A Strategy to Improve the Success of Treatment Discontinuation Buprenorphine Responders

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Detailed Data and Safety Monitoring Plan

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A. PROTOCOL SUMMARY

A1. Brief description of the protocol (Study Design)

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. Several effective medications are available to treat OUD with buprenorphine becoming the primary medication used in the community. Buprenorphine is effective for approximately 50-70% of patients and better results are achieved with the longer duration of treatment. However, the prospect of long-term opioid maintenance is not acceptable to some patients and they eventually request to stop treatment or discontinue it on their own. As many patients who had good treatment response desire to discontinue the medication there is a need to collect evidence about the best strategy to accomplish that. Opioid receptor antagonist naltrexone is approved for relapse prevention following detoxification off opioids. Naltrexone can be started as a first-line treatment following discontinuation off illicit opioids and it may also be used as an adjunct for patients who wish to discontinue buprenorphine maintenance and would like to be protected from relapse. We propose an open-label randomized outpatient trial to evaluate feasibility and efficacy of rapid buprenorphine discontinuation followed by brief course of treatment with long-acting naltrexone (XR-NTX) and to compare it to the standard method of gradual buprenorphine taper.

Individuals with 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, approximately 50 individuals, will be randomized 1:1 to: Regimen 1) buprenorphine discontinuation and outpatient transition to XR-NTX with 3 monthly injections, or Regimen 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.

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. Participants will be seen in the clinic daily where they will be monitored for up to 8 hours.

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

Regimen 2 will include a 5-week BUP taper from the maintenance dose of 8, 6, 4, or 2mg (wk 1: 6, 5, 3 or 2 mg/d, wk 2: 4, 4 , 2, or 2 mg/d, wk 3: 3, 3, 2, or 1 mg/d, wk 4: 2 or 1 mg/d, wk 5: 1 mg/d). A buprenorphine/naloxone generic product will be used.

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.

Additional injections of XR-NTX will be offered to patients who continue to express interest in remaining on the medication and are adherent to the time scheduled for the injection (4 weeks after the prior injection). In participants who use opioids and test positive, study physician will determine if it is safe to proceed with the next injection, which may involve administration of naloxone (0.8 mg im).

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 of XR-NTX 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. At each

study visits vitals and a urine toxicology for opioids (morphine, oxycodone, buprenorphine, methadone, propoxyphene, and fentanyl), THC, cocaine, benzodiazepines, amphetamines, and metamphetamines will be collected. 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.

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. A positive signal that transition from maintenance buprenorphine to XR-NTX is feasible and prevents relapse would encourage a larger trial to replicate and perhaps extend to multiple community based treatment settings. A feasible, well-tolerated, and effective method of helping patients wishing to discontinue treatment with BUP has the potential to expand the population of opioid-dependent individuals benefitting from treatment.

A2. Primary and Secondary Outcome Measures

Primary Outcome: percent of patients successfully transitioned off buprenorphine and abstinent from any opioids at the 25-week trial endpoint.

Secondary Outcomes: 1) Measures of weekly opiate withdrawal (SOWS), mood (Ham-D, BDI), anxiety (HAM-A, STAI), and sleep (MOS-SS) (continuous, longitudinal); 2) Time to relapse (survival outcome); 3) Continuing abstinence at 12 and 25 weeks (dichotomous); 4) Dichotomous weekly summary measure of use (derived by combining urine and self-report, as measured by TLFB) reflecting whether each patient had urine-confirmed opiate-free weeks over the course of treatment and urine-confirmed abstinence from all drugs (dichotomous, longitudinal); 5) Adverse events (SAFTEE) (dichotomous).

Covariates/Predictor variables: 1) Length of BUP treatment prior to randomization and the average dose; 2) Demographic characteristics (e.g., gender, age); 3) Baseline presence of co-occurring mood or anxiety disorders; 4) Baseline severity of opioid use (measured by the primary opioid, route, and quantity of illicit opioid use per using day prior to starting BUP treatment); 5) Duration of OUD, 6) Other substance use during treatment period.

A3. Inclusion/Exclusion Criteria

The following inclusion/exclusion criteria will be used for selection of participants in the proposed study.

Inclusion Criteria	**Method of Ascertainment**
1. Individuals between the ages of 18-60	ID with birth date
2. 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 patient's self-report with the prescribing records (PMP) with patient's permission

3. 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
4. Seeking buprenorphine discontinuation and willing to accept randomization to either taper from buprenorphine or injection naltrexone	Clinical interview by psychiatrist
5. Able to give written informed consent to participate in the study	Clinical Interview by psychiatrist

Exclusion Criteria	**Method of Ascertainment**
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 that is stable for the last 3 months is not exclusionary.**	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 disorder other than opioid, nicotine, and alcohol use disorder. Physiological dependence on alcohol is exclusionary. periods, blackouts)	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	Participant self-report, Clinical interview by psychiatrist, C-SSRS "yes" answers on questions 5 and/or 4
8. Currently meets DSM-5 diagnosis for an eating disorder or is underweight (BMI <18.5)	MINI interview by therapist, Clinical interview by psychiatrist
9. History of accidental opioid overdose in the last year 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) or impaired renal function (GFR<60 ml/min)	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

A4. Power calculation and sample size

The primary purpose of this proposed R21 is to estimate the 95% confidence interval (CI) for the treatment effect size, in this case the odds ratios of treatment success. The resulting 95% CIs provide considerably more information than hypothesis tests; it provides a range of plausible parameter estimates. Such range of effect sizes (especially the estimates from the lower end of the 95% CIs) can be used to conservatively estimate potential effect size in larger clinical trials. The following power calculations are only in support of this study proposal and for the purpose of sample size calculation. We assume that the observed proportion of successful BUP discontinuation in the buprenorphine taper group ranges from 30-50% (we assume higher success rate than in the previous buprenorphine taper studies due to longer period of stabilization). With 25 subjects in each arm, we have 80% power to detect a significant treatment success difference of 37% (e.g. 40% of treatment success in BUP compared to 77% treatment success in XR-NTX arm) on 5% level of significance. This is a robust effect that would be clinically meaningful.

The primary aim of this pilot study is to evaluate feasibility, tolerability, acceptability, and safety of two methods of discontinuing treatment with buprenorphine. The proposed sample size of 60 enrolled and 50 individuals randomized to two treatment arms can provide useful information for subsequent confirmatory clinical trial. We have chosen this sample size to minimize the cost and also to reach the study end within two years. 50 randomized subjects will provide large enough sample size to estimate the potential effect size in 95% confidence interval with reasonable precision.

B. TRIAL MANAGEMENT

B1. Data Collection Centers

All data will be collected at one site: New York State Psychiatric Institute's Outpatient Substance Abuse Research Service (STARS)-downtown at 3 Columbus Circle, New York, NY 10019. In our center, we have adopted StudyTrax, a comprehensive electronic system for clinical trials, which we will use to collect and manage data. As many entry forms and study calendars are already programmed, starting of a study can be expedited. Data will be analyzed using SPSS-PC, SAS, and HLM.

B2. Projected Time Table

Based on the recent rate of recruitment in our center and the planned sample size the study is estimated to take 24 months to complete.

B3. Target Population Distribution

We plan to enroll 60 participants into the study. Both males and females will be recruited. All eligible subjects are accepted; however, past experience with recruitment for other studies in this population, it is estimated that the sample will be 75% male, 60% Caucasian, 30% Hispanic or Latino, and 10% Black or African-American. These proportions are consistent with the clinical population of heroin or prescription opioid users in the city of New York and participants that we recruited in our recent treatment studies. We will make every effort to recruit minority patients in order to ensure the generalizability of our findings to the overall treatment population.

C. DATA MANAGEMENT AND ANALYSIS

C1. Data Acquisition and Transmission

Potential subjects will undergo a screening visit which will include a demographics questionnaire, medical history, physical examination, psychiatric evaluation, laboratory testing, and electrocardiogram. The MINI International Neuropsychiatric Interview will be conducted to determine current DSM-5 diagnoses. Eligible participants will be offered the opportunity to participate in the research treatment study and informed consent using the IRB-approved consent form will be obtained by the research psychiatrist.

This is an open-label randomized outpatient trial to evaluate feasibility and efficacy of a new strategy that involves rapid discontinuation of the maintenance buprenorphine dose followed by a brief course of treatment with XR-NTX and to compare it to the standard method of gradual buprenorphine taper. All patients will be followed for 25 weeks to evaluate longer-term outcomes. This is an exploratory study to collect evidence that could be used in designing a definitive efficacy trial.

The study will be entirely outpatient. Upon study entry, participants will begin clinic visits at the Substance Treatment and Research Service (STARS) clinic. All participants will visit the clinic twice weekly to provide urine toxicology, report on adverse events, and complete additional assessments (Table 1). All participants will also receive medical management, a medication adherence focused psychosocial intervention that facilitates compliance with study medication and other study procedures, and promotes abstinence from opioids and other substances.

All data will be obtained specifically for research purposes. Data will be entered and maintained in the clinical trials electronic database coded with a unique identifier assigned to each participant. Departmental, HIPPA-compliant Research Subject Registration System, will however contain participants' names.

C2. Data Entry Methods

Data collection will be achieved using a structured, integrated, network-based computerized system. Specifically, data management will include: 1) protocol management; 2) patient scheduling; 3) regulatory reporting and 4) management of research organizations, personnel, and collaborators. The research staff will collect and input data on a daily, basis to reduce the likelihood of errors. Information collection and analysis and study-specific data collection will be easily retrievable, organized, and reviewed on an ongoing basis as well.

Table 1. List and Schedule of Assessments Carried out During the Treatment Trial

	Screen	Base-line	BUP Stabiliza-tion/Taper (weekly)	NTX Induction (Daily)	Relapse Prevention (weekly)	End of study (week 25)
Medical assessments						
Blood chemistry, hematology, hepatitis panel, thyroid panel, urinalysis, ECG, physical exam	X					X
Vital Signs	X	X	X	X	X	X
Pregnancy Test	X	X	q month		q month	
Urine Toxicology	X	X	X	X	X	X
ETOH Breathalyzer	X	X	X	X	X	X
Medication Form		X	X	X	X	X
Time Line Follow Back		X	X	X	X	X
Participant						
Clinical Global Impress Scale - Self		X	X		X	X
Craving Scale		X	X	X	X	X
Spielberger State-Trait Anxiety Test		X	X		X	X
Beck Depression Inventory		X	X		X	X
Subjective Opiate Withdrawal Scale		X	X	X	X	X
Medical Outcomes Study Sleep S.		X	X	X	X	X
Locator Form	X				q month	
Investigator/Therapist						
MINI Interview for DSM-5	X					
Therapist Contact Log			X		X	
Investigator/Psychiatrist						
Systematic Assessment for Treatment Emergent Effects			X		X	X
Hamilton Depression Scale		X	X		X	X
Hamilton Anxiety Scale		X	X		X	X
Global Impression Scale -Observer		X	X		X	X
Treatment Service Review			X		X	X
End of Study Form						X

C3. Data Analysis Plan

Study Aim #1: To estimate the difference in the rate of successful transition off BUP at 25 weeks post randomization between the group that received naltrexone post-buprenorphine and the one that did not. We hypothesize that more patients will be transitioned off BUP and stable at the end of trial in the group that received XR-NTX.

Study Aim #2: To determine whether treatment with XR-NTX reduces severity of protracted withdrawal seen following BUP discontinuation.

Significance testing and preliminary analysis:

All tests for main effects will be performed at two-tailed significance α=5%. We will examine all variables for outliers, the distributions of all continuous variables will be checked for normality and if needed transformations will be used before applying parametric techniques. The distribution of demographic variables and other covariate measures at baseline in the treatment arms will be examined (means, standard deviations, proportions and 95% confidence intervals). The analysis will be adjusted by three preselected covariates (primary opioid type, length of BUP maintenance, and average dose).

Primary Analyses

Subjects treated with XR-NTX will have significantly higher rates of successful transition off BUP at the end of study compared to subjects tapered off BUP. The effect of treatment on the primary outcome will be examined using logistic regression adjusted for specified covariates (primary opioid type, length of BUP maintenance, and average dose), and described using the estimated coefficients of the treatment term in the model, the corresponding odds ratios, and 95% confidence intervals.

Secondary Analyses

Longitudinal dichotomous and continuous outcomes will be modeled with generalized linear mixed effects models using appropriate link function (logit for dichotomous outcomes) with treatment, time, treatment by time interaction, and applicable baseline outcome measure as predictors. Time to relapse will be analyzed using survival analyses and Kaplan-Meier estimators. Dichotomous outcomes will be analyzed similarly to primary hypothesis with logistic regressions. The within subject correlation will be modeled using autoregressive AR(1) structure and random effects of subject. Significant time by treatment interaction indicates different change over time between treatment groups. If the interaction between time and treatment is not found to be significant, the interaction term will be omitted and an overall treatment effect will be tested.

D. QUALITY ASSURANCE

D1. Procedures in place to ensure the validity and integrity of the data

In order to assure that collected data is valid, all raters undergo an extensive training process prior to beginning independent assessments. This involves an initial period when a trainee is a witness to evaluations and ratings conducted by an experienced rater. Subsequently trainees will conduct a series of evaluations and ratings in the presence of the trainer until a desired proficiency is obtained. Finally, all junior raters will take part in ongoing individual and group research supervision meetings where evaluation done by a trainee are presented and discussed with senior research staff.

D2. Procedures to guarantee the accuracy and completeness of the data, during data collection, entry, transmission, and analysis

In order to maximize data quality, all ratings and notes will be checked for completeness and accuracy and errors or queries are brought back to the raters for correction or clarification the same day or as soon as possible thereafter. The clinic has a Quality Assurance person who is responsible for ongoing quality

assurance. Every three months, the PI will review the number of participants enrolled, the number who completed the protocol, the number who dropped out of the protocol prior to completion (and reason why), any adverse events, procedures for assuring participant privacy and confidentiality, and the quality and integrity of the data collected. Corrective action will be taken if needed. The Quality Assurance team of the New York State Psychiatric Institute also provides semi-annual reviews of all studies to ensure completeness of data, and compliance with administrative procedures. This team regularly reports their findings to the IRB, and may prevent continuing approval for a study that is shown to have defective documentation of procedures.

E. REGULATORY ISSUES

E1. Reporting of Adverse Events

All adverse events (AE) reported by the participant or observed by the investigator will be individually listed on the Adverse Event Form (AEF). The signs and symptoms, time of onset, duration, severity, medical intervention, follow-up procedures, and suspected relationship to study drug will be reported. Any AE (clinical signs and symptoms or laboratory test) associated with the use of study drug, whether or not considered drug related, will be documented by the study psychiatrist.

All AE reports will be reviewed weekly by the clinical research staff, including Dr. Nunes, study Medical Monitor and Dr. Mariani, the medical director at STARS, and other staff physicians. If necessary, changes to the protocol or consent form to address risks suggested by the AEs will be made. Subsequently these will be reported to the Psychiatric Institute IRB.

In the event of any "serious" and/or "unexpected" adverse drug experiences, the Psychiatric Institute IRB, NIDA, and the Food and Drug Administration will be notified within 48 hours. In addition, all serious adverse events are reported to the Data and Safety Monitoring Board (DSMB). The DSMB, together with Drs. Bisaga and Nunes, will determine whether the seriousness of the event warrants removal of any participant from the study.

E2. Reporting of IRB actions to NIDA

All proposed changes/amendments to the protocol will be discussed with the NIDA Project Officer prior to IRB submission. Amendments will then be filed with the IRB. IRB approval of such amendments and updated DSM Plan will be forwarded to the NIDA project officer, and the original amendment approvals will be filed in the primary document manual.

All major IRB actions related to the protocol, will be reported to NIDA via email to the Project Officer (PO) Dr. Ann Anderson and the Science Officer (SO) Dr. Tanya Ramey within 48 hours. This communication will include a copy of the original communication from the IRB. Reportable actions of the IRB include the initial study approval, annual approvals for continuation, approvals of the proposed protocol amendments, and IRB responses to the SAE reports.

E3. Trial stopping rules

The study Data and Safety Monitoring Board may decide to recommend stopping the trial if there is an indication that a substantial proportion of participants are not able to tolerate study medication or if there is an unusually high proportion of individuals experiencing SAEs. This may be determined during weekly meetings with Dr. Bisaga (PI), Dr. Nunes (MM), and the other study investigators and discussed with NIDA's PO and SO.

E4. Disclosure of any potential conflict of interest

Any potential conflict of interest (COI) is reviewed regularly by the IRB.

F. TRIAL SAFETY

F1. Potential Risks and Benefits of Study Participation

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 relapse to use of opioids and risk of overdose. Participants who discontinued BUP will be monitored closely for signs of destabilization such as increase in cravings, or opioid use initiation. Participants who are unable to maintain abstinence off opioids will be offered resumption of maintenance treatment with buprenorphine, and once stable will be transferred to a provider in the community.

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 occurs 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 the recommended 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 limit 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 resumption of maintenance treatment with buprenorphine or with 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 overdose with its attendant risks including respiratory depression and death. Patients will be warned of the severe danger of using opiates, including trying to over-ride the blockade. Also patients who have stopped naltrexone and resume opiates will not be tolerant initially, so that the quantities of opiates self - administered prior to treatment, when they were tolerant, may be quite dangerous in the non-tolerant state. Patients will be warned of this at treatment outset and during treatment, when receiving subsequent naltrexone injections. Patients who self-administer opiates to the point of somnolence or stupor will be removed from the trial and placed back on buprenorphine or referred to inpatient unit for stabilization. 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 close monitoring of vital signs and mental status for up to 8 hours daily.

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.

Other Risks

Blood draws may cause slight discomfort at the site of needle entry, can result in infection at the site if hygienic/sterile techniques aren't used, or can result in a small bruise.

Participants will receive cash card compensation and incentives during the study that could pose a risk of providing more available funds to purchase illicit opioids. However, the form of compensation- a cash card limits this risk.

Potential Benefits of the Proposed Research

Participants will receive up to 25 weeks of free treatment.

F2. Collection and Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs)

Definitions

An **adverse event** is any unwanted experience or event occurring during the course of a clinical trial. An adverse event is defined as **unexpected** whenever the nature and severity of the event is not consistent with the known product information.

Relationship to Study Drug

The investigator will document his/her opinion of the relationship of the event to the study drug as follows:

None- the event can be readily explained by the participant's underlying medical condition or concomitant therapy, and no relationship exists between the study drug and the event. In this event, an alternative etiology must be indicated.

Unlikely-the temporal relationship between the event and the administration of the study drug is uncertain and the event can be probably explained by the participant's medical condition or other therapies.

Possible- there is some temporal relationship between the event and the administration of the study drug and the event cannot be explained by the participant's medical condition or other therapies.

Probable- the temporal relationship is compelling between the administration of the study drug and the event cannot be explained by the participant's medical condition or other therapies.

Severity

Adverse events should be graded for severity and noted in the description of the event. A severity category of mild, moderate or severe, as defined below, should be determined and entered on the appropriated AEF.

Mild- causing no limitation of usual activities.

Moderate- causing some limitation of usual activities.

Severe- causing inability to carry out usual activities

Definition of Serious Adverse Event (SAE)

An SAE is any AE, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening; the subject is at immediate risk of death from the reaction as it occurs.
- Is significantly or permanently disabling or incapacitating;
- Requires or prolongs inpatient hospitalization;
- Results in permanent disability; results in a congenital anomaly;

Significant medical events that may not result in death, be immediately life threatening, or require hospitalization may be considered to be SAEs when, based on the medical judgment, they may jeopardize the participant and may require intervention to prevent one of the outcomes defined above as SAE.

Reporting of Serious or Unexpected Adverse Events

In the event of any **"serious"** and/or **"unexpected"** adverse drug experiences during this study, the Principal Investigator will notify the following:

Amy Bennett-Staub, Department of Quality Management New York State Psychiatric Institute 1051 Riverside Drive, Unit 101 New York, NY 10032

In addition to the report to quality management, relevant data on the event and any available follow-up reports will be reported to NIDA's Project Officer Dr. Ann Anderson via email and also via using the Serious Adverse Event Tracking and Reporting System (SAETRS) within 72 hours of the event occurrence. The initial notification will indicate that the event occurred and the IRB/DSMB was notified. The PI will follow-up with the PO as the evaluation of the SAE proceeds, on whether the SAE was related or not to the trial. These follow-ups will occur as the evaluation moves forward, and not wait until the final conclusions are determined.

The Investigator will also provide written notification of the SAE to the IRB. The Incident Review Committee will also review the SAE and suggest appropriate actions and, if necessary, study modifications.

The DSMB and study PI will determine whether the seriousness of the event warrants removal of any participant from the study. Appropriate diagnostic and therapeutic measures will be instituted and the participant will be kept under observation for as long as is medically indicated. IRB actions following the

occurrence of an SAE will be reported to NIDA. Any conflict of interest in the data and safety monitoring will be disclosed. The SAEs and AEs will be reviewed by the DSMB on a regular basis.

F3. Management of SAEs and other study risks

Procedures for Minimizing Risks**:**

1) Screening Procedures

In order to minimize the risk associated with the study, subjects undergo a comprehensive medical and psychiatric evaluation during the screening procedure. The baseline medical evaluation consists of a physical examination, blood chemistry profile (including liver function tests), complete blood count, urinalysis, serum pregnancy test, urine toxicology and is designed, along with the clinical history, to detect chronic and/or unstable medical illnesses. A comprehensive psychiatric assessment is performed during the screening process, and is intended to detect and assess all past and current psychiatric disorders. The eligibility criteria (see above) are designed to minimize the medical and psychiatric risks to participants by excluding those for whom participation would place them at an increased risk. Special attention will be given to patient's concurrent use of medications. Participants on medications that meet exclusion criteria will not be included in the study. If participants have recently completed another study at STARS, we will ensure, as with other medications, that there are no drug-drug interactions with the possible recent exposure to other study medications or will ensure proper time for wash-out between studies.

2) Study Procedures

Participants will be informed about the possible side effects and risks (listed above) of taking buprenorphine and extended-release naltrexone both alone and in combination with other medications through extensive discussions with staff psychiatrist during the consent process. Participants will be told to contact the clinic if they experience any adverse effects and given the number for the 24-hr physician on-call. Participants' mental status and physical health are monitored weekly during the study period by a psychiatrist. Vital signs will be obtained at each study visit. At clinic visits, a physician will assess participants for signs and symptoms of adverse effects of study medications, noting which if any symptoms are present, the severity of the symptoms, make adjustments to study medication dose, discontinue study medication, or withdraw the participant from the study if needed.

Female participants who are engaging in sexual activity with men must use adequate methods of contraception which will be discussed repeatedly during the screening process. Serum pregnancy tests will be conducted during screening and urine pregnancy tests will be performed monthly during the study. If a female participant does become pregnant or wishes to become pregnant, study medication will be immediately discontinued, she will be withdrawn from the study, and offered continuing non-pharmacological treatment (psychotherapy).

3) Procedures to Minimize Other Risks:

With regards to the risks of blood draws, only staff trained in phlebotomy will draw blood from participants to minimize risks of infection. Participants will be warned of the possible associated discomfort and slight bruising following blood draws. They can decline blood draws at any time.

We aim to reduce the risk of using cash card reimbursements and incentives to buy drugs by keeping reimbursements at a low monetary value. The monetary incentives for completion of study related activities are felt to be modest, appropriate, and limited and also in card form. This payment schedule has been used successfully in treatment studies in our clinic and others with no observed effect of increased drug use.

With regards to risks associated with interviews, rating scales, and questionnaires, patients are informed that they may refuse to answer any questions and may ask to stop at any time. If participants become upset during the interviews/assessments, assistance will be made available to them.

4) 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, including buprenorphine, 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.

5) 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.

6) Relapse during post-medication follow-up phase

It is possible that some patients may have difficulty remaining abstinent after XR-NTX or buprenorphine are discontinued. All participants will be monitored closely during the follow-up period for signs of destabilization such as increase in cravings, or opioid use initiation. Participants who are unable to maintain abstinence off opioids will be offered resumption of maintenance treatment with buprenorphine, and once stable will be transferred to a provider in the community.

Psychiatric Monitoring and Removal from Study

Participants' mental and physical status is monitored weekly 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 throughout the study at a time.

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.

Opioid Overdose Responder Training

The Substance Abuse Treatment and Research Service (STARS) is a registered opioid overdose prevention program through the New York State Department of Health since June 2015. Our program is in compliance with 10 NYCRR 80.138 that permit non-patient specific prescriptions for naloxone, as well as shared access to and use of naloxone by appropriately trained individuals. As part of this program we offer free intranasal naloxone and training for overdose responders to any patient who self-identifies as an opioid user.

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.

Study Discontinuation

Criteria for removal from the study will include:

(1) substantial alcohol and other drug use that endangers the patient or requires a higher level of care such as inpatient or residential treatment; (2) psychiatric or medical deterioration that cannot be managed safely in the context outpatient treatment offered at the study clinics (e.g., acute suicide risk, acute medical problems); (3) Ongoing non-adherence with recommended clinical visits, absence from the clinic for more than 21 days; and (4) Pregnancy.

Patients who are exited from the trial for any reason will be offered a 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. Participants will be offer a weekly supply of buprenorphine for up to 30 days if they are being transitioned to another treatment program if they are removed from the trial. 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.

Management of SAE's

Serious adverse events (SAEs), as defined by the FDA, will be systematically evaluated at each clinic visit. Any SAE, whether or not related to study medication, will be reported to the IRB and NIDA. The initial SAE report will be followed by submission of a completed SAE report to both institutions.

In the event that a patient either withdraws from the study or the investigator decides to discontinue a patient due to SAE, the patient will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to study medication, or results in death. Outcome of SAEs will be reported to NIDA as soon as this information becomes available. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA.

G. TRIAL EFFICACY

Interim analyses are not planned for this study.

H. DATA AND SAFETY MONITORING PLAN ADMINISTRATION

H1. Responsibility for data and safety monitoring

The study Principal Investigator, Dr. Adam Bisaga, is primarily responsible for the data and safety monitoring. He will be assisted by Dr. Edward Nunes, study Medical Monitor, and other STARS staff physicians.

H2. Frequency of DSM

Ongoing data and safety monitoring will be conducted weekly during research meetings. Every three months, the PI and the medical monitor will review the number of patients enrolled, the number who completed the protocol, the number who dropped out of the protocol prior to completion (and reason why), any adverse events, procedures for assuring patient privacy and confidentiality, and the quality and integrity of the data collected. Corrective action will be taken if needed. IRB protocols and informed consent documents will be reviewed annually by the IRB. Reports of enrollment and retention and reporting of adverse events are required with these renewals. In addition, all studies involving human subjects are periodically and systematically reviewed by the New York State Quality Assurance Staff. These procedures assure protocol compliance by conducting unannounced reviews of participants' research charts, comparing research charts to the IRB protocol. All serious adverse events will be reported to the DSMB in a timely fashion. This report will also be forwarded to the NIDA's Project Staff Dr. Ann Anderson (PO) upon receipt.

In addition, a separate Data Safety and Monitoring Board (DSMB; see below for details) will meet yearly.

H3. Content of DSM report

Annually, the DSMB will prepare and submit a report to NIDA. This report will include the following:

1. Brief description of the trial
2. Baseline socio-demographic characteristics
3. Retention and disposition of study participants
4. Q.A. Issues
5. Regulatory Issues
6. AEs
7. SAEs
8. Efficacy

I. DSM BOARD PLAN

The proposed study will have a Data Safety and Monitoring Board (DSMB), that will be chaired by Dr. Frances Levin, a Division Chief, and will include Dr. Herbert Kleber, a senior investigator in the Division, and Dr. John Mariani who is a Director of the research clinic. In addition, Dr. Erik Gunderson, an experienced investigator based in the University of Virginia School of Medicine, who published research involving buprenorphine maintenance, will join the DSMB. The DSMB will meet before the study launch and annually afterwards to conduct initial and ongoing study review and review all Adverse Events that occurred in the study. The DSMB will meet within a week of the occurrence of any Serious Adverse Event (SAE). For each SAE, the Principal Investigator and covering physician will present a synopsis of how it occurred and how the incident was handled clinically. In this way the team can assess how the event was managed and if there are any recommendations that will maintain the high quality of the care that we provide to our research participants. All DSMB members will be ask to submit in writing any potential conflict of interest pertaining to the study. DSMB will prepare a report to NIDA in response to any SAE review meetings, and will submit a DSM report annually (as outlined above in section H3).