



NCT02445339

NOVEL INTERVENTIONS FOR ALCOHOL DEPENDENT FREQUENT EMERGENCY DEPARTMENT USERS:

A phase IV, randomized, open-label, non-placebo-controlled, single-center study of the feasibility, acceptability, and effect of extended-release naltrexone 380mg intramuscular injection compared to standard care on healthcare utilization, drinking, and quality of life in subjects with severe alcohol use disorders and frequent emergency department use.

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List of Abbreviations

AASE	Alcohol Abstinence Self-efficacy Scale
AST, ALT	Liver transaminase serum concentration (Aspartate and Alanine aminotransferase)
AUD	Alcohol Use Disorder
CBRD	Center for Biospecimen Research and Development
CDT	Carbohydrate deficient transferrin (quantitative measure of drinking)
CM	Care Management
CoC	Certificate of Confidentiality
CTSI	Clinical and Translational Science Institute
DSMB	Data and Safety Monitoring Board
DSM-IV/V	Diagnostic and Statistical Manual of Mental Disorders (versions 4 and 5)
EtG	Ethyl glucuronide concentration test (quantitative measure of drinking)
ED	Emergency Department
EQ-5D	EuroQoL-5D
GGT	Gamma-glutamyl transpeptidase
hcG	Pregnancy test (human chorionic gonadotropin)
HHC	New York City Health and Hospitals Corporation (Public Hospital System)
HIPAA	Health Insurance Portability and Accountability Act
IM	Intramuscular injection
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous injection
MM	Medical Management (largely based on the COMBINE study model)
MUSC	Medical Center of the University of South Carolina Laboratory
NIAAA	National Institute of Alcohol Abuse and Alcoholism
NIH	National Institutes of Health
NYU	New York University
PHI	Protected Health Information
SCID	Structured Clinical Interview for DSM disorders
SIP-2R	Short Inventory of Problems
TLFB	Timeline Follow Back
UBACC	University of California-San Diego Brief Assessment of Capacity to Consent to Research
XR-NTX	Naltrexone, extended release preparation (brand name Vivitrol)
XR-NTX+CM	Intervention arm of enhanced care consisting of XR-NTX plus care management and harm-reduction based motivation interviewing

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Study Summary

Title	Novel Interventions for Alcohol Dependent Frequent Emergency Department Users: A phase IV, randomized, open-label, non-placebo-controlled, single-center study of the feasibility, acceptability, and effect of extended-release naltrexone 380mg intramuscular injection compared to standard care on healthcare utilization, drinking, and quality of life in subjects with severe alcohol use disorders and frequent emergency department use.
Short Title	XR-NTX in ED users with AUDs
Protocol Number	S13-00928
Phase	4
Methodology	Randomized, Open Label, non-placebo (compared to standard care)
Study Duration	8 years
Study Center(s)	Single-center
Objectives	To conduct a feasibility and acceptability study of XR-NTX+CM treatment in alcohol dependent patients with frequent ED use and explore its effect on healthcare utilization, drinking, and quality of life.
Number of Subjects	300 (Pilot, N=50; Subsequent trial N=250)
Diagnosis and Main Inclusion Criteria	Alcohol use disorder and frequent emergency department use
Study Product, Dose, Route, Regimen	Extended-release naltrexone (Vivitrol) 380mg intramuscular injection every 4 weeks
Duration of administration	12 months
Reference therapy	Reference is treatment as usual (No medications)
Statistical Methodology	Formal statistical analysis is not planned for the primary aim, in which we will a) further develop and pilot procedures and b) descriptively document feasibility and acceptability of XR-NTX for frequent ED users with alcohol use disorders. To explore the intervention effect, we will generate descriptive statistics and calculate changes in scores within and between groups.

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1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

1.1 Background

Alcohol use disorders (AUDs) are common, costly, and undertreated. They exact a tremendous toll in morbidity, mortality, and suffering with far reaching implications for patients, families and society.¹⁻¹⁵ In the US, excessive alcohol use is the third leading cause of preventable death and accounts for an estimated \$223.5 billion annual cost to society.^{16,17} An estimated 4% of U.S. adults meet DSM-IV criteria for alcohol dependence,¹⁸ and the vast majority of persons with AUDs do not succeed in accessing specialty treatment.^{19,20}

Alcohol dependent patients with frequent emergency department (ED) use often receive their care exclusively in EDs. They account for a disproportionate share of healthcare visits and costs, leading to increased service demands for treatment settings and suboptimal healthcare delivery for these patients.²¹⁻³⁶ Typically, these individuals are brought to the ED involuntarily by EMS for public intoxication and have not sought care. Almost always, the ED visit represents a missed intervention opportunity as these patients are dismissed quickly with limited medical or social interventions.³² Their unabated frequent ED visits further providers' therapeutic nihilism, patients' loss of motivation for treatment, and stigma.^{32,37-39} Despite the extraordinarily high prevalence of alcohol use among ED patients, treatment or referrals for AUDs are rarely initiated in the ED, and research to develop and practically implement effective interventions is even less common.^{36,40,41} In fact, ED patients with severe AUDs are currently excluded from most research studies as they are often difficult to engage in care, are non-adherent to treatment, and suffer from alcohol-related and other comorbidities, as well as psychosocial dysfunction.^{32,42,43}

The infrastructure to support timely data-sharing and coordination of services between health and social service institutions is underdeveloped, resulting in failed navigation, frustrating providers and patients. By helping to address these difficulties, care management (CM) interventions targeting frequent ED users, including our pilot, have demonstrated reductions in the use of costly health services but have not reported an effect on drinking.^{21,32-34,44-46} Low-barrier, non-abstinence based, housing programs that include intensive care management (e.g. Housing First) have been associated with reduced use of costly public resources as well as alcohol use and alcohol-related harm.^{29,35,47-49} These community-based programs, however do not yet partner directly with EDs to coordinate care or to identify program subjects.

Well-controlled clinical trials— such as the “Combining Medications and Behavioral Interventions for Alcoholism” (COMBINE) study— have demonstrated the efficacy of behavioral and pharmacologic treatments for alcohol dependence.⁵⁰⁻⁵³ Specifically, naltrexone, an FDA-approved opioid receptor antagonist, has been shown to reduce craving, heavy drinking, and healthcare utilization and associated costs.^{51,53-63} The pharmacokinetic properties of the extended-release preparation (XR-NTX), providing steady-state medication concentrations with injections every 4 weeks, are promising and particularly well suited for this often medically disengaged population at risk of non-adherence.⁶⁴ It is safe and effective among both individuals who are abstinent and actively drinking.⁵⁴ Its feasibility in primary care and other non-specialized medical settings has been demonstrated at our institution, where effectiveness studies are ongoing.^{57,65,66} A recent pilot of XR-NTX plus harm reduction counseling in a community-based low-barrier housing program (in which abstinence is not required and intensive care management is provided) suggests a potentially more robust effect and high acceptability among a population similar to the one we are studying.⁶⁷ However, neither XR-NTX nor other pharmacotherapy for alcohol dependence has been studied in the ED. A critical need exists to refine and test the use of medications to treat alcohol dependent individuals in clinical settings where they frequently present, such as the ED.

Demonstrating that efficacious pharmacotherapy can be initiated practically in the ED, ideally as a bridge to ambulatory care, would offer a powerful boost to efforts to expand the delivery and impact of evidence-

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based alcohol treatment.

In preparation for a large definitive trial of a multimodal intervention that includes XR-NTX, we developed and tested a multidisciplinary CM intervention targeting homeless, alcohol dependent frequent ED users that coordinated healthcare, housing, and other social services through collaboration with NYC health and public health agencies.³¹ Upon each ED visit, prompted by an automated page, our ED social worker and the homeless outreach team met with participants, guided by previously developed care plans, to help coordinate ED care and offer shelter upon discharge. Assigned outreach caseworkers attempt to relocate participants into increasingly supportive settings. Care plans are informed by a cross-departmental, multidisciplinary team and updated with community partners during biweekly meetings. Plans were updated based on participants' medical, psychosocial, and housing needs, safety, and barriers to rehabilitation. In this prospective, nonequivalent pre-test post-test control group trial, we consecutively enrolled 20 participants with alcohol dependence, chronic homelessness, and 2 years of frequent ED use to receive the CM intervention. We compared this group to 20 patients recruited prospectively who received standard care, and 20 patients identified retrospectively from the previous year using the same algorithm for patient identification. ED visits, inpatient days, and direct hospital costs were reduced by medians of 35%, 56%, and 50% respectively in the six-month period after intervention ($p=0.024$; 0.20 ; 0.09). The differences-in-differences of visits in the 6 months before and after intervention compared to the two control groups are shown below (and published). Eighteen participants accepted shelter; no controls were housed. No deaths occurred in the CM group, whereas in the 2 control groups, 9 subjects died and were excluded from the visit analysis.³¹

We now propose an ED-based feasibility study comparing enhanced care that includes XR-NTX to



Table 1: Acute healthcare use was reduced in those receiving CM. The difference-in-differences of visits in the 6 months before and after intervention were compared to 2 control groups to attenuate the threat of regression to internal validity.

standard care. Our study incorporates components of efficacious interventions into a multimodal intervention customized for this unique population, including CM, housing facilitation, and pharmacological and behavioral therapy (XR-NTX, harm reduction-based motivational interview, CM). **Our overarching hypotheses are that XR-NTX + multidisciplinary care management (CM) will be feasible and will decrease acute healthcare utilization, days of heavy drinking, and improve quality of life** in a population of alcohol dependent frequent ED users.

Several aspects of this study are novel, including:

- **Initiation of pharmacotherapy for alcohol dependence in the ED.** There are no published studies of initiating treatment for alcohol or drug dependence in the ED (excluding withdrawal).
- **Potential use of ED observation** to facilitate alcohol treatment, research enrollment and procedures, and aftercare coordination. Observation units are becoming increasingly common for patients whose length of stay is expected to require 8 - 23 hours, which supports the generalizability of this model.^{68,69}
- **High degree of collaboration between health and public health institutions.** Our innovative service model will use existing social services through collaboration with the NYC Departments of Homeless Services, Fire and EMS, and Health and Mental Hygiene, as well as with community outreach providers. It is therefore feasible given limited resources. Receiving data from collaborators,

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through agreements that include database management support, will allow more robust tracking and outcomes analysis.

- **We will use an adapted, validated case-finding algorithm** to identify a cohort whose ED use is less likely to decline based on their past utilization patterns and comorbidities.^{28,70-74}
- **We will use an innovative, automated alert system, linked to hospital registration, to recruit and track participants.** This will allow us to communicate with partnering institutions and intervene in the ED, 24-hours/day, 7 days/week, rather than directing subjects to social and medical services elsewhere, when they have failed to adhere to referrals in the past.

This work is of great significance because it may provide efficacious treatment and social stability to a population that has a disproportionate impact on healthcare and societal costs, and one that traditionally does not seek or receive care in medical settings offering addiction treatment. This proposal supports the National Institute of Health–National Institute on Alcohol Abuse and Alcoholism’s (NIAAA’s) priorities to limit health disparities by expanding access to effective alcohol treatments in general clinical settings through the increased use of emerging pharmacotherapies, while disseminating treatment principles endorsed by the NIAAA Clinicians Guide.^{75,76} It has the potential to transform revolving door ED visits into an effective point of public health intervention and to incorporate the ED and its unique populations into a more integrated healthcare system.

Background: Alcohol Biomarkers

Laboratory measures of heavy drinking are needed to assist clinicians in identifying and monitoring the treatment of patients suffering from alcohol use disorders and to provide investigators with objective outcome measures in clinical trials. Recent research has provided new insights into the relationships between alcohol intake, biomarkers, and factors affecting their diagnostic validation. However, the diagnostic validation of alcohol biomarkers is incomplete and information on the sensitivities and specificities of the even the most commonly used tests have remained controversial.⁷⁷

Currently, carbohydrate-deficient transferrin (CDT) is the most specific indicator of heavy drinking and is used as a marker of excessive and chronic alcohol consumption.^{77,78} Based on the literature, the correlation between the CDT level and self-reported alcohol consumption using validated, reliable methods among alcohol consumption in alcohol dependent patients ranges from approximately $r = .35$ to $r = .60$.⁷⁹⁻⁸⁵ However, the relationship between CDT levels and alcohol intake may be influenced by age, gender, BMI, cirrhosis, smoking status, flushing, and other factors, such that the correlation among these subgroups groups is less (although, typically not powered to reach statistical significance).^{81,84} Because of potential inter-individual variation, measuring the change in CDT from an individual’s baseline as a continuous variable appears to improve performance. Recent studies have also suggested that the combination of CDT and gamma-glutamyl transpeptidase (GGT), via the equation $[0.8 \cdot \ln(\text{GGT}) + 1.3 \cdot \ln(\text{CDT})]$, has higher diagnostic sensitivity and stronger correlation with the actual amount of alcohol consumed than either of the parent compounds alone; in one study the correlation of CDT-GGT was $r = .76$; $p < .001$.^{79,82,84,86} CDT represents a ‘cutting edge’ alcohol biomarker, and one not previously studied in the context of an XR-NTX treatment trial until a current trial being conducted by Joshua Lee, MD from NYU (R01AA020836; S12-02263).

Background: OPRM1 Genomic Polymorphism

Naltrexone’s relative ineffectiveness in African American clinical trial sub-populations, including in the COMBINE trial,⁸⁷ is possibly mediated by low rates of the Asp40 OPRM1 functional allele in persons of African descent, who are primarily Asn40 homozygous.⁸⁸ This Asp40 (A118G, ‘G’ allele) OPRM1 functional single nucleotide polymorphism has been shown to be associated with successful treatment with naltrexone.^{89,90} Currently, Joshua Lee, MD from NYU (R01AA020836; S12-02263) in partnership with Charles O’Brien and Dr. Wade Berrettini’s lab from the University of Pennsylvania are prospectively assessing whether this allele is associated with retention and treatment effectiveness, potentially representing one of the first studies to assess the impact of Asp40 on XR-NTX treatment outcomes.

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1.2 Investigational Agent

Naltrexone is a pure opioid antagonist that acts as a competitive antagonist at opioid receptor sites, showing the highest affinity for mu opioid receptors.

Naltrexone for extended-release injectable suspension (XR-NTX, Vivitrol®) is an FDA-approved alcohol treatment medication. It is supplied as a microsphere formulation of naltrexone for suspension, to be administered by intramuscular injection. Naltrexone is an opioid antagonist with little, if any, opioid agonist activity.

Naltrexone is designated chemically as morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-(5 α) (CAS Registry # 16590-41-3). The molecular formula is C₂₀H₂₃NO₄ and its molecular weight is 341.41 in the anhydrous form (i.e., < 1% maximum water content). XR-NTX is provided as a carton containing a vial each of XR-NTX microspheres and diluent, one 5-mL syringe, one ½-inch 20-gauge preparation needle, and two 1½-inch 20-gauge administration needles with safety device.

XR-NTX microspheres consist of a sterile, off-white to light tan powder that is available in a dosage strength of 380 mg naltrexone per vial. Naltrexone is incorporated in 75:25 polylactide-co-glycolide (PLG) at a concentration of 337 mg of naltrexone per gram of microspheres. The diluent is a clear, colorless solution. The composition of the diluent includes carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection. The microspheres must be suspended in the diluent prior to injection.

CLINICAL PHARMACOLOGY:

Pharmacodynamics

Mechanism of Action: Naltrexone is an opioid antagonist with highest affinity for the mu opioid receptor. Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism. The administration of XR-NTX is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, XR-NTX will precipitate withdrawal symptomatology.

Occupation of opioid receptors by naltrexone may block the effects of endogenous opioid peptides. The neurobiological mechanisms responsible for the reduction in alcohol consumption observed in alcohol-dependent patients treated with naltrexone are not entirely understood. However, involvement of the endogenous opioid system is suggested by preclinical data. Naltrexone blocks the effects of opioids by competitive binding at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of opioids may result in non-opioid receptor-mediated symptoms such as histamine release.

XR-NTX is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or ethanol ingestion.

Pharmacokinetics

Absorption

XR-NTX is an extended-release, microsphere formulation of naltrexone designed to be administered by intramuscular (IM) gluteal injection every 4 weeks or once a month.

After IM injection, the naltrexone plasma concentration time profile is characterized by a transient initial peak, which occurs approximately 2 hours after injection, followed by a second peak observed approximately 2 - 3 days later. Beginning approximately 14 days after dosing, concentrations slowly decline, with measurable levels for greater than 1 month. Maximum plasma concentration (C_{max}) and area under the curve (AUC) for naltrexone and 6 β -naltrexol (the major metabolite) following XR-NTX administration are dose proportional. Compared to daily oral dosing with naltrexone 50 mg over 28 days, total naltrexone exposure is 3 to 4-fold higher following administration of a single dose of XR-NTX 380

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mg. Steady state is reached at the end of the dosing interval following the first injection. There is minimal accumulation (<15%) of naltrexone or 6 β -naltrexol upon repeat administration of XR-NTX.

Distribution

In vitro data demonstrate that naltrexone plasma protein binding is low (21%).

Metabolism

Naltrexone is extensively metabolized in humans. Production of the primary metabolite, 6 β -naltrexol, is mediated by dihydrodiol dehydrogenase, a cytosolic family of enzymes. The cytochrome P450 system is not involved in naltrexone metabolism. Two other minor metabolites are 2-hydroxy-3-methoxy-6 β -naltrexol and 2-hydroxy-3-methoxynaltrexone. Naltrexone and its metabolites are also conjugated to form glucuronide products. Significantly less 6 β -naltrexol is generated following IM administration of XR-NTX compared to administration of oral naltrexone due to a reduction in first-pass hepatic metabolism.

Elimination

Elimination of naltrexone and its metabolites occurs primarily via urine, with minimal excretion of unchanged naltrexone. The elimination half-life of naltrexone following XR-NTX administration is 5 to 10 days and is dependent on the erosion of the polymer. The elimination half-life of 6 β -naltrexol following XR-NTX administration is 5 to 10 days.

Special Populations

Hepatic Impairment: The pharmacokinetics of XR-NTX are not altered in subjects with mild to moderate hepatic impairment (Groups A and B of the Child-Pugh classification). Dose adjustment is not required in subjects with mild or moderate hepatic impairment. XR-NTX pharmacokinetics were not evaluated in subjects with severe hepatic impairment.

Renal Impairment: A population pharmacokinetic analysis indicated mild renal insufficiency (creatinine clearance of 50-80 mL/min) had little or no influence on XR-NTX pharmacokinetics and that no dosage adjustment is necessary. XR-NTX pharmacokinetics have not been evaluated in subjects with moderate and severe renal insufficiency.

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

Age: The pharmacokinetics of XR-NTX have not been evaluated in the geriatric population.

Race: The effect of race on the pharmacokinetics of XR-NTX has not been studied.

Pediatrics: The pharmacokinetics of XR-NTX have not been evaluated in a pediatric population.

Drug-Drug Interactions

Clinical drug interaction studies with XR-NTX have not been performed.

Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations and opioid analgesics.

1.3 Preclinical Data

According to the FDA prescribing information in all controlled and uncontrolled trials during the premarketing development of XR-NTX, more than 1100 patients with alcohol and/or opioid dependence have been treated with XR-NTX. Approximately 700 patients have been treated for 6 months or more, and more than 400 for 1 year or longer. In controlled trials of 6 months or less in alcohol-dependent patients, 9% of alcohol-dependent patients treated with XR-NTX discontinued treatment due to an adverse event, as compared to 7% of the alcohol-dependent patients treated with placebo. Adverse events in the XR-NTX 380 mg group that led to more dropouts than in the placebo-treated group were injection site reactions (3%), nausea (2%), pregnancy (1%), headache (1%), and suicide-related events (0.3%). In the placebo group, 1% of patients withdrew due to injection site reactions, and 0% of patients withdrew due to the other adverse events.⁸⁷

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1.4 Clinical Data to Date

A recently published meta-analysis of XR-NTX found an association with reduction in heavy drinking days (weighted mean difference -4.6%; 95% CI, -8.5% to -0.56%).⁸⁸ **XR-NTX is safe and effective among both individuals who are abstinent and actively drinking.**⁵⁴

The efficacy of XR-NTX in the treatment of alcohol dependence was evaluated in a 24 week, placebo-controlled, multi-center, double-blind, randomized trial of alcohol-dependent (DSM-IV criteria) outpatients. Subjects were treated with an injection every 4 weeks of XR-NTX 190 mg, XR-NTX 380 mg or placebo. Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Psychosocial support was provided to all subjects in addition to medication. Subjects treated with XR-NTX 380 mg demonstrated a greater reduction in days of heavy drinking than those treated with placebo. Heavy drinking was defined as self-report of 5 or more standard drinks consumed on a given day for male patients and 4 or more drinks for female patients. Among the subset of patients (n=53, 8% of the total study population) who abstained completely from drinking during the week prior to the first dose of medication, compared with placebo-treated patients, those treated with XR-NTX 380 mg had greater reductions in the number of drinking days and the number of heavy drinking days. In this subset, patients treated with XR-NTX were also more likely than placebo-treated patients to maintain complete abstinence throughout treatment. The same treatment effects were not evident among the subset of patients (n=571, 92% of the total study population) who were actively drinking at the time of treatment initiation.⁸⁷

There are no published trials of pharmacotherapy for alcohol dependence that have been conducted in the ED. Its feasibility in primary care and other non-specialized medical settings has been demonstrated at our institution, where effectiveness studies are ongoing.^{57,65,66} Our team's studies of XR-NTX for alcohol treatment include participating as a site in Garbutt's pivotal trial, an observational study demonstrating the feasibility, acceptability and likely effectiveness of 3- and 15-month courses of XR-NTX among 72 adults in Bellevue primary care clinics, and a newly initiated NIAAA R01 trial comparing it to oral NTX in primary care. Opioid treatment studies have included 4 recently completed or on-going XR-NTX vs. no medication or Buprenorphine (Joshua Lee, MD). All studies have used a simple Medical Management platform to deliver XR-NTX in general care settings. A recent pilot of XR-NTX plus harm reduction counseling in a community-based Housing First program suggests a potentially more robust effect and high acceptability among a population similar to the one we are studying.⁶⁷

1.5 Dose Rationale

XR-NTX 380mg intramuscular injection every 4 weeks is the FDA approved and recommended dosage for the treatment of alcohol dependence. We will administer XR-NTX according to these guidelines. As per the above data, the extended release preparation is favorable to the oral formulation because it helps address non-adherence. The dosage of XR-NTX 380mg has demonstrated the best efficacy while maintaining safety. The treatment duration is variable in research and clinical practice; the minimum duration is typically 3 months. Duration is generally extended in patients with more severe or refractory alcohol dependence, such as the patients we will be studying. We will plan for each subject to receive 6 months of medication and will explore continuing treatment for up to 12 months of XR-NTX.

1.6 Research Risks & Benefits

1.6.1 Risk of Study Drug

The study medication (XR-NTX, Vivitrol) was FDA approved in 2006 and will be used for the approved indication(s), so it is not an investigational drug, per se. The FDA has reviewed the protocol and determined that it meets all of the requirements for exemption from the Investigational New Drug (IND) regulations and, therefore, an IND is not required to conduct the investigation. This exemption was requested by the PI because the administration of XR-NTX may deviate slightly from its labeled-use.

XR-NTX is typically recommended for people who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment. The duration of abstinence is not specified. Patients who receive XR-NTX

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in the study may be intoxicated from alcohol when they arrive in the emergency department, but will not be enrolled until medically stable and clinically sober. Patients (potential subjects) may be placed into ED observation for the extended duration of care necessary to achieve this state. If this represents a minor deviation from the VIVITROL labeling, it may affect efficacy but should not represent an additional safety concern. XR-NTX is not aversive therapy and does not cause a disulfiram-like reaction as a result of ethanol ingestion. XR-NTX has been shown to be safe and effective among both individuals who are abstinent and actively drinking.⁵⁴ A subject's ability to abstain from drinking prior to an initial XR-NTX injection may predict treatment response.⁸⁹ However, this association has not been seen in all studies, including an XR-NTX pilot conducted in Bellevue Hospital primary care.⁶⁵ Further, the administration of XR-NTX for the treatment of alcohol dependence users in this study is consistent with current clinical care for alcohol dependent patients in other clinical settings, including Bellevue Hospital Ambulatory care. The administration of XR-NTX in our protocol is based on protocols of ongoing studies of XR-NTX for alcohol dependence in other clinical and community settings, including Dr. Joshua Lee's XR-NTX study in Bellevue Hospital ambulatory care (R01AA020836; S12-02263) and Susan Collins' study in a Seattle community housing program (R01 AA022309), which the FDA also determined was exempt from IND reporting. Also of note, the investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling or advertising of the drug. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk associated with the use of the drug product.

XR-NTX: This study provides enhanced care management and XR-NTX for treatment of alcohol dependence. According to the FDA prescribing information in all controlled and uncontrolled trials during the premarketing development of XR-NTX, more than 1100 patients with alcohol and/or opioid dependence have been treated with XR-NTX. Approximately 700 patients have been treated for 6 months or more, and more than 400 for 1 year or longer. In controlled trials of 6 months or less in alcohol-dependent patients, 9% of alcohol-dependent patients treated with XR-NTX discontinued treatment due to an adverse event, as compared to 7% of the alcohol-dependent patients treated with placebo. Adverse events in the XR-NTX 380 mg group that led to more dropouts than in the placebo-treated group were injection site reactions (3%), nausea (2%), pregnancy (1%), headache (1%), and suicide-related events (0.3%). In the placebo group, 1% of patients withdrew due to injection site reactions, and 0% of patients withdrew due to the other adverse events. Theoretically naltrexone can cause transient liver inflammation and its packaging has a boxed warning regarding the possibility of serious injury to those with active liver disease and liver function. However, recent clinical trials have demonstrated that does not appear to be hepatotoxic at recommended doses, including in individuals with mild-moderate liver impairment.^{50,54,57,65,90,91} Liver function will be monitored throughout the trial. We will accommodate (in the ED or clinic) unexpected visits related to side effects and adverse events, and the PI will be available by phone for emergency consultation at any time.

It is thought that mis-injection of XR-NTX into subcutaneous adipose tissue may cause injection site reactions. The PI has been carefully trained on the proper techniques of medication administration, including in his role as medical clinician for the National Institute on Drug Abuse Clinical Trials Network #0048 CURB study (August 2011). Any provider administering XR-NTX to study subjects will receive training as well. The PI will providing training personally and has access to supplemental webinar training resources as part of his membership in the National Institute on Drug Abuse Clinical Trials Network. Providers administering XR-NTX may include physicians, physician assistants, and registered nurses.

XR-NTX also introduces a prolonged mu opioid antagonist blockade, complicating the treatment of acute or chronic pain with opioid medications. Persons receiving XR-NTX will be provided a wallet card identifying them as an XR-NTX patient and containing the PI's name and study phone number. XR-NTX blockade can be 'overridden' due to competitive mu receptor pharmacodynamics with increasing doses of full mu agonists, which should be provided only in a monitored medical setting such as an ED. Persons with chronic pain conditions requiring opioid medications are excluded from enrollment.

Otherwise this is a study of treatment for alcohol dependence, and there is no guarantee subjects will benefit from the intervention, and thus remain chronic, heavy drinkers, with all of the short- and long-term

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risks and hazards alcohol dependence entails. The XR-NTX study represents an evidence-based, FDA approved intervention designed to treat alcohol dependence and minimize these risks, and the PI expects most subjects to derive some minimal benefit from treatment. At the index visit and any point in the trial, subjects who appear to be unable to stop drinking due to severe withdrawal symptoms or who are experiencing severely detrimental consequences of heavy drinking (i.e., job loss, homelessness) will be encouraged to seek admission to inpatient detoxification and specialty treatment through Bellevue Hospital. Withdrawal will be treated in the ED during the index visit as needed per standard of care. As per usual care, detoxification and intensive outpatient alcohol specialty services are immediately available to all subjects through the Bellevue Hospital Chemical Dependency programs, including same-day admissions to our detoxification unit, regardless of insurance status or ability to pay. Most of the risks described are well defined side effects naltrexone and XR-NTX or of on-going alcohol dependence. The additional risks of naltrexone treatment are small.

Protection against Risk (XR-NTX): As per exclusion criteria, the PI will avoid administering XR-NTX in patients with medical conditions that would contraindicate its use. Specifically, XR-NTX will not be used in: active opioid dependence (including any individual whose urine drug screen is positive for opioids), acute or chronic pain requiring opioid treatment, acute liver injury/failure (liver aminotransferase concentrations >5 times the upper limit of normal), any medical condition considered by the PI to be incompatible with or unsafe for study inclusion (e.g. expectation of future opioid needs), lack of decisional capacity, refusal to consent, currently being prescribed outpatient addiction pharmacotherapy (other than treatment of alcohol withdrawal), previous significant adverse reaction to naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or any other components of the diluent, body habitus that precludes safe injection, children, or pregnancy. The PI will assess liver function prior to enrollment; persons with liver aminotransferase concentrations >5 times the upper limit of normal will not be eligible for enrollment. Subjects will be monitored for signs and symptoms of liver injury at subsequent XR-NTX administration visits and research visits. Subjects in both arms will have their liver enzymes tested at enrollment and at the 3-, 6-, and 12-month research visits. The PI will repeat liver enzyme testing if subject receiving XR-NTX through the study has signs or symptoms of liver injury. If the liver aminotransferase concentrations rise to >5 times the upper limit of normal, the laboratory tests will be repeated in one week. If liver enzymes are persistently elevated or if the individual is symptomatic, study medication will be discontinued and the subject will be referred for a Hepatology evaluation.

In case of an emergency situation requiring opioids, subjects will be provided with a card showing that they have (or have not) received XR-NTX. This card will provide detailed information to medical personnel describing the special precautions necessary in the event that the subject should require pain management. Specifically, the amount of opioids necessary for analgesia may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged. As a result, a rapidly acting analgesic that minimizes respiratory depression is preferred and the amount of the analgesic administration titrated to the needs of the patient in a setting equipped and staffed for cardiopulmonary resuscitation. The name of and contact information for the study PI and phone number of will be listed on the card in the event of an emergency. Unexpected visits related to side effects and adverse events will be accommodated (in the ED or clinic), and the PI will be available by phone for emergency consultation at any time.

1.6.2 Other Risks of Study Participation

Confidentiality: Risks to subjects include possible loss of confidentiality/privacy pertaining to their protected health information. Subjects will be asked to provide sensitive information, including alcohol and drug use.

The PI has completed requisite IRB Human Subjects and HIPAA trainings. Any future staff will have completed requisite IRB Human Subjects and HIPAA trainings. The PI will provide any future staff with training in their responsibilities for maintaining subject confidentiality.

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The PI has obtained a Federal Certificate of Confidentiality to encompass protocol activity and subject data and ensure against the release of confidential information.

Research records will be distinct from the medical record and enrollment in the study will not be stated in the medical record to help ensure the protections of the Certificate of Confidentiality. Rather, we will state that the patient (subject) is being followed in the CPI Program (Compassion, Protection, Intervention Program- a collaborative initiative led by the PI to improve care for ED patients identified to be vulnerable. Currently, this program focuses on patients with alcohol use disorders, also known as Chronic Public Inebriates.)

The diagnosis of an alcohol use disorder will already exist in the medical record of each eligible subject prior to enrollment; this is, in part, how subjects are identified for potential eligibility (i.e. we will not be adding a new diagnosis). Including treatment for this medical condition with naltrexone and care management in the medical record should not have additional ramifications (i.e. legal, stigma), particularly since naltrexone does not have abuse potential or mind altering effects. Therefore, the receipt of XR-NTX will be noted in the patient's/subject's medical record. Study assessments (e.g. questionnaires related to alcohol and drug use, legal and social problems, healthcare utilization, quality of life, consequences of alcohol use) will only be entered into the research record (using a unique identifier). There will be no mention of these research assessments or inclusion of the data resulting from them in the medical record. Any authorizations for release of information to partnering institutions that are included in the medical record to facilitate care management (e.g. Department of Homeless Services for housing facilitation) will also not include the study title (also to ensure that the protections provided by the Certificate of Confidentiality are not jeopardized).

All research data will be entered into NYU-internal REDcap surveys administered on iPad tablet PCs using Bellevue's secure network for any data containing subject protected health information. The iPad devices have security protections that are HIPAA compliant. Data will be stored on secure servers and/or in locked filing cabinets in my locked research office with access only to authorized study personnel as identified by the principal investigator and project manager for this study. Unique identifiers will be used to identify subjects in the password- protected database. Study findings will utilize only aggregate data and no publication or presentation will involve any use of individual information.

All safeguards for storage of information on password-protected servers with HIPAA compliant firewall will be in place to ensure data are secure. There is a risk that if the iPad tablet PC is lost, it will compromise study information. To prevent this, the iPad tablet PC devices used in this research will have security features that are designed to protect the device and data while enforcing strict network and platform security including strong passwords, remote and local wipe, network security, and certificate based authentication. The extensive precautions available to iPad tablet PCs will minimize the risk involved with maintaining research databases on portable devices.

Emotional Discomfort: There is a small chance that subjects may become upset during assessments that include their history of alcohol problems, psychosocial, and other potentially sensitive topics. These risks are not beyond usual clinical procedures in alcohol treatment. We will discontinue administration of research instruments if a subject shows great discomfort or asks to terminate an interview.

Venipuncture: Subjects will have their blood drawn at the time of enrollment and during subsequent research visits to test for biomarkers genes that may predispose individuals to alcohol use disorders and/or alter the effectiveness of naltrexone. Potential risks associated with drawing blood include slight discomfort and/or bruising. Though highly unlikely, there is also the possibility of local infection, excess bleeding, clotting or fainting occurring.

Protection Against Overall Risks:

This trial will be conducted in compliance with the current version of the protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. We will obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for subject recruitment from the NYUMC IRB. Any amendments to the

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protocol or consent materials must be approved before they are implemented. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

This study offers patients randomization to FDA-approved naltrexone treatment for alcohol dependence vs. standard care. As such, the potential risks of study participation are chiefly that of data collection (time and effort, confidentiality), and otherwise consistent with the usual care and use of these medications in everyday primary care practice.

Risks from data collections and rating scales are not beyond usual clinical procedures in alcohol treatment. All appropriate actions will be taken by staff members in order to minimize the risks associated with loss of confidentiality (see above). To minimize any discomfort associated with reporting on sensitive behaviors, subjects will be informed that they may refuse to answer questions that they are not comfortable answering. Questions related to eligibility determination and monitoring of safety and treatment response are not optional. If a person declines to answer these questions, the PI will advise him/her that he/she will not be able to participate and will make a referral to other treatment if interested. As described above, the PI has obtained a Federal Certificate of Confidentiality from NIAAA/NIH to encompass protocol activity and subject data and ensure against the release of confidential information. The PI and any future staff will have completed requisite IRB Human Subjects and HIPAA trainings. The PI will provide any future staff with training in their responsibilities for maintaining subject confidentiality; we will use unique identifiers to identify subjects in the database; all data will be kept in locked filing cabinets in my locked research office or on our secure server to which only the investigators and project manager will have access. Study findings will utilize only aggregate data and no publication or presentation will involve any use of individual information.

1.6.3 Potential benefits

The benefits outweigh the risk of participation in this study. All subjects will have the opportunity to altruistically help to advance healthcare quality for others through their participation, which has been shown to be a strong motivating factor for study participation. Subjects will receive substance use treatment resources and an expedited referral to Bellevue (or other) ambulatory care for alcohol treatment and medical management. Subjects in the intervention arm will also benefit from their participation by obtaining FDA-approved treatment for alcohol dependence without the cost of medication. The individuals to be recruited traditionally receive their medical care in the ED and do not access primary or specialty ambulatory care. Thus, they are otherwise unlikely to receive and benefit from efficacious treatment for alcohol dependence. Subjects will receive care management that will include coordination with homeless outreach teams and other community peer supports and social service providers as needed. Several studies using similar interventions, including the PI's prior pilot-clinical trial, have demonstrated a range of promising outcomes that have included decreased ED use, hospitalizations, accessing benefits and housing, entry into primary care, and improved quality of life. Most of the risks described are well defined side effects of XR-NTX or of on-going alcohol dependence. The additional risks of XR-NTX treatment are small compared to the expected benefit of discontinuing alcohol use.

Importance of knowledge gained: This study will assist us in evaluating the effects of initiating treatment for alcohol dependence in the ED with XR-NTX for patients with frequent ED use and alcohol dependence. Individuals with alcohol dependence often receive their care exclusively in EDs, where referrals for substance use are rarely initiated, resulting in significant healthcare costs and diminished access to treatment of this and other chronic conditions.^{7,24-29,32-36,92-97} A critical need exists to refine and test the use of medications to treatment alcohol dependent individuals in clinical settings where they frequently present such as the ED. Knowledge gained from this study will be invaluable towards decreasing individual illness and injury as well as societal costs of dependence. This information is important in order to develop and submit a full-scale research project looking at XR-NTX in ED patients, including assessment of cost-effectiveness, which ultimately would be of great benefit to society. By examining methods to improve the feasibility and acceptability of alcohol research and treatment in the ED, this study will help improve the access to quality treatment for alcohol dependence. It also has implications for the quality and safety of research involving alcohol, vulnerable populations, and the ED

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setting. The study will examine of methods to assess and enhance decisional capacity, including the use of instruments previously validated in other populations. It will also provide information on the practical use in this population and setting of previously validated instruments commonly used in research. Informed consent procedures should provide adequate subject protection without placing unnecessary restriction on scientific advances. Investigators have an ethical responsibility to disclose information to potential subjects and to ensure that the subject has the capacity to reach a decision on the basis of the information provided. The process by which this is done is often vague; a more rigorous method will be developed in this study to help elevate the standards. Given the anticipated benefits to subjects and to society, the low risks to subjects are reasonable.

2 Study Objectives

Our primary aim is to assess the feasibility of initiating treatment in the ED with XR-NTX+CM (vs. standard care) and continuing care in cooperation with clinic providers as well as how best to assess outcomes. Secondly, we will explore its effect on various health outcomes (healthcare utilization and engagement, expenditures, drinking and consequences, quality of life) as well as the association of patient-level characteristics (e.g. sex, race, baseline drinking, health and psychosocial factors, mu opioid receptor genotype) with effectiveness. Determining both how to implement XR-NTX+CM and rigorously test its effects in the ED (phase 1) is essential before planning a large-scale effectiveness trial (phase 2).

Aim #1: To conduct a feasibility and acceptability study of XR-NTX+CM treatment in alcohol dependent patients with frequent ED use.

Hypothesis: Enrollment of a limited number of subjects will allow identification of optimal processes for a definitive trial.

Aim #2: To conduct an analysis of the effect of this intervention on healthcare utilization and engagement, drinking outcomes, quality of life, and consequences of drinking (initial analysis will be exploratory).

Hypothesis: Measuring changes in healthcare utilization, drinking metrics, and indicators of quality of life and consequences will provide preliminary data on intervention effect size on various outcomes of interest to inform the second phase, definitive trial.

Aim #3: To identify patient-level characteristics associated with effectiveness.

Hypothesis: Exploratory analysis of patient and system-level characteristics possibly associated with effectiveness will inform treatment choice to maximize the probability of successful outcome. Factors assessed will include data collected in ongoing investigations of pharmacotherapy for alcohol dependence, including mu opioid receptor (OPRM1) genotypes, to facilitate comparison across study populations and settings.

XR-NTX+CM is a potentially powerful treatment for this population that suffers poor health and psychosocial outcomes and has a disproportionate impact on public resource utilization. We will identify methods to enhance the feasibility and acceptability of its implementation in the ED as well as to ensure that future study can be carried out efficiently and rigorously. We anticipate using this data to support a future R01 application to test the intervention's effectiveness as well as other health services research that uses the ED to extend the reach of AUD treatment. This data is essential to influence policy and practices regarding evidence-based treatment for AUDs and to ensure this necessary care is provided in an integrated health system, particularly for those who only present to EDs under gravely compromised circumstances.

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3 Study Design

3.1 General Design

This a phase IV, randomized, open-label, non-placebo-controlled, single-center study of the feasibility, acceptability, and effect of initiating treatment in the ED with extended-release naltrexone 380mg intramuscular injection compared to standard care in subjects with severe alcohol use disorders (i.e. alcohol dependence) and frequent emergency department use. In the first two years, we will finalize study preparations, recruit and randomize 50 subjects for the pilot phase of this study. The duration of each subject's participation will be 12 months. Thereafter, in the second phase of study, we will enroll an additional 250 subjects (for a total of 300 subjects) to address remaining feasibility and acceptability concerns and test effects.

The study investigators (PI and RA) will collect process data, including barriers and facilitators encountered in the completion of all study procedures. For the following study procedures, study investigators (the PI and RAs) will enter data directly into NYUMC-internal REDCap system for use on portable tablet computers. NYUMC internal REDCap is HIPAA compliant and data will be stored on secure servers with access only to authorized study personnel.

Brief Synopsis of Study Procedures: The following study procedures are described in greater detail elsewhere in this protocol.

Patients will be prescreened for potential eligibility and added to an automated alert system linked to ED registration by Bellevue Care Managers as part of an ongoing quality improvement initiative. When a potentially eligible patient presents to the ED, an automated page and/or email will be delivered to the study PI and Bellevue ED social work and care management staff, prompting consultation and potential referral of the patient to study investigators (PI/RA) for recruitment (See 4.3 Subject Recruitment and Screening). ED medical providers (inclusive of ED physicians, nurses, social workers, and care managers) may also refer patients by notifying study investigators (PI/RA) when potentially eligible patients are present in the ED. The medical provider will introduce the PI/RA to clinically sober and medically stable patients who have given their permission to be approached. The PI/RA will describe the study, confirm capacity to consent using the University of California San Diego Brief Assessment of Capacity to Consent to Research (UBACC), and obtain written informed consent. The PI/RA will confirm eligibility by performing a chart and laboratory review (liver enzymes, pregnancy, urine drug screen), history and examination, and diagnostic interview to confirm alcohol dependence and assess for opioid use and chronic pain. The PI/RA will conduct research intake assessments and interview and collect blood for biomarker (17mL) and genetic (17mL) analyses. The PI/RA will randomize subjects to intervention (XR-NTX+CM) or Standard Care using a random number generator with randomly permuted blocks embedded and performed within the secure REDCap software electronically.

1. For subjects randomized to the Intervention Arm, the PI/RA will confirm the drug screen is negative for opioids prior to administering XR-NTX 380mg as an intramuscular gluteal injection. The PI/RA will facilitate a person-centered, harm-reduction-based motivational interview, and psychosocial assessment/interview to inform subjects' care-management plans. Subjects will receive a one-week referral to Bellevue ambulatory care and/or another suitable substance use treatment program for for initial Alcohol-Medical Management (MM) and will also be scheduled every 4 weeks (after most recent XR-NTX injection) for MM and XR-NTX injections. When possible, subjects who miss MM-injection visits will be navigated to clinic upon their next ED presentation and/or may receive MM and XR-NTX in the ED. XR-NTX will be administered by the PI or a provider (physician, physician assistant, or registered nurse) who is trained in the administration of XR-NTX. The schedule for MM-Injection visits is weeks 4, 8, 12, 16, 20, and 24. Subjects may be offered to continue XR-NTX treatment through this study for as many as 12 injections in total as we explore the feasibility, acceptability and potential benefits of extending treatment duration to 12 months. The schedule for potential additional MM-Injection visits is weeks 28, 32, 36, 40, and 44. The schedule for research assessment visits is weeks 12, 24, and 48; the time-window during which these research assessments may be conducted will be extremely liberal. If a scheduled date has passed, we will perform a research assessment at the

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next available opportunity (up to 6 months after the 48 week visit). During research visits, the PI/RA will repeat the assessments that were conducted at the initial enrollment visit plus adverse events and subject satisfaction and we will collect a 17mL blood sample to examine alcohol consumption biomarkers. Subject participation ends after the week-48 research visit.

2. For subjects randomized to the Standard care arm, the PI/RA will provide referral to Bellevue ambulatory care and/or another suitable substance use treatment program for MM. Facilitating this referral (and offering another referral at the close of the study) is the extent of intervention for this arm. The schedule for research assessment visits is weeks 12, 24, and 48; the time-window during which these research assessments may be conducted will be extremely liberal. If a scheduled date has passed, we will perform a research assessment at the next available opportunity (up to 6 months after the 48 week visit). During research visits, the PI/RA will repeat the assessments that were conducted at the initial enrollment visit plus adverse events and subject satisfaction and we will collect a 17mL blood sample to examine alcohol consumption biomarkers. Subject participation ends after the week-48 research visit.

Schematic Diagram of Trial

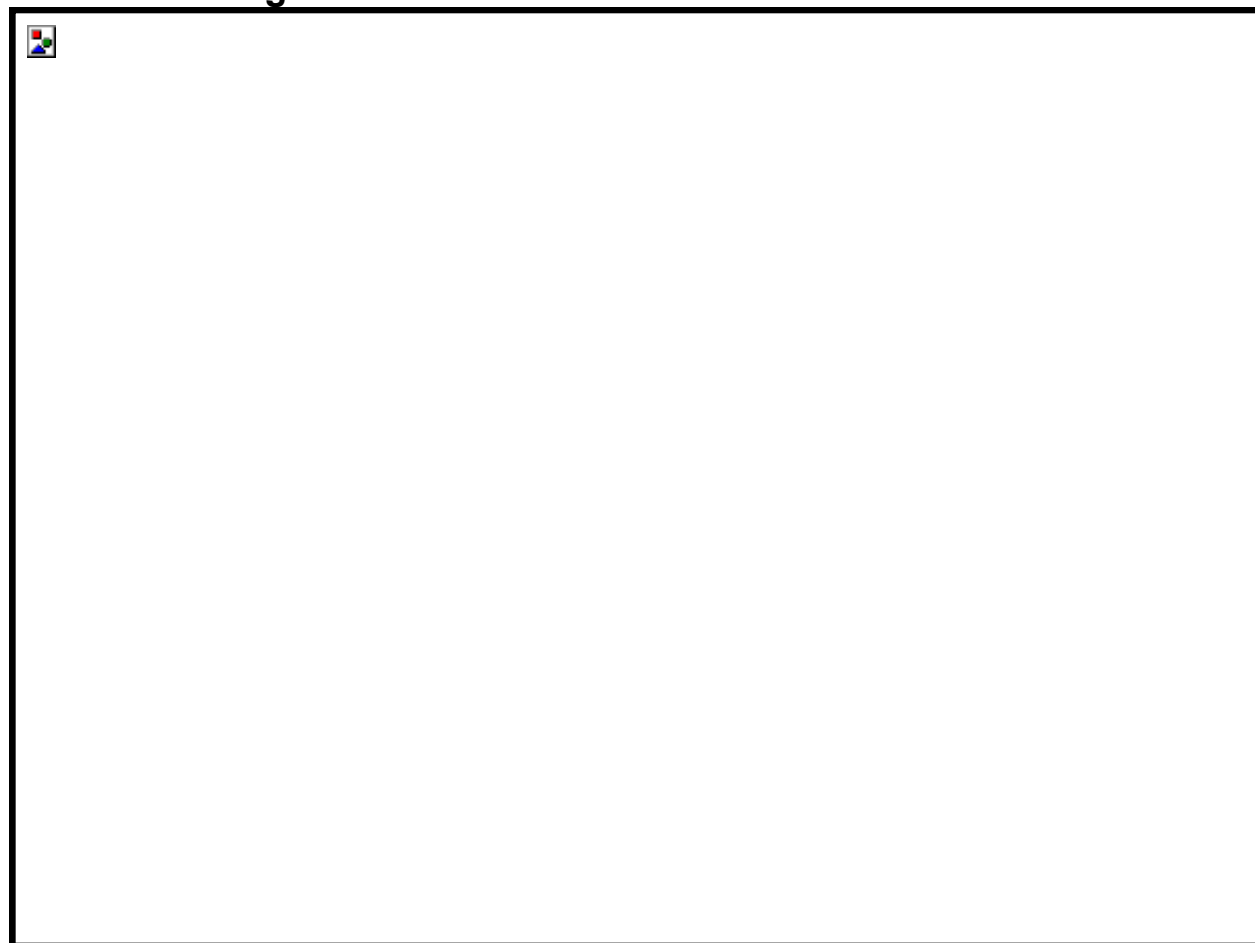


Figure 1: Schematic Diagram of Trial

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Timeline of Study Procedures:

Week	0	1	4	8	12	16	20	24	28	32	36	40	44	48
Enrollment (ED) Consent, Capacity Assessment (UBACC), DSM Diagnostic Interview (Alcohol Use), History & Physical Exam, Demographics, Below Assessments, Labs (AST, ALT, GGT, hCG, Drug Screen, genetics, CDT,), XR-NTX Arm*: Psychosocial Assessment, Interview, Care Management intake, XR-NTX injection	X													
Research Visits (ED, ED Office Space) • Broad Range of Assessments: Alcohol and Substance Use, Health Status, Psychosocial (Housing, Legal, etc.), Quality of Life, Craving, Self-efficacy, Healthcare and Services Utilization, Adverse Events • Qualitative Assessments/Interview • Laboratory: Biomarker to Quantitate Drinking	X				X			X						X
Clinical Visits (Clinic or ED) Adverse Event Form Medical Management Note		X	X*	X*	X*	X*	X*	X	X^	X^	X^	X^	X^	
Pre-Injection Labs (as needed): AST,ALT,GGT, hCG, Drug Screen	X*		X*	X*	X*	X*	X*	X^	X^	X^	X^	X^	X^	
XR-NTX 380mg injection	X*		X*	X*	X*	X*	X*	X^	X^	X^	X^	X^	X^	
Subject Compensation	40	10	25*	25*	40	25*	25*	40	25^	25^	25^	25^	25^	40

Table 2: It is expected, particularly in this challenging cohort, that subjects will not be present for all clinical (and research) visits. The pragmatic study design allows considerable flexibility—allowing delayed and missed visits. Similarly, the timing of certain clinical services (e.g. psychosocial assessments and care management intakes) will vary because they depend on the availability of existing clinical staff. The window for subjects to receive XR-NTX injections will not close until the 48th week after subject enrollment. Key: [Green] is both arms; *[Turquoise Blue] is intervention arm; ^[Grey-Blue] is intervention arm subjects that extend XR-NTX treatment.

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Anticipated Study Timeline



Figure 2: Anticipated Study Timeline: Initial phase of study – to assess feasibility and acceptability and to explore effect of XR-NTX will inform the subsequent definitive trial.

3.2 Primary Study Endpoints

To conduct a feasibility and acceptability study of XR-NTX+CM treatment in alcohol dependent patients with frequent ED use. Data will be collected to determine optimal processes for enrollment, medication administration and treatment duration, navigation to ambulatory care, and refinement of the CM model for acceptance and continuing treatment engagement.

Amongst the most pressing questions to answer in this study are the following:

1. Screening and Recruitment: We will determine which potential subjects are willing and able to provide informed consent for study participation and how to improve enrollment, including through brief remediation and placing patients in an ED observation unit.
2. XR-NTX: We will identify practical steps to maximize safety, acceptability, and adherence, and will explore extending treatment duration beyond 6 months.
3. Continuity of Care: We will explore practical measures to engage subjects in their personal healthcare and improve continuity of care, including care coordination between hospital departments and community agencies (housing case workers), scheduling flexibility, and overnight placements in ED observation with direct entry into clinics.
4. Quality Improvement: We seek to sustain and expand partnerships to improve the performance of services, tracking, and data sharing. We will explore adding components, such as emerging technologies for brief customizable interventions and tracking, and health record alerts.
5. Outcomes Analysis: We will explore various sources of data to determine the most pragmatic, rigorous approaches to analyzing outcomes in this and future studies. We will assess the performance of biomarkers as objective measures of alcohol consumption. We will continue to explore which methods of assessing patient-level characteristics are most practical in this population and comparable to measures being collected by potential collaborators.

3.3 Secondary Study Endpoints

To conduct an exploratory analysis of the effect of this intervention on healthcare utilization and engagement, drinking outcomes, and quality of life. We will also explore patient-level predictors of effectiveness.

We will explore the relative efficacy of XR-NTX+CM to standard care on decreasing acute healthcare use (ED, inpatient, Emergency Medical Services), associated expenditures, and cost-effectiveness. Secondly, we will explore effects on healthcare engagement (clinic use, medication adherence, motivation to change), alcohol quantity/frequency, alcohol-related problems, and quality of life measures.

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See Attachment #2. We will evaluate and compare the performance of CDT and the combination of CDT-GGT as an objective measure of alcohol consumption and its correlation to self-report. We will also conduct an exploratory analysis of patient and system characteristics possibly associated with effectiveness. These data will be used to inform the individualization of treatment choice to maximize the probability of successful outcome. Factors assessed will include data collected in ongoing investigations of pharmacotherapy for alcohol dependence to facilitate comparison across study populations and settings. This specifically includes the analyses modeled on those performed in an ongoing study directed by Dr. Joshua Lee (R01AA020836; S12-02263) at NYU. All data analyzed will be de-identified and linked by a unique identification number.

3.4 Primary Safety Endpoints

XR-NTX is already FDA approved for the indication of alcohol dependence for which it will be used in this study. We will repeat laboratory analyses (liver enzymes (AST, ALT, GGT), pregnancy, urine drug screen) as specified and maintain an adverse-effect profile and drug accountability log. Clinical assessments completed at week 1 and at Medical Management-Injection visits will include progress notes and Adverse Event Forms. We will use vital statistics to track mortality in the event of drop-out.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study enrollment:

- 1) English or Spanish speaking*
*Non-English Spanish speaking patients will not be enrolled initially until study documents have been translated, back translated, and approved by the IRB. This will be done through a subsequent amendment.
- 2) Emergency Department patient
- 3) Aged 18-80
- 4) Have had 6 or more emergency department visits in the last 24 months, with at least 3 visits in the last 12 months. Period of time can be extended by up to 6 months if incarcerated or institutionalized for ≥ 6 months.
- 5) Meet DSM-IV criteria for alcohol dependence or & DSM-V criteria for alcohol use disorder, moderate or severe.
- 6) Have ≥ 2 days/week of heavy drinking (>4 drinks/day)
- 7) Capable of giving informed consent.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be ineligible for study enrollment:

- 1) Current physiologic dependence to opioids
- 2) Acute or chronic pain requiring opioid treatment
- 3) Acute liver injury (liver aminotransferase concentrations >5 times the upper limit of normal)
- 4) Health condition considered unsafe for inclusion (at discretion of PI and/or attending physician)
- 5) Lack of capacity or willingness to consent
- 6) Currently prescribed pharmacotherapy for alcohol dependence (not including treatment of acute alcohol withdrawal syndrome)
- 7) Currently enrolled in research in which the intervention includes treatment for alcohol or substance use disorders, pharmacotherapy, or that may otherwise interfere with the study or patient safety.
- 8) Previous significant adverse reaction to naltrexone or diluent
- 9) Pregnant, nursing, or not using effective methods of birth control
- 10) Prisoners (as defined by Office of Human Research Protection) at the time of enrollment ARE NOT ELIGIBLE for study entry.
 - However, subjects who become prisoners after being enrolled will be included and not be withdrawn from the study

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- Patients on parole or probation are eligible for enrollment.

4.3 Subject Recruitment and Screening

All research will be performed on the NYU School of Medicine campus and Bellevue Hospital Center by study investigators. Recruitment will take place in the Bellevue ED (inclusive of Department of Emergency Medicine clinical and nonclinical space to ensure privacy and to minimize disruption of ongoing ED care). Follow up visits will occur in the Bellevue ED, Bellevue ambulatory care clinic, or the Clinical and Translational Science Institute Clinical Research Center. If it is only possible for subjects to conduct research assessments off site (e.g. due to mobility, health, or legal reasons), investigators may follow up with subjects off site.

4.3.1 Prescreen:

Potentially eligible patients will be identified in part through an administrative database search of Bellevue Hospital billing records. The data received includes a list of patients (name, date of birth, medical record number, number of visits) who had 6 or more ED visits within a 24-month period, with at least 3 visits in the past 12 months, and who were assigned an alcohol-related diagnosis; we will receive two years of data at a given time. Patients who have met this threshold are considered high-risk and added to an automated alert system to facilitate potential intervention. This alert system was first developed as part of a Medicaid High Cost Care Initiative demonstration project (PI: Raven, R# 06-336 and 06-412).⁷³ It remains in use for various quality improvement initiatives, including for the population being studied-frequent ED users with alcohol dependence. Dr. McCormack remains involved in the process of identifying high-risk patients with substance abuse diagnoses via his role as a member of Bellevue Hospital care management committees.

The high-risk patients added to the alert system are “Prescreened” as potentially eligible for study inclusion because, by definition, all will meet the visit threshold and were previously assigned an alcohol-related diagnostic code. They will be added to the briefly, aforementioned alert system. Upon registration of potentially eligible patients in the ED, an automated alert will be delivered by secure email to the ED social worker, care manager, and the study PI (Dr. McCormack). This alert triggers consultation by the social worker or care manager (as part of the quality improvement initiative) and alerts Dr. McCormack of a potential candidate for study inclusion. This system also ensures patients are identified promptly to facilitate for enrollment and for follow-up assessments.

ED staff/providers (inclusive of ED physicians, nurse practitioners, nurses, social workers, health coaches, and care managers) also may notify study investigators (PI/RA) of potentially eligible ED patients, who may not have been identified through the alert system (e.g. due to miscoded diagnoses, outdated patient lists, and/or the alert system being unavailable for maintenance, etc.). These patients may be added to the alert system (if appropriate). Staff referrals to the study do not necessarily need to originate from the alert system, as long as eligibility criteria are met. Research staff will remind ED clinical staff about the study and its eligibility criteria to help ensure appropriate referrals.

4.3.2 Screen (in Bellevue ED):

Recruitment will be triggered primarily by the aforementioned alert system or ED staff referral. Screening will be performed via convenience sample, dependent on the availability of the study investigators (PI/RA). Recruitment during days, nights, and weekends will be scheduled to capture a representative sample. A limited number of patients may be held overnight in ED observation, providing additional opportunities for enrollment. We may oversample women and minorities to reach enrollment targets.

Prior to approaching a patient for potential enrollment, the PI/RA will speak with ED staff/provider caring for the patient to ensure that the patient is appropriate and willing to be approached. The provider will introduce the PI/RA to clinically sober and medically stable patients who have given their permission to be approached. The PI/RA will describe the study to the patient.

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4.3.3 Capacity Assessment, Informed Consent, and Enrollment

The PI and RA will obtain subjects' written informed consent only after assessing their capacity to consent using the following stringent procedures. The recruitment process will specifically address the likelihood that the subjects may have a compromised capacity to consent. Subjects will not be enrolled until clinically sober and medically stable. Subjects may be (re)assessed multiple times during their ED visit(s) as needed—and therefore will have multiple opportunities to be enrolled. We will use techniques shown to improve comprehension in informed consent procedures such as using a lower reading level, using larger typeface, quizzing and having multiple individuals providing the information. The PI will provide sensitivity training of investigators/RAs regarding difficult behaviors and limited comprehension and assessment of subject capacity to consent.

The PI/RA will assess subject's understanding of the study and capacity to consent to it using the **University of California San Diego Brief Assessment of Capacity to Consent to Research (UBACC)** (Attachment #2). The UBACC 10-item questionnaire is a 5-minute, easy-to-use, and validated tool, which we have studied in this population.^{43,98} It rates the basic elements of capacity (understanding, appreciation, reasoning, and ability to express a choice) to identify subjects with questionable capacity to consent to a specified research project. The UBACC assessment occurs after informing potential subjects about the study. Thus, first the RA/PI will review each page of the informed consent document with the patient, pausing to reassess comprehension throughout the process. Then, the RA/PI will administer the UBACC. Once the RA/PI confirms the subject's comprehension (with the UBACC), the RA/PI will request the patient's signature and provide the patient with a copy of the signed consent document. If, at any point during the consent process, the RA/PI does not believe the subject comprehends the study procedures the patient will not be enrolled at that time, but he or she may be eligible in the future. Patients who are not able to successfully complete ("pass") the UBACC may be further assessed by psychiatry consultation.

In addition, the PI/RA will ask the subject to consent to being audio recorded (for qualitative interviews, counseling sessions, and quality assurance monitoring). If the patient declines to provide their written informed consent to be recorded, the subject may still participate in the study (i.e. audio recording is optional).

Subjects may be required to sign separate authorization forms for release of their personal health information to and from entities involved in their care, including care managers, case workers, housing facilitators, health providers, and government agencies/institutions. These data will be used to help coordinate and facilitate health and social needs and track outcomes. The purpose of this will be primarily clinical, rather than research. Each institution will ensure protection of PHI. All institutions, with the exception of the NYC Department of Homeless Services, are HIPAA covered entities. All Institutions will consult their respective IRBs; the NYC Fire Department Emergency Medical Services will use the IRB of the NYC Department of Health and Mental Hygiene.

4.3.4 Additional Post-Consent Eligibility Assessment

After obtaining informed consent, we will confirm eligibility by performing a chart and laboratory review (liver enzymes, pregnancy, urine drug screen), history and examination, diagnostic interview to confirm alcohol dependence, and assessment of opioid use and chronic pain.⁹⁹ See also Sections 4.1 and 4.2 for Inclusion and Exclusion Criteria.

4.3.5 Subject Randomization

Subjects will be randomly assigned to one of two arms: Intervention or Standard Care. The randomization will be completed using a random number generator with randomly permuted blocks in blocks of 2, 4, and 6 subjects. Randomization is embedded and performed within the secure REDCap software electronically. After subjects have provided their informed consent to participate in the study, are determined to be eligible for it, and have completed all baseline assessments, the RA or PI will click on the randomization button in REDCap for the treatment assignment.

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4.3.6 Expected Human Subjects Characteristics

Based on preliminary studies, this population will have a mean age 50 ± 10 , and be predominantly male, ethnically diverse, be without other usual source of care, and be precariously housed or homeless. Approximately forty-five percent of Bellevue patients are of Hispanic/Latino ethnicity (representing many countries), 40% are African American (including Caribbean and African immigrants), 10% are Asian American. Overwhelmingly, the major payers are Medicaid, Bad Debt and Charity Pools from state and federal programs. Based on studies of this population, including our own, comorbidities are expected to include concurrent mental illness, nicotine and other substance use, and untreated chronic conditions, often related to chronic alcohol dependence. In a recent dataset of 129 individuals with frequent Bellevue ED use an assigned alcohol-related diagnosis, 124 were male and 5 were female. This marked disparity among frequent ED users with AUDs has been consistently observed at Bellevue and internationally.^{34,100-}

¹⁰³ There will be no special outreach programs to recruit females or minorities since subjects will be drawn from patients receiving care at the Bellevue Hospital Emergency Department and must meet study inclusion criteria. We will purposefully recruit females by using a lower threshold of baseline visits for their addition to the alert system used in the recruitment procedure (but all subjects will meet inclusion criteria as defined). This same procedure will be performed, as needed to ensure ethnic diversity that is representative of the overall Bellevue population.

Prisoners (at the time of enrollment), pregnant females, persons under the age of 18 or over the age of 80, and persons who lack decisional capacity, or do not consent to the study will not be included. Additional exclusionary criteria exist for those recruited for the clinical intervention trial, including active opioid dependence, acute or chronic pain requiring opioid treatment, acute liver injury/failure (liver aminotransferase concentrations >5 times the upper limit of normal), any medical condition considered by the PI to be incompatible with or unsafe for study inclusion (e.g. expectation of future opioid needs), previous significant adverse reaction to naltrexone, body habitus that precludes safe injection, or individuals currently being prescribed outpatient addiction pharmacotherapy. If a woman becomes pregnant during the study she will be removed from the study and appropriately referred. We have chosen to include an age range to 18 to 80 to reduce confounding influences. To our knowledge, XR-NTX has not been studied in persons over the age of 80 or under the age of 18; persons of this age will not be included in this pilot study. All Federal rules regarding vulnerable subjects will be incorporated into the study protocol, and reviewed by the NYU IRB.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

- Subjects will be withdrawn from the study who: withdraw consent, become pregnant, develop a health condition in which XR-NTX is contraindicated (including need for opioid pain control). Abrupt termination of study treatment should not affect subject safety beyond its disease mitigating effects on alcohol dependence. Appropriate referral will be made for ongoing and/or alternative addictions treatment for all subjects withdrawn from the study.
- Subjects who are not adherent to the research protocol treatment schedule will not be withdrawn. XR-NTX administration will be allowed to resume after missed visits/injections, which is expected in this patient population due to subject-level factors such as psychosocial challenges, potential incarceration or transient medical conditions that may prevent or delay safe injection (e.g. elevation in aminotransferase elevation >5 times the upper limit of normal). The window for subjects to receive XR-NTX injections will not close until the 12th month after subject enrollment. Contraindications to treatment re-initiation (opioid dependence) will be reassessed.
- To help minimize attrition and departure from protocol, we will provide incentives for subject visits, use previously piloted care coordination and subject tracking measures, and allow considerable flexibility through the pragmatic design of the study.

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4.4.2 Data Collection and Follow-up for Withdrawn Subjects or Lost to Follow-Up Subjects

If a subject withdraws consent to participate in the study, we will attempt to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period. We will also seek permission to record the full data set on such subjects to fully support the analysis. At the time the subject consents to participating in the study, we will obtain their permission to contact additional sources as described below in the event we are unable to collect survival data from the subject. Methods to contact subjects will include, if possible, several phone calls on different days of the week and time of day, calls to next of kin, communication with community peer supports (case-worker, case manager, housing outreach personnel, etc.), electronic messaging, and certified letters. We will also use locator information available in health records, (e.g. Bellevue Hospital Medical Record, New York City Department of Homeless Services outreach data, New York City Fire Department and Emergency Medical Services transport data). We will track mortality data through vital statistics for subjects who are lost to follow up.

5 Study Drug

5.1 Description

Extended-release naltrexone (XR-NTX) 380mg (4 mL) will be administered as an intramuscular gluteal injection. Naltrexone is an opioid antagonist with little, if any, opioid agonist activity. This study will use an extended-release depot form of naltrexone (XR-NTX, Vivitrol®) that is FDA-approved treatment for alcohol dependence. XR-NTX is supplied as a microsphere formulation of naltrexone for suspension, to be administered by intramuscular injection. The microspheres consist of a sterile, off-white to light tan powder that is available in a dosage strength of 380 mg naltrexone per vial. The microspheres will be suspended in a clear, colorless diluent (polylactide-co-glycolide) prior to injection.

Pharmacodynamics/Kinetics

Duration: I.M.: 4 weeks

Distribution: V_d : ~1350 L; widely throughout the body but considerable inter-individual variation exists

Metabolism: Extensively metabolized via noncytochrome-mediated dehydrogenase conversion to 6-beta-naltrexol (primary metabolite) and related minor metabolites; glucuronide conjugates are also formed from naltrexone and its metabolites

Protein binding: 21%

Half-life elimination: I.M.: naltrexone and 6-beta-naltrexol: 5-10 days

Time to peak, I.M.: Biphasic: ~2 hours (first peak), ~2-3 days (second peak)

Excretion: Primarily urine (as metabolites and small amounts of unchanged drug)

5.2 Treatment Regimen

Extended-release naltrexone (XR-NTX) dose at 380mg (4 mL) will be administered as an intramuscular gluteal injection every 3 to 4 weeks for a total of as many as 12 doses. XR-NTX administration will be planned to occur every 28 days, but XR-NTX may be given as early as every 21 days depending on subject's clinical response and scheduling needs, which is consistent with usual clinical care. We will plan for each subject to receive 6 months of medication and will explore continuing treatment for up to 12 months of XR-NTX.

The duration of XR-NTX has not been established. We expect this population having a severe form of AUD may benefit from a longer duration of treatment.

5.3 Method for Assigning Subjects to Treatment Groups

Subjects will be randomized to intervention or standard care using a random number generator with randomly permuted blocks, in blocks of 2, 4, and 6 subjects. Randomization is embedded and performed within the secure REDCap software electronically. After subjects have provided their informed consent to

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participate in the study, are determined to be eligible for it, and have completed all baseline assessments, the RA or PI will click on the randomization button in REDCap for the treatment assignment.

5.4 Preparation and Administration of Study Drug

Extended-release naltrexone (XR-NTX, VIVITROL) dose at 380mg (4 mL) will be administered as an intramuscular gluteal injection. XR-NTX (VIVITROL) will be prepared and administered by a healthcare professional (trained physician, physician assistant, or registered nurse) using aseptic technique at the FDA approved dosage using recommended administration techniques detailed below.

The PI has been carefully trained on the proper techniques of medication administration, including in his role as medical clinician for the National Institute on Drug Abuse Clinical Trials Network #0048 CURB study (August 2011). Any provider administering XR-NTX to study subjects will receive training as well. The PI will providing training personally and has access to supplemental webinar training resources as part of his membership in the National Institute on Drug Abuse Clinical Trials Network. Providers administering XR-NTX may include physicians, physician assistants, and registered nurses.

The entire carton should be stored in the refrigerator (2-8 °C, 36-46 °F). Unrefrigerated, XR-NTX (VIVITROL) Microspheres can be stored at temperatures not exceeding 25 °C (77 °F) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25 °C (77 °F). XR-NTX (VIVITROL) should not be frozen.

Parenteral products should be visually inspected for particulate matter and discoloration prior to administration.

1. Remove the carton from refrigeration. Prior to preparation, allow drug to reach room temperature (approximately 45 minutes).
2. To ease mixing, firmly tap the XR-NTX (VIVITROL) Microspheres vial on a hard surface, ensuring the powder moves freely.
3. Remove flip-off caps from both vials. DO NOT USE IF FLIP-OFF CAPS ARE BROKEN OR MISSING.
4. Wipe the vial tops with an alcohol swab.
5. Place the 1 inch preparation needle on the syringe and withdraw 3.4 mL of the diluent from the diluent vial. Some diluent will remain in the diluent vial.
6. Inject the 3.4 mL of diluent into the XR-NTX (VIVITROL) Microsphere vial.
7. Mix the powder and diluent by vigorously shaking the vial for approximately 1 minute. Ensure that the dose is thoroughly suspended. A PROPERLY MIXED SUSPENSION WILL BE MILKY WHITE, WILL NOT CONTAIN CLUMPS, AND WILL MOVE FREELY DOWN THE WALLS OF THE VIAL.
8. Immediately after suspension, withdraw 4.2 mL of the suspension into the syringe using the same preparation needle
1. Select the appropriate needle for an intramuscular injection based on subject's body habitus:
 - a. 1.5 inch TERUMO® Needle
 - b. 2 inch NEEDLE-PRO® Needle
2. Remove the preparation needle and replace with appropriately selected administration needle for immediate use.
3. Peel the blister pouch of the selected administration needle open halfway. Grasp sheath using the plastic pouch. Attach the luer connection to the syringe with an easy clockwise twisting motion.
4. Seat the needle firmly on the needle protection device with a push and clockwise twist.
5. Pull the sheath away from the needle - do not twist the sheath because it could result in loosening the needle.
6. Prior to injecting, tap the syringe to release any air bubbles, then push gently on the plunger until 4 mL of the suspension remains in the syringe. THE SUSPENSION IS NOW READY FOR IMMEDIATE ADMINISTRATION.
7. Administer the suspension by deep intramuscular (IM) injection into a gluteal muscle, alternating buttocks per monthly injection. Remember to aspirate for blood before injection.

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8. If blood aspirates or the needle clogs, do not inject. Change to the spare needle provided in the carton and administer into an adjacent site in the same gluteal region, again aspirating for blood before injection.
9. Inject the suspension in a smooth and continuous motion. XR-NTX (VIVITROL) must NOT be given intravenously or subcutaneously.
10. After the injection is administered, cover the needle by pressing the needle protection device against a flat surface using a one-handed motion away from self and others. Visually confirm needle is fully engaged into the needle protection device. DISPOSE OF USED AND UNUSED ITEMS IN PROPER WASTE CONTAINERS.

5.5 Subject Compliance Monitoring

We know this is a challenging population to work with, and anticipate that part of the feasibility study will be to address expected difficulties specific to this population for enrollment, initiating pharmacotherapy, coordinating aftercare, and collecting outcomes data necessitates additional feasibility and exploratory work. We will make substantial efforts to maximize participation and adherence and minimize attrition by incorporating strategies used successfully by our research team and network of collaborators.^{57,65,104-106} We expect our flexible, patient-centered approach, achieved through robust collaboration, feedback, and technology, will significantly help achieving these goals. Measures to facilitate success are informed by our qualitative interviews and our pilot study; measures will include simplifying navigation to health and social services by intervening directly through pre-formulated care plans at all hours and days – contemporaneous with subjects' ED visits- and building trust by addressing basic needs (food, hygiene, shelter, transportation). Our approach incorporates the fundamental principles of addiction treatment and emphasizes improving access to effective treatment tailored to address the unique needs of each individual.^{76,107} Methods to ensure subject contact subjects will include, if possible, reminder phone calls on different days of the week and time of day, calls to next of kin, communication with community peer supports (case-worker, case manager, housing outreach personnel, etc.), electronic messaging, and letters. We may also use locator information available in health records, (e.g. Bellevue Hospital Medical Record, New York City Department of Homeless Services outreach data, New York City Fire Department and Emergency Medical Services transport data).

If a subject misses a dose, he/she should be instructed to receive the next dose as soon as possible. There are no data to specifically address re-initiation of treatment. Subjects reinitiating treatment with XR-NTX need to be opioid-free at the time of dose administration.

5.6 Prior and Concomitant Therapy

As per eligibility criteria, patients actively being treated with pharmacotherapy for opioid or alcohol dependence (not including treatment of alcohol withdrawal syndrome) will not be eligible for study inclusion. Otherwise, subjects may receive any concomitant medical therapy.

5.7 Packaging

Dosage Form: XR-NTX (VIVITROL) is an injectable suspension for single use. VIVITROL contains 380 mg of naltrexone in a microsphere formulation per vial (337 mg of naltrexone per gram of microspheres) and 4 mL diluent.

XR-NTX (VIVITROL) is supplied in single use cartons. Each carton contains one 380 mg vial of XR-NTX (VIVITROL) microspheres, one vial containing 4 mL (to deliver 3.4 mL) diluent for the suspension of VIVITROL, one 5-mL prepackaged syringe, one 1-inch 20-gauge needle, two 1.5-inch 20-gauge needles and two 2-inch 20-gauge needles with needle protection devices: NDC 65757-300-01.

For additional information, visit www.vivitrol.com or call 1-800-848-4876

Manufactured and marketed by: Alkermes, Inc. 852 Winter Street Waltham, MA 02451-1420. Revised: October 2010.

5.8 Blinding of Study Drug

There will be no blinding in this open-label study.

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5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Drug will be provided at no cost to the subject. Alkermes (manufacturer) will provide 225 VIVITROL kits (XR-NTX doses) free of charge. If additional kits are required, we will approach Alkermes to request donation of additional kits or we will purchase the kits. Drugs will be obtained from Alkermes and shipped to the PI, Dr. McCormack, via Fisher through a site called Cenduit, and stored in non-Article 28 Space within a locked refrigerator (purchased specifically for use in this study) within secure administrative office space in the NYU Department of Emergency Medicine within Bellevue Hospital Center.

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site. We will maintain a drug accountability binder, which includes temperature logs, medication inventory logs, a standard operating procedure document, drug destruction forms/logs, manuals for study-drug and refrigerator management, package inserts, shipping receipts, and original prescriptions (as requested by the CTSI pharmacy). This binder is stored in a locked cabinet in the PI's office.

5.9.2 Storage

Study medication will be stored in non-Article 28 Space within a locked refrigerator (purchased specifically for use in this study) within secure administrative office space in the NYU Department of Emergency Medicine within Bellevue Hospital Center. The entire dose pack should be stored in the refrigerator (2 - 8°C, 36 - 46°F). Unrefrigerated, XR-NTX (VIVITROL) can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose the product to temperatures above 25°C (77°F). VIVITROL should not be frozen. A temperature log will be maintained.

Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. A properly mixed suspension will be milky white, will not contain clumps, and will move freely down the wall of the vial.

For additional information, visit www.vivitrol.com or call 1-800-848-4876.

5.9.3 Dispensing of Study Drug

Study medication, XR-NTX, will be obtained by study investigators from the locked study refrigerator. XR-NTX will be administered directly to each subject by a trained physician, physician assistant, or registered nurse. Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site or shipped back to Alkermes will be documented in the study files. (Alkermes, Inc. 852 Winter Street Waltham, MA 02451-1420)

6 Study Procedures

See also:

Section 3: *Study Design (also contains study overview and Attachments #4-6)*

Section 4.3: *Subject Recruitment and Screening.*

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Attachment 4: Schematic Diagram of Trial (also in Section 3.1)

Attachment 5: Timeline of Study Procedures (also in Section 3.1)

Attachment 6: Anticipated Study Timeline (also in Section 3.1)

It is expected, in this challenging cohort, that subjects will not be present for all clinical (and research) visits. The pragmatic study design allows considerable flexibility—allowing delayed and missed visits. The window for subjects to receive XR-NTX injections will close 52 weeks after enrollment. The schedule for research assessment visits is weeks 12, 24, and 48; the time-window during which these research assessments may be conducted will be extremely liberal. If a scheduled date has passed, we will perform a research assessment at the next available opportunity (up to 6 months after the 48 week visit). Research visits may be conducted up to 28 days prior to- or 90 days after- date in which research visits are due. The below described procedures are the “ideal” conditions that are not expected in this “real world” study. Non-completion of all procedures and deviation from intended schedule is expected and will not be considered protocol violations.

For the following study procedures, study investigators (PI/RA) will enter data directly into NYUMC-internal REDCap system for use on portable tablets or computers. NYUMC internal REDCap is HIPAA compliant and data will be stored on secure servers with access only to authorized study personnel. Any paper forms containing protected health information will be stored in a locked filing cabinet within the locked office of the PI. Data will be linked to the subjects using a unique identifier.

Study Setting: Research will be performed on the NYU School of Medicine campus and Bellevue Hospital Center by study investigators. Recruitment will take place in the Bellevue ED (inclusive of Department of Emergency Medicine clinical and nonclinical space to ensure privacy and to minimize disruption of ongoing ED care). Follow up visits will occur in the Bellevue ED, Bellevue ambulatory care clinic, or the Clinical and Translational Science Institute Clinical Research Center. If it is only possible for subjects to conduct research assessments off site (e.g. due to mobility or health), investigators may follow up with subjects off site.

Study Personnel: The PI will be responsible for all aspects of the study. The study investigators (PI, Co-Investigators, and RAs) will collect process data, including barriers and facilitators encountered in the completion of all study procedures. The PI and RA will conduct study procedures related to screening, the enrollment visit (week 0), and the research visits at weeks 12, 24, and 48. Biologic samples (blood/urine) will be collected by the PI, study clinicians, or clinical staff on duty. Providers administering XR-NTX may include physicians, physician assistants, and registered nurses. Medical Management and subsequent XR-NTX injections will be performed by trained Bellevue ambulatory care or ED providers. Care Management will be facilitated by Bellevue staff and/or community support staff.

Subject Compensation: Subjects will be compensated \$40 at enrollment and upon completion of research visits at months 3, 6, and 12. Subjects in both arms will also be compensated \$10 after the first (week 1) medical management visit. Subjects in the intervention arm will receive \$25 for each XR-NTX injection/clinical visit. In the event that the subject has a research visit and injection visit on the same day, the subject will only be compensated for the research visit. Certain costs associated with arranging transportation of subjects, study personnel, and/or other staff will be reimbursed for paid by covered by the study when necessary. Subjects will also receive food and small gifts in an effort to build trust.

Laboratory Procedures

Whenever possible, blood specimens to be collected for the purposes of this study will be collected at the same time as blood that is being collected for the clinical management of the patient (i.e. to avoid repeat venipuncture). In some instances, this venipuncture will occur before the patient (potential subject) has provided his or her written informed consent to participate in the study. The specimen(s) will not be processed and will be destroyed if the patient does not consent to the study. The rationale for this is to minimize study-related risks; it has been discussed with and recommended by the Data and Safety Monitors.

1. It is possible to eliminate the risks of venipuncture for the study by collecting the research specimens with venipuncture that is planned already for clinical purposes. Potential risks

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associated with drawing blood include slight discomfort and/or bruising. Though highly unlikely, there is also the possibility of local infection, excess bleeding, clotting or fainting occurring.

2. The quantity of blood being obtained for research purposes, 34mL (2.3 tablespoons) is negligible and loss of this volume of blood poses no added harm.
3. Because of the nature of the ED setting and need to address acute problems rapidly, delaying initial venipuncture may disrupt or delay clinical care and/or negatively impact ED staff productivity. Thus, delaying venipuncture in order to first complete the lengthy informed consent process would be potentially harmful.

Clinical Laboratory Analysis

Laboratory studies that are necessary to assess subjects' eligibility to receive XR-NTX will be performed as part of their clinical care and performed through the Bellevue laboratory. These tests include serum liver function tests and urine hCG (pregnancy test). We may elect to use urine pregnancy tests purchased with study funds (at no cost to subjects) to expedite procedures. As an added safety measure, we will purchase and use urine drug screens that are capable of detecting opioids, like methadone and buprenorphine, that may not be detected using the earlier generation drug screens. This will be performed at no cost to subjects.

Serum Collection and Processing for Biomarker Analyses

Carbohydrate-deficient transferrin (CDT), and gamma-glutamyl transpeptidase (GGT). will be used to quantitate heavy drinking.^{79,80,82,83,108,109} Co-investigator Joshua Lee, MD, will serve as advisor in this aspect of the study.

Biomarker analyses will be conducted for research purposes primarily at 4 time points per subject (enrollment, months 3, 6, and 12). Each blood sample will be labeled with a unique subject ID number and the visit number obtained. No identifiable information will be included on the specimen tubes and only the PI and RA will have access to the list linking subjects to their ID Number assignment. Upon collection, the blood specimens will be delivered to the NYULMC Center for Biospecimen Research and Development (CBRD) where they will be stored until processed. The serum will be divided and aliquoted into multiple vials. Cryovial(s) containing at least at total of at least 400 microliters of serum will be shipped in batches to the Medical University of South Carolina Center (MUSC) laboratory for CDT analysis. Serum specimens (cryovials) in excess of what is required by the MUSC laboratory to perform the CDT analysis will be retained in the NYULMC CBRD until the end of the study (or until processed). This procedure of retaining the "left-over" vials will help ensure that serum is available perform additional analyses, including in the event that a specimen is lost or damaged, and/or for further biomarker, protein, or genomic analyses. GGT will be processed immediately as part of the liver enzyme analysis (see above, Clinical Laboratory Analysis); however, GGT may be processed with the specimens collected for CDT analyses (by MUSC or NYULMC) if not obtained clinically. The whole blood specimens (for genomic analyses) will be stored in the NYULMC CBRD for future processing. (Laboratory is to be determined.) Only study team members and CBRD/Clinical Laboratory staff will have access to the stored specimens. Samples will be destroyed once processed; all samples will be destroyed prior to the end of the study.

- 8.5mL of whole blood will be collected and will be stored in a -20C or -80C freezer.
- 8.5ml of blood will be collected in a serum separator vacuum tube. Centrifuge at 1500 X g for 10 minutes until clot and serum are separated. Pipette serum into the appropriately labeled plastic cryovials, cap cryovial tightly. Place into small microaliquot freezer storage boxes (or similar) and place in -30 to -80 freezer for storage. Vial(s) containing at least at total of at least 400 microliters of serum will be sent to MUSC for analyses. Remaining serum-containing vials will be stored at NYULMC CBRD as stated above. Samples will be destroyed once processed; all samples will be destroyed prior to the end of the study.

Blood Collection and Processing for Genomic Analyses

Of the patient-level characteristics analyses we will conduct (Aim 3), the OPRM1 genotypic analysis is of particular interest, because the Asp40 (A118G, 'G' allele) OPRM1 functional single nucleotide polymorphism (i.e. the mu opioid receptor genotype, where naltrexone acts) has been shown to be associated with successful treatment with naltrexone.^{89,90} The association this and other genomic polymorphisms, biomarkers, and protein level changes is an active area of research with new data and

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laboratory techniques emerging constantly. As such, the laboratory and exact procedures we will use to process the specimens is to be determined.

Whole blood for genomic analyses will be obtained once; this will occur at enrollment typically, but may be obtained at a later visit. Genomic blood draws will not be performed on subjects who become prisoners. As mentioned in the previous section, we will also store serum (the excess of what is drawn for biomarker analyses), which may be suitable for biomarker, protein, and genomic analyses. Each blood sample will be labeled with a unique subject ID number and the visit number of the specimen obtainment. No identifiable information will be included on the specimen tubes and only the PI and RA will have access to the list linking subjects to their ID Number assignment. Upon collection, the blood specimens will be delivered to the NYULMC CBRD, where they will be stored for future processing. (Laboratory is to be determined.) Only study team members and CBRD staff will have access to the stored specimens. Samples will be destroyed once processed; all samples will be destroyed prior to the end of the study. Whole Blood Collection, Processing, Storage for DNA OPRM1 analysis Instructions:

- 17mL of whole blood will be collected for DNA processing. The sample will be stored in a -20C or -80C freezer.

6.1 Visit 1: Day 0

Enrollment; Bellevue ED (PI and RA perform)

- Upon presentation of a potentially eligible patient to the ED, an automated page will be delivered to the Bellevue ED social worker, care manager, and study PI triggering enrollment procedures. Alternatively, ED staff may directly refer a patient to the study team (PI/RA) for potential enrollment. (See 4.3 Subject Recruitment and Screening)
- The ED staff/provider will introduce the PI/RA to potentially eligible patients who have given their permission to be approached.
- The PI/RA will obtain written informed consent for study after confirming capacity to consent using the UBACC (Described in Section 4.3), and obtain optional consent for audio recording. Subjects who decline to participate in audio recording may remain in the study.
- The PI/RA will confirm eligibility by performing a chart and laboratory review (liver enzymes, pregnancy, and urine drug screen - if already completed), history and examination, and diagnostic interview to confirm alcohol dependence and assess for opioid use and chronic pain.
- Draw blood for liver enzymes (AST, ALT, GGT) (8.5mL), biomarker/CDT (17
- mL), and genomic (17mL) analyses as per instructions above (Section 6.0: Laboratory Procedures). As stated above, in cases when blood is being collected clinically, research specimens may be collected prior to a subject providing written informed consent- in order to prevent repeat venipuncture.
- Conduct research intake assessments and interview.
 - Data collected will include demographic information and assessment of a broad range of subject characteristics using validated, reliable instruments and qualitative interviewing techniques that are widely-used. We will use questionnaires to assess heavy drinking days and other substance use (TLFB, Form 90),¹¹⁰⁻¹¹³ craving,¹¹⁴ and quality of life and health, consequences, psychosocial status, and utilization of services (SIP-2R, EuroQoL-5D (EQ-5D), Form 90).¹¹⁴⁻¹¹⁸ Attachment #2 contains the full instruments from which selected questions and measures have been taken. Additional instruments are included that will serve as “back-up” instruments to replace measures that cannot be reliably completed by subjects (i.e. ongoing feasibility testing).
- Randomization of subjects to intervention (XR-NTX+CM) or Standard Care using a random number generator with randomly permuted blocks with allocations embedded within REDCap software.
- Collect process data on enrollment procedures.
 - We will collect data and reason for non-inclusion for all subjects approached but not enrolled and time and attempts required for enrollment (e.g. delayed enrollment due to inebriation, instability, capacity).

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- We will collect data on barriers and facilitators and other data related to completion of assessment measures (with some refinements made during pilot phase).

Intervention Arm:

1. PI will administer XR-NTX 380mg as an intramuscular gluteal injection (after urine drug screen is confirmed to be negative for opioids).
2. PI/RA will facilitate a harm-reduction based motivational interview and psychosocial assessment with the social worker or care manager (if available) that focuses on harm reduction and identification of subjects' goals and needs to inform ongoing care management plan. PI will train future staff. See therapy manual - Attachment #3. Subjects' healthcare, housing, and social assistance will be coordinated through the CM model.³¹
3. Notify homeless services outreach of subject if homeless. Subject will be assigned a homeless outreach case worker and be offered shelter if eligible.
4. Provide referral to Bellevue Chemical Dependency clinic (or a suitable alternative) for ongoing alcohol-medical management. Subjects will be navigated directly to the clinic on their enrollment visit if possible. Subjects will receive a one-week referral to Bellevue ambulatory care for initial Alcohol-Medical Management (MM) and will also be scheduled every 4 weeks (or after most recent XR-NTX injection) for MM and XR-NTX injections (for a total of up to 12 injections).
5. Provide card containing the PI's contact information, dates of XR-NTX administration, and relevant medication information for medical personnel.

Standard Care Arm:

- Typical care consists of patients being discharged once clinically sober/stable with or without an unscheduled referral to primary care clinic. Patients may receive limited care management or counseling. In this changing healthcare environment, we expect standard care to evolve naturally and may include care management for this patient population.
- We will provide expedited referral for follow up care and substance use resources.

Subjects in both the intervention and standard care arms will be compensated \$40 at the completion of the enrollment visit.

6.2 Visit 2: Week 1

Both Arms, Clinical Visit - Medical Management (MM) Visit (Ambulatory Care or ED)

- Subjects in both arms will be referred to Bellevue ambulatory care as scheduled for an initial visit for Alcohol-Medical Management (MM) to assess and manage adverse events, treatment effects, and support the goals of reducing the harms associated with alcohol use.
- Data will be extracted from the clinical note, including adverse events or concerns.
- Subjects in intervention arm who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care. Subjects will be given a week 4 appointment.
- Subjects in the Standard Care Arm have no further clinical intervention beyond the initial referral but will have research assessments at weeks 12, 24, and 48. Any ongoing medical care will be left to the discretion of their (non-study) treating providers.

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6.3 Visit 3: Week 4

Intervention Arm Only: Clinical Visit- Medical Management and Injection Visit (Ambulatory Care or ED)

- Assessment of adverse events, medical management note.
- Repeat laboratory analysis according to XR-NTX prescribing guidelines, (urine pregnancy test if of childbearing potential; liver enzyme analysis if exhibiting signs or symptoms of liver injury). Approximately 8.5ml of blood will be drawn if applicable.
- Administer XR-NTX 380mg as an intramuscular gluteal injection.
- Those who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care.

6.4 Visit 4: Week 8

Intervention Arm Only: Clinical Visit- Medical Management and Injection Visit (Ambulatory Care or ED)

- Assessment of adverse events, medical management note.
- Repeat laboratory analysis according to XR-NTX prescribing guidelines, (urine pregnancy test if of childbearing potential; liver enzyme analysis if exhibiting signs or symptoms of liver injury). Approximately 8.5ml of blood will be drawn if applicable.
- Administer XR-NTX 380mg as an intramuscular gluteal injection.
- Those who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care.

6.5 Visit 5: Week 12

Intervention Arm Only: Clinical Visit- Medical Management and Injection Visit (Ambulatory Care or ED) and Research Visit

- Assessment of adverse events, medical management note.
- Repeat laboratory analysis according to XR-NTX prescribing guidelines, (urine pregnancy test if of childbearing potential; liver enzyme analysis if exhibiting signs or symptoms of liver injury). Approximately 8.5mL of blood will be drawn if applicable.
- Administer XR-NTX 380mg as an intramuscular gluteal injection.
- Those who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care.

Both Arms: Research Visit (ED)

- Repeat research assessments and interview that was conducted at the initial intake/enrollment visit (see above, Week 0) plus assessment of adverse events and subject satisfaction.
- Draw 17mL of blood serum to test for biomarkers (CDT) and 8.5ml of serum for liver function tests (AST, ALT, and GGT).
- If a scheduled research visit date has passed, we will perform a research assessment at the next available opportunity (up to 6 months after the 48 week visit). Those who miss appointment will be contacted through methods described in Section 4.4.2.

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6.6 Visit 6: Week 16

Intervention Arm Only: Clinical Visit- Medical Management and Injection Visit (Ambulatory Care or ED)

- Assessment of adverse events, medical management note.
- Repeat laboratory analysis according to XR-NTX prescribing guidelines, (urine pregnancy test if of childbearing potential; liver enzyme analysis if exhibiting signs or symptoms of liver injury). Approximately 8.5mL of blood will be drawn if applicable.
- Administer XR-NTX 380mg as an intramuscular gluteal injection.
- Those in intervention arm who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care.

6.7 Visit 7: Week 20

Intervention Arm Only: Clinical Visit- Medical Management and Injection Visit (Ambulatory Care or ED)

- Assessment of adverse events, medical management note.
- Repeat laboratory analysis according to XR-NTX prescribing guidelines, (urine pregnancy test if of childbearing potential; liver enzyme analysis if exhibiting signs or symptoms of liver injury). Approximately 8.5mL of blood will be drawn if applicable.
- Administer XR-NTX 380mg as an intramuscular gluteal injection.
- Those who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care.

6.8 Visit 8: Week 24

Intervention Arm Only: Clinical Visit- Medical Management and Injection Visit (Ambulatory Care or ED)

- Assessment of adverse events, medical management note.
- Repeat laboratory analysis according to XR-NTX prescribing guidelines, (urine pregnancy test if of childbearing potential; liver enzyme analysis if exhibiting signs or symptoms of liver injury). Approximately 8.5mL of blood will be drawn if applicable.
- Administer XR-NTX 380mg as an intramuscular gluteal injection.
- Those who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care.

Both Arms: Research Visit (ED)

- Repeat research assessments and interview that was conducted at the initial intake/enrollment visit (see above, Week 0) plus assessment of adverse events and subject satisfaction.
- Draw 17mL of blood serum to test for biomarkers (CDT) and 8.55ml of serum for liver function tests (AST, ALT, and GGT).
- If a scheduled research visit date has passed, we will perform a research assessment at the next available opportunity (up to 6 months after the 48 week visit). Those who miss appointment will be contacted through methods described in Section 4.4.2.

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6.9 Visit 9: Week 28

Intervention Arm Only: Clinical Visit- Medical Management and Injection Visit (Ambulatory Care or ED)

- Assessment of adverse events, medical management note.
- Repeat laboratory analysis according to XR-NTX prescribing guidelines, (urine pregnancy test if of childbearing potential; liver enzyme analysis if exhibiting signs or symptoms of liver injury). Approximately 8.5mL of blood will be drawn if applicable.
- Administer XR-NTX 380mg as an intramuscular gluteal injection.
- Those who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care.

6.10 Visit 10: Week 32

Intervention Arm Only: Clinical Visit- Medical Management and Injection Visit (Ambulatory Care or ED)

- Assessment of adverse events, medical management note.
- Repeat laboratory analysis according to XR-NTX prescribing guidelines, (urine pregnancy test if of childbearing potential; liver enzyme analysis if exhibiting signs or symptoms of liver injury). Approximately 8.5mL of blood will be drawn if applicable.
- Administer XR-NTX 380mg as an intramuscular gluteal injection.
- Those who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care.

6.11 Visit 11: Week 36

Intervention Arm Only: Clinical Visit- Medical Management and Injection Visit (Ambulatory Care or ED)

- Assessment of adverse events, medical management note.
- Repeat laboratory analysis according to XR-NTX prescribing guidelines, (urine pregnancy test if of childbearing potential; liver enzyme analysis if exhibiting signs or symptoms of liver injury). Approximately 5mL of blood will be drawn if applicable.
- Administer XR-NTX 380mg as an intramuscular gluteal injection.
- Those who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care.

6.12 Visit 12: Week 40

Intervention Arm Only: Clinical Visit- Medical Management and Injection Visit (Ambulatory Care or ED)

- Assessment of adverse events, medical management note.
- Repeat laboratory analysis according to XR-NTX prescribing guidelines, (urine pregnancy test if of childbearing potential; liver enzyme analysis if exhibiting signs or symptoms of liver injury). Approximately 8.5mL of blood will be drawn if applicable.
- Administer XR-NTX 380mg as an intramuscular gluteal injection.
- Those who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care.

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6.13 Visit 13: Week 44

Intervention Arm Only: Clinical Visit- Medical Management and Injection Visit (Ambulatory Care or ED)

- Assessment of adverse events, medical management note.
- Repeat laboratory analysis according to XR-NTX prescribing guidelines, (urine pregnancy test if of childbearing potential; liver enzyme analysis if exhibiting signs or symptoms of liver injury). Approximately 8.5mL of blood will be drawn if applicable.
- Administer XR-NTX 380mg as an intramuscular gluteal injection.
- Those who miss appointment will be contacted through methods described in Section 4.4.2. Follow up will be performed in the ED if subject cannot be navigated to ambulatory care.

6.14 Visit 14: Week 48 – Study closure

Both Arms: Research Visit (ED)

- Repeat research assessments and interview that was conducted at the initial intake/enrollment visit (see above, Week 0) plus assessment of adverse events and subject satisfaction.
- Draw 17mL of blood serum to test for biomarkers (CDT) and 8.5ml of serum for liver function tests (AST, ALT, and GGT).
- If a scheduled research visit date has passed, we will perform a research assessment at the next available opportunity (up to 6 months after the 48 week visit). Those who miss appointment will be contacted through methods described in Section 4.4.2.
- We will also provide subjects in both arms a referral for follow up care and substance use resources (if needed).

7 Statistical Plan

7.1 Sample Size Determination

Naltrexone has not demonstrated a robust treatment effect; however, most studies did not use the XR-preparation, are limited by poor adherence, and did not include this higher-severity population or other intervention components. We do not know what the “ideal” population for XR-NTX is, but posit that it may have a greater effect size in this more severely affected population than amongst the higher socioeconomic status population historically targeted. A recent pilot of XR-NTX suggests a possible greater effect (and acceptability) in a population similar to ours.⁶⁷ Our literature search yielded no studies of initiating pharmacotherapy for alcohol dependence in the ED. There are only limited data on XR-NTX effects on several long-term outcomes of interest, including healthcare use, treatment engagement, and quality of life measures. ED-based case management studies demonstrate promising healthcare utilization outcomes, but most were uncontrolled and overestimated effect because of regression to the mean. The heterogeneity in study designs, interventions, and cohort characteristics precludes meta-analysis.^{21,31,33,34,44-46}

Determining sample size is challenged by limitations in the existing data and heterogeneity of populations. Definitively testing the relative effects of intervention components may require additional arms with as many as 75 to 200 subjects in each.^{51,54,57,60,65,90,119,120} Thus, we chose to start with the strongest intervention and compare it to standard care to maximize the likelihood of seeing an effect and of exploring effect size on various outcomes. The 2-arm design will minimize the loss of power and allow us to focus on the primary goal of assessing feasibility.

The first phase of study will be a feasibility and acceptability study, through which we will obtain preliminary data to inform the power analysis for the subsequent definitive trial. In the first phase, we plan to pilot the study in 50 subjects. In the second phase of study, we project enrolling 125 subjects in each of the two arms to definitively test the intervention’s effect on multiple outcomes of interest. Thus, we

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project enrolling a total of 300 subjects in both phases. These estimates are founded in the current literature and the analyses, hypotheses, and predictions of experts in the field.

Joshua Lee, MD's ongoing study (R01AA020836) comparing the effectiveness of oral naltrexone to XR-NTX in alcohol dependent primary care patients has a targeted enrollment of n=117 in each of the two arms to detect a 20% absolute difference in primary clinical outcomes based in the Fisher's exact test with a projected power of 90%. Susan Collins, PhDs' (R01 AA022309) four-arm RCT of alcohol dependent homeless individuals recruited from a community housing program (XR-NTX + Counseling, Placebo + Counseling, Counseling alone, Treatment as Usual) will enroll a total of 300 patients (N=75/arm). This study population is similar to the one we will be studying.

A sample of 125 subjects per arm would allow us to detect a moderate effect size (Cohen's d of slightly less than 0.40) to provide power of 0.80 or greater at $\alpha < .05$. Another consideration when determining sample size is to power the study to detect the reduction in ED visits that would entirely offset the cost of medication. The institutional costs of a dose of Vivitrol (XR-NTX) is comparable to the estimated institutional cost of a single ED visit to Bellevue Hospital (according to the New York State Institute Cost Review). To detect a difference of ≥ 6 ED visits (i.e. a 6 month course of Vivitrol) between study arms comprised of subjects having a mean of 22 ± 15 ED visits per year (per our pilot study data), would require 100 subjects per arm with $\alpha = 0.05$; $\beta = 0.20$ or, more conservatively, 133 subjects per arm with $\alpha = 0.05$ and $\beta = 0.10$.

Sample Size - Performance of Biomarkers as an objective measure of Alcohol Consumption:

Based on the literature, the correlation between the CDT level and self-reported alcohol consumption using validated, reliable methods among alcohol consumption in alcohol dependent patients ranges from approximately $r = .35$ to $r = .60$.⁷⁹⁻⁸⁵ However, the relationship between CDT levels and alcohol intake may be influenced by age, gender, BMI, cirrhosis, smoking status, flushing, and other factors, such that the correlation among these subgroups groups is less (although, typically not powered to reach statistical significance).^{81,84} Because of potential inter-individual variation, measuring the change in CDT from an individual's baseline as a continuous variable appears to improve performance. Recent studies have also suggested that the combination of CDT and gamma-glutamyl transpeptidase (GGT), via the equation $[0.8 \cdot \ln(\text{GGT}) + 1.3 \cdot \ln(\text{CDT})]$, has higher diagnostic sensitivity and stronger correlation with the actual amount of alcohol consumed than either of the parent compounds alone; in one study the correlation of CDT-GGT was $r = .76$; $p < .001$.^{79,82,84,86}

We will determine the correlation between serum biomarker values and self-reported alcohol intake ascertained using the timeline followback method, which is reliable, validated, and widely used in addictions research. For our sample size calculation, the null hypothesis is there is no correlation between CDT value and reported consumption. The alternative hypothesis uses the values found in literature. The sample size calculation for each of these studies uses a type I error of 0.05. The correlation between alcohol intake and CDT level with a sample size 49, a correlation coefficient 0.39 can be detected with power 0.8. Correlation between change in CDT to change in drinking with a sample size 61, a correlation coefficient 0.35 can be detected with power 0.8. All sample size calculations are done by PASS (Power Analysis and Sample Size) 2008. See also Table 3. The first phase of study, N=50, has the approximate power required to test the primary hypotheses. We will also pool the results of Phase 1 subjects with those enrolled in phase 2.

Author	Study Results		N required
	r	p	
Mikkelsen	0.39	0.006	49
Hietala	0.59	<.001	20
Anton (all)^	0.35	<.05	61
Anton (outliers removed)^	0.54	0.001	24
Kim (flushers only)#	0.608	<.01	18

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Kim (non-flushers only) [#]	0.274	<.01	102
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Table 3: Sample size calculation results. Ha: $R0 < > R1$. The value “N required” shows the required sample size with power 0.8 and Type I Error 0.05. ^The correlation increased from $r=.35$ to $r=.54$ after removal of three outliers. #The Asian cohort was stratified into persons who do and do not flush upon alcohol consumption.

7.2 Statistical Methods

7.2.1 Data Collection and Variables: (Table 2)

Study investigators/RAs will enter data directly into NYUMC-internal REDCap for use on iPad portable tablet computers.

Feasibility: The PI/RA will collect process data, including barriers and facilitators encountered in the completion of all study procedures, including data and reason for non-inclusion for all subjects approached but not enrolled.

Clinical Assessments: We will also extract data from assessments completed by clinical staff, which will include Medical Management and XT-NTX administration progress notes, Adverse Event Forms,¹²¹ and laboratory data (liver enzymes (AST, ALT, GGT), pregnancy, urine drug screen), which is consistent with prior and ongoing XR-NTX studies at our institution (PI: Joshua Lee).^{57,65}

Research Assessments (Aim 2): We will collect demographic information and assess a broad range of subject characteristics using validated, reliable questionnaires and other instruments that are widely-used, including in ongoing XR-NTX studies, and for which trainings are available. Data collection at enrollment and months 3, 6, and 12 will include several outcome variables of interest that we have broadly classified as drinking metrics, healthcare utilization, and quality of life. The 30-day Timeline Follow-Back (TLFB) for heavy drinking days is the standard method for assessing self-reported alcohol consumption.^{110,111} The Economic Form 90 notably was used in the COMBINE study and is currently in use by in ongoing alcohol research for assessment of a broad range of health and public sector services utilization (including medical, self-help, legal services) and cost-effectiveness analyses.^{112,113,119,120} The Short Index of Problems Related to Alcohol (SIP-2R),¹¹⁷ and EuroQol-5D (EQ-5D) will be used for quality of life assessments.^{115,116} We will also conduct a 30-minute semi-structured qualitative interview and assess craving (Penn Alcohol Craving Scale),¹¹⁴ Self-Efficacy (Alcohol Abstinence Self-Efficacy Scale (AASE)),¹²² and Patient Motivation and Satisfaction scales. We will collect blood levels of carbohydrate deficient transferrin and GGT, which are biomarkers used together to objectively quantitate heavy drinking.^{79,80,82,83,108,109} We will ascertain healthcare utilization by triangulating data from Bellevue/HHC hospitals databases, EMS ambulance transports to all NYC EDs, Medicaid claims data, and subject self-report.

Attachment #2 contains the full instruments from which selected questions and measures have been taken. Additional instruments are included that will serve as “back-up” instruments to replace measures that cannot be reliably completed by subjects (i.e. ongoing feasibility testing). Of note, we have included assessments and measures used by other investigator’s studying XR-NTX for alcohol dependence so that we may perform similar analyses and draw comparisons through potential future collaboration. These investigators (potential future collaborators) specifically include Drs. Joshua Lee at NYU and Susan Collins at University of Washington (R01AA020836; R01 AA022309). To clarify, we will not use data from their studies nor share any identifiable data with these investigators, but rather perform analyses similar to those employed in their investigations.

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7.2.2 Statistical Analysis Plan

Aim 1: Feasibility and Acceptability:

Formal statistical analysis is not planned for this primary aim, in which we will a) further develop and pilot procedures and b) descriptively document feasibility and acceptability of XR-NTX for frequent ED users with severe AUDs. Process data collected will be used to determine optimal processes for enrollment, medication administration, navigation to ambulatory care, and conducting assessments. Proportions will be generated for potential subjects who (1) are able and willing to consent; (2) accept injections, (4) attend clinic appointments, (5) complete planned 3-, 6-, and 12-month assessments. Subjects' acceptability will be assessed via interviews and questionnaires. We will extract qualitative themes from interview transcripts to inform the further development of intervention and improve acceptability.¹²³

Safety Monitoring: We will repeat laboratory analyses as specified and maintain an adverse-effect profile and drug accountability log.¹²¹ We will use vital statistics to track mortality in the event of drop-out.

Aim 2: Analysis of Effect:

- a. We will explore the relative efficacy of XR-NTX+CM to standard care on decreasing acute healthcare use (ED, inpatient, other (ambulance, detoxification)) and associated expenditures.
- b. Secondly, we will explore effects on healthcare engagement (clinic use, medication adherence, self-efficacy, motivation to change), alcohol quantity/frequency, alcohol-related consequences, quality of life measures, and cost-effectiveness.
- c. We will triangulate data sources for outcome measures to explore their correlation and to address missing data. Of specific interest, we will assess the performance of biomarkers (CDT and GGT, combinations) as an objective measure of changes in heavy drinking, which will inform the design of the second phase of study (definitive trial).

Although randomization would predict equal distribution of cofounders, we will examine their distribution and adjust accordingly. Interactions or confounding may occur between outcome domains (e.g. quality of life may have an effect on healthcare utilization); other cofounders may include age, race, sex, socioeconomic status, comorbidities, and social stability. See Figure 3.

We will ascertain healthcare utilization by triangulating data from subject self-report (Form 90)^{112,113} and from various other sources (pending availability), including Bellevue Hospital and New York City Health and Hospitals Corporation databases, partnering hospital medical records, EMS database of ambulance transports to all NYC EDs, and Medicaid claims data. We will report expenditures as reimbursement payments and/or using Medicaid payment rates as a cost proxy.

We will use a mixed-methods approach with questionnaires and instruments (See 7.2.1) that are widely-used as well as database analyses to assess heavy drinking days and other substance use (TLFB, Form 90),¹¹⁰⁻¹¹³ craving (Penn Alcohol Craving Scale),¹¹⁴ self-efficacy (AASE),¹²² and quality of life (EQ-5D), consequences related to drinking (SIP-2R, Form 90), health and psychosocial status and utilization of services (Form 90).¹¹⁴⁻¹¹⁸ Changes in heavy drinking will also be assessed (secondarily) via analysis of biomarkers (CDT and GGT combinations will be tested); described below in Aim 2c (below).^{112,113} Multiple endpoint variables will not be normally distributed. We will generate descriptive statistics to characterize subjects, describe the distribution of baseline health and functioning, and calculate changes in severity scores. We will adopt a mixed methods approach to identify relationships between these variables. We will use independent t-tests or Wilcoxon rank-sum tests to compare pre-treatment variables of the two groups, and paired t-tests or Wilcoxon signed-rank tests to test pre- to post-treatment changes within each group. We will conduct an intention-to-treat analysis of healthcare use and expenditures for the 6- and 12-month periods before and after intervention using differences-in-differences multivariate linear regression modeling and repeated measures analysis. Correlations between the triangulated outcome measures will be assessed and inform the second phase of study.

Short-term estimates of costs and effectiveness will be obtained using a combination of pre-specified medical record and survey endpoints using methods described by Dr. Joshua Lee in his protocol # S12-

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02263. Cost assessment will be conceptually similar to recently published analyses of the COMBINE interventions and will include medical and non-medical costs as well as payer and societal costs (Form 90.^{112,113} Effectiveness assessment will include alcohol consumption measures, quality of life, consequences, and the EQ-5D. The EQ-5D is among the most commonly used quality-of-life measure for informing cost-effectiveness analyses because it has minimal respondent burden, is well validated, and it yields utilities (preference-based measures on a scale of 0 to 1), the desired input for cost-effectiveness models. Because costs are skewed, incremental costs will be assessed using ordinary least squares and median regression models with covariates for treatment intervention and other relevant factors, and conditional models may be used because of cost data that may include “zeros.”

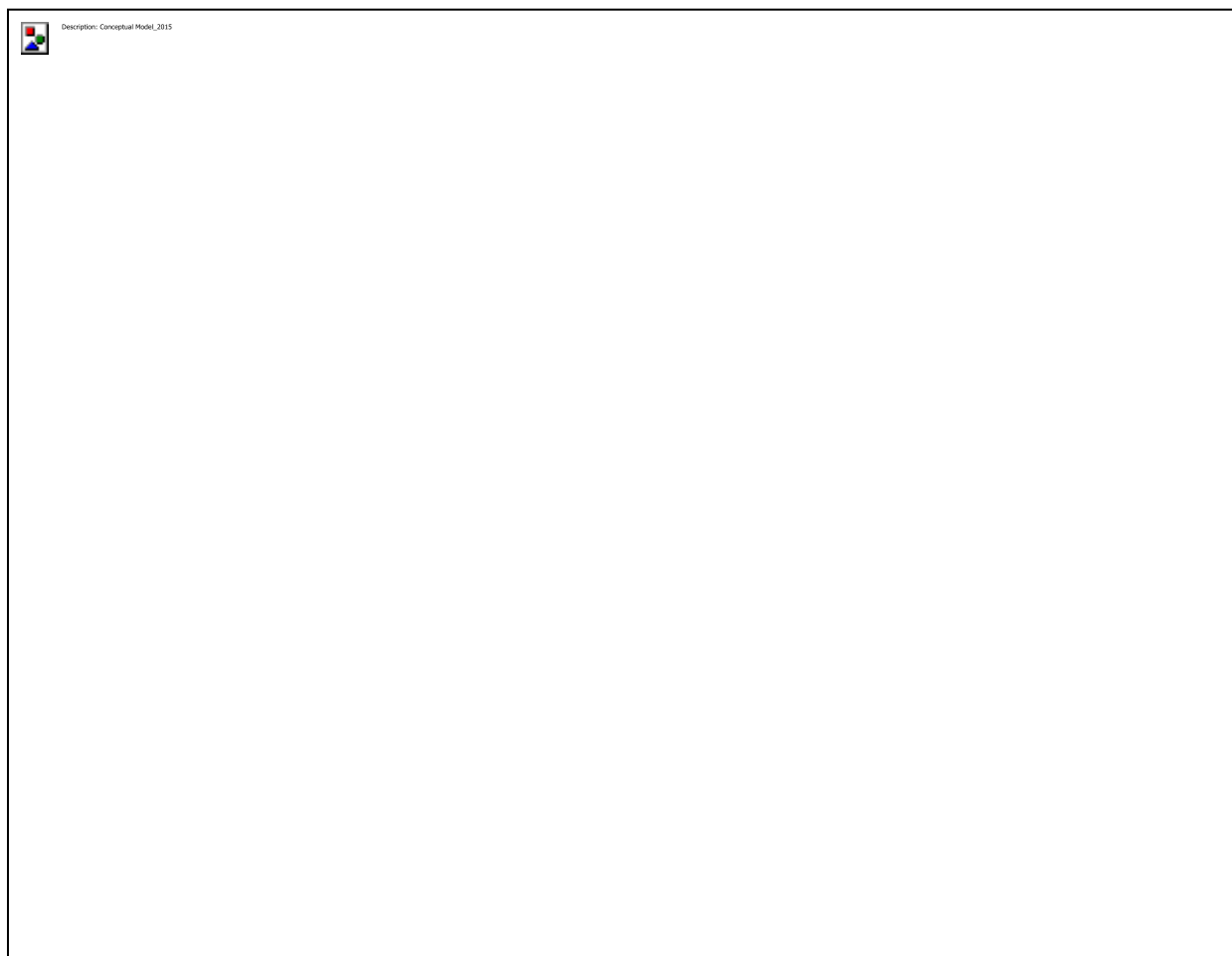


Figure 3: The Predictor variables (study arms) are shown on the left and four outcome domains on the right (Healthcare utilization, Drinking, Quality of Life, and Consequences) with the specific measures noted alongside each domain. The outcomes may be mediated by the subjects' development of engagement (assessed by AASE scale, motivation visual analogue scale, adherence to treatment arm, and participation in clinic). Several potential interactions are hypothesized, some of which may also act as confounders. Interactions or confounding may occur between outcome domains (e.g. quality of life may have an effect on healthcare utilization); other cofounders may include age, race, sex, socioeconomic status, comorbidities, and social stability. Randomization will be employed to help mitigate potential threats.

Aim 2c: Correlation of Biomarker and Self-Reported Alcohol Consumption:

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For this substudy, data from subjects in both arms (N=50 in phase 1) will be pooled as a single cohort to assess the performance of %CDT and the %CDT-GGT combination as a marker of heavy alcohol use. We will determine the correlation between serum biomarker values and self-reported alcohol intake ascertained using the timeline follow-back (TLFB) method (within the Form 90), which is reliable, validated, and widely used in addictions research.¹¹¹ Correlations between the measures will be assessed and inform the second phase of study.

- I. We will measure the correlation between biomarker levels and self-reported alcohol consumption using the Timeline Followback method of obtaining (a) 30-day average alcohol intake, and (b) 7-day alcohol intake. We hypothesize that biomarker levels will be correlated with alcohol intake for both periods of time.
- II. We will measure the correlation between changes in biomarker levels and changes in alcohol intake. We hypothesize that changes in alcohol intake will be correlated to the associated changes in biomarker levels.
- III. We will compare the performance of biomarkers in subjects for whom CDT has been shown to have higher diagnostic accuracy (males, low BMI, non-smoker, non-cirrhotic liver) to subjects having at least one characteristic previously found to lower the accuracy of CDT (women, high BMI, smokers, cirrhotic liver).

We will calculate correlations using Pearson product-moment coefficients for continuous non-skewed parameters or the Spearman's rank correlations for non-continuous variables, as required. To reduce the effect of baseline variation and to allow each subject to be evaluated in relationship to his own drinking status, and initial blood level, CDT and GGT will be expressed at each treatment week as a percentage of their baseline level. Therefore, at each treatment evaluation, every individual's levels would either decrease or increase. A multivariate approach to repeated-measures ANOVA will be conducted for the biomarker levels using the percentage of baseline at the three treatment evaluations (Months 3, 6, and 12) as the dependent units for analysis in comparing the outcome groups. Multiple sensitivity analyses will be conducted to address missing data.

Aim 3: Patient-Level Predictors of Effectiveness:

Baseline and longitudinal predictors of interest in naltrexone alcohol treatment efficacy and effectiveness trials include gender, ethnicity, mu opioid receptor genotype, and ancillary alcohol behavioral treatment involvement. Naltrexone's relative ineffectiveness in African American clinical trial sub-populations, including in the COMBINE trial,¹²⁴ is possibly mediated by low rates of the Asp40 OPRM1 functional allele in persons of African descent, who are primarily Asn40 homozygous.¹²⁵ This Asp40 (A118G, 'G' allele) OPRM1 functional single nucleotide polymorphism has been shown to be associated with successful treatment with naltrexone.^{126,127} A pilot conducted by Dr. Lee at Bellevue did find a strong association between persons involved at baseline or who became involved during primary care XR-NTX treatment with specialty alcohol treatment and/or Alcoholics Anonymous.⁶⁵ Thus, we hypothesize a priori that there will be less robust effectiveness among African Americans; voluntary specialty alcohol treatment and Alcoholics Anonymous involvement, and presence of the Asp40 OPRM1 SNP will be associated with treatment effectiveness. We note, however, that these analyses will be exploratory, as the study is not powered to carefully test these secondary hypotheses.

We will collect patient-level characteristics data to explore the association of patient-level characteristics (e.g. sex, race) with effectiveness. We will be able to carefully track prior detox admissions and concurrent 12-step and specialty alcohol treatment involvement in the proposed trial in order to estimate associations with treatment effectiveness. Multivariate models will be used to identify patient characteristics associated with treatment success. The analysis will utilize a logistic regression with an indicator variable for treatment and covariate terms for baseline potential prognostic indicators, including African American ethnicity, baseline drinking severity, and status of housing, social support, quality of life, and OPRM1 genotype. Odds ratios will be calculated to quantify the risk to treatment failure of significant predictors. As originally proposed, naltrexone appears most effective at reducing heavy drinking, as opposed to producing complete abstinence. A harm reductionist perspective delineating treatment success from failure is particularly important in this population having a greater severity of AUD and psychosocial dysfunction. All traditional alcohol treatment trial clinical endpoints, including continuous

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drinking and heavy drinking variables, as well as the %CDT biomarker, the change in CDT, and the combined CDT-GGT equation, which are specific for heavy drinking, are of great interest, and will be reported.

7.3 Subject Population(s) for Analysis

For both the primary and secondary aims/outcomes, we will study an all-randomized population: Any subject randomized into the study, regardless of whether they received study drug.

We will also collect process data, including barriers and facilitators encountered in the completion of all study procedures. This data will include reason for non-inclusion for all subjects approached but not enrolled.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events.

Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

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

Serious Adverse Event

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

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

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

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

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. By definition, all subjects in this study population have the pre-existing condition of frequent use of acute medical services, including ambulance transports, emergency department visits, and inpatient and outpatient admissions for detoxification and other alcohol-related problems, injuries, and consequences.)

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

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8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

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

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible. Events that will be reported include, but are not limited to events that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

For Narrative Reports of Safety Events

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

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

8.3.1 Investigator reporting: notifying the study sponsor

The following describes events that must be reported to the study sponsor in an expedited fashion.

Initial Report: within 48 hours:

The following events must be reported to the study sponsor within 48 hours of awareness of the event:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

Study Sponsor: NIAAA Program Officer: Brett Hagman, 301-443-0638, Brett.Hagman@nih.gov

Follow-up report: within 48 hours:

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

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Other Reportable events:

- **Deviations from the study protocol**
Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but **no later than 5 working days** of the protocol deviation.
- **Withdrawal of IRB approval**
An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but **no later than 5 working days** of the IRB notification of withdrawal of approval.

8.3.2 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, to which we will adhere.

Report Promptly, but no later than 5 working days:

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- **Unanticipated problems including adverse events that are unexpected and related**
 - Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
 - Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.
 - Harmful: either caused harm to subjects or others, or placed them at increased risk

Other Reportable events:

The following events also require prompt reporting to the IRB, though **no later than 5 working days**:

- **Complaint of a research subject** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- **Protocol deviations or violations** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
 - one or more subjects were placed at increased risk of harm
 - the event has the potential to occur again
 - the deviation was necessary to protect a subject from immediate harm
- **Breach of confidentiality**
- **New Information indicating a change to the risks or potential benefits** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)
- **Report of Changes or Amendments to the Protocol**

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All proposed changes/amendments to the protocol will be filed with the IRB. IRB approval of such amendments will be forwarded to the NIAAA project officer, and the original amendment approvals will be filed in the primary document manual.

Reporting Process

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.3.3 Sponsor reporting: Notifying the FDA

N/A

8.3.4 Sponsor reporting: Notifying participating investigators

N/A

8.4 Unblinding Procedures

N/A. Study is not blinded.

8.5 Stopping Rules

During the review process, the DSMB will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the principal investigator, DSMB, or the NYU IRB have the authority to stop or suspend the study or require modifications.

DSM Plans typically include stopping rules that specify the outcome differences detected between groups during an interim analysis that can result in stopping the clinical trial. In general, stopping rules will reflect one of the following conditions: 1) there is clear evidence of harm or harmful side-effects of the treatment; 2) there is not likelihood of demonstrating treatment benefit; 3) there is overwhelming evidence of the benefit of the treatment. The current trial is not blinded, so the DSMB would be able to compare the outcome of the two groups during each review without decoding the subject's group and determine whether the study should have an early termination. However because we are comparing an alternative paradigm of delivering a medication that is already FDA-approved for the indication in question, and regarding which preliminary data do not suggest significant safety considerations, early stopping on the basis of clear benefit (yes/no) is not anticipated.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Data Monitoring Committee

Although the PI has assessed the proposed study as one of moderate risk (consistent with prior XR-NTX studies), the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods.

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The PI will have overall responsibility for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency.

A Data and Safety Monitoring Board (DSMB) will be established for ongoing protocol review, including data, protocol compliance, safety and efficacy data, in compliance with NIH and NIAAA guidelines. The DSMB will be comprised of two individuals during phase 1 of study and 2-5 members during phase 2 of study, DSMB members will meet NIH requirements regarding background and experience, and none will have ethical conflicts, including financial interest related to study outcome. Individuals invited to serve on the board will disclose any potential conflicts in writing.

For the initial phase of study, the DSMB will be composed of:

1. Robert S. Hoffman, MD (Chair)
Professor, Departments of Emergency Medicine and Medicine
NYU School of Medicine
455 First Ave, Room 123, New York, NY 10016
Phone: 212-447-8153
2. Scott E. Sherman, MD
Associate Professor, Departments of Population Health, Medicine, and Psychiatry
NYU School of Medicine
227 East 30th St, Room 642, New York, NY 10010
Phone: 212-686-7500, ext 7386

The DSMB will conduct a review of the initial study protocol. It will make certain that the protocol captures the information necessary to evaluate the safety and efficacy of the study when it is ongoing and completed. The DSMB may provide recommendations to improve upon the protocol. The board will meet at least annually (unless more frequent meetings are deemed necessary).

At these meetings, Dr. McCormack and other research personnel will report on the trial status, followed by a closed session under the direction of the DSMB chairperson, during which time the investigators and research team may be present. This will be followed by an executive session restricted to DSMB members. Issues discussed may include those related to subject safety and benefit, whether the primary study question is being answered, conflict of interest, confidentiality, and ongoing study review (including AEs, SAEs, and regulatory issues).

All adverse events and unanticipated problems during follow-up will be reported to the IRB, DSMB, and NIAAA. Serious adverse events and unanticipated problems will be reported to the IRB and to the NIAAA project officer within 48 hours of it becoming known to the investigator, using the appropriate forms found on the website. The PI and DSMB will conduct a review of all adverse events upon completion of study subjects. The PI will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

During the review process, the DSMB will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the principal investigator, DSMB, or the NYU IRB have the authority to stop or suspend the study or require modifications. Following each DSMB meeting, recommendations will be made by the chairperson to Dr. McCormack and a final report (edited by all DSMB members) will be prepared and submitted to NIAAA, the NYUMC IRB, and (if required) the FDA.

Stopping the trial due to safety concerns or interim analysis of the primary outcome are not anticipated; the study medication, XR-NTX, is FDA-approved, its use in this trial is consistent with its FDA labeling, and no significant safety issues have arisen in national post-marketing use. DSM Plans typically include stopping rules that specify the outcome differences detected between groups during an interim analysis that can result in stopping the clinical trial. In general, stopping rules will reflect one of the following conditions: 1) there is clear evidence of harm or harmful side-effects of the treatment; 2) there is not

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likelihood of demonstrating treatment benefit; 3) there is overwhelming evidence of the benefit of the treatment. The current trial is not blinded, so the DSMB would be able to compare the outcome of the two groups during each review without decoding the subject's group and determine whether the study should have an early termination. Again however, because we are comparing an alternative paradigm of delivering a medication that is already FDA-approved for the indication in question, and regarding which preliminary data do not suggest significant safety considerations, early stopping on the basis of clear benefit (yes/no) is not anticipated.

Procedures in Place to Ensure the Validity and Integrity of the Data

Study clinicians and research staff will undergo the same baseline training at the inception of the study. The PI will ensure the quality of the clinicians' and the research assistants' administration of study assessments and instruments and of integrity of the data recorded through regular reviews and on-going data monitoring. Integrity of collected data: The identification key linking the separate charts containing the Informed Consent document and subject identifiers (name, signature, DOB, address, phone numbers) and the assessment instruments and study dataset will be stored in a locked cabinet (paper copy) as well as on a password-protected file stored on a secure NYUMC server, accessible only to the study staff. The study dataset will be otherwise de-identified and securely stored as described below. Only authorized study staff will have access to the dataset. All reasonable requests for data-sharing will be accommodated after study close.

Procedures to Guarantee the Accuracy and Completeness of the Data during Data Collection, Entry, Transmission, and Analysis

Study data will be entered directly into NYU-internal REDcap surveys administered on iPad tablet PCs over a cloud using Bellevue's secure Wi-Fi network for any data containing subject protected health information and the cellular network for de-identified data. The iPad devices have security protections that are HIPAA compliant. Data will be stored on secure servers and/or in locked filing cabinets in my locked research office with access only to authorized study personnel as identified by the principal investigator and project manager for this study. Unique identifiers will be used to identify subjects in the password-protected database. Quality control is performed as the data are being entered, and then at further stages of the storage and management process. Study findings will utilize only aggregate data and no publication or presentation will involve any use of individual information.

Reporting of Serious Adverse Events

Death, disability, hospitalization (or prolongation hospitalization), congenital defects, and life threatening events including drug overdose will be deemed serious adverse events (SAEs) and immediately reported (orally and by fax) to the NYU School of Medicine Institutional Review Board (IRB), at the time they are identified by the investigators or research staff. In addition, a written report will be filed within 72 hours to the IRB and to the NIAAA program office (and FDA as indicated by applicable regulations). When additional clinical information becomes available, a follow-up and/or final SAE report will be filed with the IRB, NIAAA, and the FDA (if indicated).

Reporting of IRB Actions to NIAAA

The initial IRB approval will be forwarded to NIAAA for review, as will all subsequent approvals and any amendments to the protocol. All proposed protocol amendments will be presented to the IRB and communicated to the NIAAA project officer if approved. Documented IRB approval of amendments will be forwarded to the NIAAA project officer, and the original amendment approvals will be maintained in the regulatory file.

Report of Changes or Amendments to the Protocol

All proposed changes/amendments to the protocol will be filed with the IRB. IRB approval of such amendments will be forwarded to the NIAAA project officer, and the original amendment approvals will be filed in the primary document manual.

In the present protocol, there are no plans for interim analysis of safety or effectiveness data (see above). However, the PI and Key Personnel will examine safety data on an ongoing basis. Adverse experience

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and safety contrasts will be performed as indicated, in response to recommendations by the PI. If interim analysis of safety data is deemed advisable by NIAAA or our IRB, we will enact such a plan.

Disclosure of Any Conflict of Interest

The investigator, co-investigators, and consultants will report on an annual basis or more frequently if indicated any conflicts of interest or apparent conflicts of interest to the IRB as well as to NIAAA. On an annual basis, the above individuals will sign a disclosure statement. There are currently no declared conflicts of interest with the proposed study among all Key Personnel.

9 Data Handling and Record Keeping

9.1 Confidentiality

The PI has obtained a Federal Certificate of Confidentiality to encompass protocol activity and subject data and ensure against the release of confidential information. Any future staff will have completed requisite IRB Human Subjects and HIPAA trainings. The PI will provide any future staff with training in their responsibilities for maintaining subject confidentiality; unique identifiers will be used to identify subjects in the database; all data will be kept in locked filing cabinets in my locked research office or on our secure server to which only the investigators and project manager will have access. Study findings will utilize only aggregate data and no publication or presentation will involve any use of individual information.

9.2 Confidentiality and HIPAA

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

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

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

9.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.4 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is

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not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.5 Records Retention

For non-FDA regulated studies, summarize the record retention plan applicable to the study (taking into account any applicable NYULMC Department, Division or Research Center requirements, or applicable funding sponsor requirements.)

For FDA-regulated studies the following sample language is appropriate:

The Principle Investigator will retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by an agreement with the sponsor.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan in Attachment #8. As described in Section 8.6.1, a DSMB will be established for ongoing protocol review, including data, protocol compliance, safety and efficacy data, in compliance with NIH and NYU guidelines. Dr. McCormack and other research personnel report on the trial status, followed by a closed session under the direction of the DSMB chairperson, during which time the investigators and research team may be present. This will be followed by an executive session restricted to DSMB members. Issues discussed may include those related to subject safety and benefit, whether the primary study question is being answered, conflict of interest, confidentiality, and ongoing study review (including AEs, SAEs, and regulatory issues). Following each DSMB meeting, recommendations will be made by the chairperson to Dr. McCormack and a final report (edited by all DSMB members) will be prepared and submitted to NIAAA, the NYUMC IRB, and (if required) the FDA. Stopping the trial due to safety concerns or interim analysis of the primary outcome are not anticipated; the medication is FDA-approved, its use in this trial is consistent with their FDA labeling, and no significant safety issues have arisen in national post-marketing use.

10.2 Auditing and Inspecting

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

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) or independent Ethics Committee (EC) in agreement with local legal prescriptions, for formal

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approval of the study conduct. The decision of the IRB/EC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB/EC members and their affiliate to the sponsor.

The patient population being studied is at risk of transient and long-term cognitive impairment that may limit potential subjects' ability to consent and benefit from this study. Individuals with AUDs often receive their care exclusively in EDs, where referrals for substance use are rarely initiated, resulting in significant healthcare costs and diminished access to treatment of this and other chronic conditions.^{7,24-29,32-36,92-97} Research to develop and practically implement effective interventions is even less common, particularly in those with severe AUDs in whom attrition and exclusion is expected.⁴² Inclusion of this patient population in study is of great significance because it may provide efficacious treatment and social stability to a population that has a disproportionate impact on healthcare and societal costs, and one that traditionally does not seek or receive care in medical settings offering addiction treatment. It has the potential to transform revolving door ED visits into an effective point of public health intervention and to incorporate the ED and its unique populations into a more integrated healthcare system.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment #9 for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent. The enrollment process will be documented in the study's Subject Screening and Enrollment log.

The study investigator will use a process of informed consent that will be structured to be conducive to rational and thoughtful decision making by the subject. The PI and RA will obtain subjects' written informed consent after assessing their capacity to consent using the stringent procedures described in Section 4.3.3 and restated here:

The recruitment process will specifically address the likelihood that the subjects may have a compromised capacity to consent. Subjects will not be enrolled until clinically sober and medically stable. Subjects will be (re)assessed multiple times during their ED visit(s) as needed—and therefore will have multiple opportunities to be enrolled. We will use techniques shown to improve comprehension in informed consent procedures such as using a lower reading level, using larger typeface, quizzing and having multiple individuals providing the information. The PI will provide sensitivity training of investigators/RAs regarding difficult behaviors and limited comprehension and assessment of subject capacity to consent.

The PI/RA will assess subject's understanding of the study and capacity to consent to it using the **University of California San Diego Brief Assessment of Capacity to Consent to Research (UBACC)** (Attachment #2). The UBACC 10-item questionnaire is a 5-minute, easy-to-use, and validated tool, which we have studied in this population.^{43,98} It rates the basic elements of capacity (understanding, appreciation, reasoning, and ability to express a choice) to identify subjects with questionable capacity to consent to a specified research project. The UBACC assessment occurs after informing potential subjects about the study. Thus, first the RA/PI will review each page of the informed consent document with the patient, pausing to reassess comprehension throughout the process. Then, the RA/PI will administer the UBACC. Once the RA/PI confirms the subject's comprehension (with the UBACC), the RA/PI will request the patient's signature and provide the patient with a copy of the signed consent document. If, at any point during the consent process, the RA/PI does not believe the patient comprehends the study procedures the patient will not be enrolled at that time, but he or she may be eligible in the future. Patients who are not able to successfully complete ("pass") the UBACC may be further assessed by psychiatry consultation.

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In addition, the PI/RA will ask the subject to consent to being audio recorded (for qualitative interviews, counseling sessions, and quality assurance monitoring). If the subject declines to provide their written informed consent to be recorded, the subject may still participate in the study (i.e. audio recording is optional).

Subjects may be required to sign separate authorization forms for release of their personal health information to and from entities involved in their care, including care managers, case workers, housing facilitators, health providers, and government agencies/institutions. These data will be used to help coordinate and facilitate health and social needs and track outcomes. The purpose of this will be primarily clinical, rather than research. Each institution will ensure protection of PHI. All institutions, with the exception of the NYC Department of Homeless Services, are HIPAA covered entities. All Institutions will consult their respective IRBs; the NYC Fire Department Emergency Medical Services will use the IRB of the NYC Department of Health and Mental Hygiene.

Individuals who are authorized to obtain consent must be listed on the protocol. If necessary to use 'Auditor/Witness' and/or translator, these roles would be described in this section. During follow-up visits subjects capacity will be reassessed and subjects will be asked to provide assent to continue participating in the study.

12 Mandatory Biomarker and Genetic Testing

Whole blood (17mL) for genomic analyses will be obtained once; this will occur at enrollment typically, but may be obtained at a later visit. The 17mL of blood will be obtained from consenting subjects for genetic analysis to test predisposition to alcohol use disorders and naltrexone effect mediation (e.g. via OPRM1 genomic analysis).^{79,112,113,129} During the initial enrollment visit and subsequent research visits (week 0,12,24,48), 17mL of blood will be obtained for analysis of biomarkers associated with alcohol consumption and alcohol use disorders. Each blood sample will be labeled with a unique subject ID number and the visit number of the specimen obtainment. No identifiable information will be included on the specimen tubes and only the PI will have access to the list linking subjects to their ID Number assignment. Upon collection the blood specimens will be delivered to the NYULMC CBRD, where they will be stored until shipped in batches to the Medical University of South Carolina (MUSC) Laboratory for analysis. Only study team members and CBRD staff will have access to the stored specimens. Samples will be destroyed after analysis.

13 Inclusion of Prisoners

"Prisoner" is defined to include any individual involuntarily confined in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. Persons receiving care in a medical treatment setting, who are also "prisoners" as defined above, can be considered for enrollment in research only as permitted for other prisoners as subjects.

This study involves research on conditions that particularly affect prisoners as a class. These conditions include alcoholism, unstable housing, and fragmented health and social services with frequent ED use and often without other usual source of care. There are considerable data, including our own studies, describing the pattern of frequent contacts this patient population typically has with both the hospital and the criminal justice system as well as the limited coordination of services between institutions.^{128,129} Although medical, social services, criminal justice, and public health institutions are eager to assist this difficult, high cost and resource utilizing population, large institutions typically operate in silos, lacking the

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coordination necessary to respond cohesively and effectively to the needs of the population. These individuals are arrested typically for minor charges related to alcohol consumption (e.g. open contain, public intoxication) and unstable housing (e.g. loitering). The resulting brief periods of incarceration are unlikely to negatively impact study procedures or outcomes consequentially. Further, recurrent episodes of incarceration can be disruptive to the delivery of healthcare (e.g. missed appointments) and social services (loss of housing); thus, it is critical to learn about these challenges that specifically affect prisoners as a class in order to develop strategies to intervene more effectively.

As an extension of our preliminary work to develop and pilot a broadly defined care management intervention, this study will explore how to better address the inadequacies of current systems of care that affect prisoners. As is reflected in the primary study aim of assessing and enhancing feasibility, we will gain valuable insight into improving continuity and coordination of care of prisoners. Specifically, we will establish linkages with the NYC Department of Health-Corrections and NYC Homeless Services and their contracted agencies to coordinate care among these high users of ED, criminal justice system, and homeless services. Each institution has caseworkers designated for high-risk, high-service utilizers; we are developing a mechanism for timely communication between these institutions to allow patient/client tracking and coordinated discharge planning. For example, selected individuals could potentially be released from jail into the care of their housing outreach case-worker and brought directly to a supportive housing facility and have medical aftercare plans established prior to release. Even in the event that the study medication cannot be administered, which we do not anticipate being a problem (for the below reasons), continued study participation could benefit the subjects through enhanced continuity of care – including upon release from incarceration.

This paragraph describes which prisoners will be eligible for enrollment and under what circumstances prisoners will be withdrawn from the study. Patients on parole or probation are eligible for enrollment. Patients who are prisoners at the time of potential enrollment will NOT eligible for study entry/inclusion. Enrolled subjects who become prisoners will remain in the study.

Extensive provisions are incorporated in the study protocol to ensure adequate protections of the subjects, all of who are considered to be vulnerable. No persons who are prisoners will be eligible for enrollment. In other words, all subjects will be entering the study as non-prisoners. Thus, there is no risk of coercion of prisoners to enroll/participate in the study. All patients will have a rigorous assessment of their capacity to consent to research participation, as described in section 4.3.3. The risks involved in the research are commensurate with the risks that would be accepted by non-prisoner volunteers. There are no added safety risks should subjects become prisoners. No additional advantages accruing to a prisoner through his/her participation in the research are of such magnitude that his/her ability to weigh the risks and benefits of the research will be impaired.

As medication (XR-NTX) is being administered in this study, it is important to explicitly state that there are no additional safety concerns for subjects in the arm receiving medications should they become prisoners. This FDA-approved medication is being administered in accordance with its safe prescribing guidelines. We do not anticipate that administration of XR-NTX will be disrupted as a result of incarceration; this is because Bellevue Hospital has an existing clinic dedicated to the care of prisoners (mostly from Rikers Jail). Protocols for the transfer of prisoners from detention centers to Bellevue Hospital for clinical care have existed many years. Subjects who are prisoners will return to Bellevue Hospital for their medical management, which may include laboratory testing and XR-NTX administration. XR-NTX is not administered unless the requisite pre-administration laboratory testing is completed. . Thus, if the subject is unable to return to our medical clinics for medical management and laboratory testing, then the subject will not receive the subsequent dosage of XR-NTX. There are no adverse effects associated with disrupted treatment (other than the lack of benefit provided by the medication); XR-NTX may be discontinued at any time.

Commensurate with non-incarcerated subjects, all Alcohol-MM clinical follow-up visits and Research Visits will be conducted at Bellevue Hospital Center when possible. Research assessments (Visits 5, 8, and 14) will be conducted at Bellevue when subjects return for their clinical appointments. For incarcerated subjects who will not be coming to Bellevue Hospital for an Alcohol-MM or other clinical

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reasons, we will arrange through the jail administrators for the subjects to return to Bellevue for a Research Visit. When making arrangements with prison administrators and disclosing that the prisoner is a research subject, we will not disclose the title or purpose of the study – as we have done in the past to ensure the subjects' privacy. For security reasons, subjects/prisoners will not be notified of the specific time of the visit, which will be coordinated through the jail.

As mentioned above, there are existing systems in place for New York City prisoners to receive outpatient care in Bellevue clinics that are specifically designated for prisoners. Thus, a new workflow does not need to be established. While we know the procedures and regulations for Riker's jail and New York City detention centers, it is possible that subjects will be incarcerated outside of New York City and/or in facilities that may not participate in bringing prisoners to Bellevue for care. In the event that a subject is unable or unwilling to return for an Alcohol-MM visit, this will not pose additional medication safety risks because the subject cannot receive the medication (XR-NTX) without presenting to Bellevue. If the subject is unable or unwilling to return to Bellevue for Research Visit(s), we will attempt to make arrangements with jail administrators for us to meet with the subjects at the jail or by phone to conduct the research assessments as we have done in other studies. If it is not possible to speak with a prisoner in private and without being recorded by the jail/prison, then we will remind the subject that he/she does not need to answer any questions that he/she does not wish to answer, and we will limit research assessments to include non-incriminating data only (e.g. no questions related to drug use or criminal behavior), such as healthcare utilization, medication side effects, and quality of life. This may result in not completing research assessments for some subjects. We will address how to handle the missing data with our DSMB. Our justification for retaining prisoners in the case of data not being collected is that these are important feasibility data that should be captured in this study whose goals include assessing and enhancing feasibility. Plus, the subject/prisoner may be able to participate in a subsequent research assessment (if released during study timeframe). Further, we do not anticipate encountering these difficulties (because of the aforementioned arrangements with local jails), and are including their potential in the protocol now so that we can maximize the retention of subjects and quality of data without jeopardizing the safety, privacy, or confidentiality of the subjects.

We will make sure the parole boards will not take into account a subject's participation in the research in making decisions regarding parole. Again, we will not disclose the title or purpose of the study to jail administrators. This anonymity also helps to ensure that research participation does not influence parole boards. Subjects are also informed verbally and in the written informed consent document that we will not provide input on their behalf to parole boards. We have received a Certificate of Confidentiality so that we cannot be compelled to provide testimony if subpoenaed.

If the subject is currently on parole, he or she must determine if their monitoring can include their scheduled follow-up visits to the Bellevue clinic. If these visits are not permitted, the subject will not be able to continue his or her participation in the study. As with all subjects enrolled in the study, all measures will be taken to ensure confidentiality is maintained. To protect the rights of this vulnerable patient population, study staff will only disclose the minimum amount of information required by prisoners. Study staff, for example, will never mention the title or content of the study or disclosure that a specific individual is participating in the study. Details of the nature of the research will not be shared with the staff at the jail/prison, and visits whether in person or by phone, will only be conducted if the subject's confidentiality can be maintained and no audio-taping occurs. In the event the research staff would want to conduct visits via phone, they will submit a request to have the study phone number placed on the "Do Not Record" list".

Incarcerated subjects will receive the same financial incentives for participating in the study as non-incarcerated subjects (as long as permitted by the prison, detention center, or other governing body within the criminal justice system). Depending on the prison/detention center's policies, the stipend may be provided directly to the subject, provided to the prison to retain until the subject's release, stored at the study site until the subject is released and can come retrieve it, debited to the prison commissary, paid to a relative, or mailed upon the subject's release. At the completion of the study, subjects in both arms of the study will be provided with harm reduction counseling and health care resources, including referral for alcohol-MM.

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14 Audio Recording

After subjects sign the initial informed consent document, they will also be asked to sign a consent document for audio recording. If the subject does not consent for audio recording, he or she can still participate in the study. If the patient provides consent, the study's RA may audio record subject interviews during the initial and follow up medical management and research visits. The sessions will be recorded for quality assurance and for training approved study personnel in qualitative interviewing. Data will also be collected from the recordings if any information was not captured during the in-person interview.

Each recording will be labeled with a unique identifier, encrypted, and stored in a locked cabinet in the Principal Investigator's office or electronically on a secure, HIPAA-compliant NYULMC server. If the subject verbally states their name, or any other identifying information, during the recording editing software will be used to expunge this information from the file, if possible. All recordings will be destroyed upon the study's conclusion.

15 Study Finances

15.1 Funding Source

The PI has received an award from the US National Institute of Health – National Institute on Alcohol Abuse and Alcoholism (NIAAA) to finance the initial phase of study, 1K23AA022989. Alkermes, Inc.TM has approved the PI's Investigator Initiated Trial application and will provide 225 VivitrolTM kits (each containing a single dosage) at no cost. The PI has been awarded funding through the New York University CTSI to cover certain CTSI-related expenses (CBRD, laboratory, pharmacy). The NYU School of Medicine Department of Emergency Medicine will also provide study support. The PI will apply for additional funding to provide additional study support, including financing the second phase of study (definitive trial) and biomarker and genomic analyses.

15.2 Conflict of Interest

Currently no investigators have a conflict of interest with this study. Any investigator who has a conflict of interest with this study will have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable University conflict of interest policies.

Cost to Subjects

Subjects will not incur any cost for the study medication. The drug manufacturer, Alkermes, Inc will provide the medication free of cost. Subjects and/or their insurance companies will be billed for medical management visits and associated laboratory tests per standard of care. Subjects will not be charged for biomarker or genetic testing.

15.3 Subject Stipends or Payments

Subjects will be compensated \$40 at the completion of the enrollment visit (Week 0) and the research visits at Weeks 12, 24, and 48. Subjects will be compensated \$10 after the first (week 1) medical management visit. Subjects in the intervention arm will receive \$25 for each Medical Management/XR-NTX injection clinical visit. Compensation for incarcerated subjects will not exceed maximums allowed by penal institutions.

16 Publication Plan

The Principal Investigator has the primary responsibility for publication of the results of the study. Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the

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information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

Our plan to share data and our management of intellectual property will be in accordance with NYUMC and NIH policies and guidelines. All investigators involved in this project will adhere to NIH's Data Sharing Policy and Implementation Guidance of March 5, 2003 and NIH Grants Policy on Sharing of Unique Research Resources including the "Sharing of Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Grants and Contracts" issued in December, 1999. The final research data will be available in acceptable formats commonly accepted for documenting and supporting research findings (i.e., .csv, .xls). The final research data will not contain any subject identifiers. Research data that documents, supports, and validates research findings will be available after the main findings from the final research data set are accepted for publication and/or presented at national meetings. Individual researchers, government, or other not-for-profit organizations petitioning Dr. McCormack for access to the data who document both a commitment to use the data for legitimate research purposes and not to identify an individual study subject, and a commitment to secure use of the de-identified data including not making unauthorized copies of the dataset available to others, will be provided the study dataset at no charge.

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18 Attachments

1. Selected diagnostic codes related to alcohol use
2. Assessment Measures – Note: Sections and Questions from selected instruments will be used.
3. Motivation Interview Therapy Manual
4. Schematic Diagram of Trial
5. Timeline of Study Procedures
6. Anticipated Study Timeline
7. MEDWATCH Form, FDA Form 3500A

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8. Data and Safety Monitoring Plan
9. Sample Consent
10. Consent – A/V

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