Title: E**X**tended-Release vs. **O**ral **N**altrexone for Alcohol Dependence Treatment in Primary Care (X:ON)

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PROTOCOL OUTLINE

1.0 Rationale

Though integration of alcohol pharmacotherapy into primary care settings is receiving increasing emphasis and support, rigorous data to inform clinicians' treatment choice is lacking. The most recently FDA-approved alcohol treatment medication, an extended-release depot form of naltrexone (XR-NTX, Vivitrol®), could greatly simplify the medical home-centered alcohol treatment emphasized in the NIAAA Clinician's Guide.[1] Injected once a month, XR-NTX offers a long-acting and thus potentially more effective form of pharmacotherapy than oral naltrexone (O-NTX),[2] which, despite the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) trial and systematic reviews supporting some efficacy,[3,4] has been characterized by low rates of overall prescribing, poor adherence, suboptimal monthly refill and inadequate treatment retention.[5,6,7,8] Yet while promising as an alternative to O-NTX, XR-NTX is substantially more expensive (~$1100 vs. ~$100 per month),[9] and no head-to-head trials have compared the two forms of naltrexone. A comparative effectiveness approach is required to systematically evaluate the following key questions: In primary care settings, what is the relative clinical effectiveness of XR-NTX vs. O-NTX? What are the benefits and costs of XR-NTX relative to O-NTX? And can patient and system characteristics be identified to inform treatment choice to maximize the probability of successful outcome?

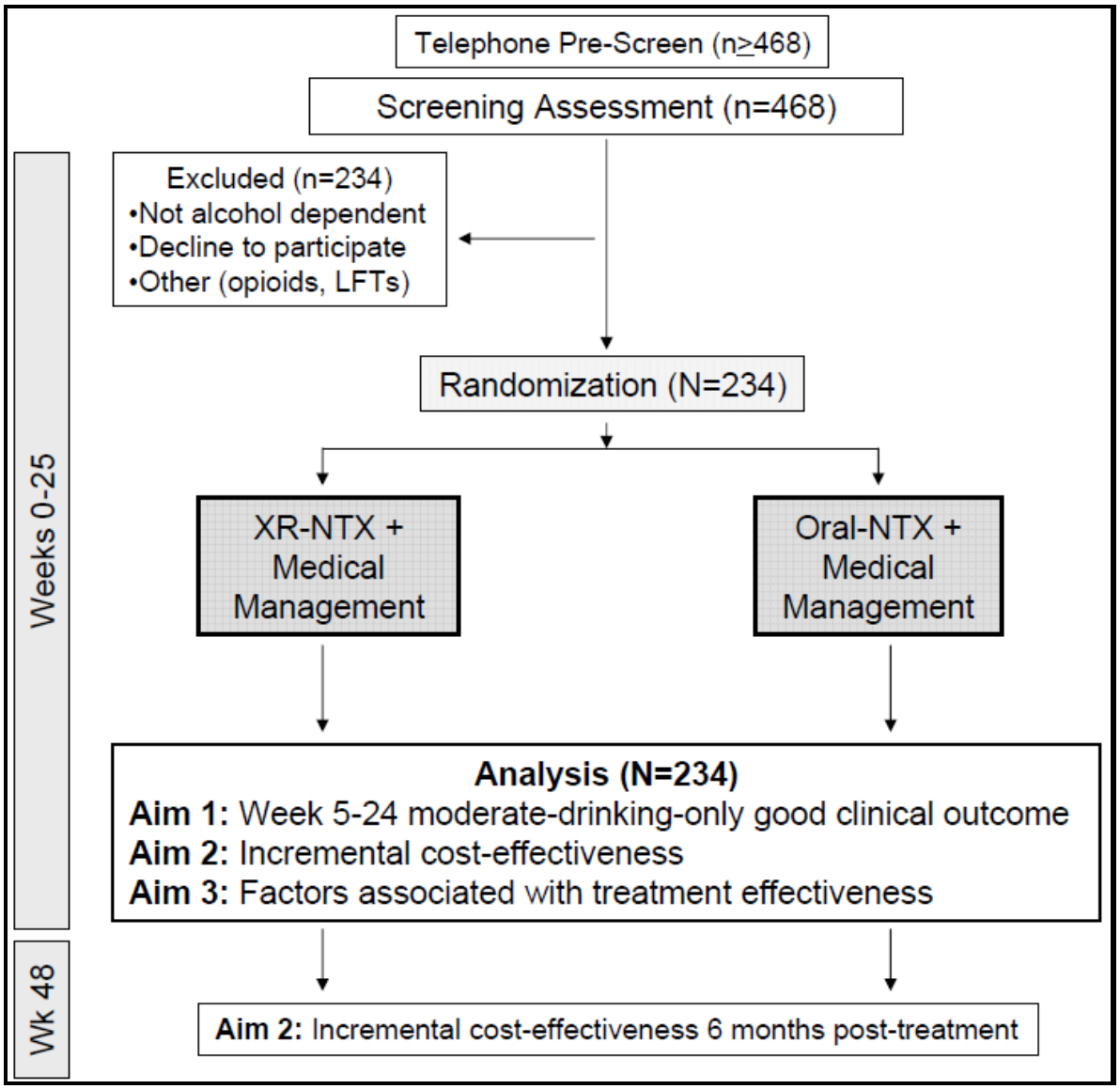
Primary Aim: Treatment Effectiveness. To evaluate the effectiveness of XR-NTX vs. O-NTX in producing a primary good clinical outcome, defined as abstinence or moderate drinking (≤2 drinks/day, men; ≤1drink/day, women; and ≤2 heavy drinking occasions/month), during the final 20 of 24 weeks of primary care-based Medical Management for alcohol dependence.
Hypothesis: The rate of this good clinical outcome will be approximately twice as great among participants receiving XR-NTX compared with those receiving O-NTX.

Secondary Aim 1: Cost Effectiveness. To estimate the incremental cost effectiveness of XR-NTX vs. O-NTX, both in conjunction with primary care-based Medical Management.
Hypothesis: XR-NTX treatment will be more cost effective than O-NTX.

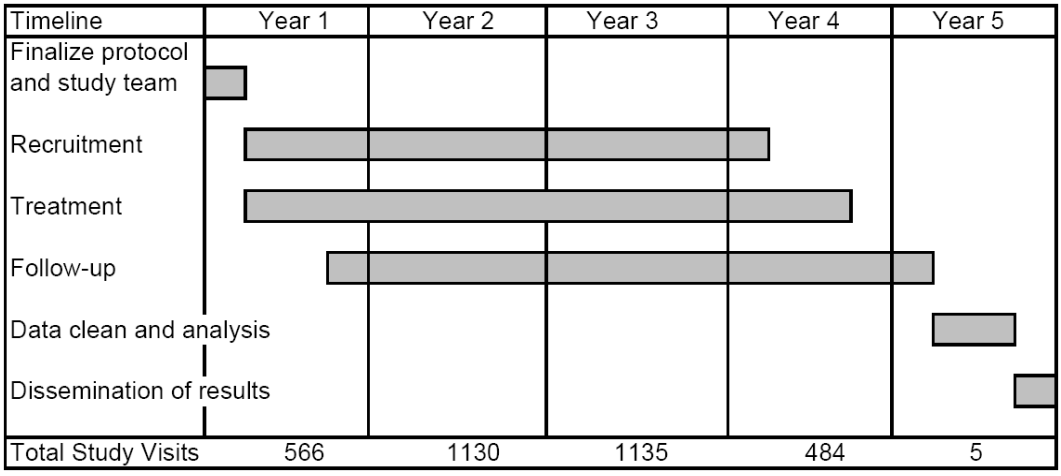
Secondary Aim 2: Patient-Level Predictors of Effectiveness. To identify patient-level characteristics associated with effectiveness in both arms.

This proposed study is a pragmatic, randomized, open-label clinical trial of 24 weeks of XR-NTX vs. O-NTX using a COMBINE-adapted Medical Management primary care treatment model. 234 adults ≥18yo with alcohol dependence will be recruited from the community into treatment at a major New York City primary care site (Bellevue Hospital Center's Adult Primary Care Clinic). The primary outcome which powers this study is a dichotomous good clinical outcome defined by abstinence or moderate drinking, and as measured by the Timeline Followback and analyzed using an intention-to-treat approach among all randomized participants. Secondary outcomes include the incremental cost effectiveness of the two arms, differences between arms by continuous measures of alcohol intake (drinks/day, % days abstinent, time to first heavy drinking day, biomarkers), and the exploratory analysis of factors possibly associated with effectiveness, including gender, pre-treatment abstinence, and mu opioid receptor (OPRM1) genotypes.

Study Schema



2.0 Study Timeline: This NIAAA notice of grant award was issued on July 18, 2013, award number: 1R01AA020836-01A1. We expect a 3-month start up phase during which we will complete the protocol approval process, hire study personnel, assemble study supplies and complete local SOPs. Recruitment of 234 enrolled and randomized participants will take place over 3 years, or approximately 6-7 persons randomized monthly, based on our pilot study. The final 6 months of Year 5 will be devoted to the tail end of study visits, data cleaning and analysis, study close out, preparation of initial manuscripts, and dissemination and national presentations of results.



3.0 Introduction

3.1 Significance and Innovation

The projected impact of this proposal has not changed since the original proposal: despite several years of experience, the comparative effectiveness of XR-NTX compared to older alcohol medications remains uncertain, particularly in a mainstream, primary care treatment model that is generalizable and broadly accessible. Newer, novel, expensive medications for addiction disorders are historically greatly underutilized by primary care physicians. This study is innovative both as a 'head-to-head' evaluation of XR- vs. O-NTX in primary care, and because expected participants will be primarily Medicaid-covered or uninsured persons who will not be excluded based on medical and psychiatric co-morbidities that often preclude participation in efficacy studies. If health insurance expansion, parity reforms, medical homes and accountable care organizations are to define primary care as a core alcohol treatment setting in the coming decade, exactly this type of study is required to guide treatment protocols and resource allocation. Ultimately, more widespread adoption of cost-effective alcohol pharmacotherapies will result in longer, healthier lives and lower costs.

3.2 Optimizing Primary Care Alcohol Treatment

This study addresses the comparative effectiveness of alcohol pharmacotherapies and associated treatments, a high priority area at NIH/NIAAA as evidenced by PAS-10-273, 'Clinically Relevant Comparative Effectiveness of Alcoholism Treatments.' This proposal is in keeping with NIAAA's FY09-14 priorities of expanding effective alcohol treatments in primary care and patient-centered medical home settings through the increased use of emerging pharmacotherapies, while further disseminating the treatment principles endorsed by the NIAAA Clinicians Guide.[10,1] Stronger evidence of the clinical benefit and ease-of-use of medications like XR-NTX in a Medical Management primary care model should further activate the generalist workforce to screen and treat alcohol dependence.

Alcohol disorders are common, costly, and undertreated: Unhealthy alcohol use exacts a tremendous toll in morbidity, mortality, suffering and cost.[11] An estimated 23% of U.S. persons aged 12 or older reported binge drinking (5 or more drinks on any once occasion) at least once in the last 30 days, and an additional 7% reported "heavy use" (binge drinking on 5 or more of the last 30 days) in the 2008 National

Survey on Drug Use and Health.[12] An estimated 4% of U.S. adults aged 18 or older met DSM-IV criteria for alcohol dependence in the most recent published NESARC data; 5% met criteria for abuse.[13] The vast majority of persons with alcohol use disorders never attempt or succeed in accessing specialty treatment.[14] Though they do present frequently to emergency rooms, primary care clinics, mental health clinics, and other general care settings,[15] alcohol pharmacotherapy is rarely offered in such settings. Data demonstrating the practicality and effectiveness of pharmacotherapy for alcohol dependence in routine primary care would offer a powerful boost to efforts to expand the impact of evidence-based alcohol treatment.[16]

3.3 Oral naltrexone pharmacotherapy is under-prescribed and plagued by poor 'real-world' adherence, yet O-NTX plus Medical Management was superior in the recent COMBINE trial

Despite efficacy data, pharmacotherapies for alcohol disorders are not widely prescribed by either generalists or addiction specialists.[17] Daily oral medications including disulfiram, oral naltrexone, and acamprosate remain in limited use, reflecting a paucity of specialty treatment centers or generalists prescribing these medications.[5] The 2001 publication of the large Veterans Administration (VA) RCT of O-NTX showed daily naltrexone adherence of 44% and 43%, respectively, in participants randomized to 12 and 3 months of O-NTX.[18] Commercial HMO prescription data has shown <15% rates of persistent O-NTX refills through 6 months, [6,19] while one analysis of New England VA pharmacy data reported <25% of O-NTX prescriptions persisting through this same timeframe.[7]

The recent COMBINE study has renewed interest in combining naltrexone prescribing with Medical Management (MM), a physician-, nurse-, or other ancillary staff-led counseling approach that focuses on support for drinking abstinence and medication adherence, and that does not explicitly incorporate ancillary treatment or formal therapeutic approaches (i.e., 12-step facilitation, motivational interviewing, or cognitive behavioral therapy).[20] Naltrexone, a full μ opioid receptor antagonist, reduces alcohol related euphoria, and craving and relapse among abstinent drinkers, in particular reducing heavy drinking episodes as opposed to slips.[21,22,23] In COMBINE, oral naltrexone-treated alcohol dependent participants demonstrated a greater percent of days abstinent, fewer heavy drinking days, and a higher proportion of patients achieving a composite good clinical outcome (abstinence/moderate drinking) vs. placebo or acamprosate arms, and oral naltrexone with MM was more effective than other combinations of pharmacotherapy and behavioral treatment. This data echoed earlier, smaller trials which also supported an O-NTX plus primary care MM approach.[24,25]

Mean adherence to oral naltrexone in COMBINE was initially reported as high (85% of prescribed drug was not returned and assumed to have been taken), though these results are somewhat difficult to interpret as a large proportion of participants assigned to 16 weeks of naltrexone at some point discontinued the medication (96 of 154 participants assigned to naltrexone + MM discontinued the medication). A subsequent secondary analysis of COMBINE medication adherence data reported 72% total daily adherence among MM patients receiving active naltrexone and placebo acamprosate, with better adherence to both naltrexone and placebo associated with favorable drinking outcomes.[26] This highlights an important tension in the oral naltrexone literature: randomized trials of select alcohol dependent patients (typically excluding those with co-morbid substance use and psychiatric disorders, as was the case in COMBINE) report relatively high levels of medication adherence and moderate effect sizes, while commercial pharmacy data and naturalistic observational studies demonstrate quite low levels of oral naltrexone adherence and little real-world effectiveness.

Importantly, the COMBINE trial's Medical Management protocols standardized (and certified) the MM physicians, nurses, and pharmacists providers in a recovery support and medication adherence enhancement counseling approach delivered in an initial 45 min. session, and then in 20 min. follow-up visits, totaling 8 visits in 16 weeks (Weeks 1, 2, 4, 6, 8, 10, 12, and 16). This basic approach to counseling strategies and follow-up visit frequency is summarized by the NIAAA Clinician's Guide, which forms the basis of the physician-led Medical Management platform used as this study's active psychosocial treatment.

3.4 Extended-Release Naltrexone: Effective and Cost-Effective?

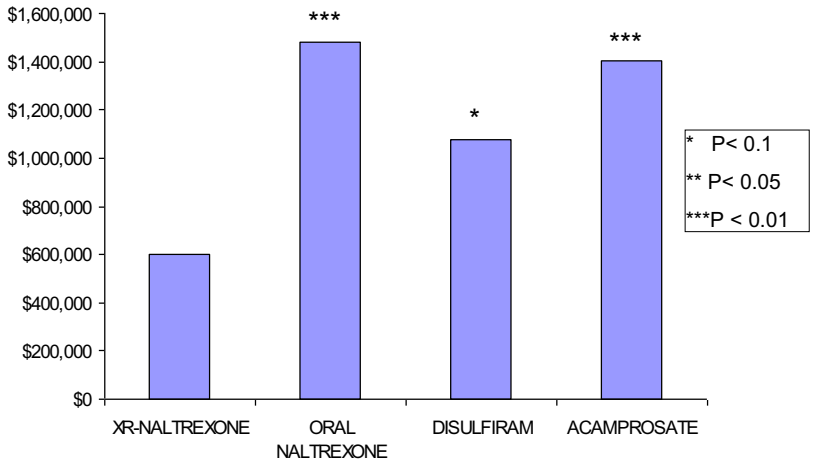
Efforts to expand alcohol treatment options and improve adherence to naltrexone treatment contributed to the development of a long-acting, polylactideco-glycolide-based (PLG) naltrexone formulation

(XR-NTX, Vivitrol®, Alkermes, Inc). Shown to be efficacious vs. placebo at reducing heavy drinking days in a dose-dependent fashion over 6 months (with 64% of all participants receiving 6 of 6 monthly injections),[27] XR-NTX gained FDA approval for alcohol dependence in 2006 (a separate opioid dependence indication was approved in 2010). Despite its promise in eliminating daily adherence concerns, only one additional study has further estimated the efficacy of XR-NTX in general adult populations,[28] and none have compared its effectiveness advantages vs. oral naltrexone.[29] Our own pilot of XR-NTX in primary care is discussed below (Approach, 3.2 Preliminary Studies and Investigative Team) and demonstrated high rates of retention and significant decreases in daily and heavy drinking.[2]

3.5 Cost-Effectiveness of Naltrexone

Overviews of economic evaluation methods and empirical economic studies of addiction treatment provide compelling evidence of societal benefits from broadening the reach of effective alcohol treatment.[30,31,32] Health system and societal cost-effectiveness estimates for specific alcohol pharmacotherapies including oral and XR-NTX are scant, however, with none based on a prospective randomized pharmacotherapy trial until the COMBINE study.[33,34,35] Analysis from COMBINE ranked MM plus naltrexone as the more cost effective of the active intervention arms, including other pharmacotherapy combinations, at achieving two of the study's primary endpoints (no heavy drinking and a 'good clinical outcome').[36,37,38]

Figure 1. Charges for Detoxification Days Per 1,000 Patients
(*** = comparison of other meds against XR-NTX)



There are no prospective, randomized data comparing the cost-effectiveness of XR-NTX against O-NTX. Data from commercial managed care examined by Marks suggest an encouraging impact of XR-NTX on costs through lower rates of high-cost emergency services and alcohol detoxification (**Fig. 1**).[39] Importantly, this recent analysis was commissioned by Alkermes, the manufacturer of XR-NTX. The proposed study aims to address these vital cost issues more rigorously in a randomized control clinical trial including a long-term drinking and cost assessment at week 48 following the initial 24 weeks of treatment. Prospective, independent verification of these projected cost savings is warranted.

3.6 What predicts good clinical outcomes in XR-NTX vs. O-NTX treatment?

Baseline and longitudinal predictors of interest in naltrexone alcohol treatment efficacy and effectiveness trials include gender, ethnicity and mu opioid receptor genotype, pre-treatment abstinence, and ancillary alcohol behavioral treatment involvement. Female gender has been shown to be associated with increased nausea and diminished oral naltrexone adherence[40] and less overall treatment effect, including sub-group results from the pivotal Garbutt XR-NTX efficacy trial, and gender remains a stratification variable at randomization.[27]

Naltrexone's relative ineffectiveness in African American clinical trial sub-populations, including in the COMBINE trial,[41] is possibly mediated by low rates of the Asp40 OPRM1 functional allele in persons of African descent, who are primarily Asn40 homozygous.[42] This Asp40 (A118G, 'G' allele) OPRM1 functional single nucleotide polymorphism (SNP) has been shown to be associated with successful treatment with naltrexone.[43,44] We will be able to determine prospectively whether this allele is associated with retention and treatment effectiveness in both arms, potentially representing one of the first studies to assess the impact of Asp40 on XR-NTX treatment outcomes, which we feel adds to this proposals significance and

innovative potential. This will be in partnership with Charles O'Brien (consultant) and Dr. Wade Berrettini's lab at the University of Pennsylvania, which will perform the genotyping in this proposal.

Lead-in drinking abstinence (3 days prior to initiating medications) will be analyzed a priori as a predictor of effectiveness in both medication arms. A participant's ability to abstain from drinking prior to an initial XR-NTX injection may predict treatment response and is highly relevant to the initiation of naltrexone treatment in monitored detox settings,[45] though we did not observe this same association in our smaller XR-NTX primary care pilot, which is described below and included few patients with pre-treatment abstinence or recently discharged from a detox unit.[2] Our pilot 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. We will be able to carefully track prior detox admissions, pre-treatment abstinence, and concurrent 12-step and specialty alcohol treatment involvement in the proposed trial in order to estimate associations with treatment effectiveness. Likewise, while we will recruit only participants willing to try either form of naltrexone, participants will be queried at baseline for a strong preference of oral vs. XR.

3.7 What outcomes matter most in primary care alcohol treatment?

We clearly feel a dichotomous 'good clinical outcome' best defines a patient's progress to 'goal' in a primary care comparative effectiveness trial, and represents innovation. Our choice of a moderate-drinking-only good clinical outcome reflects: a) the use of this same outcome in the COMBINE trial,[3] b) its ability to capture both abstinence and reduced heavy drinking, and, c) a preference for a dichotomous success/failure primary outcome, which neatly deals with drop-outs and missing data as 'failures.' A dichotomous, success/failure primary outcome is in keeping with other recent and important comparative effectiveness trials.[46,47,48,49,50] Further, this study will track and report all drinking rates over time based on TLFB, facilitating easy comparisons to other alcohol trials, and also analyze XR-NTX's impact on biomarkers, including carbohydrate-deficient transferrin (CDT). CDT is highly specific to heavy drinking and compliments well the primary good clinical outcome. CDT has not been tracked in an XR-NTX clinical trial, a secondary outcome we feel adds substantially to this proposal's innovative potential.

Few studies have examined smoking cessation among heavy drinking smokers, or during naltrexone therapy for alcohol use disorders. Smoking continues to be an enormous health crisis within the United States. Those with alcohol use disorder are more likely to smoke than the general population and account for more than 6 million people in the United States.[51,52] Additionally, smokers with concurrent alcohol use disorder are more likely to have a higher degree of tobacco addiction, smoke more heavily, and have significant morbidity and mortality from tobacco related diseases.[53,54,55,56] Most studies investigating smoking cessation exclude people with current alcohol use disorder bringing into question their generalizability to this population.[57] Of the studies that include current alcohol use, smoking cessation rates were much lower than the general population.[58] These studies tended to have small sample sizes, failed to show long-term results, and have rarely investigated combination therapies.[59] Given the prevalence, the burden of disease, and the limited success in treating heavy drinking smokers, further research is needed to discover effective therapeutic options. Our study will explore rates of quitting and reduced smoking in all active and new patients during NTX + MM alcohol treatment.

A history of trauma and current post-traumatic stress symptoms and disorders are believed to be overly prevalent among addiction disorder patients and alcohol use disorder patient samples. A survey conducted on a nationally representative sample of the United States population showed that approximately 46.4% of individuals in the United States with PTSD have a comorbid alcohol or drug use disorder.[60] PTSD and substance use disorder comorbidity is associated with a poor prognosis in both disorders (increased psychiatric comorbidity, exacerbated PTSD symptoms, and greater risk of relapse during or after substance

use treatment.)[61,62,63] There is a growing need in treatment interventions of co-occuring PTSD and AUD but the current literature provides inconclusive and contradictary results of various phamacologic treatments.[64,65] The interaction of PTSD symptoms with active naltrexone alcohol treatment is one that is not well known or studied.[66] We will pilot in all remaining new patients and existing active patients validated brief screeners for trauma history and PTSD symptoms for estimations of prevalence and changes over time during active NTX treatment of alcohol use disorders.

3.8 Preliminary Studies and the Investigative Team: Alcohol and XR-NTX Research at NYUMC

The foundation for our proposal was a single-arm evaluation of XR-NTX in monthly primary care medical management of alcohol dependence, led by Drs. Lee, Gourevitch, and Rotrosen (Co-Is).

XR-NTX plus Medical Management in Primary Care: This recent pilot showed evidence of the feasibility, acceptability and likely effectiveness of a 3-month course of XR-NTX plus MM for treatment of alcohol dependence among 72 community-recruited adults using an open-label, single-arm, proof-of-concept design.[2] Rates of uptake, retention and adherence with monthly XR-NTX were robust within the same two clinical settings we now propose and among a study population which was 15% African American, 22% Latino, and 60% Medicaid/Medicare or uninsured. *Baseline drinking in this cohort (57%, % heavy drinking days) was similar to that of the COMBINE (63%) and Garbutt (64%) trials.* Most eligible, consented patients initiated (90%) and completed (62% of those initiating injections, 56% of N=72 patients) three months of treatment not involving monetary or other incentives, excepting a single $20 payment at the last visit, and medications and medical care at no cost (**Table 1**). The 3-month adherence rate we observed was only slightly lower than in the relatively intensive Garbutt efficacy trial of XR-NTX (74%).[26] These rates of adherence and treatment retention were also similar to uptake and adherence rates expected in primary care patients initiating pharmacotherapy for common chronic conditions, such as hypertension or high cholesterol.[67,68,69] Finally, reductions in self-reported drinking reductions, including significantly fewer heavy drinking days, were significant and sustained among persons retained in treatment (**Table 1)**. Thus, in this single-arm observational pilot, treating alcohol dependence in primary care settings with XR-NTX and monthly physician medical management appeared a feasible and possibly effective model of alcohol treatment.

Table 1. XR-NTX + MM in Primary Care[2]	Baseline	Month 1	Month 2	Month 3
% retained in treatment (received monthly injection)	N=72	90%	68%	56%*
% heavy drinking days, last 30 days (median), if retained	57%	2%	3%	7%
*62% of participants initiating XR-NTX injections completed 3 of 3 injections				

Additional research by Dr. Lee in collaboration with Drs. Gourevitch and Rotrosen has also involved addiction pharmacotherapies in primary care settings. Related work includes primary care MM plus pharmacotherapy for opioid dependence, including, 1) piloting 'at-home' buprenorphine induction;[70] 2) buprenorphine/MM following release from jail;[71] 3) XR-NTX plus MM for opioid relapse prevention among criminal justice-involved participants;[72] and, 4) participation as one of 12 sites in the NIDA CTN 0030 Prescription Opioid Addiction Treatment Study, a comparative effectiveness and cost effectiveness trial of buprenorphine/MM plus intensive individual counseling vs. buprenorphine/MM. Additionally, Dr. Rotrosen's team at NYU and the Manhattan VA was a site in Garbutt's XR-NTX pivotal trial.[26]

Dr. Scott Braithwaite (Co-I, Cost Effectiveness), Chief of NYU's Section of Value and Comparative Effectiveness, is an accomplished decision scientist with an strong record of NIAAA funding, including his current R01-AA017385, "Computer Simulation of the HIV Epidemic in sub-Saharan Africa." Incremental cost effectiveness models and simulations for this proposal will draw on this team's experience creating, validating, and using other computer simulations assessing the impact of alcohol interventions specifically on long-term costs and benefits.[73,74,75] Dr. Laska (Co-I, Biostatistician) will provide core statistical advice as the study's biostatistician and in keeping with his expertise and successful role as such in recent mental health and addiction trials;[76,77,78,79] James Robinson will head data management, while two consultants, Dr. Charles O'Brien and Dr. Raymond F. Anton, will lend decades of expertise in naltrexone and alcohol

treatment effectiveness research to the design and interpretation of the study, including COMBINE MM adaptation (Anton), and assisting with measurements of baseline OPRM1 genotypes (O'Brien) and CDT analysis (Anton).

3.9 Investigative Team Roles and Study Management

Dr. Lee as PI will oversee all aspects of the study. As detailed in the Budget Justification, each Key Personnel will perform specific and distinct roles. Our economic analysis team will plan and analyze the cost-effectiveness components. Dr. Lee along with our study statistician will conduct the analyses of the primary and secondary effectiveness outcomes, based on the dataset collected and managed by our data managers. Our team will also include co-investigators who will serve as study physicians and assist in all aspects of study conduct. Dr. Rotrosen, a senior mentor to Dr. Lee and Director of the NIDA CTN NY Node, will serve as a co-investigator and assist with all aspects of the study in a senior advisory role. Dr. Anton and Dr. O'Brien, consultants, will assist with CDT analysis, COMBINE MM implementation and OPRMI genomic analysis.

Dr. Lee will be in daily contact with the Program Manager, Project Manager, Research Coordinators, and study clinicians. Weekly meetings will bring together core staff to trouble-shoot study implementation and daily management. Monthly conference calls will bring together all of the key personnel and, as needed, the two consultants, to discuss study conduct and eventual analysis and manuscript preparation. Separately, Dr. Lee will meet monthly or more frequently, depending on the study phase, with the study statistician and data manager regarding data management and analysis.

4.0 Study Aims

4.1 Primary Aim: Treatment Effectiveness. To evaluate the effectiveness of XR-NTX vs. O-NTX in producing a primary good clinical outcome, defined as abstinence or moderate drinking (≤2 drinks/day, men; ≤1drink/day, women; and ≤2 heavy drinking occasions/month), during the final 20 of 24 weeks of primary care-based Medical Management for alcohol dependence.
Hypothesis: The rate of this good clinical outcome will be approximately twice as great among participants receiving XR-NTX compared with those receiving O-NTX.

4.2 Secondary Aim 1: Cost Effectiveness. To estimate the incremental cost effectiveness of XR-NTX vs. O-NTX both in conjunction with primary care-based Medical Management.
Hypothesis: XR-NTX treatment will be more cost effective than O-NTX.

Secondary Aim 2: Patient-Level Predictors of Effectiveness. To identify patient-level characteristics associated with effectiveness in both arms.

5.0 Study Design: A Randomized Comparative Effectiveness Trial to Evaluate XR-NTX vs. O-NTX for Alcohol Dependence in Primary Care

We propose a pragmatic randomized controlled trial to compare the effectiveness and incremental cost-effectiveness of XR-NTX vs. O-NTX as a component of primary care-based Medical Management of alcohol dependence among 234 adults. The 24 week treatment trial will assess monthly treatment retention, self-reported drinking outcomes, biomarkers, and costs. The primary effectiveness outcome is a moderate drinking good clinical outcome, defined as abstinence or moderate drinking (≤2 drinks/day, men; ≤1 drink/day, women, and ≤2 heavy drinking occasions/month), during weeks 5-24. A long-term follow-up assessment at week 48 will gather further drinking and cost data. The MM visit schedule and research assessment visits will occur as follows over 48 weeks (Table 2):

Table 2. Visit Frequency (weeks)	0	1+	3	5+	7	9+	13+	17+	21+	25	26	48
XR-NTX vs. O-NTX + MM visits	x#	x#	x	x	x	x	x	x	x	x	x*	
Research-only assessment visits							x#			x#		x#

*Safety documentation research visit
Compensation provided
+ Medication Dispensed

6.0 Study Population

This study will attempt to recruit a general adult population of alcohol dependence, with few strict exclusion criteria in keeping with a 'real-world' comparative effectiveness design.

6.1 Inclusion Criteria

1. Adults (age >18 y.o.)
2. Spanish- or English-speaking and able to understand study procedure and provide informed consent
3. Current (within the last year) DSM-V diagnosis of alcohol use disorder as determined by the study physician and standard DSM-V checklist.
4. Endorses goal of alcohol abstinence, and is able to achieve alcohol abstinence without inpatient detoxification, per study physician.

6.2 Exclusion Criteria

1. Current opioid dependence and/or positive urine toxicology for extended opioids.
2. Pregnancy or female and planning conception.
3. Allergy to naltrexone or the PGL XR-NTX formulation or diluent.
4. Severe liver disease, liver failure, or liver function test levels greater than three times normal.
5. Other severe, untreated or uncontrolled medical illness (e.g., severe heart failure or dementia).
6. Untreated psychiatric disorder that might make participation hazardous (e.g. untreated psychosis, bipolar disorder with mania, significant suicide risk).

7.0 Study Procedures

7.1 Recruitment and Pre-screening

Recruitment will consist of both in-clinic referrals of existing primary care patients, as well as community recruitment of patients new to primary care. Recruitment will rely on the successful blend of 'in-reach' (meetings with clinicians, detailing, systematic communication) and local area outreach (ads, external detailing) that we employed during our pilot study to prescreen 116 persons, consent 76, and enroll 72 eligible persons over a 13-month period (a rate of 5.5 persons enrolled per month, similar to that of the current study). Routine screening for alcohol use is not presently standard practice at the study site. However, if routine alcohol screening launches during the course of the study (SBIRT implementation efforts are on-going within the HHC system), eligible persons identified through SBIRT efforts could be referred to the study. Persons interested in study enrollment will call an intake number, or consult with a research coordinator in-person. A brief eligibility pre-screen will determine probable eligibility, after which patients will be scheduled for a baseline screening visit. Recruitment will be patient- or provider-initiated rather than initiated by the research team. Potential subjects will not be approached at random by research staff at Bellevue clinic or in any other setting unless patient-initiated. Most referrals will come from in-clinic referrals by physicians or by local outreach recruitment ads. Potential participants will call the research team phone number advertised or received from referring physician. Research coordinators will complete a pre-screening on the phone with potential subjects to do an initial assessment of eligibility. If potential participants are deemed initially eligible (based on phone-screen) by study staff and the PI, research coordinators will schedule the initial Screening Visit with subject at Bellevue Hospital. All documents containing PHI on pre-screen interviews of potential subjects pre-screened on telephone and found to be ineligible or not interested in study will be destroyed. The only information that will be retained from ineligible pre-screens will be gender and age. Participants will also be recruited through word of mouth referrals. Participants can earn a $50 referral bonus for each eligible person referred and successfully

randomized into this study. All participants will be provided travel reimbursements in the form of MetroCards at the end of every study visit.

7.2 Screening and Randomization

At the baseline visit, informed consent will be obtained and eligibility confirmed by the research coordinator and study physician. A subsequent randomization/treatment visit will then be scheduled within a 2 week time period. Several factors may be associated with naltrexone treatment success/failure. We will stratify urn randomization by gender and recruitment status (in-clinic vs. community referrals). Stratifying further, however, yields increasingly smaller cells, given 117 per arm; AA ethnicity, medication preference (monthly injectable vs. daily oral), and lead-in (3-day) abstinence will be analyzed as a priori predictors of effectiveness. Randomization is the starting point of the study (day 1, week 1).

7.3 Study Interventions: Medical Management plus XR-NTX vs. O-NTX

Existing primary care physicians, all board-certified in internal medicine, physician assistants, and registered nurses at an adult primary care clinic, Bellevue Hospital, will be recruited to participate in this trial as MM clinicians. As in our previous studies with XR-NTX and buprenorphine in these sites, study participants may see different individual providers over the course of 24 weeks, thus optimizing visit flexibility as well as enhancing generalizability to multi-provider practice settings. The same study clinicians will provide both XR- and O-NTX treatment. The study site relies primarily on physician visits as the core modality for primary care encounters, and it is expected study visits will be primarily with physicians. Study clinicians will provide all XR-NTX injections in clinic (Ambulatory Care, 2nd floor, Rm. #2111) each month for each participant randomized to the XR-NTX arm. O-NTX, which is a daily oral pill formulation of naltrexone, will be self-administered on a daily basis by O-NTX participants.

The content of the Medical Management component will be the same in both arms, and will be based on the initial and follow-up MM visits outlined in the COMBINE MM manual and adapted by the NIAAA Clinician's Guide.[20] MM emphasizes: a) education surrounding the alcohol dependence diagnosis, b) a recommendation and emphasis on drinking abstinence, c) support for 12-step involvement (referrals to specialty outpatient treatment will not be part of the MM strategy – patients interested in such will not be prohibited from self-referral, and specialty referrals will be made in cases of relapse/treatment failure), d) self-efficacy counseling surrounding medication adherence, e) education and trouble-shooting of medication side effects, f) feedback on the success of drinking reductions, g) and non-specific support and motivational enhancement to make further changes toward abstinence.

MM clinician's will be trained at start-up and through quarterly calls and booster session in an adaptive approach consistent with the NIAAA COMBINE trial (see NIAAA COMBINE manual) and in consultation with Dr. Anton. Strict standardization and certification of MM clinicians, as was done in COMBINE, will not be pursued, as this would diverge from a pragmatic clinical trial attempting to reflect the adoption of, but not absolute fidelity to COMBINE MM.

7.4 Study Care vs. Usual Care: Participants in both arms may schedule additional MM visits as needed to address medication side effects or unanticipated study-related events. Any such additional visits required will be tracked carefully as service utilization. Telephone support with research coordinators and study clinicians will be available at all times during the study and also tracked as utilization. However, clinicians cannot provide or bill for other routine primary care services, such as blood pressure management or cancer screening, during MM visits. This is a conundrum in any NIH-funded, patient-level clinical trial in primary care, which cannot budget for comprehensive care. Patients can initiate or continue access to all primary care services through the same clinician and in the same clinics, it will simply occur as a non-study visit at either clinical site, both of which are public clinics providing access to all patients regardless of insurance status or ability to pay.

7.5 XR-NTX Plus Medical Management

XR-NTX will be delivered at the point of care as a single, 380mg IM injection (4cc) to alternating upper, outer, gluteal (buttock) quadrants. Injections occur every four weeks. Between-injection MM visits will assess and manage adverse events, treatment effects, and support the goal of alcohol abstinence.

7.6 Oral NTX Plus Medical Management

O-NTX will be provided by the facility's pharmacy following each monthly medication dispensing/injection MM visit, and in keeping with standard ambulatory prescribing practices of a recommended 50mg daily dose.[80] Participants with means or adequate insurance coverage may instead present their written prescription to an outside commercial pharmacy if they prefer.

7.7 Research-only Assessment Visits

As in any large clinical trial of usual care, some participants in both arms will not be present for all scheduled treatment visits. In an attempt to 'de-link' complete cost, utilization, and longitudinal drinking data collection from a naturalistic observation of these same usual care patterns, we will conduct 3 Research-only Assessment visits at week 13, 25 and 48. These visits will not hinge on a participant's treatment retention status, will be heavily incentivized to encourage participation ($100 for time and travel), and will be conducted preferably in-person but alternatively by telephone if a participant is otherwise unwilling or unable to appear in clinic. These visits will be carefully scheduled apart from MM treatment visits, which are otherwise not incentivized beyond the provision of no-cost care and medication, so as to minimize the influence of extra assessments, attention, and the monetary research participation incentive on a participant's willingness to continue with MM. Participants will be paid $20 for the initial screening visit after completion of all research assessments and $20 after completing the randomization visit.

7.8 Rescue Strategies among Treatment Non-Responders

Clearly many outcomes will occur among the 234 planned participants, beyond drinking reductions, and include: remaining in treatment and tolerating either medication but without beneficial changes to baseline alcohol intake levels; dropping out of all treatment but reporting diminished drinking; or wishing to remain in primary care treatment but unable to tolerate either form of naltrexone. Regarding continued heavy alcohol use, MM already informs and encourages interested patients to access AA, and this recommendation would be particularly relevant to those not responding to pharmacotherapy and amenable to an external referral to more intensive treatment. At any point in the trial, patients 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 detox and specialty treatment through Bellevue Hospital. Detox and intensive outpatient alcohol specialty services are immediately available to all participants through the Bellevue Hospital Chemical Dependency programs, including same-day admissions to our detox unit, regardless of insurance status or ability to pay. All enrolled participants, however, will be encouraged to remain in their assigned treatment protocols and continue follow-up in primary care for the entire 24 week treatment period, independent of medication side effects, on-going drinking, or intermittent detox or other alcohol-related inpatient treatment episodes. There is little risk, in other words, at keeping participants engaged in primary care MM regardless of on-going, frequent heavy drinking, in which case they would qualify as a primary good clinical outcome failure, or the need for further, more intensive specialty treatment, access to which the MM clinician and study staff may be crucial in facilitating. At the conclusion of the 24 week treatment trial, all patients will be offered further primary care follow-up within the same clinics and referrals to specialty alcohol treatment, if indicated, through these universally accessible addiction specialty services at Bellevue Hospital.

8.0 Assessments and Outcome Measures (Table 2)

Table 2. Visit Frequency (weeks)	0	1+	3	5+	7	9+	13+	17+	21+	25	26	48
XR-NTX vs. O-NTX + MM visits	x#	x#	x	x	x	x	x	x	x	x	x*	
Research-only assessment visits							x#			x#		x#

*Safety documentation research visit
Compensation provided
+ Medication Dispensed

A comprehensive panel of measures is planned including standard measures of drug and alcohol use, medical status, and on-going treatment services utilization. The Timeline Follow Back (TLFB), Alcohol Use Disorders Identification Test (AUDIT), and Obsessive-Compulsive Drinking Scale (OCDS) are all validated measures used to identify alcohol and drug use along with regular urine toxicology and breathalyzer tests. The ASSIST will be used to assess for substance abuse or dependence and PHQ-9 for psychosocial diagnoses. The Seek, Test, Treat and Retain (STTR) assessment will collect various demographic information for each participant. The Economic Form 90, Cost Survey, and World Health Organization Quality of Life Survey (WHOQOL) will be used to assess treatment and criminal history as well as to ascertain economic data for cost-effectiveness outcome measures. The Morisky Medication Adherence Scale (MMAS-8) will be administered to the O-NTX arm only, providing information on adherence to self-administered medications. Fagerström's test for nicotine dependence and recall of cigarettes per day will be used to assess smoking cessation measures. Adaptations of the Stages of Change Questionnaire (SOC) and Responses to Stress Questionnaire (RTS) will look towards patient motivation, self-efficacy, and coping skills. The DSM-V criteria for PTSD, Generalized Anxiety Disorder 7-Item Scale (GAD-7), and Perceived Stress Scale (PSS) will be used to assess PTSD. Throughout the treatment phase, all adverse events (AEs) will be recorded on an AE form at all treatment visits.

Screening Visit (week 0): Informed Consent Form, Consent Quiz, medication preference question, DSM-V diagnostic interview and checklist, demographics, ASSIST, PHQ-9, WHOQOL, Alcohol Use Disorders Identification Test (AUDIT), Obsessive-Compulsive Drinking Scale, Fagerström, SOC, RTS, Questionnaire, DSM-V checklist for PTSD, GAD-7, PSS, history and physical exam, vital signs, liver function (AST, ALT, GGT), urine toxicology, pregnancy test, blood alcohol breathalyzer.

Randomization Visit (week 1): Medical Management initial visit progress note, baseline biomarkers (CDT, Asp40 OPRM1 genotyping), urine toxicology, and Economic Form 90.

Treatment Visits (week 3-25): Timeline Followback (TLFB), recall of cigarettes per day, Morisky Medication Adherence Scale (MMAS-8, O-NTX arm only), Medical Management follow-up visit progress note, Adverse Event form, labs (weeks 13 and 25 only, AST, ALT, GGT, CDT).

Research-only Assessments* (week 13, 25, 48): TLFB, Economic Form 90, AUDIT, OCDS, WHOQOL, Fagerström**, SOC**, RTS**, DSM-V checklist for PTSD**, GAD-7**, and PSS**.

**Only at weeks 13 and 25.

Banked Genetic and Biomarker Testing: At randomization, participants will provide two separate blood draws (3 teaspoons blood for each) for genotyping and biomarker testing. Each of these blood samples will be labeled with the subject ID number and the date of blood draw only. No identifiable or private health information will be included on the labs prior to and when sent out for testing. Blood samples for a single biomarker (CDT) for heavy alcohol use will be drawn at randomization, weeks 13, and 25, and kept frozen at secure NYUMC facility freezer. At the conclusion of enrollment for study, samples will be sent in large batches to the Medical University of South Carolina (MUSC) and Dr. Raymond Anton's, a consultant on this protocol, laboratory. Results filed under the study ID only will be communicated and entered into the study database. Whole blood samples for a single nucleotide polymorphism (SNP) at the mu opioid receptor, the A118G OPRM1 SNP, will likewise be frozen, banked, and shipped in batch fashion for analysis at MUSC by

Dr. Anton. All samples will be destroyed following analysis and not preserved for future use. Results from either CDT or OPRM1 will be for research purposes only, will not be considered in real-time or used for participant counseling, and will be analyzed at conclusion of the study as secondary biomarkers and genetic baseline predictors of treatment outcomes.

8.1 Primary Outcome: The primary outcome measure of this study is a binary measure of success/failure consisting of a composite good clinical outcome (yes/no) through the final 20 weeks: abstinence or moderate drinking (≤2 drinks/day, men; ≤1 drink/day, women; ≤2 heavy drinking episodes every 4 weeks [heavy drinking is ≥5 drinks/occasion, men; ≥4 drinks/occasion, women). Abstinence, drinks/day, and heavy drinking days will be assessed by the TLFB calendar[81] administered at each MM and Research-only visit. As the final MM visit (week 25) does not involve medication prescribing or constitute active treatment, the week 26 research-only assessment visit TLFB will be used to capture complete heavy drinking data among participants missing the final week 25 MM visit.

Rationale: Why a binary good clinical outcome of abstinence or moderate drinking only as the primary outcome, vs. % days abstinent or time to first heavy drinking day? As stated earlier and in the original proposal, we are interested in all of these important alcohol treatment outcomes, and which we will track and report. Our strong preference is to anchor the design of this comparative effectiveness trial on a pragmatic good clinical outcome that would have genuine face validity for both patients and treatment providers. This analytic approach is consistent with pragmatic comparative effectiveness trial designs focusing on simple and important behavioral outcomes, such as post-intervention cancer screening, appropriate post-stroke smoking cessation treatment, or self-reported pain control over time.[46,47,48,49,50]

8.2 Secondary Drinking, Adverse Events, and Measures: drinking measures will be evaluated at each monthly visit (TLFB), along with self-reported O-NTX adherence (MMAS-8) and adverse events. Liver function tests (aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT) and carbohydrate-deficient transferrin (CDT) will be measured every three months (week 0/1, 13, and 25), with AST, ALT, and GGT results available in real-time to study physicians. CDT, a validated biomarker for heavy drinking,[82,83,84] is not in use or available at either facility, and will not be reported to participants or study physicians, but rather used as a secondary marker of baseline and in-treatment heavy drinking. CDT represents a 'cutting edge' alcohol biomarker, and one not previously studied in the context of an XR-NTX treatment trial. Analysis and interpretation of CDT results will be coordinated with Dr. Anton and his laboratory. Likewise, baseline assessments of drinking severity and psychiatric function (OCDS,[85] MINI-SCID,[86] Form 90[87]) and naltrexone mu receptor susceptibility (Asp40 OPRM1 genotyping) will be captured for research purposes only, and not integrated into the clinician's MM strategies.

8.3 Cost Effectiveness Outcomes: Economic data will be derived primarily from the Economic Form 90,[88] Non-Study Medical Service and HHC electronic medical records assessments, EQ-5D (functional status),[89] and a cost survey or standardized question querying patient reports of specific non-medical related costs (including lost/gained work, lost/gained dependent care, transportation costs, arrests, motor vehicle accidents) collected at baseline and at week 13, 25, and 48 assessments. The week 48 assessment is included to gain longitudinal, post-treatment cost, drinking, and functional data at a small cost to the overall study budget. Whenever possible, verification of productivity (paystubs) and medical costs (medical records) will be sought to corroborate self-report.

9.0 Power and Sample Size

As in the original proposal and based on our recent feasibility study of XR-NTX in primary care[2] and the O-NTX treatment retention and adherence literature,[6,7,19] including the single review by Roozen comparing the two medications, [28] we are powering this study on the assumption that XR-NTX is approximately twice as effective as O-NTX at achieving drinking reductions, including a good clinical outcome of abstinence or moderate-drinking-only during weeks 5-24, and also increased days abstinent and reduced rates of heavy drinking, drinks per drinking day, and drinks per day overall. This is

hypothesized to be mediated by superior naltrexone adherence. We predict based on our pilot data and the literature that 40-50% of patients will complete 24 weeks of treatment on XR-NTX, compared to <20% on O-NTX, based on O-NTX clinical trial and commercial refill data. We then estimate rates of the primary good clinical outcome of approximately 20% in O-NTX participants and 40% in the XR-NTX arm, roughly the same as adherence rates. This is based on our pilot data, in which 36 of 40 persons completing 12 weeks of XR-NTX qualified for the moderate-drinking-only good clinical outcome, and COMBINE, in which adherent oral naltrexone/MM patients reported high rates of the same moderate-drinking-only good clinical outcome during the final 8 of 16 weeks of the study. With 100 subjects per group, we anticipate power of 0.84 to detect a 20% absolute difference in the primary outcome based on the Fisher's exact test. These projected rates, however, are not well established, nor based on large datasets of heterogenous alcohol populations, and therefore we have increased the target screening n to 468, with a very conservative assumption of 2 subjects screened for every 1 enrolled, for a target sample of N=234 and n=117 per arm, which increases the projected power to 0.90.

10.0 Statistical and Cost Effectiveness Analysis

Preliminary analyses of balance: balance across the study on potentially prognostic baseline variables will be appraised using analyses of variance for continuous variables and log-linear models for discrete and ordinal responses. Variables for which significant differences were observed will be included as covariates in later analyses. Sometimes variables with strong clinical associations with the primary outcome are identified post hoc, and usually included in the analysis to reduce bias and improve efficiency (yielding smaller p-values and narrower CIs). Further, in mixed models there is always a possibility that an analysis will not converge. This danger is minimized by including in the model only essential covariates. Hence, before analyzing the primary outcome measure, the plan is to determine which predictive variables rise to a sufficient level of importance.

10.1 Hypothesis 1: The rate of the primary good clinical outcome will be approximately twice as high among participants receiving XR-NTX compared with those receiving O-NTX. (Primary Aim, Treatment Effectiveness: To evaluate the effectiveness of XR-NTX vs. O-NTX in producing a primary good clinical outcome defined as abstinence or moderate drinking ($\leq$2 drinks/day, men; $\leq$1drink/day, women; and $\leq$2 heavy drinking occasions/month), during the final 20 of 24 weeks of primary care-based Medical Management for alcohol dependence)

The primary outcome measure of this study is a binary measure of success defined by abstinence or moderate drinking only, as measured by the TLFB, with drop-outs from MM and research-only assessments assumed to have resumed baseline rates of heavy drinking, and therefore defined as good clinical outcome failures. Our analytic approach will be an intention-to-treat comparison of all randomized participants (N=234). The analysis will utilize a logistic regression with an indicator variable for treatment and covariate terms for baseline potential prognostic indicators that are not stratified for at randomization, including AA ethnicity, lead-in abstinence, medication preferences, baseline drinking severity, in-trial specialty treatment involvement, clinical site, and OPRM1 genotype. If the coefficient of treatment is significant the null hypothesis of equal treatment effect is rejected. Odds ratios will be calculated to quantify the risk to treatment failure of significant predictors (Secondary Aim 2: Patient-Level Predictors of Effectiveness: To identify patient-level characteristics associated with effectiveness in both arms). To differentiate time to a good clinical outcome failure, we will use a "cure model." The form of a cure model is $H(t) = 1- p + pS(t)$; where H(t) is the probability of failure at a time greater than t, p represents the probability of failure, and S(t) the distribution of time to failure, conditional on failure occurring. The parameters will be estimated based both on Kaplan Meier methods and parametrically. The equality of the values of p for the two treatment arms will be tested using a nonparametric likelihood ratio test. For the parametric test, a logistic will be used to model p and a Weibull survival distribution will be used to model time to failure, S(t). Both allow the use of covariates, which will complement the above logistic regression approach.

As originally proposed, naltrexone appears most effective at reducing heavy drinking, as opposed to producing complete abstinence, and all traditional alcohol treatment trial clinical endpoints, including continuous drinking and heavy drinking variables, as well as the CDT biomarker, which is specific for heavy drinking, are of great interest, and will be reported in the primary publication from this trial. In addition, rates

of medication treatment adherence, and an alternative good clinical outcome, treatment retention AND no heavy drinking, will be reported. Treatment differences in % days abstinent, overall % heavy drinking days, time to first drink, and time to first heavy drinking day, will be compared using mixed model repeated measures (MMRM) analysis including terms for subject, treatment, and time by treatment interaction, and covariate terms for baseline variables. To examine differential treatment effects at each week, we will perform tests of simple main effects. The MMRM will assume a means model, an unstructured covariance matrix and estimation will be based on restricted maximum likelihood. The baseline values will be adjusted by the overall mean. The assumptions relating to the mixed-effects model will be reviewed by examining residual scatter plots to examine deviations from normality and to assess lack-of-fit. In case of violation of assumptions, a randomization test will be performed based on the same MMRM.

10.2 Hypothesis 2: XR-NTX treatment will be more cost effective than O-NTX. (Secondary Aim 1: Cost Effectiveness. To estimate the incremental cost effectiveness of XR-NTX vs. O-NTX both in conjunction with primary care-based medical management of alcohol dependence).

We will estimate the incremental cost-effectiveness of XR-NTX compared to O-NTX. In technical terms the incremental cost-effectiveness is the ratio of incremental costs to incremental benefits; in lay terms, the incremental cost-effectiveness indicates the 'bang for the buck' of XR-NTX compared to O-NTX. The incremental cost-effectiveness of XR-NTX treatment compared to O-NTX treatment is equal to (Cost of XR-NTX minus Cost of O-NTX) divided by (Effectiveness of XR-NTX minus Effectiveness of O-NTX).

Cost-effectiveness analysis requires estimates of costs and estimates of effectiveness. Consequently, we will use primary data analyses from this study (Specific Aim 1 in the proposal) to inform costs and effectiveness estimates in the short-term, and we will synthesize these short-term estimates with published reports that allow us to estimate the longer-term, downstream costs and effects of the changes in alcohol consumption observed in Specific Aim 1. We will alternatively use societal and payer perspectives for assessing costs, and we will use the standard discount rate of 3% for costs and benefits.[90] The discount rate reflects the time preference with regard to costs and benefits (i.e., a dollar today is worth more to most people than an inflation-adjusted dollar at some time in the future). All costs will be inflated to 2011 US $ using alternatively the consumer price index (CPI) for all goods and services and the CPI for Medical services (reflecting the ongoing debate over whether the Medical services CPI overestimates inflation because of the difficulty of discriminating the effect of service improvement from service inflation).

Short-term estimates of costs and effectiveness of XR-NTX compared with O-NTX. Short-term estimates of costs and effectiveness will be obtained from primary analysis of data from the trial proposed in Aim 1, using a combination of pre-specified medical record and survey endpoints. Cost assessment will be conceptually similar to recently published analyses of the COMBINE interventions, [36,37,38] and will include medical and non-medical costs as well as payer and societal costs. Effectiveness assessment will include alcohol consumption measures as described elsewhere in this proposal, as well as quality of life. Quality of life will be assessed using 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 (OLS) 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."

Longer-term estimates of costs and effectiveness. To estimate the comparative effectiveness of XR-NTX relative to O-NTX over longer time horizons than are reflected by our data, we will incorporate these short-term results within a state-transition (Markov) computer simulation of outcomes that enables a cohort of hypothetical alcohol-dependent patients to be followed over time until death, and to be exposed to alternative alcohol interventions for specified time durations beyond the week 24 assessment. We will develop this simulation expressly for this proposal, drawing on our experience creating, validating, and using other computer simulations assessing the impact of alcohol interventions on long-term costs and benefits.[91,92,93,94,95] The simulation will be able to aggregate the lifetime benefit of remitting alcohol dependence for designated periods of time using trial endpoints (e.g. frequency of heavy drinking days), and also can quantify benefits of the levels of improvement short of full remission (e.g. if alcohol

dependence remits but the patient still is an at-risk drinker). The simulation will estimate lifetime costs and benefits over a lifetime horizon, measured in both life-years and quality-adjusted life-years. (Quality-adjusted life years is a preference-based, quality of life metric that considers quality of life simultaneously with quantity of life, and instantiates the notion that a typical person would trade away some quantity of life to get a greater quality of life.) In sensitivity analyses we will consider time horizons shorter than lifetime (10 year and 20 year) because these horizons are sometimes preferred by decision makers, even though the longer, lifetime horizon is advocated by the Panel on Cost-Effectiveness in Health and Medicine.[77]

Further considerations of the cost-effectiveness approach: The above simulation will assume that the costs and benefits observed in the trial have varying levels of persistence. In the most pessimistic scenario, any treatment effect observed in the trial would wane rapidly after the trial follow-up period, and therefore any benefits that accrue in the long-term would be attributable to the short-term effect, or, in the more optimistic scenario, any treatment effect observed would persist indefinitely, as long as the treatment is continued. Therefore, the simulation would aggregate incremental benefits of magnitude observed in the trial that are assumed to persist as long as the treatment is continued. The most optimistic, albeit unrealistic, scenario is that the treatment effect will persist indefinitely after the trial concludes, and no additional treatment would be necessary. Because this scenario is unrealistic, we will only perform analyses along these lines as sensitivity analyses; however, we will analyze scenarios in which persistence of treatment effect requires select treatment "boosters" of variable duration and frequency.

To aggregate the impact of remission of partial and/or complete alcohol dependence, the simulation will require estimates of the impact of alcohol dependence and other alcohol use disorders (e.g. at-risk consumption and harmful consumption) on quantity and quality of life, and on costs. These estimates will be based on published reports that have aggregated the impact of alcohol on the morbidity and mortality and costs of specific diseases with substantial risk attributable to alcohol (e.g., hypertensive heart disease, cirrhosis of liver, oral cancers, etc).[96] In addition, simulation input will also draw on published reports that have aggregated the impact of alcohol on morbidity, mortality, and costs of non-medical sequelae of alcohol consumption (e.g., motor vehicle collision, arrests)[97] As in our previously published simulation work, we develop the computer simulation for this proposal by incorporating the standard, stepwise procedure of *specification* (defining the structure and mathematical relationships of the variables in the model), *verification* (otherwise known as "debugging"; making sure the model performs consistently with expectations across a wide range of inputs, including "stress tests" when inputs may be deliberately set to extreme, clinically unrealistic values in an attempt to unmask flaws in the model), *parameterization* (inputting variable estimates based on relevant data or expert opinion), *calibration* (making sure model output is similar to observed clinical output in relevant circumstances), and *validation* (testing model performance in circumstances or clinical populations distinct from those used for model development).

Uncertainty: we will estimate 95% confidence intervals around point estimates of incremental cost-effectiveness using standard approaches in which vectors on the cost-effectiveness plane are identified corresponding to the 2.5^{th} and 97.5^{th} percentiles of incremental cost-effectiveness. We will also create corresponding acceptability curves, which denote the probability that a particular program or programmatic decision is favorable given a particular willingness to pay for health benefits.

If the trial is negative, what's the purpose of Aim 2? It might be observed that, if an intervention is not effective, it is meaningless to estimate its cost-effectiveness. Therefore, it might appear that the scientific validity of Aims 1 and 2 are inter-dependent. However, in the event that Aim 1 produces negative results, we will employ the computer simulation developed for Aim 2 for a slightly different purpose. Rather than using the simulation to estimate the cost-effectiveness of XR-NTX versus O-NTX, we will instead use the simulation to ask "what is the minimum level of incremental effectiveness required for an intervention to deliver sufficient value?" so that Aim 2 remains scientifically relevant and useful for decision makers. For example, even if XR-NTX does not deliver significant improvements in effectiveness compared to O-NTX, we would use the simulation to infer what levels of incremental effectiveness would be necessary to deliver sufficient value, given particular assumptions about incremental costs. For example, if a new intervention cost $100/month more than O-NTX, how many fewer heavy-drinking days would it need to reduce compared to O-NTX in order to deliver sufficient value (incremental cost-effectiveness ratio < $100,000/QALY)? That way, simulation results can inform future trial design. This approach is detailed in our recent publication,[98] and is concordant with principles of value-of-information analysis.[99]

10.3 Secondary Aim 2: Patient-Level Predictors of Effectiveness. The multivariate models described for Aim 1, while testing the main and subsidiary hypotheses, will also be used to identify patient characteristics associated with treatment success. We hypothesize a priori that there will be less robust effectiveness in both arms among women and African Americans, while pre-treatment abstinence, voluntary specialty alcohol treatment and Alcoholics Anonymous involvement (patients are not directly referred to ancillary treatment), and presence of the Asp40 OPRM1 SNP will be associated with treatment effectiveness. We also hypothesize that these positive associations will be more pronounced within the XR-NTX arm due to the sustained medication adherence following each injection. We note, however, that these analyses will be exploratory, as the study is not powered to carefully test these secondary hypotheses.

11.0 Data Collection and Management

Data recording and instruments will be collected by the RCs in real-time using web-based CRFs and the NYUMC data management platform. The NYU/HHC CTSI and NYULMC Clinical Research Informatics and Data Management Unit (CRIDM), led by James Robinson, M.Ed., will provide clinical research informatics and data management support for the study. Building on the a proprietary platform, CRIDM personnel will develop the additional required electronic case report forms (CRFs) to complete the data management system for this proposal, and work with study personnel to insure the completeness and integrity of all study data. All data will be checked in real-time and stored in a centralized database; all data will be reviewed and monitored for completeness and accuracy, and a final data clean will be completed following the last subject visit, following which the study database will be locked.

12.0 Protection of Human Subjects

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 participant recruitment from the NYUMC IRB. Any amendments to the 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.

12.1 Potential Risks

This study offers patient randomization to two forms of FDA-approved naltrexone treatment for alcohol dependence. 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.

All participants will receive 24 weeks of office-based naltrexone treatment. As with any patient starting naltrexone, participants in either arm may experience nausea, headache, and fatigue ('naltrexone flu'), particularly during the initial first few days of dosing. Nausea may be more likely with oral vs. injectable naltrexone. In most published naltrexone clinical trials, these side effects are well-tolerated by patients, though it is certainly possible some patients will discontinue the medications based on these common and expected naltrexone side effects, as a small percentage of patients did in our pilot, the COMBINE study, and the Garbutt XR-NTX efficacy studies.[2,3,26] Theoretically both forms of naltrexone can cause transient liver inflammation, and liver function will be monitored throughout the trial. In reality, few patients in recent clinical trials or usual care experience any naltrexone-related liver toxicity.

Injectable XR-NTX carries a unique set of adverse event risks, including injection site soreness, usually well tolerated, and more severe injection site reactions, which may be prolonged and resemble a sterile abscess. Nationally, a small number of injection site reactions have been recorded, with a very low percentage progressing to necrosis and requiring surgical debridement, according to a 2008 FDA Alert, *Naltrexone Injection Site Reactions* (www.fda.gov). Our own pilot recorded one such severe injection site reaction (1 of 154 injections), in this case an older female with substantial hip adipose tissue.[2] It is thought that mis-injection of the XR-NTX bolus into subcutaneous adipose tissue is the cause of injection site reactions, as opposed to proper intramuscular placement. Study staff will be carefully trained on this issue

and take extra caution among participants with increased hip and buttocks adipose tissue. We will not, however, exclude patients based on body habitus or BMI, as this is not a national recommendation and therefore not part of usual care.

XR-NTX also introduces a prolonged mu opioid antagonist blockade, complicating the treatment of acute or chronic pain with opioid medications. O-NTX also produces an antagonist blockade, but can simply be discontinued in the face of an unexpected painful event. Persons randomized to XR-NTX will be provided a wallet card identifying them as an XR-NTX patient and containing the PI's and study phone numbers. XR-NTX blockade can be 'overridden' due to competitive mu receptor pharmacodynamics with increasing doses of full mu agonists, which should provided only in a monitored medical setting such as an Emergency or Recovery Room. There were no such unanticipated painful events in our pilot study, and persons with chronic pain conditions requiring opioid medications are excluded from enrollment.

All participants will be given information concerning all of these potential risks prior to giving informed consent. The informed consent document and informed consent quiz will in simple and plain language detail all of the above medication-related risks. The Medical Management visit schedule may be altered to accommodate unexpected visits related to side effects and adverse events, and study staff will be available by phone for emergency consultation at any time (all patients will be given the PI's direct mobile number).

Otherwise this is a study of treatment for alcohol dependence, and there is no guarantee patients will benefit from either intervention, and thus remain chronic, heavy drinkers, with all of the daily and long-term risks and hazards alcohol dependence entails. Both arms of the study represent evidence-based, FDA-approved interventions designed to treat alcohol dependence and minimize these risks, and we expect most patients to derive some minimal benefit from treatment. However, at any point in the trial, patients 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 detox and specialty treatment through Bellevue Hospital. Detox and intensive outpatient alcohol specialty services are immediately available to all participants through the Bellevue Hospital Chemical Dependency programs, including same-day admissions to our detox unit, regardless of insurance status or ability to pay.

These 'risks,' inherent to identifying and initiating treatment in previously out-of-treatment alcohol dependent patients, are common to all alcohol intervention trials and usual care, and do not seem to complicate Medical Management protocols. Our recent pilot of XR-NTX did not, for example, refer any of the 72 patients to detox services, and none reported severe withdrawal or seizures after the initiation of XR-NTX treatment. Most likely patients with severe physiologic alcohol dependence and at greatest risk for withdrawal seizures, phenomena which occur in a small minority of alcohol dependent patients and are not thought to be opioid receptor mediated, do not experience great benefit from naltrexone treatment and continue to drink heavily.

12.2 Confidentiality

Participants will be asked to provide information regarding a number of sensitive behaviors (e.g., alcohol and drug use, sexual history, and illicit activities). We will obtain a Federal Certificate of Confidentiality from DHS/NIH to encompass protocol activity and participant data and ensure against the release of confidential information. We will provide all 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 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. Data sharing of de-identified data is discussed below.

12.3 Emotional Discomfort

There is a small chance that participants may become upset when discussing their history of alcohol problems, family conflict, prior trauma, or role failure, etc. We will discontinue administration of research instruments if a subject shows great discomfort or asks to terminate an interview. Such events were not observed in our pilot study.

12.4 Risk/Benefit Ratio

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 compared to the expected benefit of discontinuing alcohol use.

12.5 Resource and Data Sharing Plan

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 patient 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. Lee 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 participant, 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.

12.6 Data and Safety Monitoring Plan (DSMP)

12.6.1 Data Safety & Monitoring Board (DSMB)

A safety monitoring board will be established for ongoing protocol review, including data, protocol compliance, safety and efficacy data, in compliance with NIH and NYU guidelines. Constition of the DSMB is pending and will be presented to the IRB when complete. All board 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. The board will meet every six months (unless more frequent meetings are deemed necessary). Dr. Lee 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. Lee 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; both medications are FDA-approved, their use in this trial is consistent with their FDA labeling, and no significant safety issues have arisen in national post-marketing use; as a comparative and cost-effectiveness trial comparing two efficacious treatments, full recruitment and maximal follow-up is warranted to ensure complete outcome data, nor would an emerging effectiveness advantage in favor of one of the medications present an ethical issue in terms of continuation.

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

Study clinicians and research staff will be undergo the same baseline training at the inception of the study. The Project Manager and Data Management staff 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 patient 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 (see Resource and Data Sharing Plan).

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

Accuracy and completeness of the data will be ensured by the NYU/HHC CTSI and NYULMC Clinical Research Informatics and Data Management Unit (CRIDM), led by James Robinson, M.Ed., and as described in the Research Strategy. Study data will be managed by two Data Managers using a proprietary web-based e-research platform. Data will be entered using laptops with wireless broadband internet cards connected to the NYUMC secure intranet, encrypted, and transmitted to CRIDM servers at NYUMC. All data analyses for the study will be performed by the biostatistician, Eugene Laska PhD, of the Dept. of Psychiatry of NYU School of Medicine. Quality control is performed as the data are being entered, and then at further stages of the storage and management process.

12.6.4 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).

12.6.5 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.

12.6.6 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 NIDA project officer, and the original amendment approvals will be filed in the primary document manual.

12.6.7 Trial Stopping Rules

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 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.

12.6.8 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.

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