University of California, San Francisco
Clinical Research Protocol
The Better THAN Study: Targeting Heavy Alcohol use with Naltrexone among MSM
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Approval:

Glenn-Milo Santos, Ph.D, MPH

1/5/2020

Date

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

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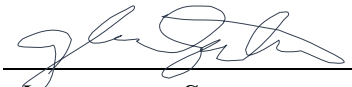

1/5/2020

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LIST OF ABBREVIATIONS

ACASI	Audio Computer Assisted Survey Instrument
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	Complete blood count
CBO	Community based organization
CCG	Community Consulting Group
CFR	Code of Federal Regulations
CRF	case report form
CPHR	Center for public health research
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual for Mental disorders
EtG	ethylglucuronide test
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	generalized estimating equations
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MM	Medical Management counseling
MSM	Men who have sex with men
NIAAA	National Institute on Alcohol Abuse and Alcoholism
PEth	phosphatidylethanol
PrEP	pre-exposure prophylaxis
PI	Principal Investigator
SAE	serious adverse experience
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	Structural clinical interview for DSM disorders
SFDPH	San Francisco Department of Public Health
SMS	Text message
TLFB	Timeline follow-back

PROTOCOL SYNOPSIS

TITLE	The Better THAN Study: Targeting Heavy Alcohol use with Naltrexone among MSM
SPONSOR	Glenn-Milo Santos
FUNDING ORGANIZATION	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
NUMBER OF SITES	1 site
RATIONALE	Oral naltrexone, FDA approved agent, was chosen because we believe it will be more acceptable to non-treatment seeking, non-alcohol dependent binge drinking men who have sex with men (MSM). Intermittent dosing makes sense for most binge-drinking MSM because data indicate that they do not binge drink daily.
STUDY DESIGN	This is a randomized, double-blind, placebo-controlled phase 2 study.
PRIMARY OBJECTIVE	To determine the efficacy of targeted naltrexone versus placebo in reducing binge drinking among non-dependent MSM, as determined by number of binge drinking days in timeline follow-back (TLFB), over the three-month treatment period.
SECONDARY OBJECTIVES	To determine the efficacy of targeted naltrexone versus placebo in reducing alcohol consumption among non-dependent MSM, as determined by the proportion of ethyl glucuronide (EtG) positive urines, over the three-month treatment period.
NUMBER OF SUBJECTS	120
SUBJECT SELECTION CRITERIA	Inclusion Criteria: (1) Male gender (2) self-reported anal sex with men in the prior three months while under the influence of alcohol (3) at least one binge drinking (five or more drinks on a single occasion) session per week in the prior three months; (4) interested in reducing binge alcohol consumption; (5) HIV-negative by rapid antibody test or medical record documentation of HIV infection (HIV positive participants); (6) no current acute illnesses requiring prolonged medical care; (7) no chronic illnesses that are likely to progress clinically during trial participation; (8) able and willing to provide informed consent and adhere to visit schedule; (9) age 18-70 years; (10) baseline CBC, total protein, albumin, glucose, alkaline phosphatase, creatinine, BUN, and electrolytes without clinically significant abnormalities as determined by study clinician in conjunction with symptoms, physical exam, and medical history. Exclusion Criteria: (1) Any psychiatric (e.g. depression with suicidal ideation) or medical condition that would preclude safe participation in the study; (2) known allergy/previous adverse reaction to naltrexone; (3) current use of/ dependence on any opioids or a known medical condition which currently requires/may likely require opioid analgesics; (4) opioid-positive urine at enrollment; (5) current CD4 count < 200 cells/mm^3 (6) moderate/severe liver disease (AST, ALT $\geq$ 3 times upper limit of normal);

	(7) impaired renal function (creatinine clearance < 50 ml/min); (8) currently participating in another intervention research study with potential overlap; (9) alcohol dependence as determined by SCID criteria (participants with non-dependent alcohol use disorders/symptoms of alcohol abuse [per DSM-IV] are *eligible*) (10) any condition that, in the principal investigator and/or study clinician's judgment interferes with safe study participation or adherence to study procedures; (11) not having a cell-phone that can send and receive text messages.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Naltrexone HCL 50 mg (ReVia), oral administration as needed.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Placebo 50 mg, oral administration as needed.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 9 months **Screening:** up to 30 days **Treatment:** 3 months **Follow-up:** 6 months The total duration of the study is expected to be nine months. One month for subject recruitment and nine months for final subject participation and follow-up.
CONCOMMITANT MEDICATIONS	Allowed: standard therapy Prohibited: current use of/ dependence on any opioid medication or current naltrexone treatments.
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• To detect 27% reductions in numbers of binge drinking occasions, as well as 10% reductions in the average numbers of drinks on drinking days among treatment arm compared to placebo arm.
SECONDARY ENDPOINTS	• To detect 15-23% reductions in the urine positivity rate in the treatment arm compared to the placebo arm.
OTHER EVALUATIONS	Potential biomarkers for alcohol: EtG and PEth
SAFETY EVALUATIONS	Change in clinical safety labs from baseline to week 12 Incidence of adverse events
PLANNED INTERIM ANALYSES	No planned interim analyses. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.

STATISTICS **Primary Analysis Plan**	We will use generalized estimating equations (GEE) to estimate treatment effects on repeated study outcomes. Primary analyses will be by intention-to-treat, without regard to adherence to treatment. In our prior trials, we had excellent retention and visit adherence. Nonetheless, in this high-risk population, missing data may be encountered.[123, 124] We will conduct sensitivity analyses imputing all missing urine samples as positive, adjusting for baseline correlates of missingness, and using inverse probability of censoring weights.[125] **Specific Aim 1:** *To determine the efficacy of targeted naltrexone versus placebo in reducing binge drinking among non-dependent MSM*, as determined by number of binge drinking days in timeline follow-back (TLFB), by arm. GEE Poisson models with robust standard errors will be used to assess reductions on weekly drinking outcomes**.** Baseline TLFB results will be included in the analysis. **Minimum detectable effects (MDEs):** In calculating minimum detectable effects, we hypothesized on pharmacologic grounds that oral naltrexone will reach full efficacy against alcohol use almost immediately; accordingly we expect treatment-control differences to be approximately constant over the 12 weeks of the trial. Based on the prior trial (93% retention), we estimate that 90% of participants will be retained at 12 weeks. Using estimates based on data from Project ECHO[92] for the within-subject correlation and over-dispersion of the outcomes, as well as the mean frequency among controls, we estimate that the proposed study will have 80% power in 2-sided tests with a type-I error rate of 5% to detect 27% reductions in numbers of binge drinking occasions, as well as 10% reductions in the average numbers of drinks on drinking days. **Specific Aim 2:** *To determine the efficacy of targeted naltrexone versus placebo in reducing alcohol consumption among non-dependent MSM*, as determined by the proportion of ethyl glucuronide (EtG) positive urines, by arm. GEE logistic models with robust standard errors will be used to assess reductions frequency of positive urine tests, accounting for within-subject correlation. **MDEs**: Using the assumptions for loss to follow-up for Aim 1, as well as estimates based on biomarker data from Batki et al's study on Topiramate for alcohol use disorders[122] for the within-subject correlation and control group urine positivity rate, we estimate that the study will have 80% power in 2-sided tests with a type-I error rate of 5% to detect 15-23% reductions in the urine positivity rate in the treatment arm. **Specific Aim 3:** *To determine the efficacy of targeted naltrexone versus placebo in reducing alcohol-associated sexual risk behaviors*, we will use GEE Poisson models with robust standard errors for the four monthly ACASI assessments on numbers of male anal sex partners, HIV-serodiscordant unprotected anal sex partners, unprotected anal sex partners while intoxicated with alcohol, and unprotected anal sex events with serodiscordant partners, including the baseline value. In the event that these outcomes are severely over-dispersed, we will analyze indicators for any self-report of each behavior, using GEE logistic models. **MDEs**: Based on estimates of within-subject correlation and control prevalence from our Project Echo trial, we estimate that the study will have 80% power to detect 31% reductions in numbers of male anal sex partners, 57% reductions in SDUA partners, 46% reductions in UA partners while intoxicated with alcohol, and 56% reductions in UA events with serodiscordant partners. In

	analyses using GEE logistic models, we will have 80% power to detect reductions of 14%, 38%, 39%, and 30% in any report of these four sexual risk behaviors, respectively.
Rationale for Number of Subjects	Given our estimate that there are 48,070 binge-drinking MSM in San Francisco[19, 20] and our prior trial enrollment rates, we are confident that we will be able to recruit 120 eligible non-dependent, binge-drinking MSM for the proposed trial.

1 BACKGROUND

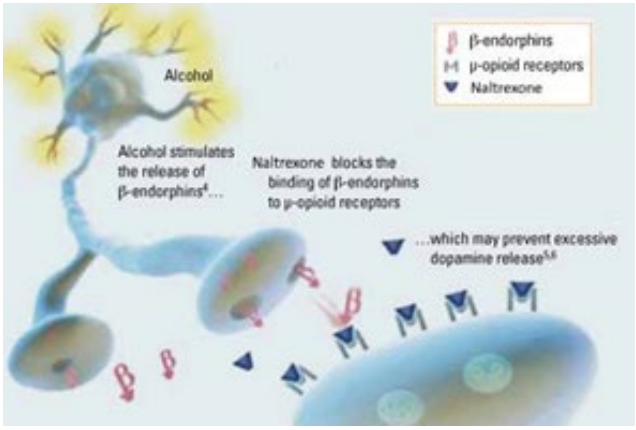
1.1 Overview of Overview of Clinical Studies

Binge drinking is a major health issue for men who have sex with men (MSM) at high-risk for acquiring or transmitting HIV. In the National HIV Behavioral Surveillance (NHBS) survey, 84% of MSM consumed alcohol in the past 30 days, and 57% reported at least one occasion of binge drinking.[3] The prevalence of binge drinking for MSM is 3.5 times the prevalence in the general US adult population.[1] **The high rates of alcohol use in MSM have been observed for decades and these rates will likely persist.**[15-17] In San Francisco, 72% and 55% of MSM reported binge drinking in the past 12 months, and the past 30 days, respectively.[18] Binge drinking is by far the most prevalent exposure attributed to HIV infections among MSM and it is estimated that there are 48,070 binge-drinking MSM in San Francisco.[19, 20] **MSM are disproportionately impacted by HIV**, accounting for 61% of new infections in 2009.[21] For San Francisco MSM, HIV prevalence is estimated at 22.7% and HIV annual incidence is estimated at 1.27% per year.[22] It is imperative to develop more evidence-based HIV-prevention interventions that are not only efficacious, but also feasible and acceptable to MSM.

Binge and other heavy drinking patterns are associated with HIV risk behaviors. NHBS data show that alcohol use before or during unprotected sex was common for MSM—41% and 43% of alcohol drinkers surveyed reported unprotected insertive and unprotected receptive anal sex while intoxicated on alcohol, respectively, during their most recent sexual episode.[3] Similarly, in Project Mix, one of the largest randomized controlled trials of MSM in the US, 40% of current drinkers reported having unprotected sex while intoxicated during their most recent anal sex episode.[23] **Interventions that can be utilized within the risk environment may be more efficacious at reducing HIV risk in this highly impacted population.** Alcohol use is deeply entwined with social activities of MSM[15] and although drinking, *per se*, does not always predict unprotected intercourse, certain risk contexts are more consistently associated with alcohol use.[4, 24] The acute effects of alcohol consumption (e.g., altered cognition, impaired judgment and increased sexual desire and confidence) may contribute to risk-taking behaviors.[25-28] A myriad of psychosocial factors (e.g., cognitive escape, impulsivity, expectancies) are believed to mediate the association between alcohol and sexual risk behaviors.[26, 29-34] Furthermore, bar and club venues frequented by MSM provide conducive environments for both meeting sexual partners and binge drinking.[12-15] **Notably, *event-level* analyses of alcohol use immediately before or during sexual episodes in two separate systematic reviews <u>consistently</u> found that binge drinking is independently associated with increased likelihood of having unprotected sex.**[4, 5] According to event-level analyses for 1,712 HIV-negative MSM, compared to non-binge drinkers, binge drinkers had three times the likelihood of having unprotected sex with non-primary partners.[35] These *event-level* assessments of alcohol use provide the most precise temporal link between these two behaviors and provide stronger evidence for causality.[5, 24] Binge drinking and other patterns of heavy alcohol use are independently associated with a variety of high-risk behaviors in MSM, including unprotected anal sex, multiple partners, and having HIV-serodiscordant partners[17, 35-44]__ a link also observed among black, Native American, and older MSM.[45-47] **Binge-drinking and heavy alcohol consumption are major causes of incident HIV infections in MSM.** Binge alcohol use was independently associated with a greater than three-fold increase in odds for new HIV diagnoses among MSM who had a previously (past 12 months) negative HIV-test in a case-control study.[48] In the Explore study of 4,295 HIV-negative MSM from six metropolitan areas, 29% of HIV incidence was attributable to use of alcohol or other drugs before sex; 6.1% was attributable to heavy alcohol use.[7] Similarly, in the Multicenter AIDS Cohort Study of 3725 HIV-negative MSM, the hazard for seroconversion among heavy drinkers was 61% greater, compared to those who abstained from alcohol during the 24 year follow-up (1984-2008).[49]

Behavioral interventions to address binge drinking to date have failed to reach MSM. Novel interventions are needed for MSM who binge drink.[8] Because excessive alcohol use is nearly ubiquitous among MSM and is commonly associated with high-risk sexual behavior and HIV infection, interventions that reduce alcohol consumption are likely to have an impact on the transmission of HIV. The primary prevention approaches to binge drinking for MSM are therapy and alcohol treatment programs. Individual[50] and couples[51] behavioral therapy approaches have been shown to reduce heavy alcohol use among MSM. However, only 20% of MSM who use alcohol or non-injection drugs have ever participated in alcohol or drug treatment programs.[3] In San Francisco, only 16% of binge-drinking MSM have sought alcohol treatment, underscoring the need for novel alcohol interventions.[18] MSM may be less likely to completely abstain from alcohol than heterosexual men,[52] emphasizing the need to consider alternative treatment outcomes including reductions in drinking. **Despite the link between binge drinking and HIV risk, the use of pharmacologic interventions to reduce alcohol-intake or alcohol-related sexual risk among MSM is almost entirely unexplored.** The absence of published studies on efficacious interventions to reduce alcohol-related sexual risk behaviors among MSM who have no desire to abstain from alcohol **presents a major gap in the field of alcohol research and HIV prevention.** Pharmacotherapy trials for methamphetamine dependence and cocaine dependence in MSM have shown that reductions in substance use can result in parallel reductions in HIV-sexual risk behaviors among MSM not seeking treatment.[53, 54] A pharmacologic intervention for binge drinking may lead to an analogous parallel reduction in alcohol-related sexual risks. **A critical challenge for HIV prevention interventions with MSM is the lack of interventions that reach MSM and effectively address HIV risk conferred through unprotected sex for MSM who binge drink.**

Naltrexone is an efficacious and effective pharmacologic treatment for alcohol dependence that blocks the reinforcing positive effects of alcohol use. Alcohol consumption results in the release of β-endorphins that bind and activate μ-opioid receptors.[55] Naltrexone competitively blocks β-endorphins from activating μ-opioid receptors[56] in the nucleus accumbens and ventral tegmental area, which mediate dopamine release (**Figure 1**, adapted from [57]). Thus, the opioid antagonistic mechanism of action of naltrexone decreases the activity of the dopamine reward pathways,[58, 59] tempering the positive neurobiological effects of alcohol.[56, 60]



Naltrexone is effective in attenuating the positive subjective effects of alcohol intoxication—including quality of "high", craving, and euphoria, supporting its efficacy among current drinkers.[61-65] A two-year longitudinal study of "heavy social drinkers" who habitually binge drink found that the positive subjective and stimulant effects of alcohol are strong predictors of sustained and increased binge drinking.[66] **Given naltrexone's efficacy in reducing the positive effects of alcohol that have been linked to future binge drinking,[66] naltrexone may be a promising option to reduce binge drinking.** Naltrexone is well-tolerated by active alcohol drinkers and has no known significant drug interactions.[56, 67-70] Naltrexone has few serious side effects, no known abuse potential, [68, 69, 71-74] and no known sexual side effects.[71]

Naltrexone's pharmacokinetic properties support targeted administration (i.e., use in anticipation of heavy alcohol use on an "as needed" basis). Naltrexone's activity is believed to be due to both the parent and the 6-β-naltrexol metabolite.[71] Naltrexone reaches peak plasma levels

within one hour of oral administration. The mean elimination half-life for naltrexone and 6-β-naltrexol are four and 13 hours, respectively.[71] Naltrexone also has high affinity to the μ-opioid receptor (Ki = 2.5 ± 0.21 nM) and a single 50 mg dose can block μ-opioid receptors for up to 72 hours[75] raising the possibility that dosing even 1-2 days prior to anticipated alcohol consumption may be effective. **Targeted administration of naltrexone on an "as needed" basis has shown promise in reducing heavy drinking among heterosexuals.** Targeted naltrexone dosing was feasible and acceptable in a small pilot study of heavy-drinking young adults not ready or willing to abstain from alcohol; the trial completion and targeted medication adherence rates were 93% and 83%, respectively.[76] Other samples of non-dependent heavy drinkers have also been successfully recruited and retained in targeted dosing studies.[11, 77-79] Targeted naltrexone administered after a period of daily dosing significantly reduced heavy-drinking relapse.[80] Similarly, in a trial conducted by Kranzler, et al., men assigned to targeted naltrexone showed significant reductions in mean drinks per day, and in number of drinks during drinking days, compared to those assigned to *daily* naltrexone administration, *daily* placebo, or targeted placebo.[11] Intermittent dosing schedules for opioid antagonists like naltrexone show similar results: targeted nalmefene reduced heavy drinking days, "very heavy" drinking days, and number of drinks during drinking days in randomized controlled trials.[81, 82] None of these studies have evaluated sexual risk behaviors or exclusively recruited binge drinking MSM at risk for acquiring or transmitting HIV. **Questions about the efficacy of targeted naltrexone to reduce alcohol-related sexual risk behavior remain unanswered; no efficacy trial has determined if targeted use of pharmacologic agents for binge drinking can reduce HIV risk behavior.**

2 STUDY RATIONALE

Oral naltrexone was chosen because we believe it will be more acceptable to non-treatment seeking, non-alcohol dependent binge drinking MSM. Intermittent dosing makes sense for most binge-drinking MSM because data indicate that they do not binge drink daily. Injectable naltrexone's opioid blockade can last a month or more and overcoming the opioid antagonism with high opioid doses requires close monitoring and expert personnel.[75, 132] Injectable naltrexone is also associated with more adverse events than oral naltrexone.[132, 133] Oral naltrexone was specifically chosen because of its mechanism of action, and safety profile. Dilsufiram is not ideal as it requires abstinence,[134] which may not be acceptable in our target population. Acamposate has been shown to sustain abstinence, although not in intention-to-treat analyses in American studies[134] and thrice-daily dosing limits its utility.[134]

Much like other chemoprophylaxis strategies, intermittent targeted dosing of oral naltrexone will not be acceptable to everyone. However, the fact remains that for most MSM, bars, clubs and other venues that serve alcohol remain the dominant setting for social interactions with other MSM.[12-15] For MSM who are interested in reducing binge drinking but do not wish to isolate themselves from these venues, targeted dosing of oral naltrexone may be an attractive alternative. *Indeed, preliminary data from our ongoing pilot, the Project iN study, suggest that taking a medication to reduce alcohol consumption is feasible and acceptable among binge-drinking MSM.* If targeted dosing is efficacious among binge-drinking MSM, it may ultimately expand strategies for MSM to reduce their alcohol consumption.

2.1 Risk / Benefit Assessment

Adverse drug effects: A primary risk of participation in this study is the potential of AEs due to taking naltrexone. These risks are seen as reasonable, given the favorable side effect profile for this medication and the fact that we will exclude persons from the trial who are at higher risk for AEs. As part of the informed consent process, participants will be informed of the potential risks of taking naltrexone.

Naltrexone is well-tolerated and has no known significant drug interactions.[54]In randomized controlled trials, naltrexone has few serious side effects; it has no known abuse potential and dependence has not been reported.[54, 66, 67, 69-72.] Naltrexone's activity is believed to be due to both the parent compound and the 6-naltrexol metabolite.[69] The mean elimination half-life of for naltrexone and 6-naltrexol are four and 13 hours, respectively.[69] Initial trials evaluating the efficacy of naltrexone as treatment for alcohol dependence raised no safety concerns.[65, 66.] Naltrexone was also well-tolerated in subsequent studies in more clinically heterogeneous populations with co-morbid conditions[67, 112.] Naltrexone has not been shown to cause significant increases in complaints in placebo-controlled trials in patients known to be free of opioids for more than 7 to 10 days.[69.] The largest safety study to date on clinical use of naltrexone as a pharmacotherapy for treatment of alcoholism was a multi-center safety trial involving 865 individuals (500 naltrexone-treated patients, 238 patients in an unmedicated control group).[68.] Results of this study demonstrated that the most commonly reported side effects were nausea (9.8%), headache (6.6%), dizziness (4.4%), nervousness (3.8%), and fatigue (3.6%); serious side effects were uncommon. [68.] Naltrexone was discontinued in 15% of the participants, with nausea being the most common reason for medication discontinuation. [68.] Studies in alcoholic populations and healthy volunteers have suggested that a small number of patients may experience an opioid withdrawal-like symptom complex including tearfulness, mild nausea, abdominal cramps, restlessness, arthralgia, myalgia, and nasal symptoms.69Naltrexone has no known sexual side-effects[69], supporting its potential acceptability for sexually-active MSM. Depression, suicidal ideation, and suicide attempts have been reported in both groups when comparing naltrexone and placebo for treatment for alcoholism. [69]There is no indication that naltrexone treatment increases the risk of suicide.[63]

A review of the literature concluded that in patients treated for heroin or alcohol dependence, naltrexone does not cause clinically significant liver disease or exacerbate pre-existing liver disease.[71.] However, naltrexone has the capacity to cause hepatocellular injury in excessive doses and is contraindicated in acute hepatitis and liver failure. [69.] Patients with these conditions will be excluded from our trial. Naltrexone is also contraindicated in patients who are currently dependent on opioids or in acute opioid withdrawal. The team anticipates that few participants will be excluded by virtue of current opioid use; for example, in our recently published mirtazapine study, only 7% of MSM met criteria for opioid dependence. Although the opioid blockade produced by naltrexone is surmountable, this situation requires careful medical management by trained personnel in settings equipped for resuscitation. Attempts by patients to overcome naltrexone's opioid antagonism may lead to an overdose. Naltrexone may also precipitate severe opiate withdrawal, including mental status change, nausea, vomiting, diarrhea, and dehydration in patients who are not opioid-free for a minimum of 7 to 10 days. [69.] For this reason, urine opioid testing is needed to screen all potential participants for opioid use. Patients who have a foreseeable need for opioid pain management (e.g. potential elective surgery in the study period) will also be excluded. Additionally, all patients will be fully informed verbally and in the written consent form about the potential for overdose by attempting to overcome naltrexone's opioid antagonism.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to determine the efficacy of targeted naltrexone versus placebo in reducing binge drinking among non-dependent MSM, as determined by number of binge drinking days in timeline follow-back (TLFB) over the three-month treatment period.

3.2 Secondary Objectives

To secondary objectives include 1) to determine the efficacy of targeted naltrexone versus placebo in reducing alcohol consumption among non-dependent MSM, as determined by the proportion of ethyl glucuronide (EtG) positive urines, over the three-month treatment period; 2) to determine the efficacy of targeted naltrexone versus placebo in reducing alcohol-associated sexual risk behaviors, we will use GEE Poisson models with robust standard errors for the four monthly ACASI assessments on numbers of male anal sex partners, HIV-serodiscordant unprotected anal sex partners, unprotected anal sex partners while intoxicated with alcohol, and unprotected anal sex events with serodiscordant partners, including the baseline value. In the event that these outcomes are severely over-dispersed, we will analyze indicators for any self-report of each behavior, using GEE logistic models.

4 STUDY DESIGN

4.1 Study Overview

This is a double-blind, placebo-controlled, two-arm trial in which 120 binge-drinking MSM will be randomly assigned to receive 12 weeks of oral naltrexone 50 mg or placebo, to be taken on an as needed basis. This efficacy study will enroll binge-drinking MSM because they are the most likely population to benefit from this intervention. A study clinician from the Center for Public Health Research (CPHR) will perform the Structured Clinical Interview for the DSM-IV (SCID) to determine eligibility and rule out alcohol dependence (the SCID for DSM-V will be used when it becomes available). Upon enrollment, 120 participants will be randomized 1:1 to naltrexone or placebo for targeted administration. Participants will be seen weekly for behavioral surveys, urinalyses, study drug dispensing and alcohol use counseling. Safety laboratory assessment, vital signs, and the audio computer assisted survey instrument (ACASI) will be completed monthly. Efficacy, tolerability, and acceptability (Specific Aims 1-4) will be assessed upon trial completion as measured by number of binge drinking occasions and numbers of drinks on drinking days via timeline follow-back at weekly visits; number of ethyl glucuronide-positive urine samples; sexual risk behavior data through monthly surveys via ACASI; frequency of adverse clinical events by treatment arm, and cumulative medication adherence data at week 12. Primary analyses are designed as “intention-to-treat” with evaluation of outcomes according to random assignment, regardless of whether participants took the medication.

5 CRITERIA FOR EVALUATION:

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is to detect 27% reductions in numbers of binge drinking occasions, as well as 10% reductions in the average numbers of drinks on drinking days among treatment arm compared to placebo arm. Using the assumptions for loss to follow-up for the primary endpoint, as well as estimates based on biomarker data from Batki et al’s study on Topiramate for alcohol use disorders[122] for the within-subject correlation and control group urine positivity rate, we estimate that the study will have 80% power in 2-sided tests with a type-I error rate of 5% to detect 15-23% reductions in the urine positivity rate in the treatment arm. The time course for the endpoints will be assessed from baseline to end of treatment period.

5.2 Secondary Efficacy Endpoints:

The secondary efficacy endpoint is based on estimates of within-subject correlation and control prevalence from our Project Echo trial, we estimate that the study will have 80% power to detect 31% reductions in numbers of male anal sex partners, 57% reductions in SDUA partners, 46%

reductions in UA partners while intoxicated with alcohol, and 56% reductions in UA events with serodiscordant partners. In analyses using GEE logistic models, we will have 80% power to detect reductions of 14%, 38%, 39%, and 30% in any report of these four sexual risk behaviors, respectively.

5.3 Safety Evaluations

Change in clinical laboratory findings, specifically the liver enzymes such as BUN or Creatinine.

Incidence of adverse events

6 SUBJECT SELECTION

6.1 Study Population

120 MSM cis-gender males who binge drink who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

(1) Male gender;

(2) self-reported anal sex with men in the prior three months while under the influence of alcohol;
(3) at least one binge drinking (five or more drinks on a single occasion) session per week in the prior three months;

(4) interested in reducing binge alcohol consumption;

(5) HIV-negative by rapid antibody test or medical record documentation of HIV infection (HIV positive participants);

(6) no current acute illnesses requiring prolonged medical care;

(7) no chronic illnesses that are likely to progress clinically during trial participation;

(8) able and willing to provide informed consent and adhere to visit schedule;

(9) age 18-70 years;

(10) baseline CBC, total protein, albumin, glucose, alkaline phosphatase, creatinine, BUN, and electrolytes without clinically significant abnormalities as determined by study clinician in conjunction with symptoms, physical exam, and medical history.

(11) Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

(1) Any psychiatric (e.g. depression with suicidal ideation) or medical condition that would preclude safe participation in the study;

(2) known allergy/previous adverse reaction to naltrexone;

(3) current use of/ dependence on any opioids or a known medical condition which currently requires/may likely require opioid analgesics;

(4) opioid-positive urine at enrollment;

(5) current CD4 count < 200 cells/mm^3 ;

(6) moderate/severe liver disease (AST, ALT $\geq$ 3 times upper limit of normal);

(7) impaired renal function (creatinine clearance < 50 ml/min);

(8) currently participating in another intervention research study with potential overlap;

(9) alcohol dependence as determined by SCID criteria (participants with non-dependent alcohol use disorders/symptoms of alcohol abuse [per DSM-IV] are *eligible*)

(10) any condition that, in the principal investigator and/or study clinician's judgment interferes with safe study participation or adherence to study procedures;

(11) not having a cell-phone that can send and receive text messages*;*

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapy is allowed except for naltrexone treatments and opioid medications as noted in the exclusion criteria described above and as noted in the prohibited medications section below.

Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation:

1) Opioid medications
2) Naltrexone treatments

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

The Better Than Study will enroll 120-participants for the double-blinded placebo controlled trial where 60 eligible participants will be randomly assigned to the treatment group receiving Naltrexone and 60 participants will be randomly assigned to the control group receiving placebo in a 1:1 ratio using a computer-generated randomization scheme developed by our biostatistician. The study biostatistician will generate a random allocation sequence list with treatment assignments associated with order of enrollment, using randomly permuted blocks with randomly selected block sizes.

8.2 Blinding

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or patients. The following study procedures will be in place to ensure double-blind administration of study treatments.

- Access to the randomization code will be strictly controlled.
- Packaging and labeling of test and control treatments will be identical to maintain the blind.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the Investigator should discuss the emergency with the Medical Director prior to unblinding.

Describe the procedures for unblinding.

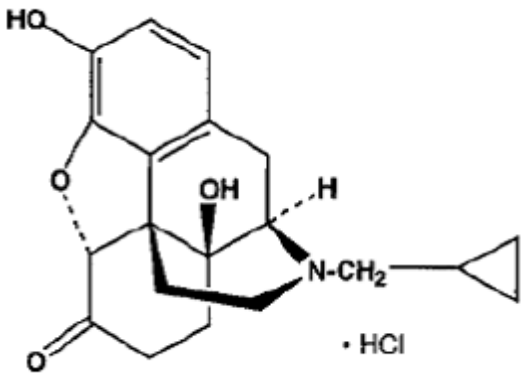
At the end of the study, the biostatistician will provide us with which study drug kits were naltrexone treatment and which study drug kits were placebo. The study drug kits will be compared to the participant enlisted in the study. Study Staff will inform the participant verbally of their study treatment assignment. For those who do not respond by phone, a letter will be sent to their address to inform the participant of their treatment assignment.

8.3 Formulation of Test and Control Products

The Safeway Compounding Pharmacy, which currently prepares our study drug for our ongoing clinical trials, will provide the study drug kits for the proposed trial. Drugs are over-capsuled in a locking capsule to ensure the same appearance across all study arms and maintain double-blind.

Formulation of Test Product

REVIA® (naltrexone hydrochloride tablets USP), an opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. REVIA is also related to the potent opioid antagonist, naloxone, or n-allylnoroxymorphone.



REVIA is a white, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/mL. REVIA is available in scored film-coated tablets containing 50 mg of naltrexone hydrochloride.

REVIA Tablets also contain: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, synthetic red iron oxide, synthetic yellow iron oxide and titanium dioxide.

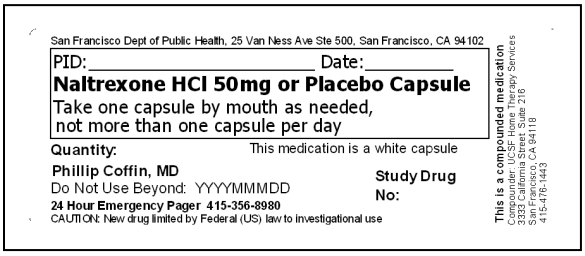
8.3.1 Formulation of Control Product

Placebo capsules will contain microcrystalline cellulose (Medisca). Placebo and active medication will be provided in capsules that are an exact match in color, so as to make the placebo and active medication indistinguishable from each other.

8.3.2 Packaging and Labeling

Study drug was initially provided by UCSF Compounding and Research Support Pharmacy, 3333 California Street, Suite 216E, San Francisco, CA, 94118. Since that pharmacy has closed, Safeway Compounding Pharmacy, 6100 Hellyer Ave Ste 100, San Jose, CA, 95138, is used to provide study drug. Each treatment bottle from the UCSF pharmacy was labeled with the study drug number, prescribing physician name (medical director), required FDA warning statement, emergency pager number, directions for participant use and storage, and expiration information. Each treatment bottle from Safeway pharmacy is labeled with the study drug number, principal investigator name, prescribing physician name (medical director), required FDA warning statement, emergency pager number, directions for participant use and storage, and lot and expiration information.

Sample label from UCSF Pharmacy:


San Francisco Dept of Public Health, 25 Van Ness Ave Ste 500, San Francisco, CA 94102

PID:_____ Date:_____

Naltrexone HCl 50mg or Placebo Capsule

Take one capsule by mouth as needed, not more than one capsule per day

Quantity: This medication is a white capsule

Phillip Coffin, MD

Do Not Use Beyond: YYYYMMMDD

Study Drug No:

24 Hour Emergency Pager 415-356-8980

CAUTION: New drug limited by Federal (US) law to investigational use

This is a compounded medication

Compounder: UCSF Home Therapy Services
3333 California Street, Suite 216
San Francisco, CA 94118
415-476-1443

8.4 Supply of Study Drug at the Site

Study medication will be supplied to the Center on Substance Use and Health (CSUH) on an as-needed basis, usually 5 or 10 study drug kits at a time. A record of drug receipt will be kept in the investigational drug accountability log. Study drug will be stored in a locked pharmacy with temperature monitoring. Study drug kits provided by the pharmacy will already be randomized, so blinding will be maintained for all staff at the study site.

8.4.1 Dosage/Dosage Regimen

The dose of naltrexone being investigated for potential as a pharmacotherapeutic on an as-needed basis to reduce binge drinking is 50 mg. It is recommended participants take one capsule of medication by mouth 1 to 2 hours before starting an episode of binge drinking. Participants will be instructed to take no more than one capsule in a 24-hour period. No adjustments for weight, age, or meals is required. The dose of naltrexone being investigated for potential as a pharmacotherapeutic on an as-needed basis to reduce binge drinking is 50 mg. It is recommended participants take one capsule of medication by mouth 1 to 2 hours before starting an episode of binge drinking. Participants will be instructed to take no more than one capsule in a 24-hour period. No adjustments for weight, age, or meals is required.

8.4.2 Dispensing

Study medications will be dispensed by the study clinician (licensed medical practitioner) in treatment bottles that are labeled with the study drug number, principal investigator name, prescribing physician name (medical director), required FDA warning statement, emergency pager number, directions for participant use and storage, and lot and expiration information.

Further, at time of study drug dispensing, the study clinician will review with the participant how to take the study medication, possible side effects they may encounter, and how to access the study clinician by emergency pager if necessary. The study clinician will also answer any questions the participant might have.

8.4.3 Administration Instructions

Training on targeted medication dosing:
During enrollment, participants will be trained on medication dosing and be provided a brief instructional leaflet for reference. Participants will be encouraged to intermittently use at least 3 capsules per week, when they believe that drinking is imminent or anticipate a session of binge drinking. At baseline and follow-up visits, study staff will assess each participant's drinking pattern and develop a plan to support intermittent dosing of study drug and maximize medication efficacy. Participants will be given twenty-eight 50 mg tablets per month and will be instructed to not exceed 1 tablet every 24 hours. This dosing is similar to the usual administration of naltrexone for alcohol dependence, except that participants will be taking study drug on an as needed basis instead of daily. Participants will be briefed about the importance of not sharing medications. We will offer participants a wallet card that explains that they may be taking naltrexone. The card provides contact information for medical professionals to seek further information from the study clinician should they have questions.

8.4.4 Storage

Study drug should be stored by the study site at controlled room temperature, Store at 15° to 30°C (59° to 86°F). If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this will be reported to the research program manager and PI and captured as a deviation. Subjects will be instructed to store the medication in the MEMs cap containers at room temperature according to the instructions outlined on the Drug Administration Instructions.

8.5 Study Drug Accountability

An accurate and current accounting of the acquisition, dispensing, return, and destruction of study drug for each participant will be maintained in an investigational drug accountability log by study staff throughout the course of the study.

8.6 Measures of Treatment Compliance

Study medications will be dispensed by the study clinician in MEMS cap dispensers with dosing instructions, date of dispensing, prescribing clinician, a 24-hour telephone study phone number for medical emergencies, and advisements against drug combinations. Each dispenser opening is recorded as a medication event in a remote database in real time. MEMs cap dispensers have been shown to be reliable for real time monitoring of medication adherence, even in resource-limited settings.[117] We have had great success with electronic medical monitoring devices in prior studies among MSM.[53, 84] The Subjects will be asked to bring in their study drug at in-office visits. The Subjects will be asked to document any adverse events that occur during the week.

9. STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study. Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at Month 1, Month 2 and Month 3 safety lab visits. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

9.1.4 Physical Examination

A complete physical examination will be performed by the clinician at Enrollment, Month 1, Month 2 and Month 3 visits. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse and weight will be performed after resting for 5 minutes on Screening, Enrollment and Month 1, Month 2 and Month 3 visits.

9.1.6 Safety Lab Assessment

Safety lab assessments will take place at screening, months 1, 2, and 3 visits. Blood specimens will be collected for monthly safety lab assessments via venipuncture by clinicians or research associates with certified phlebotomy training. Medications taken 30 days prior to enrollment and while enrolled in the study will be documented on a concomitant medications form.

9.1.7 HIV risk reduction counseling and testing

All participants will receive standard HIV risk reduction counseling at enrollment and month 3 with HIV rapid antibody test and pooled viral load (HIV-negative participants) and CD4 testing (HIV-positive participants).[104] Participants with positive rapid tests will be given a confirmatory Western Blot assay and will receive HIV-counseling and referrals to HIV service providers. Participants newly diagnosed with HIV at screen will be referred to community resources and will be contacted for rescreening in the subsequent month.

9.2 Other Clinical Procedures

9.2.1 Medical Management (MM) counseling for alcohol use:

This study's aim is to determine efficacy of a pharmacologic intervention to reduce binge drinking, against a background of relatively brief counseling that would be feasible in a clinical setting with limited resources. Thus, we will adapt a manualized version of the MM brief counseling platform used in NIAAA's COMBINE study.[72, 105] In that trial, naltrexone with MM showed the most significant reductions in heavy drinking days (Hazard Ratio: 0.72; p=0.02) compared to 7 other treatment conditions.[72] MM has been used in a targeted pharmacotherapy trial[81] and our team has successfully used MM in alcohol pharmacologic trials. MM is a low-intensity supportive program designed to increase problem recognition and enhance motivation to change maladaptive alcohol use patterns. Participants will receive individual 20 minute MM sessions weekly from trained staff supervised by a clinical psychologist, with monthly quality assurance sessions.

9.2.2 Behavioral survey measurements:

Standardized and validated behavioral measures[106-109, 111, 112, 115] will be assessed using audio computer administered surveys (ACASI) to minimize underreporting of risk activities and standardize data collection.[106, 107] To minimize potential social desirability bias, staff will not have access to data during the trial.

9.2.3 Measures of adherence:

The study will collect self-reported adherence via weekly modified TLFB assessments, similar to prior targeted naltrexone studies[11, 81] and via daily SMS text messages. Pill counts at weekly visits will also assess adherence. **MEMs cap dispensers** will be used to track medication adherence daily; each dispenser opening is recorded as a medication event in a remote database in real time. MEMs cap dispensers have been shown to be reliable for real time monitoring of medication adherence, even in resource-limited settings.[117] We have had great success with electronic medical monitoring devices in prior studies among MSM.[53, 84]

9.2.4 Ecological Momentary Assessments:

As with our Project iN pilot study, participants will receive daily SMS texts to collect data on alcohol consumption, number of drinks on drinking days, and targeted medication administration prior to anticipated drinking sessions. Messages will use short-hand notations to maintain participant confidentiality. Participants will be trained on text-messaging procedures and receive a reference guide during enrollment (see sample from Project iN study in the appendix). Participants will be encouraged to regularly delete text messages and encrypt their phone with passwords for privacy.

9.2.5 Adverse Events

Potential AEs will be monitored using a checklist of most common AEs associated with naltrexone similar to prior Phase IV naltrexone studies[11] and will follow the "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events" and UCSF IRB reporting guidelines.[116] Safety monitoring will include the assessment, follow-up, and reporting of clinical/serious AEs (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report forms as well as in the electronic database.

9.3 Clinical Laboratory Measurements

9.3.1 Hematology

Blood will be obtained and sent to San Francisco General Hospital laboratory for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count).

9.3.2 Blood Chemistry Profile

Blood will be obtained and sent to San Francisco General Hospital Laboratory for determination of (list as applicable) serum sodium, potassium, chloride, bicarbonate, random glucose, BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), albumin and LDH.

9.3.4 Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study and during the safety lab visits at month 1, month 2 and month 3 visits.

9.3.5 Urinalysis

9.3.5.1 Urinalysis for other classes of substance use: Urine samples will be collected weekly and tested for methamphetamine, cocaine, opioids, and other substances of abuse using MEDTOX EZ-SCREEN cups. Positive results will be confirmed by further urine testing through the laboratory at San Francisco General Hospital.

9.3.5.2 Urinalysis for novel alcohol biochemical markers: Urine samples will be collected at enrollment and monthly and tested for ethyl glucuronide (EtG) to determine recent alcohol consumption. EtG is a relatively novel, highly sensitive indicator for recent alcohol consumption; this alcohol biomarker is detectable in urine for approximately 72 hours).[118-121] The PI has used EtG to evaluate the efficacy of another pharmacologic intervention in reducing alcohol consumption in a trial funded by the Department of Defense [122] with Dr. Batki, a consultant in the proposed study. Urine samples will be tested via liquid chromatography-mass spectrometry through the Redwood Toxicology Laboratory, Inc., the same lab used by Dr. Batki's ongoing pharmacologic trials on alcohol dependence at the San Francisco Veteran's Affairs Medical Center. EtG quantitative results will be dichotomized using established cutoff values recommended by the Substance Abuse and Mental Health Services Administration (SAMHSA) to distinguish between positive and negative specimens.[119, 121] Whenever possible we will schedule participants for their weekly visits on Mondays and Tuesdays, given that binge drinking is likely to be higher over the weekend compared to the remainder of the week.

9.3.6 Dried Blood Spot (DSB) Testing for Phosphatidyethanol:

Phosphatidylethanol (PEth)—a phospholipid formed only in the presence of alcohol—is a novel, *direct* biochemical marker of alcohol that has shown high (>95%) sensitivity and specificity to detect heavy drinking over a period of 2-3 weeks in several studies of dependent patients and abstainers. In persons with HIV, recent validation studies found that PEth, using a cutoff of >8 ng/mL, was 88% sensitive and 89% specific for alcohol consumption in the prior 21 days (3 weeks), and 95% sensitive and 73% specific for heavy alcohol consumption (i.e., exceeding the NIAAA cutoffs). DSB samples will be collected at enrollment, weeks 3, 6, 9, 12, and post-

treatment visits at month 1, 3, and 6. Staff will use sterile lancets for fingersticks (or we will aliquot blood from a venipuncture specimen tube) to collect drops of blood (less than 5ml) to apply onto Whatman 903 filter paper (Whatman, Maidstone, UK). Samples will be dried overnight inside a drying box using standardized methods. PEth testing of DBS samples will be conducted at the United States Drug Testing Laboratories in Des Plaines, IL, one of the few laboratories that conduct this test worldwide. The testing will be conducted using an Agilent 6460 liquid chromatography-tandem mass spectrometry (LC-MS/MS) system following extraction into methanol, as previously published.

9.3.7 Genetic and Biomarker Testing: Blood samples will be stored at the University of California San Francisco, School of Nursing Genomics Lab for future genetic, epigenetic and micro RNAstudies, as well as other studies that elucidate the biologic processes by which alcohol use may contribute to morbidity and mortality. Research studies will be restricted to health conditions associated with alcohol use. These may include testing to determine the presence of the A118G SNP and other mutations relevant to the moderation of naltrexone's effects on the μ-opioid receptor gene (OPRM1). Additionally, we may test for the expression of biomarkers associated with innate immune activation (i.e., sCD14, neopterin, and tryptophan/kynurenine ratio) and inflammation (i.e., IL-6, TNF- R1).

10 EVALUATIONS BY VISIT

10.1 VISIT 1 (SCREENING VISIT—WEEK 1)

Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.

Assign the subject a unique screening number.

Record demographics data.

Record medical history, including a history of mental health, sexual behaviors and substance use, diagnosis date, and prior Alcohol treatments.

Record concomitant medications.

Perform a complete physical examination.

Collect urine sample for alcohol, opiates, and other substances test. If capable of becoming pregnant then a pregnancy test. Record results.

10.2 Visit 2 (Screening Visit – week 2)

Perform and record vital signs.

Perform and record results of blood pressure testing.

Collect blood for clinical laboratory tests (chemistry, hematology, HIV test, pooled viral load test. If HIV positive, a CD4 test).

Collect blood for Genetic and Biomarker Testing if you agreed to participate in a genetic and biomarker sub-study that will involve storage of blood samples to be used for testing. Testing will be confined for genes and biomarkers of health conditions related to alcohol use.

Collect and record contact information

10.3 Visit 3 (Enrollment Visit – month 1)

Assign randomization. You are assigned by a computer by chance to either thnaltrexone or placebo groups.

Collect urine to test for alcohol, opiates, and other substances.

If capable of becoming pregnant, we will collect urine and perform a pregnancy test.

Provide study medication (naltrexone or placebo) in medical monitoring devices ("MEMS" containers). MEMS devices will record each time you open the container to retrieve a study medication capsule.

Provided with a Wallet Card that explains that you may or may not be on a study medication (naltrexone or placebo). This card will provide the study clinician's pager number who can provide information to other doctors in the event of an emergency. The card will also instruct the emergency room or other doctor providing treatment to provide information to the study clinician about the care they provide.

Collect blood sample to test for alcohol (PEth test).

Perform ACASI questionnaire on a computer.

Meet with counselor about alcohol consumption

Initiate Ecological Momentary Assessments

10.4 Visit 4 (weeks 1, 2, 3, 5, 6, 7, 9, 10, and 11))

Record any Adverse Experiences and dosing compliance by downloading MEMs cap dispenser.

Meet with the counselor regarding alcohol consumption and use of the study medication.

Collect urine sample to test for alcohol, opiates and other substances. If capable of becoming pregnant, we will also conduct a pregnancy test.

Answer ACASI questions on a compute

Receive the study medication: if needed, you will be given more of the study medication (except at the week 12 visit).

Meet with the study doctor or nurse: to talk about any problems with the study medication or any changes in your health or medications if needed. A physical exam may be done.

Collect a blood sample (weeks 3, 6, & 9): to test for alcohol. A few drops of blood will be collected by a lancet stick to your finger or a venipuncture blood draw.

10.5 Visit 5 (Month 1, 2 and 3 with visit window 2 weeks before visit and 2 weeks after visit)

All the same procedures as the weekly visits **PLUS** these additional procedures:

Answer ACASI questions on a computer about your mood, your recent sexual behavior and drug use, and your feelings about being in the study.

Record any Adverse Experiences and dosing compliance.

Record changes to concomitant medications.

Meet with the study doctor or nurse: to talk about any problems with the study medication or any changes in your health or medications if needed. A physical exam may be done.

Collect blood for clinical laboratory tests (chemistry, hematology). At month 3 visit, collect blood for HIV test, pooled viral load test. If HIV positive, a CD4 test.

Collect a blood sample: to test for alcohol. A few drops of blood will be collected by a lancet stick to your finger or a venipuncture blood draw.

10.6 Early Withdrawal Visit

Record any Adverse Experiences and/or Review subject diary for adverse experiences and exclusionary medication use.

Record changes to concomitant medications.

Perform complete physical examination.

Perform and record vital signs.

Collect blood for clinical laboratory tests: Chemistry, Hematology, Urinalysis, Pregnancy (urine or serum).

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

11.3 Medical Monitoring

John Walker, RN, FNP-C, research clinician, should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (628) 217-6227
Pager: (415) 356-8980

Phillip Coffin, MD MIA FACP FIDSA, medical director, should be contacted directly at this number to report medical concerns or questions regarding safety.

Phone: (510) 407-2603

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

Subject withdrawal of consent (or assent)

Subject is not compliant with study procedures

Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment

Protocol violation requiring discontinuation of study treatment

Lost to follow-up

PI or clinician request for early termination of study

Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Week 8 Visit) should have an early discontinuation visit. Refer to Section 10 for early

termination procedures. Subjects who withdraw after Week 8 Visit but prior to Week 12 Visit should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.3 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

Failure to meet inclusion/exclusion criteria

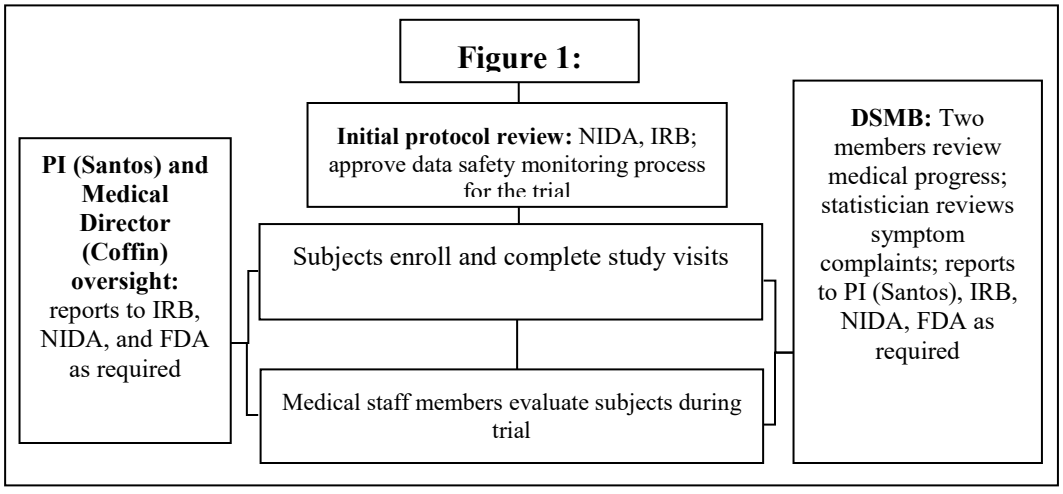
Use of a prohibited concomitant medication (such as opiate medications)

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The PI will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 DATA SAFETY MONITORING

The PI along with the site physician Dr. Coffin, will be responsible for ensuring proper monitoring of the safety and efficacy of this trial, including the execution of the DSM plan, and complying with the reporting requirements, including reports to the IRB, DSMB, NIDA and (where applicable) the FDA (see Figure 1 below).



The research team including the PI, clinicians, data manager, research associates, and recruitment coordinator, meets weekly to discuss all aspects of the study such as recruitment and retention, clinical or counseling issues, and any regulatory or operation issues. All study documents are monitored by the study coordinator for quality assurance on a weekly basis to ensure timely

corrections to charting such as missing initials or cross-outs with error-correction. Although there is no outside monitor, the clinicians review each other's charts for accuracy, consistency, and adherence to protocol. Regular audits will be conducted as well on consent forms, laboratory logs and other data collection forms.

The interim DSMB report will contain a brief description of the trial, baseline socio-demographic characteristics of participants, retention and disposition of study participants, a description of any quality assurance or regulatory issues, a report of AEs and SAES, and the status of outcome data.

Members and affiliation: We will use the existing University of California, Los Angeles (UCLA) Data & Safety Monitoring Board for Addiction Medicine (DSMBAM), which has extensive experience in monitoring pharmacologic interventions, including among vulnerable populations. The DSMBAM has monitored all of our pharmacologic trials for substance users.

To ensure that the DSMB oversight of the study remains independent from the proposed study, the PI(Santos) as well as others who serve on the DSMBAM that might be linked with the study in some way recuse themselves from review of the present study.

The purpose of the DSMBAM is to provide oversight and monitoring of Phase I and Phase II clinical trials of pharmacological and behavioral treatments for stimulant dependence. There are three fundamental charges of the board, which are:

- To ensure the safety of trial participants
- To preserve validity and integrity of research data
- To facilitate the availability of timely as well as reliable findings to the broader clinical community

Below are members who serve as committee chairs as well as clinical research experts:

• Steven Shoptaw, PhD, is Professor in both the Department of Family Medicine and the Department of Psychiatry and Biobehavioral Sciences at UCLA. Over the past 20 years, Dr. Shoptaw has conducted a series of clinical studies in community clinic settings, primarily on topics that involve developing medical and behavioral interventions to treat substance abusers.

• Timothy M. Hall, MD, PhD, is Health Sciences Assistant Clinical Professor at UCLA Department of Family Medicine and Center for Behavioral and Addiction Medicine. His research expertise is in sexual identity formation, social/sexual MSM networks, non-gay-identified MSM, ethnography and MSM substance use.

• Gayle Baldwin, PhD, is Associate Professor in the Department of Medicine at the University of California, Los Angeles. Her research focuses on how specific immune cells fight infectious diseases and cancer.

• Dominick Frosch, PhD, is an Associate Staff Scientist in the Department of Health Services Research at the Palo Alto Medical Foundation's Research Institute. He is also an Assistant Professor of Medicine at the University of California, Los Angeles. His research is focused on developing and implementing interventions to increase patient participation in clinical decision making and understanding the effects of health information in the media on behavior.

Below are members who serve as experts in biostatistics and epidemiology:

• Scott Comulada, PhD

• Sung-Jae Lee, PhD

• Jesse Fletcher, PhD

Below are members who serve as clinical research experts:

• Adam Carrico, PhD

• David Farabee, PhD

• Timothy Fong, MD

• Liz Evans, PhD

• Lara Ray, PhD

Administrative support staff:

• Uyen Kao, MPH, Director

• Oluwadamilola O. Jolayemi, MSc, Coordinator

The DSMC evaluates known risks to subjects' participation, the safety of the subjects as pre-specified in the protocol, and monitors the operational performance of the trial. The DSMC makes recommendations to continue, amend, or terminate the trial based on their findings. Recommendations are made in writing to the study investigators. The DSMC are given blinded trial data, but may request unblinding if safety data warrant. The initial review includes a review of the following items: statement of the protocol design, characteristics of the study data collection site, inclusion/exclusion criteria, randomization plan, definition of participants (e.g., screened, enrolled, randomized, treated, drop-out, lost to follow-up), intervention definition, dosage and frequency of study drug, reasons to discontinue study or to terminate individual participants, reasons to discontinue treatment, outcome measures, sample size target, key adherence and safety variables, and the data analysis plan.

Subsequent ongoing reviews include: enrollment data, including those screened, enrolled, and active; subject eligibility; demographic characteristics of participants (total, and by group), recruitment and retention (total and by group). Protocol compliance are evaluated by reviewing: the expected recruitment rate, study drop-outs and reasons for leaving the study, data quality assurance reports, overall data flow procedures, CRFs collected, received, and entered; protocol deviations; protocol violations; missing data; staff omissions; subject refusal to provide data; adherence to stopping rules. The data safety report are provided in total and by group, and include any relevant medical, psychosocial or laboratory data, AEs summarized in tables, individual SAE reports, concomitant medications, and concomitant illnesses. The outcome data report includes outcome data analyzed by group, masked or unblended, with or without statistical analyses, and include all outcome variables.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

15.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by treatment group: race, gender, age, educational attainment, employed, and HIV positivity.

15.3 Analysis of Primary Endpoint

To determine the efficacy of targeted naltrexone versus placebo in reducing binge drinking among non-dependent MSM, as determined by number of binge drinking days in timeline follow-back (TLFB), by arm. GEE Poisson models with robust standard errors will be used to assess reductions on weekly drinking outcomes**.** Baseline TLFB results will be included in the analysis. **Minimum detectable effects (MDEs):** In calculating minimum detectable effects, we hypothesized on pharmacologic grounds that oral naltrexone will reach full efficacy against alcohol use almost immediately; accordingly we expect treatment-control differences to be approximately constant over the 12 weeks of the trial. Based on the prior trial (93% retention), we estimate that 90% of participants will be retained at 12 weeks. Using estimates based on data from Project ECHO[92] for the within-subject correlation and over-dispersion of the outcomes, as well as the mean frequency among controls, we estimate that the proposed study will have 80% power in 2-sided tests with a type-I error rate of 5% to detect 27% reductions in numbers of binge drinking occasions, as well as 10% reductions in the average numbers of drinks on drinking days.

To determine the efficacy of targeted naltrexone versus placebo in reducing alcohol consumption among non-dependent MSM, as determined by the proportion of ethyl glucuronide (EtG) positive urines, by arm. GEE logistic models with robust standard errors will be used to assess reductions frequency of positive urine tests, accounting for within-subject correlation. **MDEs**: Using the assumptions for loss to follow-up for Aim 1, as well as estimates based on biomarker data from Batki et al's study on Topiramate for alcohol use disorders[122] for the within-subject correlation and control group urine positivity rate, we estimate that the study will have 80% power in 2-sided tests with a type-I error rate of 5% to detect 15-23% reductions in the urine positivity rate in the treatment arm.

15.4 Analysis of Secondary Endpoints

The analysis of the secondary endpoint to determine the efficacy of targeted naltrexone versus placebo in reducing alcohol-associated sexual risk behaviors, we will use GEE Poisson models with robust standard errors for the four monthly ACASI assessments on numbers of male anal sex partners, HIV-serodiscordant unprotected anal sex partners, unprotected anal sex partners while intoxicated with alcohol, and unprotected anal sex events with serodiscordant partners, including the baseline value. In the event that these outcomes are severely over-dispersed, we will analyze indicators for any self-report of each behavior, using GEE logistic models. **MDEs**: Based on estimates of within-subject correlation and control prevalence from our Project Echo trial, we estimate that the study will have 80% power to detect 31% reductions in numbers of male anal sex partners, 57% reductions in SDUA partners, 46% reductions in UA partners while intoxicated with alcohol, and 56% reductions in UA events with serodiscordant partners. In analyses using GEE logistic models, we will have 80% power to detect reductions of 14%, 38%, 39%, and 30% in any report of these four sexual risk behaviors, respectively.

Safety and tolerability data will be summarized by treatment group.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

15.5 Interim Analysis

There will be no interim analysis

15.6 Sample Size and Randomization

120 participants will be enrolled in the study.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject number and initials.

For paper CRFs: If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

16.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. *For paper studies:* Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, UCSF IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.6 Monitoring

Monitoring visits will be conducted by representatives according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission) and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.7 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the PI. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Board

The protocol and consent form will be reviewed and approved by the IRB prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB

in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRBs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB unconditional approval statement will be transmitted by the Investigator. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. STUDY PROCEDURES

TABLE 2. Study Procedures

	Visit Type				
	SCR	BL	Wk	Mos. 1 & 2	Mo. 3
Informed consent	X				
Safety lab assessment	X			X	X
Rapid HIV test* or CD4	X				X
HIV risk reduction counseling	X				X
Complete medical history, physical exam & SCID	X				
Vital signs, weight	X	X		X	X
Symptom driven physical exam		X			X
Targeted Medication Training		X			
Text messaging (SMS) Training		X			
Randomization		X			
Urine testing for opiates	X	X			
Urine testing for ethyl glucuronide (ETG)	X	X	X	X	X
Audio Computer Assisted Survey Instrument (ACASI)		X	X	X	X
Adverse event assessment			X	X	X
Alcohol Use Medical Management Counseling		X	X		

[a] ±2

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