STUDY PROTOCOL

Clinical protocol title	HaRP Study Protocol, Version 4
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Research project title	Harm Reduction with Pharmacotherapy (HaRP) for Homeless People with Alcohol Dependence (Short title: Harm Reduction with Pharmacotherapy [HaRP])
Phase of investigation	Phase 2 RCT assessing efficacy of extended-release naltrexone (XR-NTX) and harm-reduction counseling for alcohol harm reduction among homeless people with alcohol dependence
IND number	IND Exempt
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HaRP Study Protocol

1 Introduction

1.1 XR-NTX Background

Extended-release naltrexone (XR-NTX; Market name: Vivitrol®) is a 30-day, extended release formulation of the opioid receptor antagonist, naltrexone, and is a 380mg/vial suspension delivered monthly via intramuscular injection. It is chemically designated as morphinan-6-one, 17 (cyclopropylmethyl) 4,5-epoxy-3,14-dihydroxy-(5α) (CAS registry #16590-41-3). The molecular formula is $C_{20}H_{23}NO_4$, and its molecular weight is 341.41 in anhydrous form. Its structural formula is shown in Figure 1.

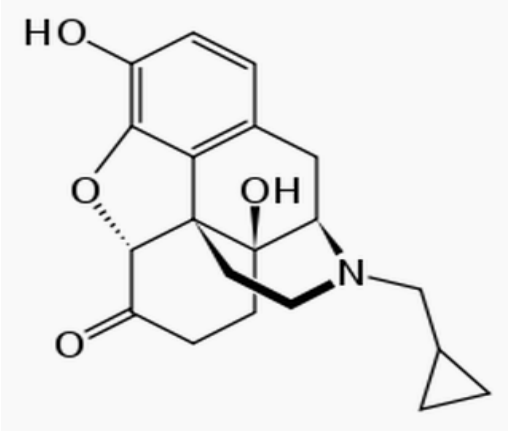


Figure 1. Molecular structure of naltrexone

Naltrexone was first used clinically to block the rewarding effects of opiates, such as heroin.[1] More recently it has been tested and FDA approved for the treatment of alcohol dependence.[2,3] In research trials, naltrexone and XR-NTX have been shown to reduce craving, heavy drinking and relapse severity.[4,5] Although its mechanism of action is not fully understood, research has suggested it may work as shown in Figure 2.[6-9]

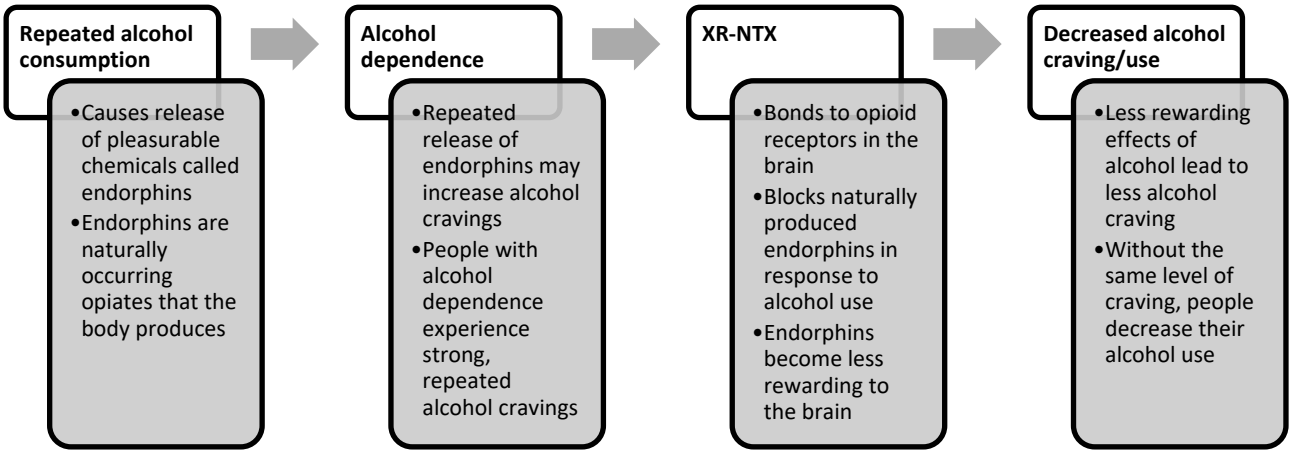


Figure 2. Naltrexone's hypothesized mechanism of action

1.2 XR-NTX Effectiveness

In understanding the effectiveness of XR-NTX, it is important to include a review of the substantial scientific literature on oral-dose naltrexone that served as its precursor. In two, initial, 12-week double-blind, placebo-controlled trials, naltrexone (plus psychosocial treatment) was found to be well-tolerated by patients. Naltrexone was also associated with significantly less alcohol craving and fewer drinking days compared to placebo plus psychosocial treatment.[2,3] Among participants who continued to drink, those who received naltrexone showed lower rates of relapse to heavy drinking,[2,3] presumably because naltrexone blocked the rewarding effects of alcohol.[6-9] A later, 6-month follow-up study showed that the naltrexone group continued to have significantly lower relapse rates and fewer alcohol dependence symptoms than the placebo group.[10] Since the early nineties, there have been dozens of published, peer-reviewed trials that have documented the effectiveness and safety of naltrexone among thousands of participants with alcohol-use disorders.[5] Larger reviews and meta-analyses have shown naltrexone's modest yet consistent effects in reducing drinking rates, relapse severity and craving.[4,11-14]

Although studies have shown support for oral naltrexone in reducing heavy-drinking outcomes, a sizeable barrier to its consistent use has been relatively low treatment compliance.[15-17] XR-NTX was introduced to overcome these challenges: it is administered by a health-care provider once a month instead of self-administered once a day. To date, a handful of XR-NTX trials have been conducted and have shown promising effects.[5,18,19] The first, large-scale randomized controlled trial of XR-NTX was conducted by Alkermes, Inc. within a multisite network of 24 US hospitals and tertiary medical centers. One of our study consultants, Dr. JC Garbutt, was the lead author on the primary publication from that trial. In addition to 12 psychosocial intervention sessions, participants (*N* = 626) were randomized to receive monthly intramuscular injections of either 380mg or 190mg of XR-NTX or matching placebo. Compared with placebo, the 380mg formulation resulted in a statistically significant 25% reduction in heavy drinking. The lower-dose (190mg) formulation did not result in statistically significant reductions compared to placebo. Participants who were initially abstinent evinced greater treatment gains. Discontinuation rates due to side effects and adverse events were 14.1% in 380mg group, 6.7% in 190mg group and 6.7% in placebo group.[5]

Secondary analyses conducted using data from the previous study indicated that XR-NTX was also associated with significant, self-reported improvements in quality of life (i.e., overall mental health, social functioning, general health, and physical functioning domains).[20] In a more recent, open-label trial, XR-NTX was deemed to be acceptable and feasible for delivery in a health-care setting.[21] XR-NTX was approved by the FDA for the treatment of alcohol dependence in 2006.[22]

1.3 XR-NTX Safety

Like oral-dose naltrexone, XR-NTX does not have addictive properties, and with the exception of opioids, evinces few interactions with other medications. Studies have shown XR-NTX to be well-tolerated and safe, even among actively drinking alcohol dependent participants.[5] Possible side effects of XR-NTX, which occur in at least 5% of patients at least twice the rate of placebo, include pain, tenderness, swelling, bruising and/or itching at the injection site, nausea, headache, fatigue, dizziness, vomiting, decreased appetite, painful joints and muscle cramps.[5,22,23]

Rare conditions that may be associated with XR-NTX can often be avoided with assessment and screening procedures. First, XR-NTX should not be taken by individuals with current opioid dependence because it will induce severe withdrawal. Similarly, because XR-NTX is an opioid antagonist, it reduces the effectiveness of opioid analgesics. There may also be a slightly elevated risk for eosinophilic pneumonia, depression and suicidality. As with any medication, there is a risk of drug hypersensitivity, although allergic reactions to XR-NTX are very rare. In some cases, reactions at the injection site may become severe. Injection sites should be monitored by a health-care provider for potential hardening, inflammation, nodules and swelling, and in extreme cases, necrosis. Injection site reactions can usually be avoided by ensuring that the needle passes through the superficial layer of fat tissue under the skin and into the gluteal muscle before the medication is injected.

Finally, until recently, there was a ‘‘black-box’’ warning on XR-NTX regarding potential hepatocellular injury. This warning was rescinded in late July 2013. The warning had originally followed from early naltrexone studies, which prescribed daily oral doses of up to 350mg for treatment of obesity and dementia—seven times the currently recommended oral dose.[24] Although current FDA labeling indicates that XR-NTX may be associated with liver injury primarily if it is administered in “excessive doses” or to patients with “acute hepatitis or liver failure,”[22] there are no reports of hepatotoxicity involving XR-NTX.[25] The large-scale, randomized controlled trial (RCT) of XR-NTX mentioned above indicated no significant differences in participants’ liver function throughout the study, even among participants with previously elevated liver enzymes.[23] Gamma-glutamyl transferase (GGT) levels were lower among those receiving XR-NTX compared to placebo during the study, likely due to decreased drinking.[23] Further, because XR-NTX is injected intramuscularly, it eliminates first-pass metabolism, further reducing the risk of hepatotoxicity and fluctuations in plasma naltrexone levels.[26] In fact, it has been suggested that there is greater risk of hepatotoxicity from continued, heavy alcohol use than from appropriate naltrexone administration.[27] That said, XR-NTX has not yet been extensively studied in patients with pre-existing, severe liver damage.

1.4 Study Rationale

Alcohol dependence among homeless individuals is a serious public health issue. A meta-analysis of international studies showed a mean of 38% of homeless individuals are affected by alcohol dependence,[28] which is ten times the prevalence of alcohol dependence in the general US population (3.8%).[29] Alcohol dependence interferes with tasks of daily living, such as attaining and maintaining housing, employment and social networks.[30-32] The more severe alcohol dependence that often affects homeless individuals is associated with both acute (e.g., accidents, falls, violence) and chronic (e.g., chronic liver disease, cancer, cardiovascular disease, encephalopathies) alcohol-related harm,[30,33] which places increased burden on the health-care and criminal justice systems,[34] and puts individuals at greater risk for alcohol-related mortality.[35-37] Considering the extent and cost of negative consequences for both affected individuals and their communities, effective approaches are needed to engage and address the issues facing homeless people with alcohol dependence.

Current abstinence-based programs do not optimally engage and treat this population. Alcohol abstinence has long been assumed to be the *sine qua non* of effective treatment, particularly for more severely affected and homeless populations. However, findings have been mixed for abstinence-based treatments among homeless individuals, ranging from no to modest improvements on substance-use outcomes.[32,38,39] Further, these improvements are only experienced by the few who are engaged and retained in treatment.[32] In fact, studies show that few homeless people start treatment (15-28%),[40,41] and even fewer complete it (2.5-33%).[42] An NIAAA review showed that treatment engagement in this population decreased as program demands—particularly abstinence—increased.[42] The end result is that the majority of homeless individuals with alcohol dependence never go to, are turned away from, or drop out of the treatments that are currently available.

Recent research has elucidated reasons why abstinence-based treatment is not optimally engaging and effectively treating this population. First, our own and other research groups’ studies show that many of the most severely affected individuals do not find abstinence-based goals or treatments to be acceptable or desirable.[43,44] Such negative evaluations of abstinence-based treatment are correlated with decreased treatment attendance[45] and poorer outcomes.[46] Thus, even if these individuals do present for treatment, they are less likely to stay in treatment and achieve positive effects. Relatedly, both theory and empirical data suggest that repeated failed treatment attempts erode self-efficacy and self-control for later behavior change.[47,48] This observation is particularly relevant for this population: one of our recent studies showed a mean of 16 past alcohol treatment attempts in a sample of homeless individuals with alcohol dependence.[49] Additionally, inpatient detoxification, typically a medical necessity for this population, is expensive and can lead to a “revolving door” of treatment,[50,51] in which abstinence-based treatment episodes are regularly alternated with resumed use. The revolving door effect is a concern in this population because an increasing number of alcohol withdrawals and medical detoxifications can precipitate increasingly severe and potentially fatal alcohol withdrawal symptoms (i.e., kindling effect),[52] which may make abstinence-based treatment a more harmful course of action for some more severely affected individuals.

New approaches are necessary that are compatible with this population's needs*.* New approaches, which remove the barrier of abstinence to treatment engagement, have recently begun to be applied with chronically homeless individuals with alcohol problems.[30,49,53,54] Such approaches have been referred to as harm-reduction interventions, because they focus on reducing alcohol-related harm without requiring abstinence.[55] Such interventions, including low-barrier housing programs and managed alcohol programs,[30,56] have shown preliminary effectiveness in reducing both alcohol-related harm and alcohol use.[57,58] However, there are few pharmacological counterparts to further enhance the effects of these promising interventions. In response to this gap in the literature, we are proposing to test a promising medication, XR-NTX, to support alcohol harm reduction among homeless people with alcohol dependence.

XR-NTX appears to be a good fit to this population's needs and harm-reduction goals. Unlike other pharmacotherapies for alcohol dependence (e.g., disulfiram), naltrexone and XR-NTX are safe and effective among both individuals who are abstinent[10,59] *and* current heavy drinkers,[5] which makes it compatible with the drinking patterns of this population. Further, in accordance with harm-reduction principles, XR-NTX has been shown to reduce craving and heavy drinking without requiring abstinence from alcohol prior to administration.[5,60] Moreover, recent studies conducted with other populations have shown that naltrexone may be safely and effectively used in the context of drinking moderation treatments.[61,62] Finally, because it is a monthly injectable versus a daily oral medication, XR-NTX may help support medication adherence and greater follow-up with health-care professionals, which often poses a challenge for homeless individuals.[63-65] Taken together, these features make XR-NTX compatible with the needs and goals of this population and with the existing harm-reduction approaches used by the community-based agencies that serve them.

Our preliminary pilot study supports the use of XR-NTX in this population. In advance of the HaRP Study, the research team conducted a single-arm, open-label, 12-week pilot trial (*N*=24). The pilot was conducted together with 2 Seattle-based, nonprofit agencies on the forefront of harm-reduction service provision for homeless people: the Downtown Emergency Service Center (DESC) and Evergreen Treatment Service's REACH Program. Both agencies expressed interest in developing and evaluating alcohol-specific treatments designed to help clients reduce their alcohol-related harm. This interest was sparked by their clients' high prevalence of alcohol dependence (approximately 33% of DESC clients and 85% of REACH clients) and the acknowledgment that most of their clients are not ready, willing and/or able to engage in abstinence-based treatment.

The aims of this pilot study were two-fold. The first aim was to develop and pilot procedures for the proposed study (i.e., study protocol, IRB application, population-appropriate measures, manuals). The second aim was to assess the initial feasibility, safety and effectiveness of XR-NTX with 2 agencies that provide services to homeless individuals with alcohol dependence. During this pilot, the proposed measures, procedures, protocols and manuals were developed and implemented and have been shown to be feasible. Of the 45 individuals approached, 42 consented to study participation, and 31 qualified for participation. Twenty-four participants received the full, 3-month treatment course. The medication and study procedures were discontinued for one participant because he voluntarily enrolled in inpatient detoxification and long-term alcohol treatment following his second injection, which was considered a positive treatment outcome. Three other participants refused the second injection due to discomfort at the injection site. All did, however, agree to continue with follow-up procedures. Additionally, one individual died (determined to be unrelated to the study medication), and two others were lost to follow-up when they were jailed over an extended period.

The extent of adverse events as measured by the Systematic Assessment for Treatment Emergent Effects (SAFTEE)[66,67] remained stable (i.e., participants endorsed a median of 6 symptoms) from baseline through the follow-up period, although the severity of these symptoms decreased over the treatment course. Serious adverse events were determined to be unassociated with the study medication. Despite the small sample size, findings showed significant baseline-to-posttest improvements on alcohol outcomes. Specifically, participants decreased their median peak drinking quantity from 29 to 19 standard drinks (Wilcoxon signed rank z=-3.00, p=.003) and their

median frequency from 30 to 25 days a month (z=-2.07, p=.04). Participants also reported a 60% reduction in alcohol-related problems (z=-3.87, p<.001), and a 33% reduction in alcohol craving (z=-3.31, p=.001). Regarding acceptability of XR-NTX, 15 of the 24 participants who completed the treatment course wanted to continue XR-NTX off-study. These participants credited the treatment for their reduced alcohol craving and for support in making changes in their drinking. One participant said, "I swear to God your program is really helping me a lot because I don't need [the alcohol]. I think your program is great. It's working on me." Another participant noted, "This program is really helping. My daughter asked me the other day, 'Mom, why didn't they make this drug years ago? You're doing so good, and I'm so proud of you.' That means a lot to me."

2 Study Objectives

The proposed Phase II study will expand upon the pilot findings within a larger, randomized controlled trial (RCT). The 4-arm RCT (N=300) will include a 24-week follow-up and will test the relative efficacy of 3 active treatment combinations—1) XR-NTX+harm reduction counseling, 2) placebo+harm reduction counseling and 3) harm reduction counseling only (HRC)—compared to the services as usual (TAU) that all participants receive from community agencies. This design will allow us to dismantle active treatment components and thereby detect potential "placebo effects" of both the administration of an injection and attention from a medical professional that have been found in previous studies.[68,69] This study is clinically significant and innovative because it seeks to engage homeless individuals, regardless of whether they have abstinence, drinking moderation or harm-reduction goals and will use a harm-reduction rather than an abstinence-based framework to guide the accompanying counseling and medication management.

Specific aim 1 is to test the relative efficacy of XR-NTX, placebo and HRC compared to TAU.

Hypothesis 1A: Compared to the TAU group, the 3 active treatment (XR-NTX, placebo, HRC) groups will evince significantly greater decreases in alcohol quantity, frequency and alcohol-related problems.

Hypothesis 1B: The XR-NTX group will evince greater decreases in alcohol quantity, frequency and alcohol-related problems than the placebo group.

Specific aim 2 is to test theory-based mediators of treatment effects.

Hypothesis 2A: Because the 3 active treatments include personalized feedback, client-driven, harm-reduction goal setting and collaborative planning for safer drinking, these groups will experience significant increases on motivation to change drinking in a way that reduces harm. In turn, these increases in motivation to change will mediate the active treatment effects on alcohol outcomes.

Hypothesis 2B: Given naltrexone's putative clinical mechanisms, the XR-NTX group will experience significant decreases on craving compared to the placebo group. In turn, these decreases in alcohol craving will mediate the effects of XR-NTX versus placebo on alcohol outcomes.

Specific aim 3 is to test treatment effects on publicly funded service costs.

Hypothesis 3A: It is hypothesized that the XR-NTX, placebo and HRC groups will show greater decreases in publicly funded service costs (i.e., costs resulting from emergency medical services, ER visits, hospital admissions, and county jail) than the TAU group.

3 Methods

3.1 Proposed design

The proposed study involves a 4-arm RCT (*N*=300) testing the relative efficacy of XR-NTX+harm reduction counseling (XR-NTX), placebo+harm reduction counseling (placebo), and harm reduction counseling alone (HRC) compared to supportive services (TAU) provided by community-based agencies (see Figure 3). Within this design, we will also compare the efficacy of XR-NTX and placebo with both participants and researchers blind to medication condition. The study features a 12-week active treatment trial with a 24-week follow-up to test for potential delayed treatment effects or treatment decay.

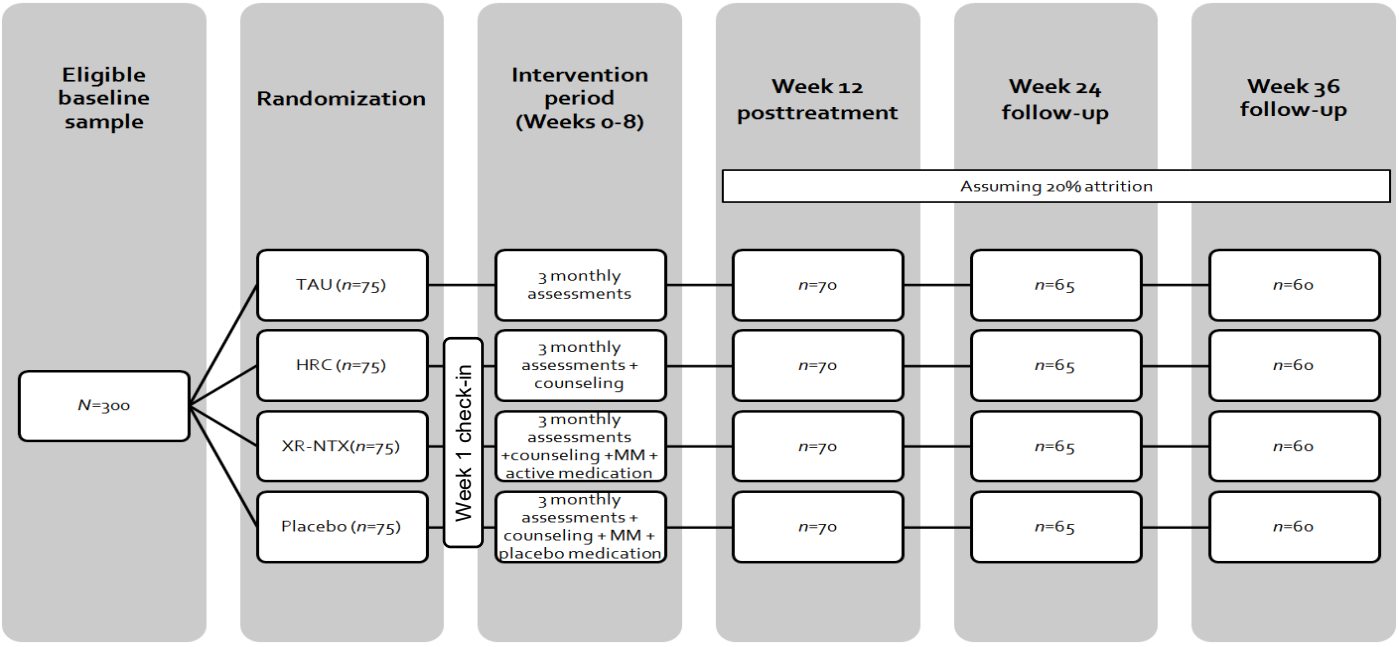


Figure 3. Intervention delivery and assessment timeline. TAU = psychosocial services as usual; HRC= harm reduction counseling only. MM = medication management.

After careful consideration of the potential benefits and drawbacks (e.g., sample size, study cost) of conducting the proposed 4-arm design versus a more traditional 2-arm (XR-NTX and placebo) design, we decided on the former for a few important reasons. First, naltrexone and XR-NTX are well-researched, FDA-approved medications for the treatment of alcohol dependence.[4,24,70,71] Therefore, it was deemed appropriate to integrate more differentiated research questions into the current study, which seeks to expand the evidence base for the use of this medication. Second, the COMBINE study evinced a "significant placebo effect" for naltrexone, which researchers attributed to participants' expectancies regarding medications as well as the effects of alcohol counseling from a medical professional, which was embedded within medication management sessions[68,69] and has become *de rigueur* in clinical drug trials for alcohol dependence.[5,71-73] It is therefore important to methodologically control for these "placebo effects" to account for the active components facilitating participants' behavior change. Third, because there is currently no generic formulation, the expense of the prescription and administration of XR-NTX is considerable. It is therefore important to determine whether the medication is not only superior to a placebo, but whether it is superior to harm-reduction counseling alone, which could be provided at lower cost. This study was therefore designed to determine the relative contributions of a) harm-reduction counseling (HRC) with a medical professional, b) the placebo effect (placebo), and c) the medication effect (XR-NTX) relative to the usual psychosocial, harm-reduction services provided by community-based agencies (TAU).

3.2 Participants

Participants (*N* = 300) will be adults (21-65 years old) with alcohol dependence who are or have been homeless in the past year. The McKinney-Vento Homeless Assistance Act[74] defines homelessness as lacking a fixed, regular and adequate nighttime residence; having a primary nighttime dwelling that is not a regular sleeping accommodation; living in a supervised shelter or transitional housing; exiting an institution that served as temporary residence when the individual had previously resided in a shelter or place not meant for human habitation; or facing imminent loss of housing when no subsequent residence is identified and insufficient resources/support networks exist.

We will not limit the sample to currently homeless individuals for the following reasons. First, agencies serving homeless individuals prioritize assisting their clients to achieve housing. It would therefore be neither ethical nor practical to limit our recruitment to only those clients who remain consistently homeless versus those who become sheltered, transitionally or permanently housed after years of chronic homelessness. Further, because a return to homelessness is not uncommon,[75,76] the proposed population is likely to be more representative of the often cyclic nature of homelessness. On the other hand, it is clinically important to understand whether treatment effects differ according to housing status. We will therefore include current housing status as a time-varying covariate in outcome analyses.

3.2.1 Inclusion criteria

Inclusion criteria will include receiving services from one of the named partnering agencies, being between 21 and 65 years of age, agreeing to use an adequate form of birth control (if female and in childbearing years; includes oral, injectable or implanted hormonal contraceptives, intrauterine devices (IUDs)/intrauterine systems (IUSs), barrier method of condoms plus spermicidal foam, true abstinence), and fulfilling criteria for current alcohol dependence according to DSM-IV-TR criteria as determined by the SCID-I/P.[77]

3.2.2 Participant exclusion criteria

Exclusion criteria will include refusal or inability to consent to participation in research, constituting a risk to safety and security of other clients or staff, known sensitivity or allergy to naltrexone/XR-NTX, current treatment with naltrexone/XR-NTX, being pregnant or nursing, concurrent participation in a clinical study involving an unapproved, experimental drug, suicide attempts within the past year, renal insufficiency/serum creatinine level > 2, current opioid dependence according to the DSM-IV-TR criteria, liver transaminases (AST, ALT) > 5 times the upper limit of normal (ULN), a clinical diagnosis of decompensated liver disease, or other condition deemed by Principal Investigator and/or Medical Director to make study participation clinically unsafe.

To increase external validity of the findings and to recruit in accordance with harm reduction principles, we have limited the exclusion criteria to only those that are necessary to minimize risks to participants' health and safety. To further reduce these potential risks, we will a) regularly assess health and safety (e.g., monthly collection/monitoring of blood and urine tests, urine toxicology and pregancy tests at baseline and prior to injections, regular suicide assessments, hospital/agency records, etc.); b) discuss participants' cases weekly; c) consult with an addiction medicine specialist and internist (Merrill) on a weekly basis to evaluate participants' health status; and d) meet and review reports biannually with a Data Safety Monitoring Board, including a psychiatrist, internal medicine physician, hepatologist (liver specialist), and clinical psychologist/statistician. By decreasing the barriers to participation, we will maximize the generalizability of the current findings to more severely affected populations[78] and will act in accordance with the agencies' existing and effective low-barrier, harm reduction approaches.[43,49,56,79]

3.3 Measures and Materials

3.3.1 Measures

Please see Table 1 below for the assessment schedule for each of the following measures.

Measures for determining eligibility. Ability to consent will be assessed during the information session using the *UCSD Brief Assessment of Capacity to Consent* (UBACC).[80] This 10-item, 3-point Likert-scale measure ensures participants understand the study protocol, potential risks/benefits and their rights as participants prior to study enrollment. The *Alcohol Use Disorders Inventory Checklist – Consumption* (AUDIT-C),[81,82] which is a three-item, psychometrically sound measure of hazardous and harmful patterns of alcohol consumption, will be used to screen participants for alcohol dependence prior to study recruitment. We will use a cut-off score of ≥ 4 points, which has optimal sensitivity and specificity for detecting alcohol-use disorders.[83,84] The *Beck Scale for Suicidal Ideation* (BSS) is a reliable and valid tool to assess suicidal ideation and behavior.[85] It will be used to assess participants' current suicidality to determine fulfillment of exclusion criteria at baseline and will be regularly assessed in weeks 4-36. Further, the *Self-injurious Thoughts and Behaviors Interview-Suicide Attempts subscale* (SITBI-SA), which measures lifetime experience of suicidal behaviors, will likewise help determine fulfilment of exclusion criteria at baseline and will be administered at all subsequent assessment timepoints (weeks 4-36).[86] The alcohol and opioid dependence parts of the *DSM-IV-TR SCID-I/P*[77] will be used to document fulfillment of inclusion/exclusion criteria and will be administered again in Weeks 4-36.

Measures for sample description. The *Personal Information Questionnaire (PIQ)* will assess age, gender, race, ethnicity, education, employment, military experience, other research study participation and experience of homelessness in the past year.[87] The *Housing Timeline Followback* (TLFB-H)[88,89] is a set of calendars that documents housing status by recording where participants resided/spent the night each day in the past 30 days or since the previous assessment, as applicable. The TLFB-H will be used to describe the baseline sample and as a time-varying covariate in efficacy analyses. The *Tracking Information Sheet* will collect contact information from participants to facilitate follow-up communication and tracking over the course of the study.

Measures of motivation outcomes. Motivation outcomes will serve as potential mediators of the hypothesized treatment effect. The *Motivation-to-change Ruler* comprises four, 10-point scales assessing participants' motivation, readiness, importance and confidence to change their alcohol use in a way that reduces harm. Such 10-point, single-item motivation scales have been shown to be valid and clinically useful measures of motivation across various populations.[90-92]

Measures of alcohol-use outcomes. The *Alcohol and Substance-use Frequency Assessment* questions were adapted from the ASI,[93] and will be used to assess frequency of use of alcohol and other drugs. The *Alcohol Quantity Use Assessment (AQUA)* was created in the context of a previous study with this population,[49] and was refined in the Project Vivitrol® pilot study. As necessary due to cognitive deficits, we will also use a set of monthly calendars to allow for prospective or retrospective evaluation of alcohol and other drugs for each day of the previous month.[88] The *Short Inventory of Problems* (SIP-2R) is a 15-item, Likert-scale questionnaire that measures social, occupational and psychological alcohol-related problems.[94] The summary score will serve as the alcohol-related problems outcome measure. Alcohol craving will be measured using the psychometrically valid, 5-item, Likert-scale *Penn Alcohol Craving Scale* (PACS).[95] The alcohol craving summary score will be used as a mediator of the hypothesized treatment effects.

Measures of quality-of-life outcomes. The Short Form – 12[96] is a well-validated, 12-item questionnaire that assesses quality-of-life outcomes in two primary areas: physical and mental health.

Measures supporting medication management. The *Case Report Form* (CRF) will be used to a) summarize clinically relevant assessment data for the study physician/nurse (e.g., alcohol-use disorder diagnosis, fulfillment of inclusion/exclusion criteria); b) compile and centralize key lab test findings; c) provide an outline during the physical exam and medication management; and d) record clinical data during the physical exam and medication management sessions. The *Systematic Assessment for Treatment Emergent Effects* (SAFTEE) interview,[66,67] which was tailored for use with this medication, includes open-ended, categorical and Likert-scale questions assessing symptoms that correspond to potential adverse events associated with XR-NTX. This measure will be embedded in the CRF.

Assessment Schedule

	S	B	0	1	4	8	12	24	36
Administered by assessment staff									
UBACC	.								
AUDIT-C	.								
Tracking Information Sheet		.			.	.	.	.	.
PIQ		.							
TLFB-H		.			.	.	.	.	.
Alcohol and Substance-use Frequency		.			.	.	.	.	.
AQA/AOD calendars		.			.	.	.	.	.
PACS		.			.	.	.	.	.
SIP-2R		.			.	.	.	.	.
DSM-IV-TR alcohol/opioid dependence		.			.	.	.	.	.
MTC Rulers		.			.	.	.	.	.
Suicide assessment (BSS and SITBI)		.			.	.	.	.	.
SF-12		.			.	.	.	.	.
Participant Satisfaction Assessment									.
Administered by study physician/nurse									
CRF		.	.	.	.	.	.	.	.
SAFTEE		.	.	.	.	.	.	.	.

Measures for utilization and cost analysis. Administrative data on publicly funded service utilization will be obtained from the King County Correctional Facility, King County Medic One/Emergency Medical Services, Harborview Medical Center (HMC), and the Washington State Comprehensive Hospital Abstract Reporting System (CHARS) for the 2-year pre-study period through the follow-up period. We will obtain participant consent and HIPAA authorizations for these data at the information session. We will collect the following data: a) number of Medic One/EMS dispatches and associated costs; b) number of ER visits and associated costs; c) number of inpatient hospital admissions, outpatient visits and total costs per admission (CHARS and HMC); d) number of bookings, length of stay and daily cost for the King County Correctional Facility. These data will be used to create overall cost outcomes.

Treatment integrity materials and measures. Manual adherence and competence for the HRC, placebo and XR-NTX sessions will be measured using the *HaRP Adherence and Competence Coding Manual* and the *HaRP Coding Scale.* The coding system, which is based on the COMBINE Study Medical Management Adherence Checklist and coding schema,[73,97] consists of 7 dimensions to assess delivery of the HaRP style and content (i.e., informativeness, direction, authoritativeness, warmth, manual adherence, avoidance of nonmanualized components, overall). Dimensions will be rated on 7-point Likert scales, where 0=absence of the characteristic and 6=very high levels of the characteristic (within top 10% of providers). The *Participant Satisfaction Assessment* is a semistructured interview with open-ended

questions and prompts to assess participants' receipt of and satisfaction with the study procedures at the final assessment.

Research staff, including bachelor-level research assistants, graduate students and postdoctoral fellows, will conduct treatment integrity rating under the supervision of the PI, who is a licensed clinical psychologist with 15 years of experience conducting treatment integrity ratings and analysis. An extensive training protocol developed during prior evaluations will be utilized. Raters will receive 16 hours of training and supervision before they begin independently recruiting and assessing participants. Training will include written instructions and group coding sessions with feedback from the PI. Sessions will be coded independently; however, regular supervision and periodic interrater consistency analyses will be conducted to reduce the risk of rater drift.

3.3.2 Lab Tests and Materials

Blood tests will be conducted on all participants at baseline and weeks 4, 8, 12, 24 and 36, and will include a complete blood count (CBC), a basic metabolic panel (CHEM 7), and a liver panel (AST, ALT, ALP, albumin, bilirubin total and direct). These tests will be conducted to assess liver and renal functioning and to detect other medical conditions that may contraindicate the use of XR-NTX or may be important to monitor during its administration. If participants in the two medication arms evince AST/ALT greater than 5 x ULN, they will be retested a week prior to the next scheduled injection. In the case AST/ALT have not decreased below that point, the study medication will be discontinued to ensure participant safety.

Urine tests will include a) complete urinalysis (UA), which will be used to detect further contraindicating conditions (e.g., renal damage) at baseline and monthly; b) a urine toxicology dipstick, which will be used in the XR-NTX and placebo conditions to detect the presence of opiates at baseline and prior to each injection; c) an hCG dipstick pregnancy test for women in childbearing years at baseline and prior to each injection; and d) ethyl glucuronide (EtG) tests,[98] which will be used to biovalidate self-reported alcohol use at each assessment and will be administered at baseline and monthly thereafter. The concentration of EtG, which is a metabolite of ethyl alcohol formed in the body by glucuronidation after ethanol exposure, will be used as a quantitative measure. Previous studies have shown that EtG is positively associated with self-reported alcohol quantity.[99,100]

3.4 Randomization Scheme

The current study will involve four treatment arms. Participants will be randomized to one of the four treatment arms using a permuted block randomization with stratification. The study PI created the scheme and randomization lists in advance using the *ralloc* program in STATA MP 11.2 (Statacorp, 2009). This program provides a sequence of treatments randomly permuted in blocks of constant or varying size with the ability to stratify the allocation. For the current study, equal blocks of four were used to minimize the risk of potential imbalance in the treatment arms, and the allocation was stratified by agency and housing status (i.e., housed or homeless at time of randomization).

The randomization scheme will be given to the University of Washington Investigational Drug Services (IDS) in the form of a series of spreadsheets. The IDS will be responsible for randomizing qualifying participants by filling the participant IDs into the corresponding spreadsheets. The two arms of the study receiving injections will be double-blinded in that the investigators will not know which participants are allocated to which group (placebo versus active medication). Further, IDS staff--not the investigators--will administer the randomization scheme so as to minimize selection bias for all groups.

3.5 Study Treatment

This study comprises four treatment conditions. The most minimal condition is *TAU*, which will comprise the agencies' harm-reduction oriented "supportive services as usual" that will be provided to all participants in all groups for the duration of the trial and beyond. One of the partnering agency's programs includes provision of emergency shelter and/or permanent, supportive housing. Both agencies provide supportive services that are tailored to the needs of individual clients and include outreach; case management; nursing/medical care; access to external service providers, as needed (e.g., more intensive medical or psychiatric treatment, chemical dependency counseling, etc); and/or assistance with basic needs (i.e., food, clothing, income, housing). Like the other treatment conditions, participants in the TAU condition will also undergo regular assessments at baseline and weeks 4, 8, 12, 24, and 36.

The remaining three conditions (XR-NTX, placebo and HRC) are considered active treatment conditions and will all include monthly, alcohol-specific, harm-reduction counseling sessions that will be delivered by study physicians/nurses. A harm reduction style, which will involve a nonjudgmental, empathetic stance, unconditional positive regard, and acceptance of clients wherever they fall on the spectrum of readiness to change,[60] will be utilized. This style has been chosen for a few reasons. First, it is compatible with the agencies' current clinical and case management approaches. Second, the research team's preliminary findings in these settings indicate that a client-centered style helps providers best align with clients and build appropriate and positive rapport to support behavior change.[43] Third, research has confirmed the superior efficacy of a client-centered versus confrontational style in therapeutic interactions.[101-103] Finally, a client-centered style has been shown to be helpful in other interventions involving homeless individuals.[104]

The HRC condition will involve harm-reduction counseling components. At appointments, study physicians/nurses will a) provide personalized feedback about alcohol assessments and lab tests, b) assess vital signs and concomitant medications, c) obtain medical history (baseline only), d) assess for adverse events using the SAFTEE, e) conduct a physical exam (baseline and as clinically indicated), f) elicit participants' harm reduction goals and progress made towards them, and g) discuss and secure commitment for safer drinking using the Safer Drinking Strategies worksheet. These components have been tested in the pilot study and are based on both harm reduction theory[55] and clinical practice[60] as well as evidence-based motivational enhancement.[92,105] Study physicians/nurses will use the HaRP treatment manual to guide the session and will record participants' in-session data on the CRF.

The XR-NTX and placebo conditions will receive harm-reduction counseling components + medication administration/management. At each appointment, study physicians/nurses will a) provide personalized feedback about alcohol assessments and lab tests, b) assess vital signs and concomitant medications, c) obtain medical history (baseline only), d) assess for adverse events using the SAFTEE, e) conduct a brief physical exam (baseline and as clinically indicated), f) provide medication management (discuss the medication, side effects and ways to manage them, including provision of 2, 25mg tabs of over-the-counter antihistamine meclizine; ensure participants have medication bracelets/dogtags; provide emergency contact information), g) elicit harm reduction goals and progress made towards them, h) discuss and secure commitment for safer drinking using the Safer Drinking Strategies worksheet, and i) administer XR-NTX/placebo. Study physicians/nurses will use the HaRP treatment manual to guide the session and will record participants' in-session data on the CRF.

Participants will take urine toxicology and pregnancy dipstick tests immediately prior to the first injection. If participants test negative for pregnancy and opioids, study physicians/nurses will administer the injection into the gluteal muscle, alternating buttocks for each subsequent injection. If participants test positive for hCG, they will be withdrawn from the study. If participants test positive for opioids, the injection will not be administered, the positive test result will be discussed, and current opioid dependence will be assessed using the SCID-I/P. If participants do not meet criteria for opioid dependence, they will be rescheduled for an additional urine toxicology test the following week. If participants test positive for opioid dependence on the repeat test, they will be withdrawn from the study. If participants test negative for opioids on the repeat test, they will receive the injection.

All participants who receive an injection will attend the Week 1 safety check-in to assess and address potential

adverse events using the SAFTEE and to allow study physicians/nurses to check for potential injection site irritation. They will also be given research staff contact information in case they need to discuss any further questions/concerns regarding the study medication/procedures at any time throughout the study. For the three active treatment groups, Week 1 appointments will also include a check-in regarding participants' progress towards their harm reduction goals and safer drinking plans.

3.6 Treatment Adherence and Compliance

Treatment adherence and study compliance will be measured by follow-up appointment attendance. If participants do not attend appointments, their absence will be noted, and research staff will work together with program staff to reschedule with participants. If this is not feasible after five failed scheduling attempts (no-shows), the participant will be counted as "noncompliant." The exception to this will be for the safety check-in at Week 1. We will work to contact participants until we can schedule them. Participants will not be withdrawn from participation or analyses unless they expressly request to be.

3.7 Study Medication

3.7.1 Formulation and labeling

XR-NTX (380 mg/vial) (n=225), which is FDA-approved and commercially available, and placebo (n=225) formulations will be provided to the investigator per agreement from Alkermes. The preparation will consist of microspheres of 100-µm diameter that either contain naltrexone or do not (placebo) and are suspended prior to administration in a PLG polymeric matrix. PLG is a common biodegradable medical polymer with an extensive history of human use in extended-release pharmaceuticals. Following the injection, naltrexone is released from the microspheres, yielding peak concentrations within three days. Thereafter, by a combination of diffusion and erosion, naltrexone is released for more than thirty days. Also provided by Alkermes, the placebo preparation will consist of an identical formulation of microspheres (not containing naltrexone) within a PLG polymeric matrix to ensure study staff and participants are blind to medication condition.

The UW IDS will receive the study medication from Alkermes and will blind and label the doses in the two intervention arms involving placebo and active medication.

3.7.2 Preparing and dispensing

XR-NTX/placebo will be dispensed by the UW IDS. IDS will randomize participants according to the prepared scheme, and will inform the research staff of participants' randomization to receive a) medication (blinded active or placebo), b) HRC or c) TAU. Research staff will pick up the blinded medication from IDS prior to the Week 0 appointment, as applicable.

Prior to administration, XR-NTX and placebo will be prepared by the study physician/nurse. Both formulations must be refrigerated prior to use, but allowed to reach room temperature before injection (removing from refrigeration approximately 45 minutes prior to use). It must be suspended in the accompanying diluent in the carton by using the preparation needle to inject the diluent into the vial containing the microspheres and shaking until the mixture is milky white in appearance (approximately one minute). At this point, XR-NTX (or the placebo formulation) is ready for administration.

3.7.3 Drug storage and accountability

XR-NTX/placebo doses will be blinded and stored in locked and secure refrigerators (2-8ºC or 36-46º F) at the IDS prior to use. Doses can be stored at room temperature (not exceeding 25ºC or 77º F) for no more than 7 days prior to administration. Doses may not be frozen.

Accurate recording of all study medication administration will be recorded at each transaction and each participant's sessions. The IDS will maintain records on Vivitrol dispensation, and the PI and Medical Director will maintain accurate and current records of all administered and returned medication. All remaining, unused XR-NTX/placebo doses will be returned to the IDS pharmacy.

3.7.4 Concomitant Medications

Naltrexone antagonizes the effects of opioid-containing medicines, including some cough and cold remedies, some antidiarrheal preparations and opioid analgesics. For this reason, use of opiates (prescription medication or street drugs) is an exclusion criterion for participation at baseline. If participants have positive opiate drug screens (after retesting) and/or fulfill opioid dependence criteria according to the DSM-IV-TR, XR-NTX/placebo administration will not proceed at week 0.

In emergency situations requiring analgesia, the use of regional anesthesia or non-opioid analgesics is recommended. If opioid therapy is required, patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure. Opioid therapy should be managed by anesthesiologists trained in the management of the respiratory effects of potent opioids (e.g., establishment and maintenance of a patent airway and assisted ventilation). In this study, patients in need of analgesia will be referred for consultation to the UW Anesthesiology & Pain Medicine Department at Harborview Medical Center. At study enrollment, all participants in the medication conditions will be given ID tags and wallet-size medical emergency information cards indicating the possible presence of the study medication. Participants will be encouraged to wear the ID tags and carry the cards with them for the duration of the study.

3.7.5 Breaking the Blind

The principles guiding the breaking of the blind must balance the protection of participants in medical emergencies with the need to maintain the integrity of the double blind for study validity. Until the study is completed, this will only be done in the event of a medical emergency where the information is necessary for the provision of care. In the absence of specific information to the contrary, it is often sufficient to assume that participants might be receiving XR-NTX, with a 50% probability among those who are receiving an injection. However, if local treatment providers believe that an emergency medical situation exists and that exact information about the participants' medication dose is required to provide emergency care, then the dose codes can be obtained. All participants will be provided with emergency information cards and ID tags and will be informed about investigator and emergency contact information. They will also be informed that identification of their blinded medication condition will not be available (except in emergency situations when the health-care provider deems it necessary) until after all participants at all sites have completed the study, including follow up visits.

The UW IDS will have the individual dose codes for each randomized participant so the dose conditions for that participant may be identified without compromising the dose codes for other participants. This information will be accessible 24 hours per day, 7 days per week. The UW IDS will contact the study PI and/or Medical Director for authorization to break the blind in the event of an emergency.

Once blind dose codes are revealed to emergency medical personnel, efforts should be made to contain the information from reaching the research staff, to the extent that such containment is possible. Prudent clinical follow-up should occur to maximize participant protections, as should sufficient investigation about the causes and consequences of the emergency event for documentation and

adverse event reporting. Participants will continue to receive the medication and harm reduction counseling for the duration of their appointments, and data will continue to be collected; however, these participants will not be included in primary analyses.

If the blind is broken, a note will be placed in the participant's study record. This note will indicate the dose code that was revealed, a brief description of the emergency situation, and the extent to which study personnel have been informed of the dose code information. Examples of emergency descriptions may include the participant's admission to a hospital intensive care unit or the need for high dose opiates due to severe pain or injuries. In almost all cases, a situation that requires breaking the blind would also warrant completion of a Serious Adverse Event (SAE) form that should be turned in to the UW IRB within 24 hours.

Note: Although there may be perceived clinical advantages to individual participants to know what medication they received, the necessity of minimizing subject-expectancy effects during the study procedures and follow-up period requires maintenance of the double-blind until study completion. In most cases, nonemergency adverse events can be managed without breaking the blind (e.g., by discontinuing study medication). If, in a nonemergency situation, a local clinician feels it is in the best interest of the participant to break the study blind, this individual will need to contact the study PI and Medical Director to discuss the specific case.

3.8 Study Procedures

3.8.1 Screening/baseline assessment

As shown in Figure 4, agency and research staff will notify agency clients of the opportunity to participate in the study, and informational flyers will be posted throughout the agencies and/or distributed to individuals. Soon thereafter, research staff will be onsite at agency centers in planned rotations to conduct information sessions and baseline assessments with interested agency clients. During the information sessions, research staff will briefly explain the study and will ask individuals about their initial interest in participation. If interested, research staff will obtain verbal consent to administer the AUDIT-C to screen for alcohol dependence. If participants meet the initial screening cut-off (≥4), the research staff will explain the study procedures, participants' rights and informed consent materials. Next, the UBACC will be administered to assess capacity to provide informed consent. Potential participants will receive $5 for attending the information session, regardless of their decision, ability or qualification to participate. If they initially screen in and agree to participate, written informed consent for the study will be obtained, and participants may elect to complete the baseline assessment or schedule it for a later date. Based on our pilot study findings, we anticipate needing to screen 480 individuals at baseline to achieve the proposed sample size (N = 300).

One primary purpose of the baseline interview with the research staff is to determine whether participants meet initial criteria for the study (see sections 4.1 for inclusion criteria and 4.2 for exclusion criteria). The baseline interview will be administered by trained research staff holding at least a bachelor-level degree in the health or social sciences. Baseline assessment sessions will take approximately 30-45 minutes and will be audio recorded (if participant agrees). Audio recordings will facilitate weekly supervision conducted by the PI and other investigators. The measures (see section 3.3) will be administered verbally in-person with participants. Responses will be recorded by the interviewer on paper-and-pencil forms.

Next, the study physician/nurse will assess the study participant in an interview that will take approximately 50 minutes. During this appointment, study physicians/nurses will a) open the session with an introduction; b) assess vital signs; c) conduct a medication reconciliation; d) take a medical

history; e) administer the SAFTEE; f) conduct a physical exam (i.e., assessment of general appearance; head, eyes, ears, nose, and throat exam; heart, lung, and abdominal exam; musculoskeletal and dermatologic exam, and neurological assessment); and g) collect blood (1 EDTA and 1 red or gold top tube for ca. 15 ml for each blood draw during the study) and urine samples for initial lab tests, labeling them with study IDs. Participants will then be scheduled for a follow-up appointment the following week (i.e., Week 0) and will be paid $20 for their time.

Following the baseline appointment, a member of the research study staff will then bring the samples to the UW Research Testing Services. The EtG samples will be returned to Sterling labs. Both the UW Research Testing Services and Sterling labs will conduct the lab testing using only study ID and will not have access to participants' identifying information. It will take approximately three days for the results of the lab tests to be processed and returned to the study staff.

During the interim week, investigators (including the PI and Medical Director) will review participants' Case Report Forms, including results from the baseline interview, physical exam and lab test results, to consider the safety and appropriateness of proceeding with the study procedures/treatments (i.e., based on the inclusion/exclusion criteria listed in sections 3.2.1 and 3.2.2). Participant information for qualifying participants will be provided to the UW IDS who will randomize participants according to the scheme described in section 3.4.

3.8.2 Follow-up

At the Week 0 appointment, the study physician/nurse will discuss findings from the baseline interview, physical exam and lab tests with participants and will discuss the participants' participation course. Participants who do not qualify for study participation will be provided with feedback regarding their lab tests, exam and assessment; will be told why they do not qualify for participation; and will be provided with brief counseling regarding safer drinking steps. They will be thanked for their time, referred back to their agency staff/primary care provider and will be paid $20 for the session.

Participants randomized to the TAU will receive feedback regarding blood/urine tests that is deemed clinically relevant, will be referred to their primary care provider (as necessary), paid $20 and scheduled for their next appointment time (i.e., Week 4 follow-up). Participants in the XR-NTX, placebo or HRC conditions will receive their specified Week 0 treatment content as described in section 3.5. They will then be scheduled for the Week 1 safety check-in and paid $20. At the Week 1 safety check-in, the study physician/nurse will perform a physical exam if clinically indicated and will complete the case report form, which will primarily comprise the SAFTEE, goals and safer drinking steps sections. This meeting will further ensure participants' safety (for those in the medication conditions) and enhance participant engagement and follow-through. All active treatment groups (XR-NTX, placebo, HRC) will receive the same treatment components they received during week 0 (see section 3.5) at weeks 4, 8 and 12. At each follow-up visit, research staff will confirm with the participants that they are in possession of their wallet cards and study ID tags, if they receive injections. If they do not have them in their possession, research staff will supply new ones to the participants.

All participants will attend assessment sessions identical to the baseline appointment at weeks 4, 8, 12, 24 and 36 (see Figure 3 and 4). Participants will be paid $20 for each appointment they attend. At the final 36-week appointment, an additional measure will be added to the assessment battery—the Participant Satisfaction Assessment—to assess participants' receipt of and satisfaction with study procedures. At the end of the final session, participants will receive a study completion certificate.

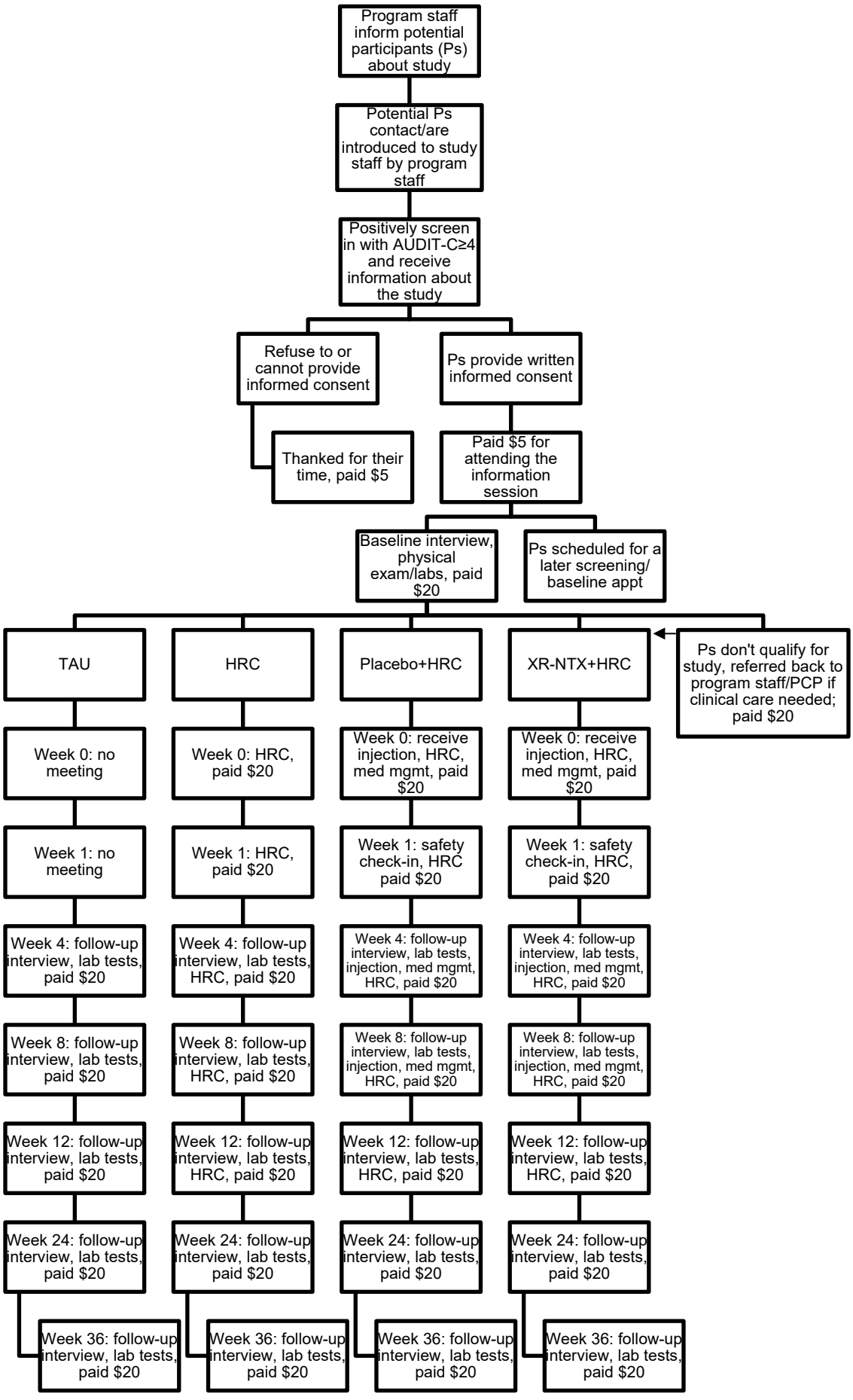
To ensure participant retention, we will use procedures honed in previous studies with these agencies. At each session, participants will be asked to update their contact information and will receive appointment slips including the time, place and contact person for their next appointment. Prior to all

appointments, reminder calls will be made to participants, or with their written permission, to agency staff at their respective sites and/or contacts of their choosing.

Further, if participants are unable to attend their sessions at the original study location or if there is concern that they may be lost to follow-up if required to come to the original location, the study treatments and other procedures may conducted at an alternate location (e.g., housing project, shelter, treatment center, hospital, etc.) as long as the implementation of study procedures in the alternate location is deemed safe and feasible by study staff.

If participants fail to appear at their follow-up appointments, we will make up to five attempts to contact them using the information provided in on the tracking form to reschedule their appointments before we consider them lost to follow-up. We will also reschedule participants for missed appointments up to 5 times before considering them lost to follow-up. For the safety appointment at Week 1, we will continue to make contact attempts until contact is made.

Given their extensive familiarity with their clients and their clients' routines, we will primarily rely on agency staff to help us locate participants. In the unlikely event they are unaware of their clients' whereabouts, we will be prepared to additionally search jail databases for King County, Pierce County, Snohomish County, Washington State Prison System, and the Federal Prison System; Harborview Medical Center; online resources (e.g., zabasearch.com, google, white pages); and death records using the Social Security Death Index or via http://www.digitalarchives.wa.gov/ for WA-specific records.


Program staff inform potential participants (Ps) about study
Potential Ps contact/are introduced to study staff by program staff
Positively screen in with AUDIT-C≥4 and receive information about the study
Refuse to or cannot provide informed consent
Thanked for their time, paid $5
Ps provide written informed consent
Paid $5 for attending the information session
Baseline interview, physical exam/labs, paid $20
Ps scheduled for a later screening/ baseline appt
Ps don't qualify for study, referred back to program staff/PCP if clinical care needed; paid $20
TAU
HRC
Placebo+HRC
XR-NTX+HRC
Week 0: no meeting
Week 0: HRC, paid $20
Week 0: receive injection, HRC, med mgmt, paid $20
Week 0: receive injection, HRC, med mgmt, paid $20
Week 1: no meeting
Week 1: HRC, paid $20
Week 1: safety check-in, HRC paid $20
Week 1: safety check-in, HRC, paid $20
Week 4: follow-up interview, lab tests, paid $20
Week 4: follow-up interview, lab tests, HRC, paid $20
Week 4: follow-up interview, lab tests, injection, med mgmt, HRC, paid $20
Week 4: follow-up interview, lab tests, injection, med mgmt, HRC, paid $20
Week 8: follow-up interview, lab tests, paid $20
Week 8: follow-up interview, lab tests, HRC, paid $20
Week 8: follow-up interview, lab tests, injection, med mgmt, HRC, paid $20
Week 8: follow-up interview, lab tests, injection, med mgmt, HRC, paid $20
Week 12: follow-up interview, lab tests, paid $20
Week 12: follow-up interview, lab tests, HRC, paid $20
Week 12: follow-up interview, lab tests, HRC, paid $20
Week 12: follow-up interview, lab tests, HRC, paid $20
Week 24: follow-up interview, lab tests, paid $20
Week 24: follow-up interview, lab tests, paid $20
Week 24: follow-up interview, lab tests, paid $20
Week 24: follow-up interview, lab tests, paid $20
Week 36: follow-up interview, lab tests, paid $20
Week 36: follow-up interview, lab tests, paid $20
Week 36: follow-up interview, lab tests, paid $20
Week 36: follow-up interview, lab tests, paid $20

4 Schedule of activities (Study Table)

	Year 1						Year2						Year 3						Year 4						Year 5					
	2	4	6	8	10	12	2	4	6	8	10	12	2	4	6	8	10	12	2	4	6	8	10	12	2	4	6	8	10	12
Hire project staff	.																													
Study organization and preparation	.	.																												
Interviewer and therapist training			.																											
Participant recruitment (cohort 1)				.																										
Baseline assessments				.																										
12-wk intervention and/or assessment only period				.	.	.																								
Posttest follow up					.	.																								
24-wk follow-up						.	.																							
36-wk follow-up							.	.	.																					
Participant recruitment (cohort 2)									.																					
Baseline assessments									.																					
12-wk intervention and/or assessment only period									.	.	.																			
Posttest follow up										.	.																			
24-wk follow-up											.	.																		
36-wk follow-up												.	.	.																
Participant recruitment (cohort 3)														.																
Baseline assessments														.																
12-wk intervention and/or assessment only period														.	.	.														
Posttest follow up															.	.														
24-wk follow-up																.	.													
36-wk follow-up																	.	.	.											
Participant recruitment (cohort 4)																			.											
Baseline assessments																			.											
12-wk intervention and/or assessment only period																			.	.	.									
Posttest follow up																				.	.									
24-wk follow-up																					.	.								
36-wk follow-up																						.	.	.						
Treatment integrity training and supervision					.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
Treatment integrity coding					.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
Administrative data management and analysis															.	.	.											.	.	.
Alcohol outcome data management and analysis																												.	.	.
Dissemination																														.

5 Safety Assessments

XR-NTX and oral naltrexone have been shown to have a favorable safety profile among adults with alcohol dependence and among current alcohol users. The known risks of taking XR-NTX are small when compared to the risks of untreated alcohol dependence. The safety assessments we have planned for the current study should provide adequate safeguards to quickly identify and respond to adverse events, should they occur.

5.1 Screening/baseline assessments

Participants will undergo extensive baseline screening procedures before they are deemed eligible for study participation. After providing written informed consent, participants' substance use will be assessed by trained research staff. Participants will also meet with the study physician/nurse and will undergo assessment of vital signs, weight, medical history, medication reconciliation, and physical exam. Clinical laboratory tests (blood chemistry, hematology, liver function, and urinalysis) will also be performed during the screening/baseline appointment. Clinical laboratory testing will be performed during the screening/baseline appointment to determine if participants

are healthy enough to receive the study medication. The laboratory testing will include a complete blood count, a basic metabolic panel, a liver panel, and a urinalysis. Urine drug screens and the SCID I/P will be used to rule out current opioid dependence prior to injections. Women who are in their childbearing years will be required to agree to use effective methods of birth control for the duration of the study. Women will undergo a serum hCG (pregnancy) test during the screening/baseline assessment. Neither pregnant nor lactating women will be included in the study. Additionally, both assessment staff and study interventionists will assess for suicidal ideation, intent, and attempts to exclude people who have made an attempt in the past year and set a baseline level of suicidal ideation for each participant and thereby facilitate tracking over time. Additionally, there is a standard suicide intervention protocol in place to be used as necessary.

5.2 Ongoing safety monitoring

Participants will undergo monthly clinical laboratory testing which will include a complete blood count, a basic metabolic panel, a liver panel, and urinalysis. Research staff will record self-reported drug and alcohol use, side effects and adverse events (as measured by the SAFTEE) at each follow-up visit. All serious adverse events and potential serious adverse events will be reported to the Medical Director and PI for determination of whether they are reportable under 45 CFR part 46 (see section 6.4 below for more information about reportable events). The study medication/placebo will be discontinued in the case of serious adverse events that are determined to be likely due to the study medication, and participants will be referred to their PCP and/or clinical case managers at the corresponding programs for appropriate follow-up care.

Women will undergo hCG tests at the baseline, and those who are in the XR-NTX/placebo groups will be tested throughout the administration period (Weeks 0, 4, 8). Women who become pregnant during the study will be withdrawn from XR-NTX/placebo and will be referred to their PCP and/or clinical case manager on the program staff for appropriate care.

Known potential side effects of XR-NTX include pain, tenderness, swelling, bruising and/or itching at the injection site; nausea; headache; fatigue; dizziness; vomiting; decreased appetite; painful joints and muscle cramps. Potential symptoms will be monitored closely during sessions with the study physician/nurse to avoid adverse consequences of participation in this study. Research staff will assess for and will help participants manage side effects during the course of the study and each of these will be explained during the informed consent process orally and in writing.

Naltrexone/XR-NTX do not have addictive properties, and with the exception of opioids, they evince few interactions with other medications. Studies have shown naltrexone/XR-NTX to be well-tolerated.[5] Rare conditions that may be associated with XR-NTX can often be avoided with assessment and screening procedures, and such procedures will be used in this study. First, XR-NTX should not be taken by individuals who are opioid dependent because it may induce withdrawal. Similarly, because XR-NTX is an opioid antagonist, it reduces the effectiveness of opioid analgesics. For these reasons, we will be conducting urine toxicology at baseline and prior to each injection and will not inject participants who are positive for opioids (see procedures described in section 3.5). There may also be a slightly elevated risk for eosinophilic pneumonia, depression and suicidality. For these reasons, research staff will conduct regular physical exams as clinically indicated and assessment of depression/suicide using the SAFTEE, BSS and SITBI. Additionally, there is a standard suicide intervention protocol in place in case a person has acute suicidal ideation and intent. As with any medication, there is a risk of drug hypersensitivity, although allergic reactions to XR-NTX are very rare. All participants will be told to call 911 in the case of an allergic reaction. In some cases, reactions at the injection site may become severe. Injection sites should be monitored by a health-care provider for potential hardening, inflammation, nodules and swelling, and in extreme cases, necrosis. The research staff will make concerted efforts to avoid injection site reactions by ensuring that the needle passes through the superficial layer of fat tissue under the skin and into the gluteal muscle before the medication is injected.

Finally, until recently, there was a ‘‘black-box’’ warning regarding potential hepatocellular injury. This warning was removed from XR-NTX in July 2013 given a lack of evidence of hepatotoxicity at the approved dosage. The warning

had followed from early naltrexone studies, which prescribed daily oral doses of up to 350mg for treatment of obesity and dementia—seven times the currently recommended oral dose.[24] Although current FDA labeling indicates that XR-NTX may be associated with liver injury primarily if it is administered in "excessive doses" or to patients with "acute hepatitis or liver failure,"[22] there are no reports of hepatotoxicity involving XR-NTX.[25] The large-scale, randomized controlled trial (RCT) of XR-NTX mentioned above indicated no significant differences in participants' liver function throughout the study, even among participants with previously elevated liver enzymes.[23] Gamma-glutamyl transferase (GGT) levels were lower among those receiving XR-NTX compared to placebo during the study, likely due to decreased drinking.[23] Further, because XR-NTX is injected intramuscularly, it eliminates first-pass metabolism, further reducing the risk of hepatotoxicity and fluctuations in plasma naltrexone levels.[26] In fact, it has been suggested that there is greater risk of hepatotoxicity from continued, heavy alcohol use than from appropriate naltrexone administration.[27] Research staff will, however, be monitoring liver function throughout the study and will discontinue the study medication if liver enzymes exceed acceptable limits (AST/ALT > 5 x ULN after a repeat test).

In addition to the research study data collection, biannual reports on adverse events (i.e., deaths, hospitalizations, illness) experienced by study participants will be compiled. These reports will be reviewed by the PI and Co-Is as well as the Data Safety Monitoring Board. Additionally, on a biannual basis, Dr. David Atkins (DSMB statistician and chair) will review the study's safety and effectiveness using a blinded, grouped analysis, which will be shared with the DSMB. Based on this review, the DSMB will make a recommendation for continuing or terminating the trial. Copies of these recommendations will be sent to the PI, Medical Director and IRB committee.

6 Adverse Event Reporting

6.1 Adverse event definitions

- *Adverse event:* Any untoward medical occurrence in a clinical study, regardless of the causal relationship of the event with the study treatment.
- *Associated with the study treatment*: Reasonable possibility that the adverse event may have been caused by the study treatment.
- *Disability*: A substantial disruption of a person's ability to conduct normal life functions.
- *Life-threatening adverse event*: Any adverse event that places participants, in the view of the investigators, at immediate risk of death from the event as it occurred (i.e., does not include an adverse event that, had it actually occurred in a more severe form, might have caused death).
- *Serious adverse event*: Any adverse event that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, congenital anomaly/birth defect, or threat to participants' health that may require medical or surgical intervention to prevent the previous outcomes
- *Hospitalization:* Any initial admission to a healthcare facility as a result of a precipitating clinical adverse event, including transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event (e.g., for a preexisting condition not associated with a new adverse event or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse event.
- *Unanticipated problem*: OHRP designation for an adverse event that a) is unexpected in nature, severity or frequency; b) is related or possibly related to participation in the research; and c) may place participants or others at a greater risk of physical or psychological harm. Under 45 CFR part 46, unanticipated problems must be reported to the IRB for report to the OHRP within 2 weeks. If the unanticipated problem is also a serious or life-threatening adverse event, it must be reported to the IRB for report to the OHRP within 1 week.

6.2 Eliciting adverse event information

Contact information for the research team and the IRB will be provided in all consent materials, and participants will be encouraged to report adverse events to research staff. Participants will be routinely questioned about adverse events at study visits using the SAFTEE, which was tailored specifically for use with the study medication. Further, lab tests and physical exams will be used to detect potential adverse events. These will be regularly reviewed by the PI and Medical Director in weekly meetings. Adverse events or abnormal test findings believed to be associated with the study treatment will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the PI and Medical Director.

In the case of a suspected unanticipated problem or serious adverse event, research staff will promptly call the PI or Medical Director, and will follow a detailed protocol which ranges from encouraging or assisting the participant to speak with his or her onsite case manager (assigned to all clients of DESC and REACH) to calling 911 or a county Mental Health Professional to assess for involuntary hospitalization, depending on the nature of the event. Research staff will record all observed or volunteered serious adverse events using the designated form in the CRF, which will be turned in to the PI and Medical director for review before it is submitted to the IRB.

If upon review, it is unclear whether an adverse event meets criteria for an unanticipated problem or serious adverse event, the PI and Medical Director will promptly seek out and review further documentation and/or abnormal test findings to determine 1) if they should be classified as adverse events; 2) if there is a reasonable possibility that the adverse events were caused by the study treatment; and 3) if the adverse events meet criteria for a serious adverse event or unanticipated problem. If causality is determined to be of "unknown and of questionable relationship" to the study treatment, the adverse event will be classified as associated with the study treatment for reporting purposes. If the determination of causality is "unknown but not related to the study treatment," this determination and its rationale will be documented in the study log. If serious adverse events/unanticipated problems are deemed to be due to the study medication, it will be discontinued and appropriate follow-up care will be coordinated.

Research staff will also obtain HIPAA authorizations/releases of information for agency and local hospital records of potential adverse and serious adverse events (e.g., hospitalizations, death, disability). Safety data will be compiled on a biannual basis and will be monitored by the PI and Co-Is as well as the Data Safety Monitoring Board. On a biannual basis during the study, the DSMB chair will generate a recommendation for continuing or terminating the trial. Copies of these reviews will be sent to the PI (Collins), the Medical Director (Ries) and the UW IRB. The report and recommendations will be discussed with research and agency staff in research meetings during the course of the RCT.

6.3 Recording requirements

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of treatment group or suspected causal relationship to the study treatments will be recorded in the participants' CRF in the appropriate space or using the adverse event form. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the study treatment. Adverse events or abnormal test findings believed to be associated with the study treatment will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the PI and Medical Director.

6.3.1 Abnormal test findings, side effects and other study occurrences

An abnormal test finding, side effect or other study occurrence will be classified as an *adverse event* if one or more of the following criteria are met:

- It is accompanied by clinically significant symptoms.

- It necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.)
- It leads to a change in study dosing or discontinuation of participant participation in the study
- It is considered an adverse event by the PI and Medical Director

6.3.2 Causality and severity assessment

The investigators (including the PI and Medical Director) will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study treatment/procedures; and 3) if the adverse event meets the criteria for a *serious adverse event*.

Relationship	Criteria for assessment
Definitely related	There is evidence of exposure to the study drug AND • The temporal sequence of the AE onset relative to the administration of the study drug is reasonable • The AE is more likely explained by the study drug than by another cause • Dechallenge (if performed) is positive • Rechallenge (if performed) is positive • The AE shows a pattern consistent with previous knowledge of the study drug or study drug class
Probably related	There is evidence of exposure to the study drug AND • The temporal sequence of the AE onset relative to the administration of the study drug is reasonable • The AE is more likely explained by the study drug than by another cause • Dechallenge (if performed) is positive
Possibly related	There is evidence of exposure to the study drug AND • The temporal sequence of the AE onset relative to the administration of the study drug is reasonable • The AE could have been due to another equally likely cause • Dechallenge (if performed) is positive
Probably not related	There is evidence of exposure to the study drug AND • There is another, more likely cause of the AE • Dechallenge (if performed) is negative or ambiguous • Rechallenge (if performed) is negative or ambiguous

Definitely not related	The participant was not exposed to the study drug OR • The temporal sequence of the AE onset relative to administration of the study drug is not reasonable OR • There is another obvious cause of the AE

6.4 Reporting of adverse events

Any observed or volunteered adverse event that is determined to be a serious adverse event or an unanticipated problem will be reported by the PI to the IRB and Alkermes within 24 hours of receipt of this information. This will be done even if a serious adverse event is determined to be "probably not related" or "definitely not related" to the study medication/study procedurs, although it is understood that it typically must not be officially reported unless it is found to be a serious adverse event that is possibly due to the study medication/study procedures. Follow-up information to the reported serious adverse event or unanticipated problem will be submitted to the IRB and Alkermes as soon as the relevant information is available—particularly regarding the association of the study medication or procedures with the serious adverse event. It is conceivable that further investigation could show that a serious adverse event or unanticipated problem that was initially determined to not require reporting does, in fact, meet the requirements for reporting. Such events will be reported to the IRB as soon as possible and no later than 24 hours after the determination was made. Unanticipated problems will be reported to OHRP as specified under federal law (45 CFR part 46).

6.5 Withdrawal of Participants Due to Adverse Events

Participants will be withdrawn from the XR-NTX/placebo treatment course if they experience an adverse event determined qualify as a serious adverse event or unanticipated problem and probably due to the medication. Other reasons for withdrawal from the medication treatment course include participants' decision to discontinue study medication; pregnancy; elevated liver enzymes (AST/ALT > 5x normal after repeat test); renal insufficiency (serum creatinine level > 2; and/or physical illness/injury that precludes following the prescribed XR-NTX/placebo course. In this case, the reason for discontinuation of medication will be noted on the participants' CRF and will be noted in safety reports. The study medication will be discontinued, and participants will be encouraged to discuss their medical condition/lab test findings with their assigned clinical case manager on the program staff and primary care physician for follow-up care. In the case participants do not have a primary care provider, they will be referred to local primary care clinics. In the case of an observed or self-reported adverse event of questionable severity, research staff will immediately contact the medical director and PI. If it is determined to fit the definition of a serious adverse event or unanticipated problem, this will be reported to the IRB as discussed in previous sections. In case of life-threatening event, research staff will immediately inform the medical director, the PI and the participants' clinical case manager at the program agency, who will take immediate, clinically appropriate action. Unless participants explicitly request to withdraw their participation altogether or the adverse event prevents participation, they will continue with follow-up assessment subsequent to treatment discontinuation.

7 Statistical Methods/Data Analysis:

7.1 Study endpoints

Primary and secondary endpoints for the current study will include alcohol (i.e., peak alcohol quantity, drinking frequency, alcohol-related problems, EtG/creatinine ratio, liver tests) and quality-of-life outcomes; process/mediational variables (i.e., motivation to engage in harm reduction, craving); and publicly funded service utilization and associated costs (i.e., Medic One/EMS dispatches; ER visits; inpatient hospital admissions; bookings, length of stay and daily cost for the King County Correctional Facility).

7.2 Sample size determination

Using Mplus 6.11,[106] we conducted Monte Carlo studies to estimate power for the primary outcome analyses to be conducted in Specific Aims 1 and 3. Data were generated from a population with hypothesized parameter values, 10,000 samples were drawn at random, and model parameters were estimated for each sample. A significance level of $\alpha = .05$ was assumed for the hypothesized treatment effects for each of the outcome variables. Residual variance was set at .09, which is a representative value for this model type[107] and corresponds to calculations based on data from our prior studies in a similar population.[49,56] For Hypothesis 1a, assuming a follow-up attrition rate of 20%,[49] a Monte Carlo study indicated power (β-1) of .92 to detect a small-to-medium effect (γ=.15) for HRC and placebo and β-1=.99 to detect a medium effect for XR-NTX (γ=.2; corresponding to Cohen's *d*=.63; following suggestions by Muthén and colleagues[107]) compared to TAU for our proposed sample size (*N*=300). For Hypothesis 1b, power was adequate (β-1=.83) to detect a medium effect (γ=.2) for XR-NTX compared to placebo (*N*=150). These estimated effect sizes were deemed appropriate given findings from prior studies with this population[49,56] and with the study medication.[5,68]

For specific aim 3, assuming no missing utilization data, a Monte Carlo study indicated adequate power (β-1=.81) to detect a medium effect (γ=.2) for XR-NTX compared to TAU.[107] This test will, however, be underpowered to detect the hypothesized small-to-medium (γ=.15) effects for placebo and HRC (β-1=.57). The fact that the weaker treatment effects are underpowered is not unexpected for cost analyses in smaller clinical trials.[108] Although the proposed population comprises relatively high utilizers of EMS, ER, inpatient hospital and jail services, the frequency of emergency and criminal justice system utilization is still statistically rare.

7.3 Proposed analyses

Outcome analyses will comprise a series of latent growth curve models utilizing appropriate probability distributions for the outcome variables (e.g., Poisson, negative binomial, Gaussian, logistic). Growth modeling examines individuals' outcome trajectories and covariate effects on these trajectories over time.[109] Growth modeling will be conducted using Mplus 6.11, which incorporates a generalized latent framework and allows for a wide array of variable types, estimation methods and longitudinal modeling options.[106] Mplus uses a multivariate approach to growth modeling in contrast to the multilevel approach proposed by Raudenbush and Bryk.[110]

Outcomes measured at each time point will serve as indicators of the intercept (i.e., baseline) and slope (i.e., change in outcomes over time). Treatment group will serve as the primary predictor of slope. Covariates (e.g., housing status, agency) will serve as additional predictors of intercept or slope, as necessary. Outcome variables are based on established standards in the alcohol-use literature[111-113] and our own studies on alcohol-use in similar populations.[49,56]

Analyses for *Specific Aim 1* will feature growth models to test treatment effects on 3, 30-day alcohol outcomes: peak alcohol quantity, drinking frequency and alcohol-related problems. In secondary analyses, we will additionally test the treatment effects on the EtG/creatinine ratio and liver values to biovalidate the primary, self-report outcomes. Although the proposed alcohol outcomes differ from those typically encountered in clinical drug trials, they were deemed appropriate for the proposed study aims and population. First, most naltrexone studies have used an abstinence-based treatment model and have thereby employed complementary, abstinence-oriented outcomes (e.g., days to relapse, percent days abstinent). Because we have proposed a harm-reduction treatment model, we, too, deemed it important to focus on complementary outcomes: reduced alcohol-use and -related harm. Second, the baseline assessment during our pilot study indicated participants had a 30-day median drinking frequency of 30 days and a peak alcohol quantity of 30 drinks. Given the extent of alcohol use in this population, abstinence-based outcomes would be blunt instruments that would not capture nuanced longitudinal changes in alcohol-use and -related problems. Finally, in keeping with the harm-reduction philosophy, we are proposing to assess multiple outcomes to reflect the various pathways by which individuals might change their drinking to achieve reductions in alcohol-related harm.

To test Hypothesis 1a, we will conduct growth models comparing the relative effects of the three active treatment groups with the TAU group on alcohol outcomes (see Figure 5). It is hypothesized that the three active treatment groups will evince significantly greater decreases across alcohol outcomes than TAU. To test Hypothesis 1B, we will conduct a second set of growth models directly comparing the XR-NTX and placebo effects on alcohol outcomes. It is hypothesized that the XR-NTX group will evince significantly greater decreases than the placebo group on alcohol outcomes over the follow-up period.

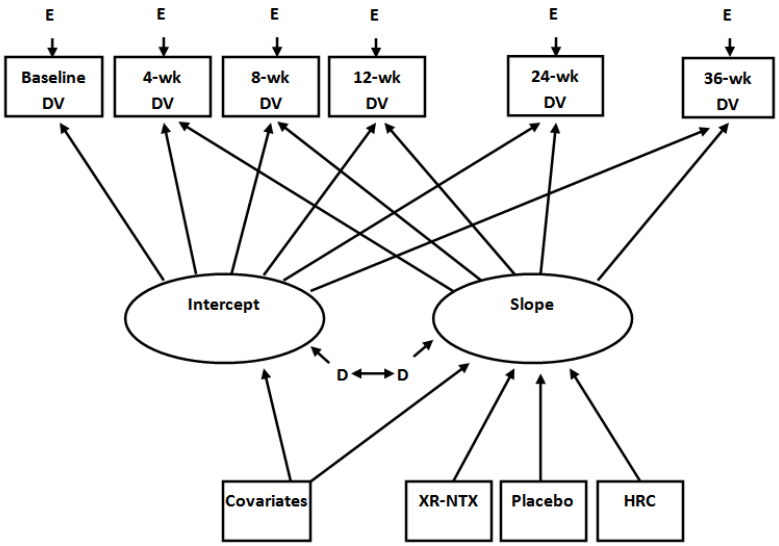


Figure 5. Hypothesized primary intervention model. "Intercept" is the baseline measurement of the outcome variable (DV). "Slope" represents change in the DV over time. DV= outcome or dependent variable. D=latent variable disturbance (error). E=measured variable error.

For *Specific Aim 2,* we will be testing longitudinal changes on secondary, theoretical variables as mediators of the treatment effects on alcohol outcomes. To test Hypothesis 2a, growth analyses will be conducted to determine whether the 3, active treatment groups are associated with significant increases in motivation to change drinking in a way that reduces harm as represented by the DBP and readiness, motivation, importance and confidence rulers. If this is the case, the alcohol growth model established in analyses for Specific Aim 1 and the motivation growth model will be combined into a single parallel process growth model.[114] The mediation effect will be tested by taking the product of coefficients (αβ), where α=the regression of the slope of the mediator on the dummy-coded intervention variables and β=the regression of the slope of the alcohol outcome variable on the slope of the mediator, using the asymmetric confidence interval (CI) approach.[115] This same procedure will be used to test hypothesis 2B or whether XR-NTX produces significantly greater decreases on alcohol craving than the placebo group, and whether those decreases in craving are in turn associated with decreases on alcohol outcomes.

Because homeless people with alcohol dependence disproportionately utilize costly medical and criminal justice services,[49,116,117] it is important to assess the impact of interventions for this population on publicly funded service costs. *Specific Aim 3* will therefore assess relative effects of the 3 active treatments (i.e., XR-NTX, placebo and HRC) compared to TAU on costs stemming from: a) the number of emergency medical service dispatches; b) number of ER visits; c) number of inpatient hospital admissions; d) number of bookings and length of stay at the King County Correctional Facility. As in Specific Aim 1, this analysis will feature a growth model in which the mean monthly costs during 3 timepoints (i.e., 2 years prior to baseline, during the 12 weeks of treatment, and during the 24-week follow-up) will serve as indicators of the latent variables. We will use the mean monthly costs to account for the differing lengths of the time points. The 3 active treatment groups will serve as dummy-coded variables predicting the cost slope, which is expected to decrease at a significantly greater rate for the XR-NTX, placebo and HRC groups (in descending order) compared to the TAU group.

8 Quality Control and Quality Assurance

This protocol and other study documentation will be reviewed and approved by the UW IRB prior to study start date. The study will involve qualified and trained professionals who will administer the clinical interviews, physical exams and study treatment according to the guidelines laid out in this protocol and in the HaRP treatment manual. Specifically, study physicians will be licensed medical doctors who have completed their residencies in psychiatry and have either completed or are completing an addiction psychiatry fellowship. Study nurses will be registered

nurses who are completing an advanced Doctor of Nursing Practice program at the UW. Research staff conducting assessments will have at least a bachelor-level degree in the health or social sciences. All study staff will receive training and weekly supervision from the PI and Co-Investigators. Training on treatment and assessment delivery will comprise 16 hours of in-person training, including review of the manual, role-plays, and feedback. Study staff will audio record all participant sessions to facilitate supervision and treatment integrity analyses, including manual adherence, therapist competence, and participants' receipt and enactment of the HaRP principles.

All adverse events will be recorded on the CRF and/or on the adverse event reporting form. These will be reported to the PI and medical director in weekly meetings and by personal consultation so the team may determine whether it constitutes an unanticipated problem and/or serious adverse event that warrants reporting to the IRB and OHRP. Additionally, the scientific team and DSMB will review the safety data on a biannual basis in report form. The DSMB will then make a recommendation, which will be sent to the PI and IRB, regarding the appropriateness of continuing the study.

9 Data Handling and Record-Keeping

9.1 Data recording/Case Report Forms

Assessment packets and Case Report Forms (CRF) will be completed for each participant enrolled into the clinical study. During weekly meetings, the PI and Medical Director will review, approve and sign/date each completed CRF. These signatures will serve as attestation of their responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in Source Documents. Source Documents are the original records (and certified copies of original records); including, but not limited to lab test results, physician or nursing session notes, evaluation checklists, participants' self-reported data, and agency/hospital records. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

9.2 Record maintenance and retention

The investigators will maintain records in accordance with Good Clinical Practice guidelines. These will include:

- FDA correspondence related to the IND status
- IRB correspondence (including approval notifications) related to the protocol, including copies of adverse event reports and annual or interim reports
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, participant recruitment advertisements
- Financial disclosure information (investigators) – Note: this is now reported and maintained in online databases through the UW FIDS
- Biosketches (investigators)
- Certificates of required training (e.g., human participant protections, HIPAA, etc.) for PI and Co-Is
- Listing of printed names/signatures of investigators
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol
- Instructions for on-site preparation and handling of the investigational drug(s), study treatment(s), and other study-related materials (i.e., if not addressed in the clinical protocol)
- Signed informed consent forms
- Completed Case Report Forms; signed and dated by investigators
- Source Documents or certified copies of Source Documents

- Copies of investigators' correspondence among one another regarding notifications of safety information and adverse events
- Participant screening and enrollment logs
- Participant identification code list
- Investigational drug accountability records, including documentation of drug disposal.
- Final clinical study report

Great care will be taken to maintain the confidentiality of data provided by participants contained in these records. Direct subject identifiers, including participants' names and contact information, will be collected to facilitate follow-up communication and thereby assess intervention safety and efficacy over time. However, all records—including lab tests—will be identified only with a randomly generated, unique ID. Master lists of IDs and direct identifiers will be stored in locked file cabinets and password-protected computers with restricted access. These lists will be available only to research staff on this project. All UW research staff (including IDS personnel) will be required to sign a confidentiality statement and complete HIPAA and human subjects training before having contact with participants or participants' identifiable private information. The linkage will be destroyed one year after study completion. All data will be collected specifically for the proposed research study.

10 Ethics

10.1 Institutional Review Board (IRB) approval

The investigators will obtain, from the UW IRB, prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research participants) prior to study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research participant(s). In such circumstances, the investigators will promptly notify the UW IRB of the deviation using the appropriate designation(s) on the Report of Other Problems (ROOP) form based on IRB counsel (i.e., unanticipated problem, protocol deviation, protocol violation or other problem).

10.2 Ethical and scientific conduct of the clinical study

This study will be conducted in accordance with the clinical protocol currently under review by the UW IRB and relevant policies, requirements, and regulations of the UW IRB, Washington State, and applicable federal agencies.

10.3 Participant informed consent

The investigators will make certain that an appropriate informed consent process is in place to ensure that potential research participants are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. Designated research staff will obtain the written, signed informed consent of each participant prior to performing any study-specific procedures. The date that the participant signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented on the consent form. The investigators will retain the original copy of the signed informed consent form, and a copy will be provided to the participant.

The investigators will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and that participants are informed of any new information that may affect their decision to continue participation in the study. In the event of substantial

changes to the clinical study or the risk-to-benefit ratio of study participation, the investigators will obtain the informed consent of enrolled participants for continued participation.

References

1. Crabtree BL. Review of naltrexone, a long-acting opiate antagonist. *Clinical Pharmacology.* 1984;3:273-280.

2. O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. *Archives of General Psychiatry.* 1992;49:881-887.

3. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry.* 1992;49:876-880.

4. Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. *The Cochrane Database of Systematic Reviews.* 2008;Issue 2:Art. No.: CD001867.

5. Garbutt JC, Kranzler HR, O'Malley SS, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. *JAMA.* 2005;293:1617-1625.

6. Froehlich JC, K LT. Opioid involvement in alcohol drinking. *Annals of the New York Academy of Science.* 1994;739:156-167.

7. Gianoulakis C. Implications of endogenous opioids and dopamine in alcoholism: Human and basic science studies. *Alcohol and Alcoholism.* 1996;S1:33-42.

8. Gianoulakis C. Influence of the endogenous opioid system on high alcohol consumption and genetic predisposition to alcoholism. *Journal of Psychiatry and Neuroscience.* 2001;26:304-318.

9. Méndez M, Morales-Mulia M. Role of mu and delta opioid receptors in alcohol drinking behaviour. *Current Drug Abuse Review.* 2008;1:239-252.

10. O'Malley SS, Jaffe AJ, Chang G, et al. Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. *Archives of General Psychiatry.* 1996;53:217-224.

11. Anton RF. Naltrexone for the management of alcohol dependence. *The New England Journal of Medicine.* 2008;359:715-721.

12. Garbutt JC. Efficacy and tolerability of naltrexone in the management of alcohol dependence. *Current Pharmaceutical Design.* 2010;16:2091-2097.

13. Rösner S, Leucht S, Lehert P, Soyka M. Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. *Journal of Psychopharmacology.* 2008;22:11-23.

14. Soyka M, Rösner S. Opioid antagonists for pharmacological treatment of alcohol dependence - a critical review. *Current Drug Abuse Review.* 2008;1:280-291.

15. Bouza C, Angeles M, Muñoz A, Amate JM. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction.* 2004;99:811-828.

16. Pettinati HM, Volpicelli JR, Pierce JD, O'Brien CP. Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. *Journal of Addictive Diseases.* 2000;19:71-83.

17. Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP. Naltrexone and alcohol dependence: role of subject compliance. *Archives of General Psychiatry.* 1997;54:737-742.

18. Dunbar JL, Turncliff RZ, Dong Q, Silverman BL, Ehrich EW, Lasseter KC. Single- and multiple-dose pharmacokinetics of long-acting injectable naltrexone. *Alcoholism: Clinical and Experimental Research.* 2006;30:480-490.

19. Johnson BA, Ait-Daoud N, Aubin HJ, et al. A pilot evaluation of the safety and tolerability of repeat dose administration of long-acting injectable naltrexone (Vivitrex) in patience with alcohol dependence. *Alcoholism: Clinical and Experimental Research.* 2004;28:1356-1361.

20. Pettinati HM, Gastfriend DR, Dong Q, Kranzler HR, O'Malley SS. Effect of extended-release naltrexone (XR-NTX) on quality of life in alcohol-dependent patients. *Alcoholism: Clinical and Experimental Research.* 2009;33:350-356.

21. Lee JD, DiRocco D, Truncali A, et al. Extended-release naltrexone for treatment of alcohol dependence in primary care. *Journal of Substance Abuse Treatment.* 2010;39:14-21.

22. Federal Drug Administration. Vivitrol, NDA no. 021897. *Label Information.* 2010:http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s021015lbl.pdf.

23. Lucey MR, Silverman BL, Illeperuma A, O'Brien CP. Hepatic safety of once-monthly injectable extended-release naltrexone administered to actively drinking alcoholics. *Alcohol Clinical and Experimental Research.* 2008;32:498-504.

24. Pettinati HM, O'Brien CP, Rabinowitz AR, et al. The status of naltrexone in the treatment of alcohol dependence. *Journal of Clinical Psychopharmacology.* 2006;26:610-625.

25. Alkermes Inc. FDA Psychopharmacologic drugs advisory committee meeting: Vivitrol (naltrexone for extended-release injectable suspension) NDA-21-897. Accessed on 6/17/11 via http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM225664.pdf. 2010.

26. Center for Substance Abuse Treatment. Incorporating alcohol pharmacotherapies into medical practice. *Treatment Improvement Protocol (TIP) Series 49. HHS Publication No. (SMA) 09-4380*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2009.

27. Berg BJ, Pettinati HM, Volpicelli JR. A risk-benefit assessment of naltrexone in the treatment of alcohol dependence. *Drug Safety.* 1996;15:274-282.

28. Fazel S, Khosla V, Doll H, Geddes J. The prevalence of mental disorders among the homeless in western countries: Systematic review and meta-regression analysis. *PLOS Medicine.* 2008;5:e225.

29. Grant BF, Dawson DA, Stinson FS, Chou SP, Dufour MC, Pickering RP. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. *Drug and Alcohol Dependence.* 2004;74:223-234.

30. Podymow T, Turnbull J, Coyle D, Yetisir E, Wells G. Shelter-based managed alcohol administration to chronically homeless people addicted to alcohol. *Canadian Medical Association Journal.* 2006;174:45-49.

31. Dietz TL. Predictors of reported current and lifetime substance abuse problems among a national sample of U.S. homeless. *Substance Use & MIsuse.* 2007;42:1745-1766.

32. Zerger S. *Substance abuse treatment: What works for homeless people? A review of the literature*. Nashville, TN: National Health Care for the Homeless Council; 2002.

33. Eyrich-Garg KM, Cacciola JS, Carise D, Lynch KG, McLellan AT. Individual characteristics of the literally homeless, marginally housed and impoverished in a US substance abuse treatment-seeking sample. *Social Psychiatry and Psychiatric Epidemiology.* 2008;43(831-842).

34. WHO. *Global status report on alcohol and health*. Le Mont-sur-Lausanne, Switzerland: WHO; 2011.

35. Hawke W, Davis M, Erlenbusch B. *Dying without dignity: Homeless deaths in Los Angeles County*. Los Angeles, CA: Los Angeles Coalition to End Hunger & Homelessness.; 2007.

36. O'Connell JJ. *Premature mortality in homeless populations: A review of the literature*. Nashville, TN: National Health Care for the Homeless Council, Inc.; 2005.

37. Public Health - Seattle and King County. *King County 2003 Homeless Death Review.* Seattle, WA: Health Care for the Homeless Network;2004.

38. Hwang SW, Tolomiczenko G, Kouyoumdjian FG, Garner RE. Interventions to improve the health of the homeless. *American Journal of Preventative Medicine.* 2006;29:311-319.

39. Orwin RG, Scott CK, Arieira C. Transitions through homelessness and factors that predict them: Three-year treatment outcomes. *Journal of Substance Abuse Treatment.* 2005;Suppl. 1:S23-S39.

40. Rosenheck RA, Morrissey J, Lam J, et al. Service system integration, access to services, and housing outcomes in a program for homeless persons with severe mental illness. *American Journal of Public Health.* 1998;88:1610-1615.

41. Wenzel SL, Burnam MA, Koegel P, et al. Access to inpatient or residential substance abuse treatment among homeless adults with alcohol or other drug use disorders. *Medical Care.* 2001;39:1158-1169.

42. Orwin RG, Garrison-Mogren R, Jacobs ML, Sonnefeld LJ. Retention of homeless clients in substance abuse treatment: Findings from the National Institute on Alcohol Abuse and Alcoholism Cooperative Agreement Program. *Journal of Substance Abuse Treatment.* 1999;17:45-66.

43. Collins SE, Clifasefi SL, Dana EA, et al. Where harm reduction meets Housing First: Exploring alcohol's role in a project-based Housing First setting. *International Journal of Drug Policy.* 2012;23:111-119.

44. Padgett D, Henwood B, Abrams C, Davis A. Engagement and retention in services among formerly homeless adults with co-occurring mental illness and substance abuse: voices from the margins. *Psychiatric rehabilitation journal.* 2008;31(3):226-233.

45. Pettinati HM, Monterosso J, Lipkin C, Volpicelli JR. Patient attitudes toward treatment predict attendance in clinical pharmacotherapy trials of alcohol and drug treatment. *American Journal on Addictions.* 2003;12:324-335.

46. Long CG, Williams M, Midgley M, Hollin CR. Within-program factors as predictors of drinking outcome following cognitive-behavioral treatment. *Addictive Behaviors.* 2000;25:573-578.

47. Marlatt GA, Gordon JR. *Relapse prevention: Maintenance strategies in the treatment of addictive behaviors*. New York: The Guilford Press; 1985.

48. Muraven M, Baumeister RF. Self-regulation and depletion of limited resources: Does self-control resemble a muscle? *Psychological Bulletin.* 2000;126:247-259.

49. Larimer ME, Malone DK, Garner MD, et al. Health Care and Public Service Use and Costs Before and After Provision of Housing for Chronically Homeless Persons With Severe Alcohol Problems. *Journal of the American Medical Association.* 2009;301:1349-1357.

50. Kertesz SG, Horton NJ, Friedmann PD, Saitz R, Samet JH. Slowing the revolving door: Stabilization programs reduce homeless persons' substance use after detoxification. *Journal of Substance Abuse Treatment.* 2003;24:197-207.

51. Richman A, Neumann B. Breaking the "detox-loop" for alcoholics with social detoxification. *Drug and Alcohol Dependence.* 1984;13(65-73).

52. Becker HC. Kindling in alcohol withdrawal. *Alcohol Health & Research World.* 1998;22:25-33.

53. Svoboda T. Measuring the 'reduction' in a harm reduction program for homeless men experiencing harms related to alochol abuse and problem behaviors. In: Toronto Uo, ed. Toronto, ON, Canada2006.

54. Tsemberis S, Eisenberg RF. Pathways to Housing: Supported housing for street-dwelling homeless individuals with psychiatric disabilities. *Psychiatric Services.* 2000;51:487-493.

55. Collins SE, Clifasefi SL, Logan DE, Samples L, Somers J, Marlatt GA. Ch. 1 Harm Reduction: Current Status, Historical Highlights and Basic Principles. In: Marlatt GA, Witkiewitz K, Larimer ME, eds. *Harm reduction: Pragmatic strategies for managing high-risk behaviors (2nd ed)*. New York: Guilford. http://www.guilford.com/excerpts/marlatt2.pdf; 2011.

56. Collins SE, Malone DK, Clifasefi SL, et al. Project-based Housing First for chronically homeless individuals with alcohol problems: Within-subjects analyses of two-year alcohol-use trajectories. *American Journal of Public Health.* 2012;102:511-519.

57. Batra A, Collins SE, Schröter M, Eck S, Torchalla I, Buchkremer G. A cluster-randomized effectiveness trial of smoking cessation modified for at-risk smoker subgroups. *Journal of Substance Abuse Treatment.* 2010;38:128-140.

58. Padgett D, Stanhope V, Henwood BF, Stefancic A. Substance use outcomes among homeless clients with serious mental illness: Comparing housing first with treatment first programs. *Community Mental Health Journal.* 2011;47:227-232.

59. O'Malley SS, Garbutt JC, Gastfriend DR, Dong Q, Kranzler HR. Efficacy of extended-release naltrexone in alcohol-dependent patients who are abstinent before treatment. *Journal of Clinical Psychopharmacology.* 2007;27:507-512.

60. Denning P, Little J. *Practicing harm reduction psychotherapy: An alternative approach to addictions (2nd edition)*. New York: Guilford Press; 2011.

61. Leeman RF, Palmer RS, Corbin WR, Romano DM, Meandzija B, O'Malley SS. A pilot study of naltrexone and BASICS for heavy drinking young adults. *Addictive Behaviors.* 2008;33:1048-1054.

62. O'Malley SS. Naltrexone for heavy drinking in young adults [published abstract]. *Alcoholism: Clinical and Experimental Research.* 2012;36(s1):334A.

63. Palepu A, Milloy MJ, Kerr T, Zhang R, Wood E. Homelessness and adherence to antiretroviral therapy among a cohort of HIV-infected injection drug users. *Journal of Urban Health.* 2011;88:545-555.

64. Kidder DP, Wolitski RJ, Campsmith ML, Nakamura GV. Health status, health care use, medication use, and medication adherence among homeless and housed people living with HIV/AIDS. *American Journal of Public Health.* 2007;97:2238-2245.
65. Copeland LA, Miller AL, Welsh DE, McCarthy JF, Zeber JE, Kilbourne AM. Clinical and demographic factors associated with homelessness and incarceration among VA patients with bipolar disorder. *American Journal of Public Health.* 2009;99:871-877.
66. Johnson B, Ait-Daoud N, Roache J. The COMBINE SAFTEE: A structured instrument for collecting adverse events adapted for clinical studies in the alcoholism field. *Journal of Studies on Alcohol.* 2005;15:157-167.
67. Levine J, Schooler NR. Strategies for analyzing side-effect data from SAFTEE--A workshop held fall 1985 in Rockville, Maryland. *Psychopharmacology Bulletin.* 1986;22(2):343.
68. Weiss RD, O'Malley SS, Hosking JD, LoCastro JS, Swift R, for the COMBINE Study Research Team. Do Patients with alcohol dependence respond to placebo? Results from the COMBINE Study. *Journal of Studies on Alcohol and Drugs.* 2008;69:878-884.
69. Anton RF, O'Malley SS, Ciraulio DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. *Journal of the American Medical Association.* 2006;295:2003-2017.
70. Anton R. Naltrexone for the management of alcohol dependence. *The New England Journal of Medicine.* 2010;359:715-721.
71. Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. *Annals of the New York Academy of Sciences.* 2011;1216:144-166.
72. Starosta AN, Leeman RF, Volpicelli JR. The BRENDA model: Integrating psychosocial treatment and pharmacotherapy for the treatment of alcohol use disorders. *Journal of Psychiatric Practice.* 2006;12:80-89.
73. Pettinati HM, Weiss RD, Miller WR, Donovan DM, Ernst DB, Rounsaville BJ. COMBINE Monograph Series, Volume 2. Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of a Treatment for Alcohol Dependence. DHHS Publication No. (NIH) 04-5289. Bethesda, MD: NIAAA; 2004.
74. The McKinney-Vento Homeless Assistance Act. 42 USC Section 11302, (2009).
75. Piliavin I, Entner Wright BR, Mare RD, Westerfelt AH. Exits from and returns to homelessness. *Social Service Review.* 1996;70:33-57.
76. Dworsky AL, Piliavin I. Homeless Spell Exits and Returns: Substantive and methodological elaborations on recent studies. *The Social Service Review.* 2000;74(2):193-213.
77. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured clinical interview for DSM-IV-TR Axis I disorders, Research version, Patient edition (SCID-I/P)*. New York: Biometrics Research, New York State Psychiatric Institute; 2002.
78. Humphreys K, Weisner C. Use of exclusion criteria in selecting research subjects and its effect on generalizability of alcohol treatment outcome studies. *The American Journal of Psychiatry.* 2000;157:588-594.
79. Collins SE, Clifasefi SL, Andrasik MP, et al. Exploring the transition from homelessness to Housing First: Qualitative evaluation and practice implications. *Journal of Health Care for the Poor and Underserved.* 2012;23:1678-1697.
80. Jeste DV, Palmer BW, Appelbaum PS, et al. A new brief instrument for assessing decisional capacity for clinical research. *Archives of General Psychiatry.* 2007;64:966-974.
81. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. *The Alcohol Use Disorders Identification Test: Guidelines for use in primary care.* 2nd ed. Geneva, Switzerland: World Health Organization; 1991.
82. Bush K, Kivlahan DR, McDonnell MB, Fihn SD, Bradley KA, (ACQUIP) ftACQIP. The AUDIT alcohol consumption questions (AUDIT-C). *Archives of Internal Medicine.* 1998;158:1789-1795.
83. Dawson DA, Smith SM, Saha TD, Rubinsky AD, Grant BF. Comparative performance of the AUDIT-C in screening for DSM-IV and DSM-V alcohol use disorders. *Drug and Alcohol Dependence.* 2013;126:384-388.
84. Reinert DF, Allen JP. The Alcohol Use Disorders Identification Test: An update of research findings. *Alcoholism: Clinical and Experimental Research.* 2007;31:185-199.
85. Beck AT. *Beck Scale for Suicide Ideation*. San Antonio, TX: Pearson; 1991.

86. Nock MK, Holmberg EB, Photos VIM, B D. Self-injurious thoughts and behaviors interview: Development, reliability, and validity in an adolescent sample. *Psychological Assessment.* 2007;19:309-317.
87. Israel Y, Hollander O, Sanchez-Craig M, et al. Screening for problem drinking and counseling by the primary care physician-nurse team. *Alcoholism: Clinical and Experimental Research.* 1996;20:1443-1450.
88. Sobell LC, Sobell MB. Timeline followback: A technique for assessing self-reported ethanol consumption. In: Allen J, Litten RZ, eds. *Measuring Alcohol Consumption: Psychosocial and Biological Methods*. Totowa, NJ: Humana Press; 1992:41-72.
89. Tsemberis S, McHugo G, Williams V, Hanrahan P, Stefancic A. Measuring homelessness and residential stability: The residential time-line follow-back inventory. *Journal of community psychology.* 2007;35(1):29.
90. Maisto SA, Krenek M, Chung T, Martin CS, Clark D, Cornelius J. A comparison of the concurrent and predictive validity of three measurs of readiness to change alcohol use in a clinical sample of adolescents. *Psychological Assessment.* in press.
91. Heather N, Smailes D, Cassidy P. Development of a readiness ruler for use with alcohol brief interventions. *Drug and Alcohol Dependence.* 2008;98:235-240.
92. Miller WR, Rollnick S. Chapter 10: When goals differ. *Motivational interviewing: Helping people change (3rd edition)*. Second ed. New York: US Guilford Press; 2012.
93. McLellan AT, Kushner H, Metzger D, Peters R. The fifth edition of the Addiction Severity Index. *Journal of Substance Abuse Treatment.* 1992;9:199-213.
94. Miller W, Tonigan J, Longabaugh R. The Drinker Inventory of Consequences (DrInC): An instrument for assessing adverse consequences of alcohol abuse. *Test manual (Vol. 4, Project MATCH Monograph Series)*. Rockville: National Institute on Alcohol Abuse and Alcoholism; 1995.
95. Flannery BA, Volpicelli JR, Pettinati HM. Psychometric properties of the Penn Alcohol Craving Scale. *Alcoholism: Clinical and Experimental Research.* 1999;23:1289-1295.
96. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey – Construction of scales and preliminary tests of reliability and validity. *Medical Care.* 1996;34:220-233.
97. Miller WR, Moyers T, Arciniega L, Ernst DB, Forcehimes A. Training, supervision and quality monitoring of the COMBINE Study behavioral interventions. *Journal of Studies on Alcohol.* 2005;s15:188-195.
98. Wurst FM, Skipper GE, Weinmann W. Ethyl glucuronide - the direct ethanol metabolite on the threshold from science to routine use. *Addiction.* 2003;98(suppl. 2):51-61.
99. Appenzeller BM, Agirman R, Neuberg P, Yegles M, Wennig R. Segmental determination of ethyl glucuronide in hair: A pilot study. *Forensic Science International.* 2007;20:87-92.
100. Jones M, Jones J, Lewis D, et al. Correlation of the alcohol biomarker ethyl glucuronide in fingernails and hair to reported alcohol consumed. *Alcoholism: Clinical and Experimental Research.* 2011;35(s1):16a.
101. Moyers TB, Martin T, Christopher PJ, Houck JM, Tonigan JS, Amrhein PC. Client language as a mediator of motivational interviewing efficacy: Where is the evidence? *Alcoholism: Clinical and Experimental Research.* 2007;31:40S-47S.
102. Moyers TB, Martin T. Associations between client and therapist behaviors: Partial validation of the motivational interviewing approach. 2003; http://casaa.unm.edu/crbposters/Associations%20between%20client%20and%20therapist%20behaviors.pdf. Accessed September 9, 2003.
103. Miller WR, Benefield RG, Tonigan JS. Enhancing motivation for change in problem drinking - A controlled comparison of 2 therapist styles. *Journal of Consulting & Clinical Psychology.* 1993;61:455-461.
104. Wain RM, Wilbourne PL, Harris KW, et al. Motivational interview improves treatment entry in homeless veterans. *Drug and Alcohol Dependence.* 2011;115:113-119.
105. Dimeff LA, Baer JS, Kivlahan DR, Marlatt GA. *Brief alcohol screening and intervention for college students (BASICS): A harm reduction approach*. New York: Guilford Press; 1999.
106. Muthén LK, Muthén BO. *Mplus User's Guide. Fifth Edition*. Los Angeles, CA: Muthén & Muthén; 2007.
107. Muthén LK, Muthén B. How to use a Monte Carlo study to decide on sample size and determine power. *Structural Equation Modeling.* 2002;4:599-620.
108. Sturm R, Unützer J, Katon W. Effectiveness research and implications for study design: Sample size and statistical power. *General Hospital Psychiatry.* 1999;21:274-283.

109. Muthen BO. Beyond SEM: General latent variable modeling. *Behaviormetrika.* 2002;29:81-117.
110. Raudenbush SW, Bryk AS. *Hierarchical linear models: Applications and data analysis*. Thousand Oaks, CA: Sage Publications, Inc.; 2002.
111. Babor TF, Stephens RS, Marlatt GA. Verbal report methods in clinical research on alcoholism: Response bias and its minimization. *Journal of Studies on Alcohol.* 1987;48:410-424.
112. Carey KB. Clinically useful assessments: Substance use and comorbid psychiatric disorders. *Behaviour Research and Therapy.* 2002;40:1345-1361.
113. Carey KB, Purnine DM, Maisto SA, Carey MP. Assessing readiness to change substance abuse: A critical review of instruments. *Clinical Psychology: Science and Practice.* 1999;6:245-266.
114. Cheong J, MacKinnon DP, Khoo ST. Investigation of mediational processes using parallel process latent growth curve modeling. *Structural Equation Modeling.* 2003;10:238.
115. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test the significance of the mediated effect. *Psychological Methods.* 2002;7:83-104.
116. Kushel MB, Perry S, Bangsberg D, Clark R. Emergency department use among the homeless and marginally housed: Results from a community-based study. *American Journal of Public Health.* 2002;92:778-784.
117. Dunford JV, Castillo EM, Chan TC, Vilke GM, Jenson P, Lindsay SP. Impact of the San Diego Serial Inebriate Program on use of emergency medical resources. *Annals of Emergency Medicine.* 2006;47:328-336.