

2. Chapter 2: Eligibility

2.1 Overview of Approach and Goals

The goal is to randomize 1375 participants over 18 years of age who meet DSM-IV criteria for alcohol dependence and are abstinent for a minimum of 4 and a maximum of 21 days prior to randomization. An upper age limit is not specified because there is no pharmacological rationale for excluding healthy older adults, extensive safety and post-marketing surveillance data are available with no indication for concern, and there is a need to treat this subgroup.

Potential participants must meet eligibility criteria to enroll into this study (see section 2.2). Participants are screened to ascertain whether they meet inclusion criteria and they undergo assessments performed by a research assistant. A medical history is obtained and a physical examination is performed. Blood is also drawn for laboratory testing.

2.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are summarized below.

2.2.1 Inclusion Criteria

People will be eligible to enroll if they meet all of the following criteria. If even one of the inclusion criteria is not met, then the prospective participant is not eligible.

2.2.1.1 Males and Females \geq 18 years of age

Potential participants must be at least 18 years old for inclusion. However, there is no upper limit on age. There of course may exist practical barriers for participants of advanced age with regard to mobility, and cognitive functioning that could serve to exclude someone.

2.2.1.2 Meet DSM-IV Dependence diagnostic criteria

Potential participants will be given the SCID Module E and must meet established DSM-IV diagnostic criteria for alcohol dependency.

2.2.1.3 Minimum Drinking Level

Potential participants must have had a minimum drinking level of an average of \geq 14 drinks per week (females) or \geq 21 drinks per week (males) over a consecutive 30-day period during the last 90 days prior to the initiation of abstinence. In addition, 2 or more days heavy drinking must have occurred during the last 90 days (4 drinks/day for females, and 5 drinks/day males).

2.2.1.4 CIWA-Ar $<$ 8

Potential participants must score less than 8 on the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) at the time of randomization.

2.2.1.5 Abstinance

Potential participants must have been abstinent between 4 and 21 days prior to randomization. If a participant is screened at 5 days of abstinence, there are 16 days remaining to begin him or her on the protocol.

- To help people achieve 4 consecutive days of abstinence (96 hours), Project Coordinators are advised to consult with their Principle Investigator and other PCs who have experience with studies of this nature. Some strategic recommendations involve:
 1. Spacing out assessments (over 2-3 days)
 2. Calling people at home in order to provide support
- If a potential participant consumes non-alcoholic beer during the 4-day abstinence period, he or she can be randomized.
- Abstinent days in a detoxification setting can count towards the 4 days of abstinence.
- Participants are allowed two attempts to meet the 4-day abstinence requirement. Two successive failures disqualify the person for 30 days from the last randomization attempt. After a 30-day wait, the site investigator can attempt to re-screen the patient for another attempt at inclusion if they wish. In any 30-day period, the site investigator is free to decide when a patient appears ready to successfully meet 4 days of abstinence before the randomization target date is set.
- Randomization post-detoxification would be acceptable even after two prior failed attempts at abstinence.

2.2.1.6 No planned absences

Potential participants must not plan to be absent for more than 21 consecutive days during the 16-week treatment period.

2.2.1.7 Literacy

Potential participants must be literate in the English language, and be able to understand and complete rating scales and questionnaires accurately. The Slossen reading test will be administered when reading ability and/or comprehension is questionable, to indicate when a participant needs to have assistance with a measure.

2.2.1.8 Written Informed Consent

Informed consent must be obtained from each eligible participant, and the document signed prior to the participant being eligible for randomization into the study. The consent form outlines the nature of the study, description of the medication, behavioral therapies, duration, procedures, risks and discomforts, benefits, alternatives, compensation and confidentiality. Each site must comply with local IRB guidelines in this regard under the aegis of the federal OHSR guidelines for clinical research with human participants. There are specific guidelines for the informed consent procedure in Chapter 4 and an Informed Consent Checklist is located in Appendix B.

2.2.1.9 Locator for Participant

The potential participant must be able to identify at least one "locator" person to assist in tracking the participant for follow-up assessment.

If a prospective participant has no fixed domicile and/or is not available via phone or beeper adherence and retention could be affected.

2.2.2 Exclusion Criteria

Potential participants will not be enrolled if they meet any of the following criteria:

2.2.2.1 Meets DSM-IV criteria for Axis I Disorder

Potential participant meets current DSM-IV criteria for a major Axis I disorder and is in need of, or currently undergoing, pharmacotherapy. Examples of disorders that would rule out a participant include: bipolar disorder, schizophrenia, bulimia/anorexia, dementia, or other DSM-IV Axis I disorder for which medications are normally prescribed (even if they are not currently taking the medication). Table 4.1 is a diagnostic grid, which outlines Axis I categories that need to be assessed.

2.2.2.2 Concomitant Drug Therapy

Participants requiring concomitant therapy with medications outlined on the disallowed concomitant medication list (Appendix C). If a urine screen is positive for disallowed substances, Quintiles will do a confirmatory test. After the second positive urine drug screen, Quintiles will consider that person ineligible. Prior to collecting and sending a second sample, staff should insure that enough time has elapsed for the disallowed medication to wash out of the candidates system.

- If a potential participant is currently taking SSRIs but is willing to discontinue the medication, there is a 7-day wash out period before s/he is eligible to begin taking study medication. The prospective participant's physician should be contacted in order to inquire about whether the medication is needed.
- If a potential participant is taking herbal supplements that fall under the antidepressant category (i.e., St. John's Wart), but is willing to discontinue use of the supplement, there is a 7-day wash out period before s/he is eligible to begin taking study medication.
- If a potential participant is taking Prozac but is willing to discontinue the medication, there is a 14-day wash out period before s/he is eligible to begin taking study medication. The prospective participant's physician should be contacted in order to inquire about whether the medication is needed.
- Potential participants taking herbal supplements not listed on the concomitant medication list (Appendix C) should be advised that the interaction with study medication is unknown but they will not be excluded.

Note: If the physician or PI has a question about whether a concomitant medication is allowed, the name of the medication should be forwarded to the Coordinating Center.

2.2.2.3 Meets DSM-IV Criteria for Dependence on other Substance(s)

Currently meets DSM-IV criteria for dependence on substances other than alcohol, cannabis, caffeine or nicotine. If not currently dependent but a positive urine screen is obtained for a disallowed substance, the urine screen may be repeated (must be negative for study inclusion). In cases where a urine screen is negative prior to detoxification, but tests positive post-detoxification for benzodiazepines, that urine test result should not exclude the participant from study participation.

- Note the exception to the latter rule is the use of benzodiazepines or other similar agents during medicated detoxification at the time of alcohol withdrawal. If a negative urine drug screen is obtained prior to the detoxification, the person is eligible. However, if the site is unable to obtain a negative urine drug screen prior to detoxification, a clean urine test must be documented after detoxification.
- If you do not have access to negative pre-detoxification urine screen, re-test needs to occur 5-7 days after detoxification to allow sufficient time for benzodiazepines to clear. If you do not wait 5-7 days and the second test is positive, Quintiles will consider the person ineligible and further tests will need to occur on site.

2.2.2.4 Opiate Dependence

Opiate dependence DSM-IV diagnosis, or abuse within the past 6 months, chronic treatment with any narcotic-containing medications during the previous month, or urine positive for opioids.

2.2.2.5 Significant Medical Disorders

Significant medical disorders that will increase potential risk of study treatment, or interfere with study participation (i.e., cancer, AIDs). Sensitivity to drug as evidenced by adverse drug experiences especially with narcotic-containing analgesics, opioid antagonists, or acamprosate is an important potential exclusion criterion.

2.2.2.6 Liver Function Tests More Than 3X ULN

Liver function tests more than 3X ULN or elevated bilirubin (>10% above ULN); tests may be repeated if initial results are out of range. The upper limit of normal for GGT is not itself relevant in the context of screening as an exclusion criteria. Instead, GGT levels and liver function should be evaluated in the light of ALT and AST, or bilirubin.

2.2.2.7 Pregnant or Breast Feeding Women

Female participants who are pregnant or nursing infant(s), and women of child bearing potential not using a contraceptive method judged by the investigator to be effective (i.e., oral contraceptives, hormonal (levonorgestrel) or surgical implants, or barrier plus spermicide).

2.2.2.8 Intent to Engage in Additional Treatment

Participants who intend to engage in additional formal treatment for alcohol-related problem, or who intend to continue in current treatment for alcohol related problems during the active treatment period. Self-help treatments are not considered formal treatment.

2.2.2.9 Inpatient Treatment prior to screening

More than 7 days of inpatient treatment (excluding detoxification) within the 30 days prior to screening for substance use disorders.

2.2.2.10 Prior Study Drug Use

Treatment within the 30 days prior to screening with an investigational drug or medications which may influence drinking outcome [i.e., naltrexone (ReVia) or other psychotropic agents] excludes the person screened from participation.

Potential participants who stopped using disulfiram (Antabuse) in order to participate in the study, will need to go through a 7-day washout period before they are eligible.

2.3 Other Eligibility Guidelines

2.3.1 Reporting Progress

Some participants may request that staff report on their progress to an outside agency (i.e., parole officer, court, etc.). If this situation presents itself, staff may report on attendance but not progress and value statements should be avoided (i.e., participant completed the study successfully). A sample form is located in Appendix B and should be used to communicate this information.

2.3.2 Probation

People on probation are eligible for study participation but if the person becomes incarcerated after randomization, s/he will be considered lost to follow-up until they are released.

2.3.3 Pilot Study Participants

Pilot 3 participants are not eligible for main trial participation. Pilot 1 participants are eligible for main trial participation.

Any question concerning the interpretation of or application of the inclusion/exclusion criteria will be referred to the medical expert at the Coordinating Center. If he is unavailable, the question will be referred to the Chairperson of the Treatment Committee.

Note: Although the Coordinating Center or Sponsor can approve a candidate for randomization even if exclusion criteria are met, this is still considered a protocol violation and should be documented as such. Document, on the Protocol Violation/Deviation Log, the exclusion criteria met and the person(s) who authorized the site to proceed with the randomization process. This log should be kept in the Investigator's Binder as the Lipha Monitor will review this.