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I. Summary of changes to the statistical analysis plan

The original statistical analysis plan is described in the original protocol below beginning on page 20.

In the original statistical analysis plan the stratification factor sex was omitted unintentionally from the primary model specification for the main outcome (percent heavy drinking days, PHDD) although sex was identified as a potential moderator in an exploratory aim. At the analysis stage, we included both stratification factors (site and sex) and their interactions with treatment in the model for PHDD consistent with prior hypothesis that men and women differ in their smoking and drinking behavior and treatment response, and with good statistical practice.

Baseline percent heavy drinking days was specified as a covariate in the original analysis plan but in response to comments by the statistical reviewer was dropped as a covariate and included in the final mixed model analyses reported in the paper. In order to make the baseline and end-point measures comparable, baseline percent heavy drinking days and end-point percent heavy drinking days were both summarized over 8 week periods. This 8-week duration was pre-planned for the end-point measure but modified from the original intention to use 30 days of the baseline period. Unstructured variance-covariance matrix was used for the errors since variances at baseline and end-point were different.

Logistic regression was planned for the abstinence from smoking outcome. However, due to zero abstinence frequency on placebo, we were not able to perform logistic regression analysis and Fisher's exact test was used instead.

Following the recommendations of the statistical review, statistical testing is reported only for the main drinking outcome (percent heavy drinking days, PHDD) and for the main smoking outcome (abstinence from smoking, PA). Effect sizes are calculated for both primary and secondary outcomes.

II. Summary of Changes in the Protocol

Amendments to the protocol	Approval Date
Changed the hosting location for the web screener and instructions to participants about how to contact us if they are interested in participating; updated advertising materials.	December 21, 2012
Changed inclusion criterion for biochemical validation of smoking from >10 ppm to either a CO reading of ≥ 6 ppm OR a plasma cotinine level of ≥ 40 ng/ml. The prior cut-off (>10 ppm) was higher than would be expected by someone meeting the entrance criterion of 5 cigarettes per day. Also, carbon monoxide readings are influenced strongly by time since the last cigarette. With clean air laws, many people do much of their smoking in the evening, yet they are seen for appointments in the daytime. Plasma cotinine provides additional information about overall tobacco exposure.	
Corrected "weight" to "waist" circumference and other typographical errors. Specified medical provider or physician in two places.	
Corrected assessments to indicate that concurrent medications will be	

<p>monitored at baseline, during treatment and at follow-up. Corrected Table 1 listing of the weeks at which the Implicit measures of alcohol craving were obtained (week 4 changed to week 5)</p> <p>Added repeat assessments of the Attitudes and Beliefs about Chantix and the Medication Adherence Questionnaire to Week 5 and EOT.</p>	
<p>Obtained approval to audio-tape treatment sessions for analysis and quality assurance.</p>	<p>March 6, 2013</p>
<p>Updated advertising methods</p>	<p>April 5, 2013</p>
<p>Due to slow recruitment, broadened the inclusion criteria from daily smoking (5 cigarettes per day for ≥ 6 months and have a CO level of ≥ 6 or a plasma cotinine level of 40 ng/mL) to include nondaily smokers who report smoking 100 cigarettes or more in their lifetime and currently smoke at least twice per week on average for the prior 90 days and have a urinary cotinine of ≥ 30 ng/mL by semi-quantitative urinalysis or equivalent plasma cotinine level (≥ 6 ng/mL). This definition is consistent with the CDC's definition of a smoker as someone who reports smoking 100 cigarettes or more in their lifetime and currently smoke some days. In 2010, the CDC reported that 21.8% of smokers were nondaily smokers. Nondaily smokers also have the highest rates of alcohol dependence (Harrison et al., <i>Alcoholism Clinical and Experimental Research</i>, 32:2081-2087, 2008).</p> <p>Because the cut-off on cotinine was lowered for purposes of selecting smokers, the cut-off on cotinine to document abstinence from smoking in the secondary aim was reduced to a plasma level less than 6 ng/mL.</p> <p>Changed exclusion criteria to define allergic reactions to varenicline; to allow occasional use of prescription sleep aids that the participant is willing to discontinue; to allow those who meet criteria for marijuana dependence to participate; and to increase the allowable upper limit on BMI from 38 to 39.99.</p> <p>Added urine cotinine at screening; corrected test of the secondary aim which incorrectly listed the MADRAS instead of the HADS, made other corrections to the protocol (e.g., positive drug screen was incorrectly listed as exclusionary in the description of screening procedures) and added new recruitment materials.</p> <p>Added information about use of the OnCore system, Yale's clinical trials management system.</p> <p>Added information about limits to confidentiality involving medical emergencies.</p>	<p>May 8, 2013</p>
<p>Removed the Rapid Visual Processing task and added the Five Facet Mindfulness Questionnaire at intake and end of treatment; added recruitment</p>	<p>June 12, 2013</p>

via the emergency department.	
Added \$20 subject payment for unscheduled study appointments for study related procedures; added recruitment through the Yale Clinical Investigation Recruitment Team.	December 11, 2013
Added recruitment through referrals from other studies.	February 6, 2013
Added transportation for extenuating circumstances, updated web screener instructions.	March 19, 2014
Updated study physician and personnel obtaining informed consent	June 23, 2014
Expanded recruitment methods to include the YCCI volunteer registry; updated procedures for making referrals from other studies.	October 23, 2014
Updated protocol and consent to address the updated label to varenicline (Chantix) which includes new warnings about the rare risk of seizures and reduced alcohol tolerance ((FDA, 3-9-15, http://www.fda.gov/Drugs/DrugSafety/ucm436494.htm). Exclusion criteria were revised to exclude those with a history of seizures or who are taking medications known to reduce the seizure threshold. We had already excluded individuals with a history of seizures related to alcohol withdrawal and individuals taking psychotropic medications, many of which reduce the seizure threshold.	April 8, 2015
Due to expiration date of study medications, the 2-week downward titration for subjects enrolled as of 4/22/15 was dropped.	June 21, 2015

III. Original Protocol at Trial Initiation (Yale Site)

Title of Research Project: ½ Multi-Site Study: Varenicline Treatment of Alcohol Dependent Smokers

Principal Investigator: Stephanie O'Malley, Ph.D.

Date: 9/11/12

Probable Duration of Project: We anticipate that this project will take approximately 5 years to complete from initiation to publication.

Targeted Enrollment: The targeted enrollment for this protocol is 160 participants; 80 participants will be recruited at Yale University and 80 will be recruited at Columbia University. We will also recruit 3 pilot subjects at Yale University. The data from these subjects will not be included in our statistical analyses.

Research Plan

1. Statement of Purpose:

The proposed project is a 16-week randomized, double-blind, placebo controlled Phase II trial of varenicline titrated to 2 mg for the treatment of alcohol drinking using a sample of 160 alcohol dependent daily smokers. We will pilot our procedures with 3 participants; they will not be randomized and will receive active varenicline titrated to 2 mg daily.

Primary Aim: To evaluate the effect of varenicline 2mg daily compared to placebo on alcohol drinking in alcohol dependent daily smokers. Our primary hypothesis is that varenicline will significantly reduce the percentage of heavy drinking days during the last 8 weeks of the 16-week treatment period. Other secondary outcomes (e.g., drinking related consequences, proportions of “responders”, biological confirmation of drinking self-reports using urine ethyl glucuronide analysis) will be examined to support the primary efficacy analyses.

Secondary Aim 1: To evaluate the effects of varenicline compared to placebo on smoking among alcohol dependent daily smokers who are not seeking treatment for smoking cessation. We hypothesize that varenicline will increase the proportion of individuals who are abstinent from smoking in the last month of the study, based on self-report and biochemical confirmation.

Secondary Aim 2: To test the hypothesis that varenicline will reduce craving for alcohol and for tobacco and the ability of cues to motivate drinking. Craving will be measured using explicit (i.e., Obsessive Compulsive Drinking Scale; Tiffany Cigarette Craving Measure) and implicit measures (e.g., the Approach Avoidance Task).

Secondary Aim 3: To compare the safety and tolerability of varenicline compared to placebo in alcohol dependent daily smokers.

Secondary Aim 4: To evaluate maintenance of improvement during post-treatment follow-up.

Exploratory Aim: To examine moderators and mediators of response to varenicline.

2. Background:

Alcohol dependence continues to be a major health problem, and individuals with alcohol dependence have high rates of cigarette smoking that further compromises their health. Although there are now three FDA approved treatments for alcohol dependence (acamprosate, naltrexone and disulfiram), their effects are small to moderate. Moreover, individuals who are daily smokers continue to have poorer alcoholism treatment outcomes even when provided these treatments. The development of effective pharmacotherapies for this high-risk group of alcohol dependent smokers could substantially advance the treatment of alcoholism. Finally, treatments that benefit drinking and smoking concurrently will be of particular value given the synergistic adverse effects of heavy alcohol drinking and tobacco use on health.

An estimated 45% of alcohol dependent individuals smoke cigarettes[1] compared with 21% of the general population[2]. Cigarette smoking when combined with heavy drinking represents a significant health burden including increased risk of liver, head, and neck cancers, liver cirrhosis, and pancreatitis,[3-6] and abnormalities in brain structure and function[7]. Alcohol dependent smokers have poorer alcohol and smoking treatment outcomes. Smoking and higher nicotine dependence levels at the start of alcohol treatment are associated with greater alcohol urge, an increased likelihood of relapsing to drinking, and a greater number of drinks consumed among relapsers post-treatment[8, 9]. Among individuals who have achieved long-term drinking abstinence, continued cigarette smoking is a predictor of alcohol relapse[10]. By the same token, alcohol dependent smokers are less likely to initiate a smoking quit attempt[11, 12] and achieve both short and long-term smoking abstinence when they quit smoking[13-15]. Thus, a pharmacotherapy that could reduce heavy drinking in this high risk group of smokers and result in reductions or cessation of smoking would be invaluable.

Nicotinic acetylcholine receptors are known to play a role in the rewarding effects of both nicotine and alcohol[16-18] and this system has been suggested as a pharmaceutical target for alcohol use disorders[19-21]. Varenicline, a partial agonist of $\alpha 4\beta 2$ nAChRs [22-24], was approved as a smoking cessation aid. Varenicline results in smoking abstinence rates as high as 50%, significantly better than bupropion or placebo[25-27]. Varenicline may also yield better smoking outcomes than NRT[28]. In a trial of varenicline versus nicotine transdermal patch, smokers who received varenicline had higher rates of continuous smoking abstinence and lower rates of craving, withdrawal, and smoking satisfaction than smokers who received the patch[29]. Among smokers, varenicline has the advantage of being a partial agonist of nAChRs that raises brain dopamine levels thereby reducing effects of withdrawal while simultaneously attenuating reinforcement from smoking. This is in contrast to mecamylamine, an antagonist of nicotinic acetylcholine receptors, that attenuates reinforcement but can result in compensatory smoking [30, 31], an effect that limits its utility for treating alcohol dependent smokers not seeking to quit smoking.

Preclinical findings and recent preliminary studies in heavy drinking smokers also suggest that it may be useful as a treatment for alcoholism as well. In a rodent model Streensland et al [32] demonstrated that acute and chronic varenicline administration selectively reduced alcohol seeking and consumption in rats but had no effect on sucrose or water reward and these effects remained after varenicline was no longer administered. Using C57BL/6J mice, Kamens et al [33] demonstrated that varenicline dose dependently reduced ethanol consumption. This effect also occurred in $\alpha 4\beta 2$ KO and $\alpha 7$ KO mice suggesting that receptors containing these subunits are not solely required for varenicline's effects on drinking. Varenicline is also a low potency agonist at $\alpha 3\beta 4$ nAChRs [34]. Others have shown that blocking this receptor subtype can reduce ethanol consumption in rodent models [35, 36]. In heavy drinking smokers, McKee [37] demonstrated that 1-week exposure to varenicline resulted in a greater

reduction in alcohol consumption and craving in a laboratory self-administration paradigm[38, 39], compared to placebo in heavy drinking smokers. Subsequently, we confirmed these findings among 30 heavy drinking smokers with current or past alcohol dependence treated with either placebo or varenicline for three weeks prior to making a smoking cessation attempt,[40]

Varenicline effects on dopamine response to nicotine or alcohol may be a mechanism for reductions in drinking. For example, Ericson et al [41] demonstrated that varenicline modulates the effects of ethanol on dopamine release. Varenicline administered acutely reduced dopamine levels in response to ethanol and semi-chronic pretreatment with varenicline abolished the additive effect of co-administration of nicotine and ethanol on accumbal dopamine levels. These data suggest that varenicline may attenuate the reinforcing properties of alcohol consumption among alcohol dependent smokers. Consistent with this hypothesis, subjects on varenicline report higher ratings of sedation [40] and lower positive effects of alcohol [37]. Reductions in the reinforcing properties of alcohol prior to becoming abstinent could help extinguish or weaken the associations between cues and alcohol drinking, resulting in reductions in cue-elicited urges. Among smokers, varenicline has been shown to blunt smoking cue elicited neural and tobacco craving responses [42]. Based on the substantial cross-reactivity between tobacco and alcohol cues [43-45] we predict that varenicline will also reduce alcohol craving in response to alcohol and smoking cues.

In the alcohol field, many clinical trials including COMBINE require abstinence prior to beginning the study and then monitor return to drinking as the outcome. Even if pretreatment abstinence is not required, protocols and clinics typically emphasize efforts to change from the start. A noteworthy exception is that of Johnson and colleagues who pioneered an approach in which actively drinking participants began topiramate and received brief counseling emphasizing adherence to the medication in order to promote gradual improvements in drinking[46, 47]. Using this model, topiramate led to significant improvements compared to placebo by the end of treatment although the percentage of individuals abstaining was relatively low. A next iteration of this model could combine a period of pretreatment emphasizing adherence followed by a period where more active efforts to change drinking are emphasized.

Smoking cessation programs typically prepare patients to quit smoking on a future “quit-date”. In addition, smoking cessation medications, such as bupropion and varenicline[25-27, 29], are initiated 1-2 weeks prior to the quit-date so that patients are on steady state level of the medication when abstinence is initiated. This pretreatment period may also promote smoking cessation success by reducing smoking reinforcement and dependence on smoked nicotine during the pretreatment period [48]. Systematic placebo-controlled investigations testing pretreatment with nicotine replacement prior to subjects actively trying to quit smoking support the value of this approach [48-51]. The possibility that varenicline may also improve quit rates through an extinction mechanism derives from the observation that 1-week point prevalence abstinence from smoking continues to increase over the first four weeks following the quit-date compared to placebo [26]. Consistent with this hypothesis, laboratory studies find that varenicline attenuates the rewarding effects of cigarettes and nicotine, potentially through its antagonist effects [52, 53]. In animal models, varenicline abolishes dopamine release to combined ethanol and nicotine [41], while other studies indicate that nicotine antagonists can reverse nicotine enhancement of conditioned reinforcement of alcohol associated cues [54].

Inclusion of an initial treatment phase emphasizing medication adherence prior to treatment emphasizing efforts to change drinking could help patients be more successful if the medication reduces alcohol reinforcement and the strength of conditioned cues. From a methodological

perspective, this initial phase also permits us to evaluate the effects of varenicline on the subjective effects of alcohol and cigarettes, changes in craving using explicit and implicit measures, and changes in drinking and smoking. This information will advance our knowledge of mechanisms of action for varenicline.

SUMMARY: Building upon knowledge about the role of nicotinic acetylcholine receptors in alcohol drinking and smoking, varenicline, a new pharmacological agent targeting these receptors, represents an exciting opportunity to intervene with alcohol dependent smokers. Integrating methods from the smoking cessation and alcoholism pharmacotherapy literatures, we hope to provide a strong test of the efficacy of varenicline for alcohol dependent smokers seeking alcoholism treatment while promoting smoking cessation as an additional benefit.

3. Research Plan Overview:

The proposed project is a 16-week randomized, double-blind, placebo controlled Phase II trial of varenicline titrated to 2 mg for the treatment of alcohol drinking using a sample of 160 alcohol dependent daily smokers. The first is a four-week treatment period in which participants receive medication but are not asked to change their drinking. Medication adherence and safety monitoring are addressed in brief weekly appointments. Using an adaptation of the Medication Manual from COMBINE, therapists then meet with participants for 12 weeks and monitor drinking, adherence and provide simple advice to address drinking and encourage support group attendance. Following termination of treatment at the week 17 appointment (end of week 16), (followed by a 2-week downward titration of study medications), there are three follow-up interviews at weeks 26, 39 and 52 from randomization.

The study will be conducted at two sites: Yale University and Columbia University. Both PIs sites will work closely together in monitoring the clinical care of participants. All of the activities will be coordinated via local weekly staff meetings, teleconference calls between PIs and site teams at the 2 sites, regular site visits and a study website.

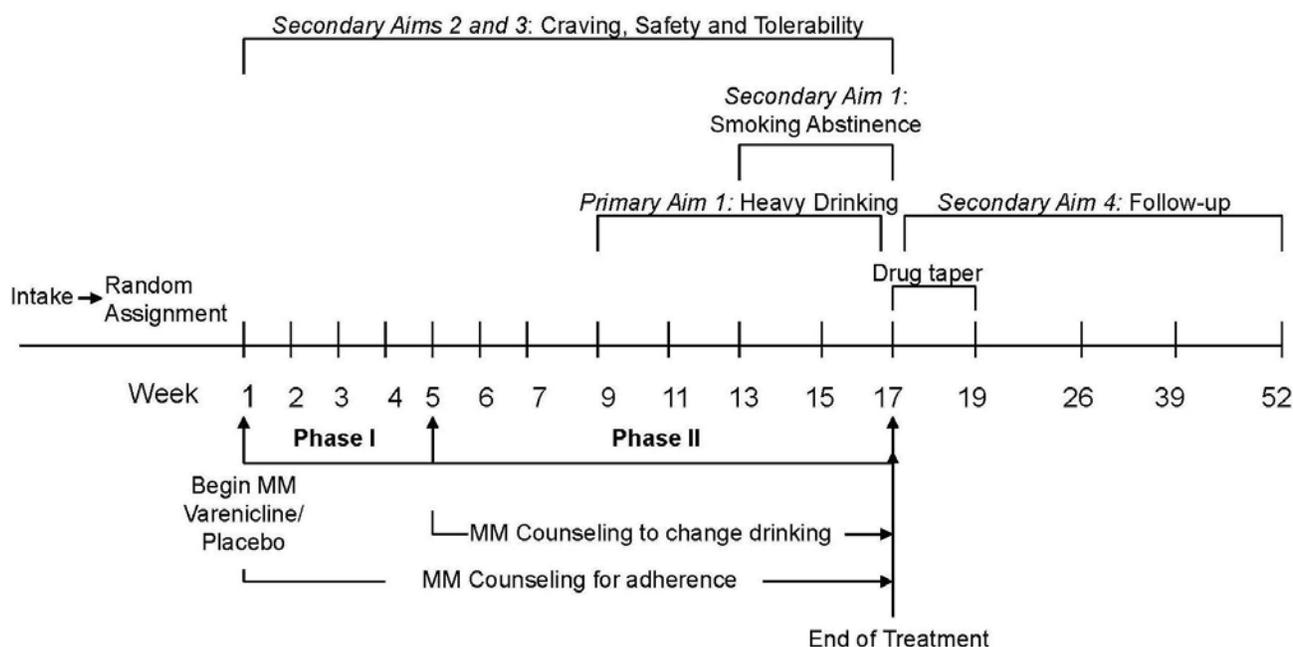
Unique to Columbia: Parallax Center is the performance site for Columbia University; all human subject research will be performed at Parallax Center. Parallax is a for-profit; New York State licensed outpatient mental health and substance abuse treatment and research facility that has served New York City and surrounding community for the past 25 years. Parallax Center has a long-standing commitment to the integration of pharmacotherapy in their behavioral treatment programs. The Columbia site will be responsible for overseeing recruitment and retention and the behavioral intervention at both at Parallax and the Yale sites. The Columbia PI will conduct the training and monitoring of the behavioral intervention and develop and implement procedures for monitoring recruitment, enrollment and the retention of participants.

Unique to Yale: The study will be conducted at Dr. O'Malley's research clinic adjacent to the Substance Abuse Treatment Unit of the Connecticut Mental Health Center at Yale. The Yale site will coordinate with pharmacy in handling medications and medication supplies and conduct assays of cotinine and ethyl glucuronide (EtG). Data management will be centralized at the Yale site. The Yale PI will be responsible for the development of the study manual of operations and monitoring eligibility and data collection procedures for purposes of quality assurance. With Dr. Petrakis, she will monitor medication related issues to ensure both sites meet regulatory and study requirements.

A. Procedures:

A detailed flow-chart of all study procedures is provided in Figure 1 below.

Figure 1: Single Subject Time-Line



i. Screening:

Participants will be recruited through advertisements, press releases, posters/flyers, scratch pads, emails and mailings to physicians and clinicians, fax referral forms from physicians and clinicians, and through websites (e.g., www.google.com,) (see Appendix A). Prospective participants will be screened either by phone or via an online screener, the link for which will be provided on the study website (http://medicine.yale.edu/psychiatry/research/programs/clinical_people/smoking.aspx).

The online screener will be hosted by the Survey Monkey service and data collected will be stored on Survey Monkey's secure servers. After indicating consent, participants will advance to the survey itself. No questions on the survey require participants to provide personally identifiable information. After completing the survey responses, participants will be asked to select a code word that is personally meaningful to them but that includes no personally identifiable information. Participants are then asked to send a message to the study's Yale email address that includes this code word. This will alert study staff that a web screener has been completed. Staff will check individuals' survey responses on survey monkey and evaluate these responses in light of the inclusion and exclusion criteria. Staff will then notify individuals as to their preliminary eligibility status. No email addresses or any other personally identifiable information will be stored on survey monkey.

The link for the online survey that will be provided on the study web-site, is used solely for screening purposes. We refer to this survey as the "Revised Preliminary Web Screener" (see Appendix for a copy of the consent and survey itself). After providing consent, participants will proceed to complete the survey itself. The survey contains items concerning where they heard about the study; demographics/residence situation (i.e., whether or not they have a permanent address and telephone;

plans to move in the next 6 months if any; age; gender); background information (whether or not they can read and write English; sexual activity/birth control use [females only]; current treatment for medical problems; current use of medication or prescription drugs; lifetime history of treatment for emotional/psychiatric difficulties); frequency and quantity of alcohol consumption during the past week and during the heaviest week of consumption in the past month (if not the prior week); history of substance abuse treatment and participation in alcohol-related research; history of alcohol withdrawal; current and past year use of a series of illicit drugs (e.g., cocaine, opiates).

Those who appear eligible either by phone or via the online screener will be invited to attend an intake appointment with a study investigator or a research assistant at the Substance Abuse Treatment Unit (SATU) where informed consent will be obtained prior to any other procedures. Following this, the participant will meet with a research assistant for an intake session. Prospective participants will be asked to provide a photo ID (i.e., driver's license, passport, state ID) to verify their identity and contact information. Complete medical, alcohol and tobacco use histories, breath CO levels, breath alcohol levels will be obtained from all participants as well as blood and urine samples for laboratory screening tests, including urine drug screening. Prospective participants who screen positive for drugs will not be eligible for the study. They will also be asked for permission to use a portion of their blood that is drawn at screening for DNA testing. They will not be required to consent to DNA testing in order to take part in the study.

If participants meet initial eligibility criteria, the research assistant will schedule a physical exam, which will include a blood chemistry profile test and an EKG. A breath alcohol test will also be administered at the time of the physical exam. Once the results of these exams become available, the participants will meet with the study advanced practice nurse to review their medical status and eligibility criteria as well as the risks, benefits and procedures involved in study participation. Eligible participants will select a drinking quit date with the nurse practitioner. Before starting varenicline, pregnancy tests will be performed on all females of child bearing potential. If a participant is found to be pregnant, she will be excluded from the study and referred for other treatment. All prospective participants will also meet with the study psychiatrist for a brief psychiatric evaluation (i.e., 15 minutes) to verify suitability for enrollment in the study.

ii. Treatment:

Those participants who meet inclusion criteria following the intake appointment and physical exam will be randomly assigned to one of two study groups (2 mg varenicline or matching placebo), with randomization stratified by gender to balance the two treatment groups on the proportion of men and women). The sites will call a central number to randomize a participant who will then be assigned a box of medications. Both participants and research staff will be blind to participant assignment.

Dosing: Catalent will create blister packs of active varenicline or placebo and dispense and distribute to the two sites. For the pilot study, active varenicline will be dispensed by the CMHC pharmacy in bottles. The titration schedule for varenicline is based on the schedule used for smoking cessation and was used in our pilot study: 0.5 mg once per day for Days 1 to 3, 0.5 mg twice per day for Days 4 to 7, then two.5 mg tablets (1 mg) twice per day (or placebo) [26, 27]. Nausea is the most common adverse event of varenicline. If nausea is intolerable, we will reduce the dose to 1 mg per day (.5 mg twice per day). While not as effective as 2 mg daily, 1 mg per day is more effective than placebo in promoting smoking cessation [25]. The treatment period is 16 weeks, including the initial titration period. At the end of treatment period, there will be a downward titration over the course of

two weeks: 1 week at 1 mg daily (.5 twice daily) followed by .5 daily. Although prescribing guidelines do not require downward titration, we believe this will enhance attendance at the end of treatment appointment (week 17) and participants are apprehensive about abruptly stopping their medications.

Counseling: The Medical Management Manual (MM) [55] for the COMBINE Study will be adapted for this project. The treatment, delivered by a medical professional (i.e., nurse or physician), monitors medication side effects, provides strategies to increase medication adherence and supports abstinence through psychoeducation and referral to self-help groups. The manual will be adapted to focus on the rationale for the medication, medication adherence, and management of side effects during the first four weeks as well as participants' tentative goals to facilitate efforts to actively change their drinking beginning week 5. During the pilot phase, treatment sessions will be audio-taped for training purposes.

Phase I – Preparation Phase: Weeks 1- 4 of Treatment: The focus of this phase is medication adherence. Participants are not asked to make changes to their drinking during this time. During these sessions, the participant meets with a medical provider (e.g., nurse practitioner or study physician) weekly. At the first session, the provider obtains baseline assessments of adverse events using the SAFTEE, reviews instructions for taking the medication and helps develop a medication adherence plan. The clinician will make a 3-day call back to check in with the participant to see how they are doing and to address any side effects or concerns. In subsequent sessions, the provider obtains reports of adverse events, reviews and emphasizes medication adherence and problem solves difficulties with medication adherence. The potential effect of the medication on reducing learned associations between cues and drinking will be presented as a rationale for this portion of the treatment. This period also helps establish a relationship between the therapist and the participant prior to actively recommending change. The pervasive problem of early dropout in traditional outpatient clinics may be an inadvertent consequence of the provider's and participant's expectation of immediate improvement. We successfully used a 4-week pretreatment period in our pilot study of heavy drinking smokers seeking to quit smoking with 87% of participants completing this period.

Phase II – Action Phase: Weeks 5- 16 of Treatment: This phase focuses on promoting participants' efforts to change their drinking while continuing to adhere to their medication. Beginning at the week 5 appointment, the clinicians will follow the COMBINE Study's MM manual, adapted to provide advice to abstain or moderate alcohol in addition to supporting medication adherence. Participants are seen weekly for 2 weeks (weeks 6 and 7), and then every other week through the end of treatment. Session structure varies according to drinking status and treatment compliance. When non-adherence occurs, the clinician evaluates the reasons and helps participants devise plans to enhance medication adherence. Participants are encouraged to attend support groups and the clinician provides common sense recommendations, such as avoiding bars. For those who discontinue medication because of intolerance, the clinician will see them for a monthly 15-25 minute "Medical Attention" (MA) meeting, which employs a similar approach, focusing on drinking and overall health. MM is a treatment approach for primary care clinicians that has been adapted by the NIAAA Clinician's Guide[56].

Goals of Treatment Regarding Alcohol Abstinence: The participants' goals for changing their drinking are discussed at the early action phase appointments. While abstinence is the most stable long-term outcome of treatment[10] particularly among individuals who are smokers[57] and will be recommended, we will adapt the MM manual to allow individuals to work toward other goals. Strong evidence exists that therapists cannot impose treatment goals on participants. In fact, participants are

more likely to drop out of treatment if such disparities are dealt with by persuasion or confrontation rather than by more indirect methods[58, 59]. For those seeking drinking reduction, we will recommend a trial period of abstinence [60], emphasizing that this period can help reduce tolerance to alcohol prior to resuming drinking [61].

Smoking Cessation: Although many alcohol dependent smokers express interest in quitting smoking in the future, recruiting a sample of individuals interested in both reducing their drinking and smoking cessation at present would limit feasibility and the ability to generalize to less motivated patients. In addition, the present design provides a unique opportunity to evaluate the effect of varenicline on smoking without requiring a quit attempt. In a study of topiramate for alcohol dependence, Johnson and colleagues [62] found that topiramate led to smoking cessation even though participants were not seeking or advised to quit. For these reasons, therapists will not provide smoking cessation counseling during the active treatment component of the study. However, all participants will be encouraged to quit smoking at the final treatment appointment. If interested, the therapist will make a fax referral to the state quitline for free telephone counseling. If a participant asks for help quitting smoking during treatment, he/she will be given the quitline number and advised that smoking cessation medications should not be used while in the study. At follow-up appointments, research assistants will monitor smoking behavior, smoking quit attempts and what kinds of interventions were used.

iii. Follow-up and Retention:

Follow-up visits will occur at weeks 26, 39 and 52 post-randomization. For the pilot, we will follow-up only at week 26. At intake, participants will provide 2 collateral contacts who could provide the whereabouts of the participant if we are unable to reach him/her. Basic locator information will be confirmed at each visit. We will meet participants at a more convenient location or collect data by phone if necessary. Using methods similar to this[63], the COMBINE study collected complete drinking timeline data on 94% of participants during treatment and 82% at one year follow-up. With substantially fewer resources, 90% of participants provided complete timeline data in our 8-week pilot study of varenicline in heavy drinking smokers. To further enhance retention, participants will be paid \$25 for research assessments at intake and treatment appointments. Compensation will be increased to \$50 at termination and follow-up. A system of increased payments has proven effective in facilitating retention[63].

B. Assessments:

Assessments include pretreatment participant characteristics, process measures, measures of treatment safety, and treatment outcomes. Baseline assessments ensure that patients meet eligibility criteria and assess important predictor variables.

i. Screening Measures

Medical History, Demographic, and Family History Questionnaires: These questionnaires will obtain: (1) basic demographic information including age, gender, marital status, employment status, occupation and (2) alcohol/drug history. Medical history, a physical examination, and laboratory will also be completed prior to randomization.

Diagnostic and Substance Use History: Sections of the Structured Clinical Interview [64] will be used to provide current and lifetime diagnoses of substance use and other Axis I psychiatric disorders at the recruitment session. Specifically, participants will be characterized on their history of

alcohol, drug, eating, panic disorder, psychosis, and mood disorders. The alcohol section of the SCID will be repeated at the end of treatment (EOT) and at follow-up appointments. The alcohol portion of the Family History Assessment Module (FHAM;[65]) will be administered to assess the extent to which participants have a history of alcohol problems in their first and second degree relatives.

Body Weight and Height: both will be measured at baseline and weight will also be measured during treatment and follow up appointments (wks 26,39,52). Weight Circumference will be measured at the Physical Examination.

Menstrual Cycle Assessment: All women will be assessed for their menstrual/gynecological status by self-report at baseline and during treatment.

The Clinical Institute Withdrawal Assessment for Alcohol (Revised) (CIWA-AR): will be used to assess alcohol withdrawal symptoms at baseline. The CIWA is a reliable 10-item instrument designed to assess severity of current withdrawal syndrome [66].

ii. Motivation Measures

The Contemplation Ladder[67]- Smoking and Alcohol versions: The Contemplation Ladders are 1-item measure of readiness to change rated on an 11-point scale (e.g., 0 = no thought of quitting to 10 = taking action to quit). The Smoking ladder will be administered at the end of treatment and the Alcohol Ladder will be administered at baseline, week 5 and end of treatment.

Commitment to Abstinence will be assessed with a single item from the Thoughts About Abstinence Scale [68], This will be assessed for alcohol at baseline, week 5 and EOT; and for smoking at end of treatment.

iii. Biochemical Markers of Tobacco Use and Alcohol Use

Breath alcohol concentration (BAC) assesses very recent alcohol consumption and will be used to determine whether participants are acutely intoxicated and unable to consent or complete assessments and for clinical management. BAC will be assessed at every appointment. Potential participants will not be able to provide consent unless they have a blood alcohol level of .00. Research assessments may be administered to participants who have blood alcohol levels of less than or equal to .04. Participants who have blood alcohol levels higher than .00 will be reassessed to determine if their blood alcohol level is rising. Participants with blood alcohol levels above the legal drinking limit, who also drove to their appointment, will be asked to take alternate transport. The study staff will arrange for a taxi for participants in this case.

Ethyl glucuronide (EtG) provides a sensitive and reliable biomarker of recent alcohol consumption and is detectable in urine for up to three days after drinking depending upon the amount consumed[69-72]. A urine sample will be obtained at each appointment. Comparison of urine EtG levels during treatment taken monthly with baseline values will provide a *within participant* quantitative approximation of relative changes in alcohol exposure. For other time-points, EtG concentrations will be assayed only if a subject self-reports abstinence or no heavy drinking and will be used in secondary analyses of composite outcomes based on self-report confirmed by EtG (see statistical section.). Heavy exposure to non-beverage sources of ethanol such as some mouthwashes and hand washes, particularly the latter, can confound interpretation of urinary EtG assays and will be monitored. Normalization to urine creatinine concentration will correct for extremes in urinary dilution.

Unique to Yale: The EtG assays will be performed at Yale for both sites. The Yale group is currently characterizing the relationship between EtG concentration over time and their inter-individual and within individual variation over a range of ethanol doses (RO1AA018664) to develop more definitive cut-offs that can be used to confirm no heavy drinking. However, current knowledge of the pharmacokinetics of EtG allows the following conclusions. A concentration <100 ng/mL indicates that any alcohol consumption during the past 24 hrs is unlikely[72]. A concentration >500 ng/mL refutes a self report of "no heavy drinking" in the past 1-3 days[73] with several unavoidable limitations intrinsic to the pharmacokinetics of EtG. A low EtG concentration could be either consistent with light drinking during the prior 24 hours or with heavy drinking several days previously. Even light drinking on the day of the clinic visit, a short time prior to sample collection, could exceed 500ng/mL. Thus, final interpretations regarding heavy drinking for biochemical confirmation of self-report require integration with information from self-reports about the recency and quantity of alcohol consumed. Dr. Jatlow and a second reviewer will make these determinations without knowledge of the participant's clinical course or treatment condition. *EtG Assay:* Aliquots of spot urine samples will be stored at -20degrees within one hour of collection and subsequently transferred to a -70 degree freezer for longer-term storage. EtG will be measured using LC coupled to tandem mass spectrometry (LC/MS/MS) in the negative ion mode with deuterium labeled EtG as internal standard. This procedure, modified from published assays [71, 74] is validated and running.

Breath Carbon Monoxide levels which have a half-life of 2 hours, will be measured using a Vitalograph Breath CO, from Vitalograph Inc. (Lenexa, Kansas). This instrument measures CO in the range of 0-500 ppm and has no cross sensitivity to hydrogen or other positive ions. CO will be assessed at baseline and all treatment appointments.

Plasma samples for cotinine (a by-product of nicotine metabolism) will be used as a marker of tobacco use. Samples will be obtained at baseline, monthly during treatment, and at follow-up, Plasma concentrations <15 ng/mL have traditionally been used as a marker of abstinence[75]. Since cotinine concentrations reflect nicotine exposure, changes in plasma cotinine concentration and cotinine concentration per cigarette smoked will provide a good measure of changes in tobacco use and intensity of smoking. Cotinine will be assayed with LC/MS/MS with deuterium labeled cotinine as the internal standard. We use an LOQ of 2 ng/mL.

Blood chemistry profiles will be obtained at baseline and monthly during treatment to assess general health and any potential adverse effects of the medication.

DNA: We recognize the value of banking biological samples for future genetic and epigenetic analyses given the care taken to establish clinical phenotypes. We will ask participants' permission to use a portion of the blood that is drawn at baseline for DNA testing. Thus, the main purpose of the DNA testing will allow us to determine whether genes predict response to varenicline. DNA testing may also be used to study genes pertinent to other medical research issues. Participants will not be required to consent to DNA testing in order to take part in the study.

iv. Alcohol and Tobacco Use Measures

Smoking and Alcohol History Questionnaire: This questionnaire will assess basic smoking and drinking history such as number of years of use, length of prior quit attempts, amount used and prior treatments at baseline. Questions about alcohol smoking interactions and goals are asked.

Timeline Follow-back Interview [76, 77](TLFB): This standardized, validated, and reliable interview will be used to obtain quantity and frequency estimates of nicotine, alcohol and drug consumption for the 90-days prior to treatment and since the last appointment during treatment and follow-up. This information will be obtained at each appointment.

The Impact of Beverage Intake on Behavior (IMBIBE): This 15-item questionnaire assesses the frequency of negative alcohol consequences in the past month. It will be administered at baseline, Week 9, end of treatment, and follow-up.

The Self-Rating of the Effects of Alcohol (SRE, [78]) is a self-administered questionnaire that asks the respondent to think back about their drinking (approximately his/her first five times of drinking; their heaviest period, and their current drinking) and to list the number of standard drinks (10–12 g of ethanol) required to experience various effects of alcohol (e.g., intoxication). This will be administered at baseline.

Protective Strategies: The protective factors questionnaire [79, 80] measures the degree to which participants use specific safety strategies while drinking (e.g., spacing drinks, having a designated driver). This will be administered at baseline, week 9 and at the end of treatment.

Others Views About Drinking (baseline, week 9, EOT): Injunctive norms will be measured using seven items comprised of general statements about alcohol consumption (e.g., “it is okay to occasionally get drunk as long as it doesn’t interfere with my responsibilities”). Participants are asked to report, on a five-point scale, the extent to which an average, same sex member of their social group agrees with each statement.

Alcohol Dependence Scale [81] (ADS) (B): This 25-item questionnaire, assessed at baseline, measures the severity of alcohol dependence.

Obsessive Compulsive Drinking Scale [66](OCDS): This 14-item questionnaire assesses thoughts about drinking, urges to drink and the ability to resist these thoughts and urges. It will be administered at each appointment.

Implicit Measures of Alcohol Craving: These measures will be computer administered by trained research assistants during research appointments at weeks 1,5 and EOT. (i) The Implicit Association Test (IAT) measures implicit affective associations (pleasant – unpleasant) with the concept of alcohol using standard IAT procedures. We will use a bipolar alcohol-related affective IAT that has good internal consistency (.79)[82] and was found to predict drinking above explicit measures and to outperform other variants of the IAT. (ii) The Alcohol Approach Avoidance Test measures approach bias for alcohol-related stimuli[83, 84]. Subjects push or pull a joy stick in response to stimuli on a computer screen, based on the tilt of the stimulus, a content-irrelevant feature. Pushing decreases and pulling increases the stimulus size. Pulling is related to more positive evaluations than pushing[85, 86]. The zooming feature also generates a sense of approach or avoidance[87]. Four categories of stimuli include: 1) alcohol-related, 2) visually-matched control non-appetitive, 3) other appetitive, and 4) matched non-appetitive stimuli for the non-alcohol appetitive stimuli. This allows for measuring whether motivation is alcohol specific. AAT difference scores are computed using the median response time for pushing minus the median response time for pulling for each stimulus class with higher scores indicating greater motivation. We will administer these measures (using alternate

versions with presentation counterbalanced across groups) to examine whether varenicline reduces motivation to drink that is outside of awareness. The IAT and AAT provide a test of the hypothesis that varenicline treatment during active drinking “extinguishes” or modifies bias toward alcohol related cues. *Unique to Yale*: Dr. Reinout Wiers will consult on adapting these measures to incorporate smoking as well as alcohol stimuli for use by both sites.

Biphasic Alcohol Effects Scale [88]. At baseline and at Weeks 1-4, participants will rate their most recent drinking experience using the 14-items of the Biphasic Alcohol Effects Scale on a scale of 0 (not at all) to 10 (“extremely”). The number of drinks and the approximate time over which drinking occurred will be recorded. These will be used for exploratory analyses of the effects of varenicline on subjective responses to alcohol.

Fagerström Test for Nicotine Dependence [89]: This six-item scale will be used to measure severity of dependence on nicotine and has an internal consistency of .61. Time to the 1st cigarette is a good predictor of smoking cessation [90] and changes in dependence may capture changes in smoking with varenicline. It will be administered at baseline, monthly during treatment, and at follow-up.

The Wisconsin Predicting Patient’s Relapse (WI-PREPARE;[91] Baseline, End of Treatment) questionnaire is a 7-item scale that assesses physical dependence, environmental factors, and individual difference characteristics of smokers. This scale predicts relapse to smoking better than the Fagerstrom Test for Nicotine Dependence (FTND).

Attitudes and Beliefs about Varenicline (Chantix) (Baseline). This seven-item questionnaire asks the participant to rate for example how important, helpful, and acceptable varenicline will be for changing their drinking, how confident they are that they will use it as prescribed and whether it can help people with their drinking and with their smoking.

Tiffany Questionnaire of Smoking Urges-Brief [92](QSU-Brief): Using 10 items rated on a Likert scale, the QSU-Brief characterizes urges to smoke in response to two factors: 1) desire and intention to smoke, and 2) relief from nicotine withdrawal or negative affect. It will be assessed at each appointment.

Modified Cigarette Evaluation Scale[93] (mCEQ): This 12-item measure will be used to evaluate the degree to which participants experienced reinforcing effects of smoking or “smoking satisfaction” for the past 24 hours at baseline and Weeks 1-5. Participants will be asked to indicate how smoking made them feel on a Likert-type scale of 1 (not at all) to 7 (extremely). The scale yields five clusters or domains: Smoking Satisfaction, Psychological Reward, Aversion, Enjoyment of Respiratory Tract Sensations, and Craving Reduction.

v. Cognitive and Motor Measures (Baseline, Week 5, EOT)

The One Leg Stand from the Health, Aging and Body Composition (Health ABC) Study is an examiner-administered test to evaluate a person’s balance. A technician asks the participant to maintain his/her balance by standing on one foot as long as possible, up to 30 seconds. The participant may choose which foot to stand on. One or two trials are attempted, depending on the participant’s willingness and how long he/she can maintain his/her balance. We have the participant perform this task on the Wii Balance board [94]which should provide a more sensitive evaluation of balance.

Impairments in gait and balance are common in alcoholism [95 {Sullivan, 2010 #346}] and case reports have found that varenicline reverses balance problems associated with other disorders [96].

The Rapid Visual Processing Task[97, 98] assesses sustained attention. This computer administered task requires the participant to detect sequences of three consecutive digits among a series of presented numbers.

vi. Psychological Related Measures

Hospital Anxiety and Depression Scale (HAD) [99] is a 14 item self-rated questionnaire used to assess levels of anxiety and depression over the previous week.

Positive and Negative Affect Schedule [100](PANAS): The PANAS, a 10-item self-report scale that contains two subscales to assess positive and negative mood, will be included to evaluate whether improvements in positive affect mediate varenicline effects at each appointment. Varenicline has been shown to enhance positive mood in smokers relative to placebo [52, 101] and to reduce depressive symptoms in patients [102]. Low positive affect [103] and increases in negative affect predict relapse to smoking [103-106] and alcohol dependence [107-109].

UPPS Urgency Scales: The Positive and Negative Urgency subscale of the UPPS Impulsive Behavior Scale [110, 111] will be administered. The items are rated on a five point scale from 0 (not at all) to 4 (very much). These subscales measure the tendency to behave rashly under strong emotional states and have been linked to alcohol consumption and problems[112].

Quality of Life- Short Version (Center for Disease Control and Prevention, 2000) (baseline, end of treatment and follow-up). The participant responds to four self-report items about his or her physical and mental health during the past 30 days.

Pain is a common complaint and may motivate both smoking and drinking (baseline, monthly). We will administer a brief pain inventory and two questions asking about the use of smoking and alcohol to relieve pain for a total of 8 questions.

vii. Safety Related Measures

We will obtain traditional measures of adverse events, but will also systematically assess specific concerns connected to varenicline:

Adverse Events Checklist (SAFTEE): This will be assessed at baseline and at each treatment appointment and will include the most commonly reported adverse events for varenicline with severity rated on a scale from 0 (minimal) to 3 (severe). In addition, participants will report any other concerns, with the severity rated on the same scale.

Columbia Suicide Severity Rating Scale[113]: This interview systematically assesses past and current suicidal ideation, intent, and attempts. It will be administered at each appointment.

The Overt Aggression Scale – Modified for Outpatients (OAS-M)[114] assesses 4 types of aggression: verbal, against objects, against self, and against others and includes an irritability subscale and will be administered at each appointment.

McGill Nausea Questionnaire[115]: This 11-item self-report scale, to be administered at baseline and during treatment, measures the extent to which an individual experiences nausea, which is the most commonly reported adverse event associated with varenicline.

Epworth Sleepiness Scale[116, 117]: Participants rate how likely they are to doze off or fall asleep in 7 situations on a 4-point scale yielding an index of daytime sleepiness. This will be administered at baseline and during treatment.

Sleep: Sleep is often disrupted in alcoholism. We will measure sleep quality to see if it improves and to monitor the effects of varenicline. Sleep measures will be administered weekly in Phase I, and then monthly. At baseline and monthly, 8 items will be used, including 4-sleep quality items and 5 questions related to sleep duration from the Pittsburgh Sleep Quality Index[118]. The shorter 4-item sleep quality measure will be administered at other appointment during phase 1. Questions about use of alcohol and medications to promote sleep will be asked at baseline.

viii. Adherence

Medication Adherence Questionnaire[119]: This 4-item self-report scale will measure typical adherence to medication regimens at baseline. It yields two factors: purposeful nonadherence and unintentional nonadherence.

Pill Counts: Daily medication adherence will be monitored at each treatment appointment using a combination of pill counts returned from blisterpacks and self-reported compliance using the time-line follow-back procedures similar to the COMBINE Study[120, 121].

Yale Adherence and Competence Scale [122]: Therapists will complete an adaptation of this checklist to assess competence and manual adherence after each treatment appointment.

ix. Termination

Termination Rating Form: Participants will rate their perceptions of the effectiveness of the different treatment components at Week 16 (or at early termination), their reasons for termination and which medication they thought they were taking during the study treatment and why.

Table 1. Schedule of Assessments

Instrument	Intake/ Baseline	Treatment (Wks 1-17)	Follow up
Demographic/Screening			
Demographic Interview	X		
SCID sections	X	EOT (Alc only)	Alc only
Family Hx of Alcohol	X		
Clinical Institute Withdrawal Assessment for Alcohol	X		
Laboratory/Medical			
Urine Drug Screen	X		
Urine Pregnancy Screen	X	Monthly	
Medical History, Physical Exam, EKG	X		
Weight and Vital Signs	X	X	X

Menstrual Cycle Assessment	X	X	
Blood Chemistry Profile	X	Monthly	
DNA	X		
Biochemical Measures of Alcohol/Nicotine Use			
Carbon Monoxide Breath Test	X	X	X
Breath Alcohol Test	X	X	X
Plasma Cotinine Level	X	Monthly	X
Urine Ethyl Glucuronide Level	X	X	X
Alcohol/Nicotine Use Measures			
Smoking and Alcohol History	X		
SRE	X		
Protective Strategies Questionnaire	X	Wk 9, EOT	
Others Views About Drinking Behavior	X	Wk 9, EOT	
ImBIBe	X	Wk 9, EOT	X
Timeline Followback	X	X	X
Alcohol Dependence Scale	X		
Obsessive Compulsive Drinking Scale	X	X	
Implicit Measures of Alcohol Craving	X	Wk 4, EOT	
Biphasic Alcohol Effects Scale	X	Wks 1-5	
Fagerstrom Test of Nicotine Dependence	X	Monthly	X
Questionnaire of Smoking Urges- Brief	X	X	X
Attitudes & Beliefs about Chantix	X		
Rapid Visual Processing Task	X	Wk 5, EOT	
One Leg Standing Test	X	Wk 5, EOT	
WI-PREPARE	X	EOT	
Contemplation Ladder-Smoking		EOT	
Contemplation Ladder-Alcohol	X	Wk 5, EOT	
TAAS Smoking		EOT	
TAAS Alcohol	X	Wk 5, EOT	
Modified Cigarette Evaluation Scale	X	Wks 1-5	
Psychological Related Measures			
UPPS Urgency Scales	X		
Quality of Life Short Version	X	EOT	X
Pain	X	Monthly	
Hospital Anxiety and Depression Scale	X	Monthly	
Positive and Negative Affect Scale	X	X	X
Safety Related Measures			
Adverse Events Checklist (SAFTEE)	X	X	
Columbia-Suicide Severity Rating Scale	X	X	X
Overt Aggression Scale	X	X	X
McGill Nausea Questionnaire	X	X	
Epworth Sleepiness Scale	X	X	
Sleep	X	Wks 1-5, monthly	X
Adherence			
Medication Adherence Questionnaire	X		

Pill Count		X	
Yale Adherence & Competence Scale		X	
Termination			
Termination Rating Form		EOT	

4. Statistical Considerations:

The intention-to-treat (ITT) sample will include all randomized participants who start the study medication (N=160).

Primary Aim 1: *To evaluate the effect of varenicline 2mg daily compared to placebo on alcohol drinking in alcohol dependent daily smokers.* Our primary hypothesis is that varenicline will significantly reduce the percentage of heavy drinking days (PHD) summarized over the last 8 weeks of the 16-week treatment period. Analyses will include all available data on an individual. Percent heavy drinking days (PHD) will be computed over four week periods. We will use a mixed-effect general linear model with treatment condition, clinical center, time and their interactions as fixed effects. Baseline PHD will be computed using the first 30 days of the 90-day retrospective timeline obtained at intake and included as a covariate. In analyses of baseline trajectories of drinking in the COMBINE Study, we determined that individuals often reduce their drinking prior to beginning treatment, and that this earlier baseline period is more representative of individual differences in drinking than a summary measure across the entire 90-day period. Subject will be the clustering factor and we will use autoregressive structure with random intercept for the covariance structure of the data as this is expected to fit the data the best [123]. We will consider a significant medication by time effect and a significant difference between groups at the last two data-points as supportive of our hypothesis.

Other secondary outcomes will be examined to support the primary efficacy analyses. Other drinking related outcomes including percent days abstinent, drinks per drinking day, and self-reported consequences from drinking (the SIP) will be analyzed using the same approach as for percent heavy drinking days.

We will explore composite outcomes of self-reported abstinence from any and heavy drinking confirmed by EtG. Cut-offs levels for confirming self-reported abstinence (< 100ng/ml) over the prior 24 - 80 hours are currently available. We can also reliably detect recent heavy drinking within the prior 24-72 hours subject to the constraints described in the Assessments section. Using self-reports of the day and amount consumed relative to the time of the EtG sample, we anticipate that we can also detect some cases in which individuals are under-reporting their use for up to 72 hours. Similar to the smoking cessation literature, a composite index of abstinence would entail self-reported abstinence (from any drinking or from heavy drinking) for the period in question (e.g., 2 weeks) with EtG confirmation. We will also report contingency tables between self-reported abstinence (or no heavy drinking) and abstinence (or no heavy drinking) determined by EtG levels as an index of the validity of the self-report data. We have extensive experience in conducting similar analyses for cotinine, CO and self-reports of smoking abstinence[124].

Finally, The U.S. Food and Drug Administration[125] recently recommended that trials include an analysis of responders as an efficacy endpoint. One responder definition proposed is the proportion of patients with no heavy drinking days (PSNHDDs) in which a grace period can be excluded if the maximal drug effect is thought to take time (e.g., as in a drug that promotes extinction of responding)[126]. We will examine the responder definition of no heavy drinking days with a grace

period of two months using logistic regression analysis with clinical site and baseline PHD as covariates. However, we will report a cumulative proportion of responder graph (CPRA) proposed by Farrar et al 2006[127]. The CPRA graph will present the cumulative proportion of patients who achieved a specific response rate based on different cut-offs for the number of heavy drinking days. These graphs allow the reader to compare the treatment groups on the response level they deem clinically significant for their patients and to compute the number needed to treat for the cut-off chosen [127].

Secondary Aim 1: *To evaluate the effects of varenicline compared to placebo on smoking among alcohol dependent daily smokers who are not seeking treatment for smoking cessation.* The primary outcome will be the proportion of participants who are abstinent from smoking based on self-report over the last 4 weeks of treatment confirmed by plasma cotinine levels less than 15ng/mL measured at the end of week 16 [128]. Abstinance verified with biochemical verification is the standard in the field. The primary analysis for this aim will be performed using logistic regression with abstinence as the response, group as the main predictor variable and covariates including site.

Secondary analyses will include a survival analysis to determine whether the treatment groups differ in the time to the first week when smoking abstinence occurs. Nicotine withdrawal, level of nicotine dependence (FTND), cotinine level and cotinine per cigarette (to evaluate compensatory smoking) over time will be analyzed using general linear mixed models as outlined in Aim 1 to understand the time-course of changes in smoking. We will compare the proportion of those in each group who agree to a fax referral to the Quitline for help in quitting smoking using chi-square or Fisher's exact tests. Utilization of smoking cessation treatment during follow-up will be examined to interpret long-term outcomes.

Secondary Aim 2: *To test the hypothesis that varenicline will reduce craving for alcohol and for tobacco and the ability of cues to motivate drinking.* Explicit measures of craving, including the Obsessive Compulsive Drinking Scale and the Questionnaire of Smoking Urges, are assessed at each appointment. These will be analyzed by the general linear mixed models as outlined in Primary Aim 1. Implicit measures (e.g., the Approach Avoidance Task and the IAT) administered at baseline, week 5 and end of treatment will be analyzed by this approach but with fewer time points.

Secondary Aim 3: *To compare the safety and tolerability of varenicline compared to placebo in alcohol dependent daily smokers.* Rates of serious adverse events and other adverse events of greater intensity than baseline as measured by the SAFTEE will be compared using exact logistic regression analysis. Other analyses will compare the groups on changes in MADRS and PANAS scores between groups co-varying for baseline scores.

Secondary Aim 4: *To evaluate maintenance of improvement during post-treatment follow-up.* We will compare percent heavy-drinking days among four time-periods: the last 2 months of the treatment period (weeks 8-16), week 17-month 6, Months 6-9 and Months 9-12. Given that variability of the measures in these four periods may differ, we will use mixed-effects models with unequal variances at each time point. We will classify patterns for missing data and use the pattern mixture approach [129] to adjust for missing data. We will also compare point prevalence abstinence from smoking (7 days of abstinence confirmed by cotinine) measured at end-of-treatment (week 16), weeks 26, 9 months and 12 months.

Exploratory Aim: *To examine moderators and mediators of response to varenicline.* We will examine moderator effects by including the moderator variable (e.g., gender) in our models above and testing the interaction between the moderator variable and treatment. Mediation hypotheses are that reductions in drinking resulting from varenicline treatment are due, in part to reductions in alcohol craving, assessed with explicit (OCDS) and implicit measures (IAT, AAT). We will perform mediational analyses for heavy drinking only if we confirm the corresponding primary hypotheses of varenicline effects on drinking. In the mediational analyses, we will follow the approach of Krull and Mackinnon [130] for multilevel data. For each of the potential mediators we will fit an HLM that assesses the effect of treatment on the mediator, and an HLM that assesses the effect of treatment on drinking when controlling for the mediator main effect. We anticipate that varenicline will reduce craving and that the effect of varenicline on drinking will be decreased when craving is accounted for in the models. Mediator effects will be entered at level 1 of the models, since they are measured at end of week 4, whereas treatment group will be entered at level 2 of the models.

2. Background Information: Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Varenicline has been used extensively in humans. It is an approved treatment for smoking cessation, and will be used at the approved dosage of 2 mg twice daily in this study. The most common side effects include nausea, insomnia, abnormal dreams, constipation, flatulence, and/or vomiting. Less frequent side effects may include dry mouth, dyspepsia, sleep disorder, anxiety, headache, dizziness, fatigue, abdominal pain, gastroesophageal reflux disease, nightmare, dysgeusia, somnolence, lethargy, rhinorrhea, dyspnoea, upper respiratory tract disorder, rash, pruritis, increased/decreased appetite, diarrhea, gingivitis, chest pain, influenza like illness, edema (swelling), thirst, abnormal liver function tests, increased weight, arthralgia (joint pain), back pain, muscle cramps, musculoskeletal pain, myalgia (muscle pain), disturbance in attention, dizziness, sensory disturbance, anxiety, depression, emotional disorder, irritability, restlessness, polyuria (increased urination), menstrual disorder, epistaxis (nosebleed), respiratory disorders, hyperhidrosis (excessive sweating), hot flush, hypertension (high blood pressure). The safety of varenicline during pregnancy has not been established.

There have been reports of agitation, hostility, depressed mood, changes in behavior and thinking, suicidal ideation, and suicidal behavior related to varenicline (Chantix). We will monitor patients for these symptoms, and ask them to contact us immediately and discontinue varenicline (Chantix) if they experience any of them.

There have been reports of angioedema [swelling of the face, mouth (tongue, lips, gums), extremities, and neck] and infrequent reports of life-threatening angioedema requiring emergency medical care due to respiratory compromise in people taking varenicline (Chantix). There have been reports of rare but serious skin reactions, including Stevens-Johnson Syndrome and Erythema Multiforme (symptoms include a blistering rash and peeling skin). Patients will be advised to discontinue varenicline (Chantix) and immediately seek medical care if they experience either of these reactions.

There have also been reports of traffic accidents, near-miss accidents in traffic, or accidental injuries in patients taking varenicline (Chantix). In some cases patients reported somnolence, loss of consciousness or difficulty concentrating that resulted in impairment or concern about impairment in driving or operating machinery. We will advise patients to use caution driving or operating machinery

or engaging in other potentially hazardous activities until they know how varenicline (Chantix) affects them.

In a review of a study of 700 patients with documented stable cardiovascular disease (other than or in addition to hypertension) diagnosed at least 2 months prior to the screening visit (120), the FDA noted that varenicline was associated with more cardiovascular events (e.g., chest pain, nonfatal heart attack, need for coronary revascularization, new or hospitalization for peripheral artery disease) than placebo (121)). The differences were small. A recent meta-analysis of studies of patients without known cardiovascular disease (122)) also found that the rate of serious cardiovascular events was higher among the patients who received varenicline (1.06% compared to the clients who received placebo (0.82) although the rate was low in both groups. Varenicline more than doubled the smoking quit rate in these studies compared to placebo. The FDA concludes that the absolute risk of cardiovascular adverse events with Chantix, in relation to its efficacy, is small (123). All participants will receive a physical examination and EKG, will be required to be medically stable, and will be advised of this risk in the consent form.

As the safety of varenicline has not been established in pregnant and nursing women, they will be excluded from participation. A urine pregnancy test will be performed at baseline and monthly during treatment. Tests will be administered at the next assessment point for all menstruating female participants who miss the pregnancy test at their prior appointment. In addition, a menstrual cycle timeline is completed at each appointment during treatment, and if their menses is late, a urine pregnancy test will be obtained. Pregnant women will be referred for other treatment.

The use of this medication with heavy drinking smokers is experimental with regard to alcohol consumption. Varenicline is approved for smoking cessation and many smokers are heavy drinkers. Alcohol use while taking varenicline is not contraindicated according to the product information for the drug.

Human Subjects

1. **Recruitment Procedures:** How will potential subjects be identified, contacted and recruited? Attach copies of any recruitment materials that will be used.

- | | | |
|--|--|---|
| <input checked="" type="checkbox"/> Flyers | <input checked="" type="checkbox"/> Internet/Web Postings | <input checked="" type="checkbox"/> Radio |
| <input checked="" type="checkbox"/> Posters | <input type="checkbox"/> Mass E-mail Solicitation | <input type="checkbox"/> Telephone |
| <input type="checkbox"/> Letter | <input checked="" type="checkbox"/> Departmental/Center Website | <input checked="" type="checkbox"/> |
| Television | | |
| <input type="checkbox"/> Medical Record Review | <input type="checkbox"/> Departmental/Center Research Boards | <input checked="" type="checkbox"/> |
| Newspaper | | |
| <input type="checkbox"/> Departmental/Center Newsletters | <input type="checkbox"/> Web-Based Clinical Trial Registries | |
| <input type="checkbox"/> Other (describe): | <input checked="" type="checkbox"/> Clinicaltrials.gov Registry (do not send materials to HIC) | |

Participants will be recruited through advertisements for participation placed in local media outlets, including newspapers (print and online), television and radio advertisements and posters/flyers. We will also utilize mailings to health care professionals, fax referrals from healthcare providers, press releases, and websites (e.g., www.google.com) (see Appendix A). Prospective participants will be screened either by phone or via an online screener, the link for which will be provided on the study

website: (http://medicine.yale.edu/psychiatry/research/programs/clinical_people/smoking.aspx), prior to attending an initial intake appointment at the Substance Abuse Treatment Unit (SATU) where informed consent will be obtained prior to any other procedures.

Copies of our advertisements and telephone and online screening forms are attached. All potential participants must contact us directly.

2. **Subject Population:** Provide a detailed description of the targeted involvement of human subjects for this research project.

Participants will be 160 male and female alcohol dependent daily smokers (80 at Yale and 80 at Columbia), 18 years or older, who seek alcohol treatment. Three additional pilot subjects will be recruited at Yale. Participants must meet inclusion/exclusion criteria as listed below. Based on the demographics of New Haven and the surrounding communities obtained from census data, we anticipate the following breakdown of the Yale sample: White (not Hispanic) 70%, Black 17%, White (Hispanic) 10%, Asian/Asian Indian 3%. Children will be excluded because the safety and tolerability of varenicline has not been proven in children under 18.

3. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion? How will eligibility be determined, and by whom?

The study physician and/or advanced practice nurse will evaluate eligibility for the study based on medically related inclusion and exclusion criteria. The principal investigator will sign off on final eligibility for the study after review of the screening data and the physician's evaluation. The following inclusion and exclusion criteria are based on varenicline efficacy studies (Gonzales et al., 2006; Jorenby et al., 2006), NIAAA guidelines defining hazardous drinking, the COMBINE Study, and our pilot study of varenicline for smoking cessation in heavy drinkers.

Participants will be eligible for the study if they:

- (1) are 18 - 70 years of age and seeking treatment of alcohol drinking;
- (2) meet DSM-IV TR Criteria for Alcohol Dependence
- (3) smoke ≥ 5 cigarettes/day for ≥ 6 months and have a CO > 10 ppm;
- (4) report heavy drinking on at least 2 days on average per week (i.e., ≥ 4 drinks on an occasion for women and ≥ 5 drinks for men) for the past 90 days and no more than 7 consecutive days of abstinence at intake.

Participants will be excluded from the study if they:

- (1) exhibit current, clinically significant physical disease or abnormality based on medical history, physical examination, or routine laboratory evaluation including:
 - (a) any unexplained elevations in liver enzymes (i.e., transaminases, bilirubin);
 - (b) clinically significant, unstable cardiovascular disease/uncontrolled hypertension;
 - (c) hepatic or renal impairment;
 - (d) severe obstructive pulmonary disease;
 - (e) diabetes mellitus requiring insulin or certain oral medications (i.e., sulfonylureas) and an A1C hemoglobin test score of > 7 for participants not prescribed these medications;

- (f) baseline systolic blood pressure higher than 150 mm Hg or diastolic blood pressure higher than 95 mm Hg;
- (2) have a history of cancer (except treated basal cell or squamous cell carcinoma of the skin);
 - (3) have a history of clinically significant allergic reactions;
 - (4) exhibit serious psychiatric illness (i.e., schizophrenia, bipolar disorder, severe major depression, panic disorder, borderline personality disorder, organic mood or mental disorders by history or psychological examination
 - (5) report current suicidal ideation (past 6 months) or lifetime hx of suicidal behavior assessed with the Columbia Suicide Severity Rating Scale [107]; or risk for aggression using a cut-off of 15 or more on the Overt Aggression Scale – Modified Aggression Scale or 6 or more on the OAS-M Irritability Subscale [114].
 - (6) have used any psychotropic drug in the past month, except individuals who are on a stable dose of a Selective Serotonin Reuptake Inhibitor for at least two months;
 - (7) have a current DSM-IV diagnosis of drug dependence other than nicotine or alcohol
 - (8) are at risk for an alcohol withdrawal syndrome as evidenced by:
 - (a) a history of seizures, delirium, or hallucinations during alcohol withdrawal;
 - (b) a Clinical Institute Withdrawal Assessment scale [131] score of ≥ 8 ,
 - (c) report drinking to avoid withdrawal symptoms;
 - (d) have required medical treatment of alcohol withdrawal within the past 6 months
 - (9) have used another investigational drug within 30 days or have used medications to treat alcohol (e.g., naltrexone, topiramate, acamprosate, disulfiram) or nicotine use (e.g., clonidine, varenicline, bupropion, nicotine replacement) in the past 3 months or intend to use these medications; (prior use of nicotine replacement in situations where smoking is not permitted (e.g., planes) without the intention to quit smoking is not exclusionary at screening)
 - (10) intend to donate blood or blood products during the treatment phase of the study;
 - (11) have a Body Mass Index (calculated as weight in kilograms divided by the square of height in meters) less than 15 or greater than 38 or weight less than 45 kg;
 - (12) are a female of childbearing potential who is pregnant, nursing, or not practicing effective contraception (oral, injectable, or implantable contraceptives, intrauterine device, or barrier method with spermicide).

Consent Procedures

1. **Consent Personnel:** List all members of the research team who will be obtaining consent/assent.

Individuals obtaining consent will include [REDACTED]. Initial consent will be obtained at the first screening appointment. At the physical exam, prior to randomization, the study nurse or study physician will again review the consent form with potential participants to discuss key study points and address any questions potential participants have.

2. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

The entire consent form will be reviewed in detail with the participant in a private, one-on-one setting at the screening appointment. All risks and potential benefits will be described. Any questions the participant may have will be addressed. If the participant wishes, they may take the consent form home and consider it further before signing. They may also request to speak to anyone on the research team

about questions they have or to consult others, including their physician and family members. Once the participant has signed the consent, they may withdraw consent at any time. Informed consent must be obtained prior to performance of any protocol specific procedures. For all participants, the advanced practice nurse or study physician will review the risks of the study medications at the time of the physical examination.

3. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

We will not be enrolling participants with limited decision-making capacity. We plan to exclude individuals with current serious psychiatric or medical illnesses.

4. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

The adult compound consent/HIPAA form will be used and is appended for your review.

Protection of Research Subjects

1. **Risks:** Describe the reasonably foreseeable risks, discomforts, or inconveniences associated with subjects participating in the research.

Varenicline is an approved treatment for smoking cessation, and will be used at the approved dosage of 2 mg/day in this study. The most common side effects include nausea, insomnia, abnormal dreams, constipation, flatulence, and/or vomiting. Less frequent side effects may include dry mouth, dyspepsia, sleep disorder, anxiety, headache, dizziness, fatigue, abdominal pain, gastroesophageal reflux disease, nightmare, dysgeusia, somnolence, lethargy, rhinorrhea, dyspnoea, upper respiratory tract disorder, rash, pruritis, increased/decreased appetite, diarrhea, gingivitis, chest pain, influenza like illness, edema (swelling), thirst, abnormal liver function tests, increased weight, arthralgia (joint pain), back pain, muscle cramps, musculoskeletal pain, myalgia (muscle pain), disturbance in attention, dizziness, sensory disturbance, anxiety, depression, emotional disorder, irritability, restlessness, polyuria (increased urination), menstrual disorder, epistaxis (nosebleed), respiratory disorders, hyperhidrosis (excessive sweating), hot flush, hypertension (high blood pressure). The safety of varenicline during pregnancy has not been established.

There have been reports of agitation, hostility, depressed mood, changes in behavior and thinking, suicidal ideation, and suicidal behavior related to varenicline (Chantix). We will monitor patients for these symptoms, and ask them to contact us immediately and discontinue varenicline (Chantix) if they experience any of them.

There have been reports of angioedema [swelling of the face, mouth (tongue, lips, gums), extremities, and neck] and infrequent reports of life-threatening angioedema requiring emergency medical care due to respiratory compromise in people taking varenicline (Chantix). There have been reports of rare but serious skin reactions, including Stevens-Johnson Syndrome and Erythema Multiforme (symptoms include a blistering rash and peeling skin). Patients will be advised to discontinue varenicline (Chantix)

and immediately seek medical care if they experience either of these reactions.

There have also been reports of traffic accidents, near-miss accidents in traffic, or accidental injuries in patients taking varenicline (Chantix). In some cases patients reported somnolence, loss of consciousness or difficulty concentrating that resulted in impairment or concern about impairment in driving or operating machinery. We will advise patients to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how varenicline (Chantix) affects them.

There may be a small increase in cardiovascular events associated with varenicline (Chantix) compared to placebo. In a review of a study of 700 patients with documented stable cardiovascular disease (other than or in addition to hypertension) diagnosed at least 2 months prior to the screening visit (120) the FDA noted that varenicline was associated with more cardiovascular events (e.g., chest pain, nonfatal heart attack, need for coronary revascularization, new or hospitalization for peripheral artery disease) than placebo (121). The differences were small. A recent meta-analysis of studies of patients without known cardiovascular disease (122) also found that the rate of serious cardiovascular events was higher among the patients who received varenicline (1.06% compared to the clients who received placebo (0.82) although the rate was low in both groups. Varenicline more than doubled the smoking quit rate in these studies compared to placebo. The FDA concludes that the absolute risk of cardiovascular adverse events with Chantix, in relation to its efficacy, is small (123). All participants will receive a physical examination and EKG to determine eligibility. Individuals with clinically significant, unstable cardiovascular disease/uncontrolled hypertension will be excluded. Consistent with guidance from the FDA, we will advise individuals of this risk and to discontinue the medication and seek immediate medical attention if they experience any of the following symptoms: Shortness of breath, Chest pain or New or worse pain in legs when walking.

Pregnant or nursing women will be excluded from this study since this medication may have harmful consequences to the baby. We also ask that you use a reliable form of birth control during the study. Acceptable methods of birth control include abstinence, the birth control pill, intrauterine device, injection of Depo-Provera, Norplant, tubal ligation, and barrier methods such as condoms or the diaphragm in combination with a spermicide. Female participants of childbearing potential will be informed to alert study staff in the event that they change from their birth control plans, or if despite their plans, think they may be pregnant. A urine pregnancy test will be done at baseline and then monthly during treatment. A positive pregnancy test will result in the participant being excluded from the study. In this case, we will provide the participant with a referral for other treatment.

Research assessments are all noninvasive, and should add no risk. The major disadvantages are the time taken to complete them and possible breach of confidentiality. Our past experience with these measures indicates that they are acceptable to participants. Careful efforts aimed at maintaining confidentiality will be made. This is described in detail below.

Breath tests and urine collections should add no risks other than those normally associated with these procedures. We will draw approximately 3 ounces of blood over the entire course of the study. Research assistants who are trained in phlebotomy will conduct blood drawing. This is a very small amount of blood. The most common risks to providing blood samples are the potential for bruising at the site, brief pain, and, rarely, infection. A rare risk is also fainting.

Risks associated with providing blood for genetic testing: Under some circumstances, it can be a risk for genetic information to be known by the subject or others. Variation in some genes is known to be directly related to risk of certain illnesses. In some cases, knowledge of genetic information could have negative psychological consequences or could affect access to or retention of certain benefits or entitlements. For example, the information could potentially be used against a person if it were revealed to insurance companies or potential employers. However, participants will not get the results of the DNA portion of the study nor will the results be made available in their medical record. Additionally, we will take precautions to ensure that confidentiality is maintained and that genetic information is not unintentionally disclosed to inappropriate third parties. There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers, except those with less than 15 employees, to discriminate against you based on your genetic information. However, it does not protect the person against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

2. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized. Effective screening will exclude all participants who would be at greater risk for complications because of medical, neurological or psychiatric illnesses. Participants will be seen regularly and will be monitored for any adverse reactions. Participants will be advised that there have been reports of agitation, hostility, depressed mood, changes in behavior and thinking, suicidal ideation, and suicidal behavior related to varenicline (Chantix). We will monitor them for these symptoms and ask that they contact us immediately and discontinue varenicline (Chantix) if they experience any of them. The Columbia Suicide Severity Rating Scale will continue to be administered weekly to assess suicidal ideation and behavior. Subjects will be advised to discontinue varenicline (Chantix) and immediately seek medical care if they experience either angioedema or serious skin reactions. We will advise participants to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how varenicline (Chantix) affects them.

With respect to recent data on cardiovascular risks and varenicline, we will give all participants an EKG prior to participation, monitor them for symptoms of cardiovascular disease, and ask them to discontinue varenicline (Chantix) and to seek immediate medical assistance if they experience any of the following symptoms: shortness of breath, chest pain, new or worse pain in legs when walking.

Given the uncertain effects of varenicline during pregnancy, the following precautions will be taken for women: 1) urine pregnancy tests will be performed at baseline and monthly during treatment, and pregnant or nursing women will be excluded from participation and referred to other treatment programs; 2) women must agree to use a reliable method of birth control while they are in the study and to alert the principal investigator if she departs from her birth control plans or if, in spite of adherence to these plans, she thinks she might be pregnant; 3) additional urine pregnancy tests will be performed as needed; if a woman becomes pregnant, she will be withdrawn from the study and referred to alternative treatments; 4) a menstrual cycle timeline is completed at each appointment during treatment, and if the woman's menses is late, a urine pregnancy test will be obtained.

All efforts will be made to protect participants' confidentiality. This is described in detail below.

3. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

- a. What is the investigator's assessment of the overall risk level for subjects participating in this study?
- b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?
- c. Data and Safety Monitoring Plan:

a) What is the investigator's assessment of the overall risk for subjects participating in this study?

We view the risks associated with the use of varenicline in alcohol dependent daily smokers as moderate. Although varenicline has not been tested extensively specifically to reduce alcohol consumption, we believe that it has been used clinically in thousands of smokers who also drink heavily given the substantial comorbidity between smoking and heavy alcohol consumption. Although alcohol consumption is not a contraindication for varenicline, heavy alcohol consumption may be associated with greater psychiatric risks. The FDA has issued a warning about serious neuropsychiatric symptoms that have occurred in patients taking varenicline including behavior changes, agitation, depression, suicidal ideation, and attempted and completed suicide [FDA warning issued 2/1/2008]. In some cases, these symptoms developed during varenicline treatment and in others they developed after withdrawal of varenicline treatment. For these reasons, participants whose psychiatric history may put them at undue risk will not be eligible to participate in this study. Furthermore, participants will be carefully monitored each week for both physical and psychological adverse events. In particular, the Columbia Suicide Severity Rating Scale and the Overt Aggression Scale will be administered at each treatment appointment to assess aggression and suicidal ideation and behavior. In our prior pilot study, "*Varenicline for Smoking Cessation in Heavy Drinkers*" (HIC# 0809004276) varenicline was well tolerated and no adverse events occurred. The potential for increased risk of cardiovascular events with varenicline appears small. We will exclude individuals whose medical history may put them at increased risk and subjects will be monitored closely. For these reasons, we do not view the proposed study as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study below.

b) If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?

Not applicable. No children will participate in this study.

c) Data Safety Monitoring Plan

Adverse events will be monitored for each participant participating in the study and attributed to the study procedures/design by study nurse, physician or the principal investigator according to the following categories:

- a. Definite: Adverse event is clearly related to investigational agent.
- b. Probable: Adverse event is likely related to investigational agent.
- c. Possible: Adverse event may be related to investigational agent.

- d. Unlikely: Adverse event is likely not to be related to the investigational agent.
- e. Unrelated: Adverse event is clearly not related to investigational agent.

The following scale will be used in grading the severity of adverse events noted during the study:

- 1. Mild adverse event;
- 2. Moderate adverse event;
- 3. Severe unanticipated adverse event resulting inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect;
- 4. Life threatening event or
- 5. Fatal adverse event.

The investigator will report the following types of adverse events to the HIC; a) serious AND unanticipated AND possibly, probably or definitely related events; and b) anticipated adverse events occurring with a greater frequency than expected. These adverse events will be reported to the HIC within 24 hours of it becoming known to the investigator, using HIC Form 6A. Adverse events will be deemed serious in nature if graded as 3 or higher according to the scale for grading severity above.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

- a. All Co-Investigators listed on the protocol.
- b. National Institutes of Health.
- c. Pfizer, Inc.
- d. Food and Drug Administration

All serious adverse events (Grade 3 or higher above) regardless of whether or not they are anticipated or related will be reported to Pfizer, NIH and the FDA.

Specific procedures for reporting of Serious Adverse Events to Pfizer follow:

Reporting of Serious Adverse Events to Pfizer. Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), Principal Investigators will report to Pfizer by facsimile any Serious Adverse Event (“SAE,” as defined below) that occurs during the SAE reporting period (as defined below) in a Study subject assigned to receive the Pfizer Product (see Section 5, Pfizer Product). Principal Investigators will report such SAEs in accordance with the approved Protocol. The *Reportable Event Fax Cover Sheet* provided by Pfizer should also be included. SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.

- a. SAE Definition. An SAE is any adverse event, without regard to causality, that is life-threatening or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity; or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical

procedure is not, in itself, an SAE.

- b. Exposure During Pregnancy, Exposure During Lactation, and Lack Of Effect. Even though there may not be an associated SAE, exposure to the Pfizer Product during pregnancy, exposure to the Pfizer Product during lactation, and lack of effect of the Pfizer Product are also reportable, as discussed in the training material provided by Pfizer. In this Agreement, SAE will be understood to include exposure during pregnancy, exposure during lactation, and lack of effect.
- c. SAE Reporting Period. The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Pfizer Product through 28 days after discontinuation of the Pfizer Product.

The principal investigator (Stephanie O'Malley, Ph.D.) and the study physician will conduct a review of adverse events upon completion of every study participant. The principal investigator and the study physician will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required. In addition, this protocol will be reviewed every six months by members of the Center for the Translational Neuroscience of Alcoholism DSMB. The DSMB will review the safety data at each meeting and will vote whether or not to continue recruitment as planned. The DSMB can also require modifications/amendments. If, after this meeting, any DSMB member votes to stop recruitment or requests a protocol modification, Dr. O'Malley will inform the Yale IRB immediately. In any case, the minutes of their meeting will be submitted to the IRB.

Research Alternatives and Economic Considerations

1. Alternatives: What other alternatives are available to the study subjects outside of the research?

Alternatives to treatment in this study are current approved alcohol pharmacotherapies such as naltrexone, acamprosate, and disulfiram. Participants may get prescriptions from their physicians for these medications; however they may not use these devices while participating in this research study. Study drugs will not be available once participants complete this study.

Individuals who request support with smoking cessation will be given the telephone number of the CT Quitline. Alternative smoking cessation treatments include more intensive counseling, nicotine replacement products (nicotine containing gum, lozenges, patches, nasal spray, inhalers), bupropion, and the use of varenicline for the purpose of smoking cessation.

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects and the conditions for receiving this compensation.

Participants will receive \$25 for attending the screening session, physical exam, and research appointments that correspond with treatment visits Weeks 1-15 (11 total). In addition, participants will receive \$50 for attending the final treatment appointment (week 17) and the 3 follow-up research appointments. Thus, the total possible payment for completion of the entire study is \$525.00.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

Participants will not be charged for any aspects of the treatment. As part of the screening procedures for the study they will receive a free physical examination from a medical doctor or an advanced practice registered nurse, and they will receive counseling and treatment with either varenicline or placebo. If subjects chose to take varenicline beyond the treatment portion of the study, these costs will not be covered by the study.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
- Will medical treatment be available if research-related injury occurs?
 - Where and from whom may treatment be obtained?
 - Are there any limits to the treatment being provided?
 - Who will pay for this treatment?
 - How will the medical treatment be accessed by subjects?

If a participant is injured as a direct result of participation in this study, treatment will be provided. The participant and/or his or her insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. Participants will not waive their legal rights by participating in this study.

If immediate information is needed about the study, participants will be instructed to contact [REDACTED].

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