New Approaches to Smoking Cessation in Heavy Drinkers

Study Protocol and Data Analysis Plan

NCT # 02151591

May 30, 2017

YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2011-1)

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://www.yale.edu/hrpp/forms-templates/biomedical.html Submit the original application and two (2) copies of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.	**HIC OFFICE USE ONLY**	
	DATE STAMPED-RECEIVED	PROTOCOL NUMBER 1106008673

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: New Approaches to Smoking Cessation in Heavy Drinkers			
Principal Investigator: Lisa Fucito, PhD			nt Professor of
Campus Address: 1 Long Wharf Drive, Box 18, New Haven, CT 06511			
Campus Phone: 974-5759	**Fax:** 974-5790	**Pager:**	**E-mail:** lisa.fucito@yale.edu
Protocol Correspondent Name & Address (*if different than PI*):			
Campus Phone:	**Fax:**	**E-mail:**	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):			
Campus Phone:	**Fax:**	**E-mail:**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☐ **N**			**tment:**
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Does the principal investigator, co-investigator, or any other responsible research team member, or any of their family members (spouse, child, domestic partner) have an incentive or interest, financial or otherwise,

that may be viewed as affecting the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? See Disclosures and Management of Personal Interests in Human Research http://www.yale.edu/hrpp/policies/index.html#COI

o Yes 4 No
If yes, list names of the investigator or responsible person:

All individuals listed as co-investigators must have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends **ONLY** to Yale University personnel. Researchers listed on the protocol who are not Yale personnel are only required to disclose to the PI any interests that are specific to this protocol.

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

- ☐ Magnetic Resonance Research Center (MR-TAC)
- ☐ Yale Cancer Center/Clinical Trials Office (CTO)
- ☐ Yale Cancer Center
- ☒ Yale-New Haven Hospital
- ☐ Specify Other Yale Location:
- ☐ PET Center
- ☐ YCCI/Church Street Research Unit (CSRU)
- ☐ YCCI/Hospital Research Unit (HRU)
- ☐ YCCI/Keck Laboratories
- ☐ Cancer Data Repository/Tumor Registry

b. External Location[s]:

- ☐ APT Foundation, Inc.
- ☒ Connecticut Mental Health Center
- ☐ Clinical Neuroscience Research Unit (CNRU)
- ☐ Other Locations, Specify:
- ☐ Haskins Laboratories
- ☐ John B. Pierce Laboratory, Inc.
- ☐ Veterans Affairs Hospital, West Haven
- ☐ International Research Site (Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☐ N/A

- ☐ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
- ☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
- ☐ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
- ☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
- ☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
- ☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
- ☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
- ☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
- ☐ Dept. of Lab Medicine request for services or specimens form

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

We anticipate that this project will take approximately 4 years to complete from initiation to publication.

3. **Targeted Enrollment:** Give the number of subjects:

a. targeted for enrollment at Yale for this protocol _ If this is a multi-site study, give the total number of subjects targeted across all sites___

The targeted enrollment all at Yale are as follows: (1) up to 30 subjects for focus groups, (2) 10 subjects for an open-label pre-pilot study and (2) 40 subjects for randomized, controlled pilot study.

b. expected to sign the consent form___

In order to achieve a randomized sample of 50, it is anticipated that 100 individuals will need to be consented. This conservative figure is based on the ratio of consents to randomizations in previous smoking cessation trials conducted by our research group.

c. expected to complete some or all interventions for this protocol?

Forty participants will be randomized and thus, 50 participants are expected to complete some or all of the intervention. There will be no randomized non-starters in this pilot. If a participant drops out prior to starting any treatment, his/her condition number will be reassigned.

4. Research Type/Phase: (Check all that apply)

a. Study Type

☒ Single Center Study
☐ Multi-Center Study
Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐
☐ Coordinating Center/Data Management
☐ Other:

b. Study Phase ☐ **N/A**

☒ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV
☐ Other (*Specify)*

c. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

Clinical Research: Patient-Oriented
☐ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study required to be registered in a public database? Yes No ☐
If yes, where is it registered?
Clinical Trials.gov registry
Other (*Specify*)

6. Will this study have a billable service as defined by the Billable Service Definition?
Yes No ☐

If you answered "yes", this study will need to be set up in Patient Protocol Manager (PPM)
http://medicine.yale.edu/ymg/systems/ppm/index.aspx

7. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes _X No _ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*
a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?

Yes – Dr. Fucito is the Director of the Tobacco Treatment Service at YNHH where routine tobacco treatment will be provided to participants.

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?

No

c. Will a novel approach using existing equipment be applied?

No

If you answered "no" to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Fun**

Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	unding	unding Mechanism
Lisa Fucito, PhD	New Approaches to Smoking Cessation in Heavy Drinkers	National Institute on Alcohol Abuse and Alcoholism	☒ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For rofit Other	☒ Grant-M# 23AA020000-01A1 ☐ Contract# ☐ Contract Pending ☐ Investigator/Department nitiated ☐ Sponsor Initiated Other, Specify:
			Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For rofit Other	Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department nitiated ☐ Sponsor Initiated Other, Specify:
			Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For rofit Other	Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department nitiated ☐ Sponsor Initiated Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To: N/A

Name:
Company:
Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

NOTE: The HIC will remove from the protocol any personnel who have not completed required training.

	Name	**Affiliation: Yale/Other Institution (Identify)**	**NetID**
Principal Investigator	Lisa Fucito, PhD	Yale Faculty	lmf35
Role: Consultant	Stephanie O'Malley	Yale Faculty	sss02
Role: Consultant	Kathleen Carroll, PhD	Yale Faculty	ernieb
Role: Consultant	Nancy Redeker, PhD, RN, FAHA, FAAN	Yale Faculty	nsr24
Role: Consultant	Ralitza Gueorguieva, PhD	Yale Faculty	rg268
Role: Study Personnel	Srinivas Muvvala, MD	Yale Faculty	sm826
Role: Study Personnel	Denise Romano, APRN, FNP	Yale Staff	dmr35
Role: Study Personnel	Elaine LaVelle, MS	Yale Staff	etl7
Role: Study Personnel	Susan Neveu	Yale Staff	sn227
Role: Study Personnel	Tess Hanrahan, MRes	Yale Staff	th473
Role: Study Personnel	Ran Wu, MS	Yale Staff	rw74
Role: Study Personnel	Ann Agro, MPH	Yale Staff	ada22
Role: Study Personnel	Phyllis Hunt	YNHH	
Role: Study Personnel	Victoria Ogbejesi	YNHH	
Role: Study Personnel	Steve Baldassarri	Yale Fellow	
Role: Study Personnel	Steve Bernstein	Yale Faculty	
Role: Study Personnel	Abedalrazaq Alkukhun	Yale Postgraduate Student	
Role: Study Personnel	Kelly DeMartini, PhD	Yale Faculty	
Role: Study Personnel	Hochang Ben Lee	Yale Faculty	
Role: Study Personnel	Maura D'Andrea	YNHH	
Role: Study Personnel	Christina Heffern	Quinnipiac University Study Intern	
Role: Study Personnel	Helen Sackler, PhD	Yale Casual Employee	
Role: Study Personnel	Lisa Blumenthal, LCSW	CMHC/Yale Casual Employee	
Role: Study Personnel	Krysten Bold, PhD	Yale Staff	

A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

Lisa Fucito, PhD _____ 5.31.17_____

PI Name (PRINT) and Signature Date

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions Prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.

_____ _____

Advisor Name (PRINT) and Signature Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____
Chair Name (PRINT) and Signature Date

_____
Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____
YNHH HSPA Name (PRINT) and Signature Date

For HIC Use Only

_____ _____
Date Approved **Human Investigation Committee Signature**

This protocol is valid through _____

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

The purpose of the proposed project is to develop and test an integrated cognitive-behavioral intervention for smoking and alcohol (*CBT for SA*) among heavy drinking smokers presenting for smoking cessation treatment. The project involves three phases. In Phase 1, focus group interviews will be conducted with 30 heavy drinking smokers to identify intervention components that are feasible and acceptable to this population. In Phase 2, an open-label pre-pilot study of *CBT for SA* will be conducted with 10 heavy drinking smokers. The primary results of this phase will be used to refine the *CBT for SA* protocol. In Phase 3, a randomized, controlled pilot study will be conducted with 40 heavy drinking smokers comparing *CBT for SA* with standard smoking counseling (SC) and standard alcohol counseling (AC). The specific aims are as follows:

Primary Aim 1.1: *In an iterative process based on detailed review of audiotaped focus group and treatment sessions,* develop and refine *CBT for SA* manual, participant materials, therapist training materials, and treatment fidelity documents.

Primary Aim 1.2: Conduct pre-pilot study of *CBT for SA* (N=10) with heavy drinking smokers to evaluate the feasibility and acceptability of the intervention.

Primary Aim 2.1: Conduct RCT pilot study of *CBT for SA* versus *SC* and *AC* (N=40) with heavy drinking smokers to obtain effect size estimate data for the two primary outcomes of:

1. *Point prevalence smoking abstinence over the last 7 days at 6 months post treatment completion.*
2. *Percentage of heavy drinking days at 6 months post treatment completion.*

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaininguseful scientific data.

Co-occurring Heavy Alcohol Use and Cigarette Smoking: An Important Co-Morbidity.
More than 50% of heavy drinkers (defined as >14 drinks per week/5 per day for men and >7 drinks per week/4 per day for women) smoke cigarettes compared with 23-39% of individuals who either abstain from alcohol or drink only moderately(1, 2). This figure increases to nearly 80% in clinical samples of alcohol dependent individuals. Cigarette smoking is the leading preventable cause of morbidity and mortality in the United States(3) and when combined with heavy alcohol has a synergistic effect on health including increased risk of liver, head, and neck cancers, liver cirrhosis, and pancreatitis(4-7), and greater abnormalities in brain structure and function(8). Combined heavy alcohol use and cigarette smoking is also associated with poor treatment outcomes. Heavy drinking smokers are less likely to initiate a smoking quit attempt(9, 10), achieve and maintain smoking abstinence (1, 11-25), and successfully moderate or abstain from alcohol use(26, 27). Thus, more effective treatments for concurrently reducing smoking and heavy drinking are warranted.

Why Integrate Treatment for Heavy Alcohol Use and Cigarette Smoking?
Several factors may limit treatment response in heavy drinking smokers. Through conditioning processes, heavy alcohol use may enhance smoking motivation and smoking may promote

motivation to drink(28-33). Heavy drinking may disinhibit individuals to smoke(33) or potentiate the rewarding effects of nicotine(34). Similarly, cigarette smoking may enhance alcohol reinforcement by reducing the sedating effects and cognitive deficits associated with alcohol use thereby enabling drinkers to consume heavier amounts of alcohol(33). Thus, treating one behavior in isolation of the other may render heavy drinking smokers' efforts to change either behavior less successful. Despite these risks, heavy alcohol use and smoking are not typically treated concurrently largely due to concerns that quitting smoking will negatively affect drinking outcomes(35) and misperceptions that smoking is less harmful. On the contrary, more heavy drinkers will die from smoking-related causes than alcohol-related causes(33, 36), quitting smoking does not jeopardize and may even promote drinking changes(37), and many heavy drinkers are motivated to quit smoking(35).

Current Combination Treatments for Heavy Drinking and Smoking of Limited Efficacy. Prior research has primarily focused on smoking interventions provided during or shortly following outpatient or inpatient alcohol treatment (37, 38). Most interventions were brief (i.e., a few sessions), not integrated into alcohol treatment, and associated with low smoking quit rates (37, 38). Adding smoking pharmacotherapy to these interventions yields higher smoking quit rates, but these effects are not sustained beyond treatment (37, 38). Only 1 study examined a brief alcohol intervention integrated into smoking cessation treatment for heavy drinkers seeking to quit smoking(39). Heavy drinkers, not currently alcohol dependent, received 8 weeks of nicotine patch therapy starting on the quit day and either 4 weeks of standard smoking counseling or standard smoking counseling plus brief alcohol advice starting 2 weeks before quitting. The integrated treatment resulted in greater smoking abstinence and alcohol use reductions but these effects were modest; smoking changes also did not persist beyond treatment and were greatest among only moderately heavy drinkers. Moreover, through personal communication with Dr. Kahler, many participants were unmotivated to discuss drinking after the first session. Despite these limitations, this protocol is a promising model for integrating smoking and alcohol treatment and highlights how smoking treatment can provide an opportunity to identify and intervene with heavy drinkers. Providing more health information to motivate them to also reduce their drinking before and after quitting smoking and incorporating skill development relevant for changing alcohol use might promote sustained smoking abstinence and greater drinking reductions in this population.

Proposed Integrated CBT Intervention for Heavy Drinking Smokers: CBT for SA. We will develop a manual that integrates smoking and alcohol treatment and incorporates empirically supported CBT techniques to support reductions in both smoking and alcohol use. Treatment will address obstacles and teach skills relevant for both issues and will be organized around two major areas of development: (1) stimulus control and (2) mood/stress management strategies. Treatment will be focused so that participants acquire high competence in two major skills in rather than poor to moderate competence in many skills. This content was selected based on data analyses and focus group interviews conducted by Dr. Fucito on the factors that predict poor smoking cessation outcomes among heavy drinkers. Stimulus control involves setting up environmental constraints to avoid exposure to cues that trigger problematic behaviors and feelings(73, 74). For smoking and drinking, stimulus control emphasizes avoiding people, places, and things that trigger urges to use (73, 74). Relative to moderate and non-drinkers, the smoking behavior of heavy drinkers appears to be more environmentally and socially cued. For these reasons, skill development will focus on recognizing and responding to cues without smoking/drinking and either changing social networks

or managing social situations without using. Mood/stress management strategies will emphasize behavioral activation - engaging in pleasant activities that do not involve smoking and drinking to reduce negative mood (i.e. stress, anxiety, boredom), specific relaxation techniques (e.g., deep breathing, progressive muscle relaxation), and anger management techniques. Behavioral activation is an empirically-supported intervention for the treatment of mood problems. Counseling will information about moderate drinking guidelines for men and women and will include specific strategies to reduce drinking (e.g., slowing the pace of drinking, substituting a non-alcoholic drink in between alcoholic drinks, counting drinks).

In initial sessions and reinforced throughout treatment, participants will be taught how problematic behaviors and feelings are the result of a learning process. By conducting a functional analysis in session (a core component of CBT), participants will understand the factors that maintain the problematic behavior or feeling and what they can do to break the cycle[79]. Discussions will focus on situations, thoughts, and feelings that maintain smoking and drinking and other problems that could affect efforts to change them (i.e., mood, social networks). They will learn general stimulus control skills (i.e., how to create an environment that supports adaptive behaviors) and how to apply them to these specific problems as well as how to identify and implement pleasant activities that do not involve smoking and drinking.

In addition to CBT skills, the intervention will incorporate motivational components to encourage participants to make changes to both behaviors. This will be provided through personalized health feedback and general feedback about smoking and drinking behaviors that will be provided at the first session and then monitored during treatment. We will first provide a number of different types of health profile information in the pre-pilot study in order to identify which components are the most motivating and helpful for participants. The highest rated health profile components among these will then be provided in the final RCT pilot study. The final components will include: (1) liver function tests using blood samples, (2) inflammation markers using blood samples, (3) blood pressure, (4) metabolic function (i.e., glucose, lipid profile) from blood samples, (6) lung function based on spirometry tests, which involve having participants exhale into a tube for 6 seconds as hard as they can, and (7) breath carbon monoxide (CO) levels, and (8) hemoglobin, hematocrit, MCV. We will also provide personalized feedback to participants about the money they are spending on cigarettes and alcohol, the extra calories they are consuming from alcohol use, typical cues that trigger smoking and alcohol use. Consistent with Dr. Kahler's intervention for heavy drinking smokers, sessions will also involve open-ended, personalized discussions of current drinking and smoking patterns, pros and cons of smoking and drinking, how drinking and smoking are associated, history of prior quit attempts for both, the role of alcohol in smoking relapse, normative feedback on current drinking, and preliminary drinking goal setting.

We will recruit heavy drinkers interested in quitting smoking or interested in changing drinking; we will not require an interest in changing both. Unlike Dr. Kahler's study(39), participants with current alcohol dependence will be eligible to participate since the aim is to evaluate smoking treatments that could be applicable to a broader heavy drinking population, though severe alcohol dependent participants who require additional alcohol treatment will be excluded (see exclusion criteria). The intention is to improve smoking and drinking outcomes among heavy- drinking smokers. Thus, participants' motivation to change their behaviors will vary. In addition to the CBT skills above, motivational strategies will be utilized to support participants who are interested in

changing and encourage those who may be more ambivalent. These strategies include eliciting and reinforcing participants' self-motivational drinking statements, using reflective listening, and expressing acceptance and affirmation(80).

Participants will be advised to consider abstaining from drinking for the first 2 weeks of quitting smoking and ideally for the duration of treatment, regardless of their long-term drinking goals. They will be provided with specific strategies for moderating their alcohol use in addition to the general skills mentioned above. Likewise, participants will be advised that reducing their smoking, and ideally quitting smoking, is helpful for promoting better long-term drinking outcomes.

We will also provide varenicline to all participants in the pre-pilot and RCT pilot studies, instead of the nicotine patch as initially planned, for several reasons. Varenicline is a highly efficacious smoking cessation pharmacotherapy that yields higher smoking quit rates than bupropion and placebo (127, 128).

Among smokers who also drink heavily, varenicline is safe and well-tolerated (129, 130). Recent evidence also suggests that varenicline reduces alcohol craving and consumption among smokers (129, 130, 131) and nonsmokers (131). The results of focus group interviews with heavy drinking smokers recently completed by Dr. Fucito suggest additional benefits of varenicline. In interviews, participants expressed greater ambivalence about changing their drinking than smoking. Varenicline can reduce alcohol use in the absence of specific advice to change drinking among smokers not actively seeking alcohol treatment (129, 130). Participants also expressed greater dissatisfaction with using nicotine replacement therapies than other smoking pharmacotherapies. In contrast, the nicotine patch yields lower smoking quit rates than varenicline among all smokers (132) and in at least one study was associated with greater alcohol use among smokers compared to varenicline (133). Taken together, providing a pharmacotherapy intervention that is efficacious for both problems along with an integrated behavioral treatment makes sense for the purposes of this study. The two studies will allow for an investigation of whether CBT for SA can improve varenicline's efficacy for smoking cessation and drinking reductions in this population.

We will also recruit heavy drinkers who are smokers as defined by the CDC: report smoking 100 cigarettes or more in their lifetime and currently smoke at least twice weekly on average in the past 90 days. To verify smoking status, they must also have a urinary cotinine level of ≥30ng/mL by semi-quantitative urinalysis, and/or ≥2 on NicAlert dipstick. We propose this flexible definition of smoking for several reasons:

(1) This is a pilot feasibility study. We do not want to miss the opportunity to learn which heavy drinking smokers are interested in an integrated treatment, perceive it to be helpful, and actually benefit from it, due to making the smoking eligibility too narrow.
(2) Heavy drinking smokers are a diverse population. A sizeable portion of heavy drinkers smoke on a non-daily basis, only during drinking episodes. In 2010, the CDC reported that 21.8% of smokers were nondaily smokers. Nondaily smokers also have the highest rates of alcohol dependence (135).
(3) and seek smoking cessation treatment (136).
(4) Nondaily smokers have similar treatment needs as daily smokers. There is evidence that they extract similar levels of nicotine as daily smokers at a given number of cigarettes

smoked per day, suggesting that this subgroup could also benefit from pharmacotherapy treatment (137).

(5) Racial and ethnic minorities are more likely to report light or non-daily smoking (138, 139) so we do not want to limit our ability to recruit these populations of smokers.

(6) The results of a pilot study showed that varenicline was more efficacious than placebo or nicotine replacement therapy for smoking cessation in light smokers (138). Likewise, a retrospective evaluation of 36,594 French smokers offered smoking cessation services demonstrated that varenicline doubled quit rates among light smokers compared to nicotine replacement therapy (140).

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths.

This project involves three phases: (1) focus group interviews with heavy drinking smokers, (2) an open-label pre-pilot study with 10 heavy drinking smokers and (3) a randomized, controlled pilot study with 40 heavy drinking smokers.

Phase 1:
Focus Group Interviews: We will recruit up to 30 heavy drinking smokers to participate in 1 of 4 focus group interview sessions (approximately 7-8 smokers per group). Prior to each focus group, smokers will provide informed consent and complete self-report assessments (approximately one hour) as part of an intake visit. The assessments will be used to determine participant eligibility and to obtain baseline information on participants' smoking and drinking behavior. Participants will not complete all of the assessments that are listed for the pre-pilot and pilot RCT. Instead, they will complete an abbreviated intake to confirm they meet study eligibility and smoking and alcohol assessments.

The focus group interview (approximately 90 minutes in length) will evaluate heavy drinking smokers' perceptions about smoking and heavy drinking and their associated consequences, strategies they find helpful for managing these problems, and their preferences for components they would prefer in an integrated intervention to address both. We will use the results of the focus groups to create the pre-pilot version of the intervention that will take place in Phase 2 of the study. The PI, Dr. Lisa Fucito, along with Denise Romano, APRN, will facilitate the focus group interviews. Dr. Fucito and Ms. Romano will provide discussion prompts, moderate discussion, and maintain an open, supportive environment. They will utilize structured group discussion with standardized procedures (including audio-taping and think aloud methods).
A research staff member will also be present to hand transcribe smokers' responses as a back-up for the audio-recorders. The focus groups will be audiotaped and later transcribed.

Participants will be compensated $15 for completing the intake and $45 for completing the focus group interview.

At the end of the focus groups, transcripts will be reviewed and analyzed according to standardized coding procedures such as noting consistent themes, their frequency, and listing representative

quotations from transcripts. We will analyze detailed field notes from interviews with a content analysis approach that incorporates data display matrices to identify themes across participants. Questionnaire data will be analyzed descriptively, focusing on severity and frequency of smoking behavior and alcohol use. Common themes among smokers' suggestions will guide the intervention components for the pre-pilot study and pilot RCT in Phases 2 and 3.

We will not directly advertise the focus groups. Instead, we will rely on referrals from the Substance Abuse Treatment Unit clinic and from an ongoing study of varenicline for heavy drinking smokers, entitled "Multi-Site Study: Varenicline Treatment of Alcohol Dependent Smokers" **(**HIC#*1106008598*). The latter study is recruiting heavy drinking smokers for a clinical trial. A high percentage of potential participants who are screened are ineligible for the trial. Individuals who are not eligible for the varenicline trial will be provided with an opportunity to screen for this focus group study upon completion of their intake for the clinical trial **(**HIC#*1106008598*).

Phase 2:
Open-label Pre-Pilot Study: Heavy drinkers interested in quitting smoking (N=10) assigned to 8 sessions over 12 weeks of CBT for SA + 12 weeks of varenicline.

During this phase of the project, Dr. Fucito will develop and refine an integrated cognitive-behavioral psychotherapy intervention for smoking and heavy drinking (CBT for SA) and related therapist training materials in collaboration with study consultants. An initial manual will be tested in an iterative fashion with a small sample of heavy drinkers interested in quitting smoking (N=10). Dr. Fucito will be the study therapist for these participants. The same sample selection criteria, recruitment methods, study procedures, and assessments described for the RCT pilot study below will be used. Dr. Fucito will then review the results of the pre-pilot study with consultants to devise the final manual, therapist training materials, and adherence/competence process rating system for the RCT.

Several strategies will be utilized to evaluate the feasibility, utility, and acceptability of the manualized interventions. All sessions will be audiotaped. Participants will complete therapy satisfaction questionnaires after each session to rate positive and negative session aspects, their comprehension of the session content, perceived utility of the material, and their intentions to follow through with session assignments and recommendations. Participants' reported utilization of previously taught strategies/techniques at the beginning of sessions will also provide an index of the utility of specific intervention components. Dr. Fucito will record her experience implementing the interventions after each session. A trained RA will conduct taped individual structured exit interviews with participants to further assess participants' satisfaction with the interventions. Descriptive statistics will be used to analyze all of these process outcomes. After conducting psychotherapy sessions, Dr. Fucito will review session tapes, participant feedback and progress, and her experience conducting the sessions with consultants at regular meetings. The sessions will continue to be modified until they are deemed acceptable by participants based on satisfaction questionnaires.

Phase 3:

RCT Pilot Study: Heavy-drinking smokers interested in either quitting smoking or reducing their drinking (N=40) will be randomly assigned to 1 of 3 treatment conditions. At intake, participants will be asked which behavior they would like to change using scores on the Contemplation Ladder (see measures section). If participants have the same score for both, we will ask them to choose which one they would like to change.

For participants who state that they would prefer to quit smoking, we will randomly assign them to:

(1) up to 12 sessions over 12 weeks of CBT for SA + 12 weeks of varenicline or
(2) up to 12 sessions over 12 weeks of standard smoking counseling (SC) + 12 weeks of varenicline

For participants who state that they would prefer to reduce their drinking, we will randomly assign them to:

(1) up to 12 sessions over 12 weeks of CBT for SA + 12 weeks of varenicline or
(2) up to 12 sessions over 12 weeks of standard alcohol counseling (AC)+ 12 weeks of varenicline .

A detailed flow-chart of study procedures for Phase 3 is provided in the tables below based on participant condition assignment for either phase (i.e., CBT for SA, SC, or AC). Phase 2 will follow the same timeline except pre-pilot participants will not be asked to attend 2 research follow-up appointments.

Table of Study Procedures - Pre-Pilot

Timeframe	Study Phase	Study Procedures
Week -1	Intake	Assessment & screening
Week 0	Treatment	Receive counseling, start varenicline, health feedback
Week 1	Treatment	Receive counseling & varenicline
Week 2	Treatment	Receive counseling & varenicline
Week 3	Treatment	Receive counseling & varenicline
Week 5	Treatment	Receive counseling, varenicline, health feedback
Week 7	Treatment	Receive counseling & varenicline
Week 9	Treatment	Receive counseling,varenicline, health feedback
Week 10	Treatment	
Week 11	Treatment	Final counseling appointment, stop varenicline, health feedback

Table of Study Procedures - Pilot

Timeframe	Study Phase	Study Procedures
Week -1	Intake	Assessment & screening
Week 0	Treatment	Receive counseling, start varenicline, health feedback
Week 1	Treatment	Receive counseling & varenicline
Week 2	Treatment	Receive counseling & varenicline
Week 3	Treatment	Receive counseling & varenicline
Week 4	Treatment	Optional treatment/research appointment
Week 5	Treatment	Receive counseling, varenicline, health feedback
Week 6	Treatment	Optional treatment/research appointment
Week 7	Treatment	Receive counseling & varenicline
Week 8	Treatment	Optional treatment/research appointment

Week 9	Treatment	Receive counseling & varenicline
Week 10	Treatment	Optional treatment/research appointment
Week 11	Treatment	Final counseling appointment, final health feedback, stop varenicline
Week 15	Follow-up	Research follow-up appointment
Week 27	Follow-up	Research follow-up appointment

The following procedures only apply to Phases 2 and 3 of the study.

Recruitment:

Participants will be recruited through advertisements, press releases, posters/flyers, scratch pads, mailings to physicians, fax referral forms from physicians, and through websites (e.g., www.quitnet.com, www.google.com, www.craigslist.com, www.facebook.com). Participants will also be recruited through the Yale New Haven Hospital Tobacco Treatment Service. Patients who enroll in the Service and meet study eligibility criteria, will be given the option to participate. Prospective participants will be screened by phone and via a web-based screener on initial eligibility criteria.

Screening (Week -1):

Those who appear eligible on the basis of a phone screen or webscreener will be invited to attend an intake appointment with a study investigator or a research assistant at the Substance Abuse Treatment Unit (SATU), Yale New Haven Hospital Tobacco Treatment Service, or the Connecticut Mental Health Center (CMHC), 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. 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 and tobacco use histories, breath CO levels, breath alcohol levels will be obtained from all participants as well as urine samples for laboratory screening tests, including urine drug screening. Participants who screen positive for drugs, other than marijuana, will not be eligible for the study. Urine drug screens are performed using dip sticks which provide immediate results. The dip sticks are disposed of after obtaining drug screening results and no urine samples are further retained for this purpose. The results of urine drug screening are not included in the participant's research record.

If participants meet initial eligibility criteria, they will then be evaluated for final medical eligibility by a study advanced practice nurse or study physician. The research assistant and nurse/physician will review the risks, benefits and procedures involved in study participation and help eligible participants select a potential quit date which they will then finalize with their smoking counselor. 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 smoking cessation treatment. Those participants who meet inclusion criteria following the intake appointment will be assigned to 1 of 3 study groups (CBT for SA, SC, or AC) depending on the study phase. In the pre-pilot study, all participants will be assigned to CBT for SA and varenicline. In the pilot study, participants will be randomly assigned to either CBT for SA, SC, or AC plus varenicline. Participants will be blind to participant counseling assignment. Research and clinical staff will not be informed of the study hypotheses. Randomization will be stratified by gender (male, female) in order to balance treatment groups with respect to the proportion of women and men.

Treatment Phase - CBT for SA (Weeks 0 to 11):
Participants will begin varenicline on the first day of counseling.
Pre-pilot: In the pre-pilot study, Dr. Fucito will work with participants to identify the ideal smoking quit date. It is anticipated that participants will quit smoking within the first 2 weeks of treatment. This date will then be finalized for the RCT pilot study. At the first session (Week 0), clients will receive their personalized smoking, drinking, and health feedback report which they will review with their study therapist. The personalized feedback information will be repeated 3 more times during treatment to monitor participants' progress (i.e., Weeks 5, 8 or 9, and 11 – end of treatment). Participants will attend appointments to complete research assessments with a research assistant and receive individual counseling with a study therapist. Sessions will be weekly for the first 4 weeks (weeks 0, 1, 2, 3), then bi-weekly (weeks 5, 7, and 9). They will then return the two weeks later (Week 11) for termination. Counseling will focus on teaching skills to manage smoking cues and create environmental conditions that promote behavior change as well as behavioral activation and anger management techniques to promote positive mood. Participants will learn these skills generally and how to specifically apply them to quitting smoking and reducing their drinking. Sessions will utilize a motivational style to minimize participant resistance and emphasize personal responsibility for change. Smoking and alcohol use will be discussed at every session and participants will monitor both behaviors outside of session. Sessions will involve open-ended discussions of smoking and drinking patterns, pros and cons of smoking and drinking, how drinking and smoking are associated, history of prior quit attempts for both, the role of alcohol in smoking relapse, normative feedback on drinking, and preliminary drinking goal setting. Participants will be advised to consider abstaining from drinking for the first 2 weeks of quitting smoking and ideally for the duration of smoking cessation treatment, regardless of their long-term drinking goals. They will also be provided with specific strategies for moderating their alcohol use. Counseling will also include a review of participants' reactions to varenicline and medication compliance. We will reduce the varenicline dose for any participants who report difficulty tolerating higher doses.

Pilot RCT:
In the pilot study, study therapists will work with participants to plan a smoking quit date within the first 2 weeks of treatment. For participants receiving treatment through the Yale New Haven Hospital Tobacco Treatment Service, Dr. Fucito will serve as the study therapist. The smoking cessation treatment provided to study participants by Dr. Fucito through the Tobacco Treatment Service in this study is a reimbursable service and not a research cost. At the first session (Week 0), clients will receive their personalized smoking, drinking, and health feedback report which they will review with their study therapist. The personalized feedback information will be repeated 2 more times during treatment to monitor participants' progress (i.e., 1 time between Weeks 5-7 and Week 11 – end of treatment). Participants will attend appointments to complete research assessments with a research assistant and receive individual counseling with a study therapist. Sessions will be weekly for the first 4 weeks (weeks 0, 1, 2, 3), then the option to have bi-weekly thereafter (weeks 5, 7, and 9) or to continue weekly sessions until termination. They will then return for a final visit for termination (Week 11). Regardless of their decision, we will inform them that in order to get a final feedback report they will need to come in at Week 9 or 10 for a blood draw. Counseling will focus on teaching skills to manage smoking and drinking cues and create environmental conditions that promote behavior change as well as behavioral activation, relaxation

skills, and anger management techniques to promote positive mood. Participants will learn these skills generally and how to specifically apply them to quitting smoking and reducing their drinking. Sessions will utilize a motivational style to minimize participant resistance and emphasize personal responsibility for change. Smoking and alcohol use will be discussed at every session and participants will monitor both behaviors outside of session. Sessions will involve open-ended discussions of smoking and drinking patterns, pros and cons of smoking and drinking, how drinking and smoking are associated, history of prior quit attempts for both, the role of alcohol in smoking relapse, normative feedback on drinking, and preliminary drinking goal setting. Participants will be advised to consider abstaining from drinking for the first 2 weeks of quitting smoking and ideally for the duration of smoking cessation treatment, regardless of their long-term drinking goals and to consider reducing their smoking during the first 2 weeks of making drinking changes and ideally for the duration of alcohol treatment, regardless of their long-term smoking goals. They will also be provided with specific strategies for moderating their alcohol use and reducing their smoking. Counseling will also include a review of participants' reactions to varenicline and medication compliance. We will reduce the varenicline dose for any participants who report difficulty tolerating higher doses.

Treatment Phase – SC (Weeks 0 to 11)

Participants will begin varenicline on the first day of counseling and plan a smoking quit date within the first 2 weeks of treatment. At the first session (Week 0), clients will receive their personalized smoking and health feedback report which they will review with their study therapist. The personalized feedback information will be repeated 2 more times during treatment to monitor participants' progress (i.e., 1 time between Weeks 5-7 and Week 11 – end of treatment). Participants will attend appointments to complete research assessments with a research assistant and receive individual counseling with a study therapist. Sessions will be weekly for the first 4 weeks (weeks 0, 1, 2, 3), then the option to have bi-weekly thereafter (weeks 5, 7, and 9) or to continue weekly sessions until termination. They will then return for a final visit for termination (Week 11). Regardless of their decision, we will inform them that in order to get a final feedback report they will need to come in at Week 9 or 10 for a blood draw. In the SC control condition, counseling will focus on teaching skills to manage smoking cues and create environmental conditions that promote behavior change as well as behavioral activation, relaxation skills, and anger management techniques to promote positive mood. Participants will learn these skills generally and how to specifically apply them to quitting smoking. Sessions will utilize a motivational style to minimize participant resistance and emphasize personal responsibility for change. Smoking will be discussed at every session and participants will monitor their behavior outside of session. Sessions will involve open-ended discussions of smoking patterns, pros and cons of smoking, history of prior quit attempts for smoking, and preliminary smoking goal setting.
. Consistent with Tobacco Clinical Practice Guidelines for smoking cessation in heavy drinkers[81], participants will also receive brief advice to consider abstaining from alcohol or moderating their alcohol use for at least 2 weeks after quitting smoking and preferably during the duration of treatment. They will be provided with specific strategies for reducing their smoking. Counseling will also include a review of participants' reactions to varenicline and medication compliance. We will reduce the varenicline dose for any participants who report difficulty tolerating higher doses.

Treatment Phase – AC (Weeks 0 to 11)

Participants will begin varenicline on the first day of counseling and plan a smoking quit date within the first 2 weeks of treatment. At the first session (Week 0), clients will receive their personalized drinking and health feedback report which they will review with their study therapist. The personalized feedback information will be repeated 2 more times during treatment to monitor participants' progress (i.e., 1 time between Weeks 5-7 and Week 11 – end of treatment). Participants will attend appointments to complete research assessments with a research assistant and receive individual counseling with a study therapist. Sessions will be weekly for the first 4 weeks (weeks 0, 1, 2, 3), then the option to have bi-weekly thereafter (weeks 5, 7, and 9) or to continue weekly sessions until termination. They will then return for a final visit for termination (Week 11). Regardless of their decision, we will inform them that in order to get a final feedback report they will need to come in at Week 9 or 10 for a blood draw. In the AC control condition, counseling will focus on teaching skills to manage drinking cues and create environmental conditions that promote behavior change as well as behavioral activation, relaxation skills, and anger management techniques to promote positive mood. Participants will learn these skills generally and how to specifically apply them to reducing their drinking. Sessions will utilize a motivational style to minimize participant resistance and emphasize personal responsibility for change. Drinking will be discussed at every session and participants will monitor their behavior outside of session. Sessions will involve open-ended discussions of drinking patterns, pros and cons of drinking, history of prior attempts at changing drinking, and preliminary drinking goal setting. Participants will also receive brief advice to consider reducing their smoking to support long-term improvements in drinking. They will be provided with specific strategies for reducing their drinking. Counseling will also include a review of participants' reactions to varenicline and medication compliance. We will reduce the varenicline dose for any participants who report difficulty tolerating higher doses.

A total of 40 participants will be randomized to the RCT.

Varenicline Titration Schedule:
Tablets contain either 0.5 mg or 1mg active varenicline. Whenever participants start the study medication their dose will be slowly increased as follows:

Days 1-3: one 0.5mg tablet once per day
Days 4-7: one 0.5mg tablet twice per day
Day 8 – Week 11: one 1mg tablets twice per day

If participants experience any unpleasant side effects their medication dosage can be decreased. The study physician or nurse will check in with you by phone three days after you start your medication.

3-Day Call Back Phone Call:
In both conditions, within 3 days of either quitting smoking or changing their drinking, , participants will be briefly contacted by their study therapist to assess their experience quitting/reducing.

Research Follow-up (Phase 3 only: Weeks 15 and 27):
Participants will return 4 weeks and 16 weeks after completing treatment to complete an exit interview and follow-up assessments.

Participants will complete a SAFTEE (Systematic Assessment for Treatment Emergent Events) at each research appointment. Medication will be dispensed at the counseling appointments, and any unused medication will be returned. Breath CO levels, breath alcohol levels, blood pressure, weight, and self-reports of tobacco and alcohol use will be obtained at each appointment, and questionnaires will be administered. Urine cotinine and ethyl glucuronide levels will be measured at intake and Weeks 0, 11, 15, and 27 to provide indices of smoking and alcohol exposure. Blood samples for health feedback will be obtained at intake, Weeks 2-3 (pre-pilot only), 5-7, and 9- 10. A urine pregnancy test will be done for all menstruating before beginning the study and monthly during treatment. A positive pregnancy test will result in the participant being excluded from the study. Four weeks and 16 weeks after the treatment phase of the study is completed (i.e., Weeks 15 and 27), participants in Phase 3 only will return to the clinic to assess cigarette and alcohol use, breath CO, urine cotinine ethyl glucuronide, weight gain, and adverse events.

Retention of Participants:

To enhance retention, participants will be paid $10 for attending the intake and research appointments, and $20 each for the research follow-up appointments. The pre-pilot study involves an intake session and 8 research appointments for a total of $90 per participant. The RCT study involves an intake session, up to 12 research appointments, and two follow up sessions for a total of up to $170 per participant. Several procedures used to enhance adherence and retention include: (1) obtaining participant contact information and ≥2 collateral informants at enrollment; (2) thoroughly explaining study procedures; (3) rapidly assigning participants to treatment; (4) uniformly implementing procedures for non-adherence across study conditions; (5) providing appointment cards and reminder calls for all appointments; (6) contacting participants who miss sessions; (7) closely monitoring side effects, symptoms, clinical status, and participant concerns; (8) ensuring availability of staff for addressing concerns; and (9) reimbursing participants for time and effort[82]. Participants who drop out of treatment or are lost to follow-up will be compared to study completers to inform the interpretation of study results and improve retention rates in the next phase of intervention testing. Scheduled research data will continue to be obtained for participants who need to withdraw from treatment or who discontinue treatment.

For participants who discontinue the study during the treatment phase and are unreachable by phone or unresponsive to phone calls, we will mail a letter with a follow-up questionnaire and self-addressed stamped envelope. Some participants may indicate that they are unable to come to the clinic for an interview. If these participants are willing to meet a member of the research team at a public place, we will meet with them to collect follow-up data, including a breath carbon monoxide test, urine cotinine and ethyl glucuronide, weight, and, questionnaire data.

Study Counselors:

Dr. Fucito will be the pre-pilot study therapist. Four to six study therapists with experience in CBT and motivational substance abuse interventions will be the RCT therapists. Dr. Fucito is available to serve as one of the study therapists for the RCT but other therapists will be prioritized over Dr. Fucito; Dr. Fucito will serve as the study therapist for participants enrolled through the Tobacco Treatment Service at Yale New Haven Hospital. Therapists will be crossed across treatment conditions (i.e., all therapists will provide all treatments). Therapists will not be informed of the study hypotheses to reduce potential demand characteristics. The crossed design has the advantage of reducing potential therapist effects on treatment outcome(83). Although a contamination across conditions is a potential disadvantage of this crossed design(83), the design has the advantage of

reducing potential therapist effects which are large and could be problematic given the small sample size (84). To reduce contamination, therapists will be carefully selected and trained, provided with close supervision, and only informed of treatment assignment on the day of the session, therapy will be delivered using treatment manuals, and therapist will also be added as a random factor in analyses(84).

Counselor Training Seminars and Guided Feedback:
Counselors will receive careful training and close supervision by Dr. Fucito. Prior to treating participants, counselors will attend a training seminar over the span of 1 week (approximately 1 hour per day for each counselor for the CBT for SA, SC, and AC conditions). Counselor training will largely focus on learning how to deliver personalized health feedback about smoking- and drinking-related risks and cognitive-behavioral techniques to promote changes in smoking and drinking for heavy drinking smokers. Treatment manuals will be developed for all counseling conditions.

Counselor Certification:
Following this training, counselors will be assigned a training case that will be audiotaped. Specialist performance on the training cases will be evaluated on the basis of ratings by Dr. Fucito on an adapted version of the Yale Adherence and Competence Scale (YACS) (85) created specifically for this study by Dr. Fucito. Dr. Fucito will listen to counseling sessions from each counselor, rate sessions using the YACS, and give guided feedback to counselors in both conditions to help them develop their skills and meet certification standards that would permit them to receive Pilot Study participants. Dr. Fucito will certify counselors who use sufficient counseling strategies (an average of 4 on a 7-point scale across all adherence items) with a minimum of adequate skill (an average of 4 on a 7-point scale across all competence items). Dr. Fucito will continue to coach counselors until they become certified. During this training phase, there will be some leeway to alter the counseling protocols based on feedback from counselors and participants.

Counselor Supervision:
The CBT for SA and SC alone counseling procedures will be overseen by Dr. Fucito, with input from study consultants on an ongoing basis, and they will respond to problems and issues as they arise. Beginning with all training cases and continuing throughout the Phase II pilot study, all counselors will receive regular supervision and re-training on an individual and group basis. Supervision sessions will include review of study procedures, updates of case materials, review of digital recordings, and opportunities to discuss supervisor ratings. Continual review and supervision will help ensure that counselors' skills remain at a high level and prevent the use of counseling techniques or strategies that are inconsistent with the counselingprotocol. Supervision will ensure that counselors are primarily providing integrated cognitive-behavioral techniques for smoking and heavy drinking in the CBT for SA condition and primarily providing standard smoking counseling for the SC alone condition and standard alcohol counseling in the AC alone condition.

Adherence and Competence Ratings:
Establishing discrimination between the three conditions (CBT for SA versus SC or AC) is a priority. After completion of intervention delivery, tape ratings for fidelity analyses will be

conducted by 5 experienced raters blind to counselors' intervention condition. All therapy sessions will be digitally tape recorded and saved for supervision and training of study counselors and fidelity analysis. Consistent with other psychotherapy studies (e.g., Project MATCH)(79), a percentage of tapes collected post-intervention will be rated and assessed [i.e., approximately 20% (88/440)] which will consist of an equal number of tapes for each rater broken down as 44/44 for CBT for SA versus SC. Prior to tape rating, raters will receive training in fidelity analysis. Following training, intrarater reliability will be established by having all 5 raters rate an initial sample of approximately 10 tapes. A second calibration sample of 5 tapes will then be conducted to focus additional training efforts on items where reliability is not adequate (i.e., 5 raters x 5 tapes). A third calibration sample of 5 tapes will be conducted midway through the study tape rating phase to ensure raters maintain high levels of reliability (i.e., 5 raters x 5 tapes). All session recordings will be accessed via a secure server. Recordings will be loaded onto this server and accessed as links after logging in with a password. All recordings will be available to play but not to download, ensuring that confidential session data is not saved anywhere but on the secure server. This method has been used successfully by our research team for fidelity analysis in prior research. Thus, the requisite knowledge, programming, and infrastructure is in place to implement this system for the current study.

Assessments

We plan to assess a range of pretreatment participant characteristics, process measures, measures of treatment safety, and treatment outcomes. Intake assessments are designed to ensure that patients meet eligibility criteria and assess important predictor variables. After the narrative description of all assessments provided below, a schedule of the assessments is presented in Table 2.

Screening Measures

Medical History and Demographic Questionnaires: These questionnaires will obtain: (1) basic demographic information including age, gender, marital status, employment status, occupation and (2) alcohol/drug history. Medical history will also be obtained prior to randomization. The medical history and demographic measures will be administered for screening.

Diagnostic and Substance Use History: Sections of the Structured Clinical Interview (SCID) will be used to provide current and lifetime diagnoses of substance use and other Axis I psychiatric disorders at the recruitment session for all study phases. Specifically, participants will be characterized on their history of alcohol, drug, eating, panic disorder, psychosis, and mood disorders. The alcohol and nicotine sections of the SCID will be repeated at the end of treatment (EOT) and at follow up appointments.

Vitals – Two blood pressure readings will be obtained at each visit; the first by a research assistant and the second by the study physician or nurse.

Body Weight: will be measured at baseline, during treatment, and at follow-up in order to evaluate the effects of treatment and smoking cessation on weight gain.

Menstrual Cycle Assessment: All women will be assessed for their menstrual/gynecological status by self-report. Additionally, retrospective assessments of premenstrual symptoms will be obtained.

The Clinical Institute Withdrawal Assessment for Alcohol (Revised) (CIWA-AR): will be used to assess alcohol withdrawal symptoms for all study phases. The CIWA is a reliable 10-item instrument designed to assess severity of current withdrawal syndrome(86).

Columbia Suicide Severity Rating Scale: This questionnaire assesses past and current suicidal ideation, intent, and attempts (97). It will be used to monitor the possible suicidality of all study participants for all study phases, as well any potential contraindications. This will be assessed at all timepoints.

Urine pregnancy – 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.

Biological Markers of Tobacco and Alcohol Use

Carbon monoxide levels and urine cotinine levels will be monitored at intake to determine participant eligibility and to verify smoking abstinence during treatment. Although CO levels are typically used to verify abstinence during treatment, measurement of urine cotinine levels should cover a wider time window than exhaled carbon monoxide. Carbon monoxide levels will be measured using a Vitalograph Breath CO, from Vitalograph Inc. (Lenexa, Kansas), which is a precision instrument for detecting carbon monoxide in exhaled breath. Carbon monoxide is known to have a half-life of 2 hours in an active human (87). This instrument measures CO in the range of 0-500 ppm and has no cross sensitivity to hydrogen or other positive ions. Dr. Peter Jatlow will measure Cotinine levels in urine. Urine samples for cotinine will be obtained at intake and Weeks 0, 11, 15, and 27. Comparison of CO and cotinine during treatment with intake values will provide a within participant quantitative measure of changes in nicotine exposure and thus allow characterization of partial responders. Only a breath CO will be obtained for Phase 1 screening.

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[117-120]. A urine sample will be obtained at intake, Weeks 0, 11, 15 and 27. 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.

The EtG assays will be performed at Yale. Yale researchers are 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[120]. A concentration >500 ng/mL refutes a self report of "no heavy drinking" in the past 1-3 days[121] 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 ofspot 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 [119, 122] is validated and running.

Breath alcohol tests (BAC) will be conducted at each appointment to assess recent alcohol consumption. Participants will be asked to blow into a small tube for five seconds. The purpose of this test is to determine if participants can give consent and/or complete assessments and to assess potential risk of harm (e.g., driving above the legal limit). 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. Blood alcohol levels will be assessed prior to screening and focus groups for Phase 1. Participants who have blood alcohol levels higher than .00 will not be permitted to participate in the focus group interview. They will be rescheduled to attend another session.

Health Profile Measures - General Health Biomarkers (these will all be measured at intake and then weeks 2 or 3 (pre-pilot only), between 5 and 7 (treatment midpoint), and 9 or 10 (treatment completion))

Blood Chemistry Profiles: This comprehensive metabolic evaluation is used to assess general health and any potential adverse effects of the medication. The profile includes an evaluation of kidney and liver functions, renal function, glucose, cholesterol levels and blood count.

C-reactive protein test (CRP) and other makers of inflammation will be conducted at intake, then weeks 2 or 3,treatment midpoint (i.e., between Weeks 5 and 7), and treatment completion (i.e., 9 or 10). A CRP test is a blood test that measures the amount of a protein called c-reactive protein in the blood, C-reactive protein measures levels of inflammation in the body. Heavy alcohol consumption and smoking can cause such inflammation, thus inflammatory markers could act as

a measure of physical damage done to the body as a result of both. By repeating the tests during treatment, we will be able to observe whether decreases in heavy drinking and/or smoking are associated with decreases inflammatory markers.

Plasma carotenoids: Carotenoids are an important component of the antioxidant defense system in humans. Blood samples will be obtained at intake, at Weeks 3, treatment midpoint (i.e, between Weeks 5 and 7), and treatment completion (i.e., 9 to measure levels of plasma carotenoids. Participants will be informed of their carotenoid levels as part of their health feedback. This is assessed for the pre-pilot only.

Lung Function will be measured using a portable spirometer. At intake and Weeks 3 (pre-pilot only), between 5 and 7, and 9 or 10, participants will be asked to exhale a deep breath into a sensor for a minimum of six seconds, three different times. Participants will be presented with a brief description of the measures and a qualitative interpretation of the test results (i.e., normal functioning, mild/moderate/severe impairment, normal or reduced airflow, lung age, etc.).

Health Profile Measures - Cancer Risk

Lung cancer and oral cancer risks: Self-report data provided at intake pill be put into empirically derived cancer risk calculators. Cancer risks will be calculated at intake. Participants will be presented with a brief description of the cancer risks and a qualitative interpretation of the calculated results in their Week 0 feedback. These risks will not be calculated for subsequent feedback weeks because the short duration of smoking cessation and reductions in drinking will not likely have an impact on this calculation in the short term. This is assessed for the pre-pilot only.

The oral cancer risk calculator models the excess odds ratio to assess risk by total exposure (pack-years) and its modification by exposure rate (cigarettes/day) (124-126).

The CLEAR lung cancer risk prediction tool (123) will be used to quantify a smoker's risk of developing lung cancer in the next five, 10, or 15 years. This tool is based on the participant's age, sex, smoking history, medical history, family history of cancer, and past exposures to asbestos or wood dust.

Nicotine and Alcohol Use Measures

Smoking and Alcohol Use History Questionnaire: At intake for all study phases, this questionnaire will assess basic smoking status and history such as number of years smoked, type of cigarettes smoked, number and length of quit attempts, amount of money spent on smoking, concomitant smoking related health symptoms and syndromes. Similar questions will be asked about drinking history: age of first use, number and length of quit attempts, amount of money spent on drinking, concomitant drinking related health symptoms and syndromes.

Timeline Followback Interview (TLFB): This standardized, validated, and reliable experimenter-administered rating scale will be used to obtain quantity and frequency estimates of nicotine, alcohol and other drug consumption for a 90-day period prior to study enrollment for all study phases (88). It uses a calendar prompt and a number of other memory aids (e.g., holiday, payday,

and other personally relevant dates) to facilitate accurate recall of drug use during the targeted period, and it has demonstrated adequate levels of reliability and validity when administered as an in-person interview. We will use the calendar to record alcohol and tobacco use on a daily basis throughout the study.

Fagerström Test for Nicotine Dependence: This six item scale (89) will be used to measure severity of dependence on nicotine at intake for all study phases. It has an internal consistency of .61, and its total score is closely related to biochemical measures of intensity of smoking. An additional dichotomous item will be added to assess whether the participant wakes in the middle of the night to smoke.

Nicotine Withdrawal Checklist: This questionnaire (90) measures the severity of eight withdrawal symptoms on five point Likert scales. This will allow an examination of the relationship between self-reported levels of nicotine withdrawal, biochemical measures of nicotine use, cigarette craving, cigarette consumption, and sleep disturbance. This will be assessed at all timepoints.

Tiffany Questionnaire of Smoking Urges-Brief (QSU-Brief): The QSU-Brief is a ten-item questionnaire that assesses the structure and function of smoking urges (91). Participants will be asked to indicate how strongly they agree or disagree with each statement on a Likert-type scale of 1 (strongly agree) to 7 (strongly disagree). The Tiffany scale characterizes urges to smoke in response to two separate factors. The first factor is characterized by both desire and intention to smoke, and the second is related to relief from nicotine withdrawal or negative affect. This will be assessed at all timepoints.

Contemplation Ladders for Smoking and Drinking: 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 and Alcohol ladders will be administered at intake.

Alcohol Dependence Scale (ADS): This 25-item questionnaire assesses the severity of alcohol dependence including withdrawal symptoms, tolerance, impaired control over drinking, compulsion to drink, and drink-seeking behavior (93). This will be assessed at intake.

Obsessive Compulsive Drinking Scale (OCDS): This 14-item questionnaire assesses thoughts about drinking, urges to drink, and the ability to resist these thoughts and urges (94). This will be assessed at all timepoints.

Alcohol Use Disorders Identification Test (AUDIT): This ten-item questionnaire developed by the World Health Organization screens for hazardous or harmful alcohol consumption (134). Participants' AUDIT score will be provided to them on their personalized feedback report to given them an indication of their potential risk of harm from drinking.

Short Inventory of Problems (SIP-2R): This fifteen-item questionnaire measures physical, social, intrapersonal, impulsive, and interpersonal consequences of alcohol consumption and will be included in participant’s personalized feedback reports (135).

Psychological Related Measures

Positive and Negative Affect Schedule (PANAS): The PANAS is a self-report scale that contains two subscales to assess positive and negative mood. Both subscales contain 10 items that are measured on a Likert-type scale of 1 (not at all) to 5 (extremely) (96). This will be assessed at all timepoints.

Coping strategies to avoid cues: A questionnaire will be designed for this study to assess the participants' use of cognitive and behavioral coping strategies to avoid smoking and alcohol cues. This will be assessed at all timepoints.

Acceptance and Action Questionnaire II (AAQ II) (114): This 7-item questionnaire will measure the construct of psychological flexibility using a 7-point Likert type scale. It will be assessed at intake, week 11, and week 27.

Avoidance and Inflexibility Scale (AIS) (115): This 13-item scale will measure distress intolerance or inflexibility in response to smoking-related thoughts, feelings, and body sensations. This scale uses a 5-point Likert-type scale and will be assessed at intake, week 11, and week 27.

Depression Anxiety Stress Scale 21(DAAS-21) (116) : This 21-item self-report contains 3 subscales to assess depression, anxiety, and stress. All subscales contain 7 items using a 4-point Likert type scale. It will be assessed at all timepoints.

Social Network Information: Participants will be asked to list up to 9 people who provide them with emotional support or instrumental support and who are important. One additional name will be allowed if participants have a romantic partner. Network sizes, therefore, can range from 0 to 10. Participants will also indicate how many of these individuals smoke cigarettes and drink alcohol.

Cognitive Measures

Stroop Task (67): This task will be used to evaluate the effect of counseling on changes in self-control strength in response to smoking cues. Participants will be shown smoking-related, drinking-related words and neutral words matched for frequency and length in the English language that are displayed in 1 of 4 different ink colors. They will be asked to identify the color that they see (i.e., the color the word is printed in) and ignore what the word says (i.e., inhibit response to read word). Words will be presented in blocks with neutral words presented before smoking- and drinking-related words. Practice sessions will be administered for both tasks before the first test trials. This task will be administered at intake and Weeks 0, 5, and 11.

Medication Related Measures

Adverse Events Checklist (SAFTEE)(100): A checklist format will be used to obtain information about adverse events. This checklist 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 be asked to report any other concerns, which will be recorded individually. This information will be collected at all study time points.

Pill Counts: The number of returned varenicline pills will be used to monitor medication adherence.

Other Psychological Measures

Pittsburgh Sleep Quality Index (PSQI)(101): The PSQI will be used to evaluate habitual sleep quality, self-reports of quantitative aspects of sleep (e.g., duration, latency) and insomnia symptoms (perceived). It has a diagnostic sensitivity and specificity for distinguishing "good" vs. "poor" sleepers. This will be assessed at all timepoints (pre-pilot only) and intake and end of treatment for the RCT pilot.

Barratt Impulsivity Scale, Version 11 (BIS-11) (105): This 30-item questionnaire will assess general impulsiveness and specific impulsiveness along 3 domains (attentional impulsiveness [attention and cognitive instability], motor impulsiveness [motor and perseverance], nonplanning impulsiveness [self-control and cognitive complexity]).Items are scored on a 4-point scale. This will be assessed at intake.

Emotion Regulation Questionnaire (ERQ) (106). The ERQ is a 10-item self-report measure designed to assess individual differences in the use of two regulation processes: cognitive reappraisal and expressive suppression on 7-point scale. This will be assessed at intake..

Brief Self-Control Scale (B-SCS) (107). This 13-item measure of self-control is correlated with better adjustment, lower scores on measures of binge eating and alcohol abuse, lower ratings of psychopathology and anger, higher self-esteem, and a number of other measures of adjustment. This will be assessed at intake..

Treatment Evaluation

Client Session Report: Participants will complete a questionnaire at the end of each counseling session that is based on selected items from the Therapy Session Report (TSR)(108). The items will include: (1) an overall evaluation of the session from perfect to very poor; 2) a rating of therapist helpfulness from completely to not-at-all; (3) a rating of how well the participant felt understood by the therapist; (4) a rating of the extent to which the participant is looking forward to the next session; and (5) a rating of overall satisfaction with the session. During the pre-pilot, participants will be asked to evaluate specific treatment components that were discussed in each session (e.g., presentation of health feedback, discussion of social networks).

Client Treatment Evaluation Form: Participants will be asked at termination to rate components of the study treatment and provide reasons for termination (where relevant).

Table 1. Schedule of Assessments

Construct	**Assessments**	**Administered**		
	Baseline and Outcome Measures	*Intake*	*Treatment (Wks 0-11)*	*Follow-Ups (Phase 3 only, Wks 15 & 27)*
Demographic /Screening	Demographic Interview	X		
	SCID-I	X	11 (alcohol & drug)	X (alcohol and drug)
	C-SSRS	X	X	X

	Medical History	X		
	Clinical Institute Withdrawal Assessment for Alcohol	X		
Laboratory/ Medical	Physical Exam	X		
	EKG (if applicable)	X		
	Urine Drug Screen	X		
	Urine Pregnancy Screen	X	0,5,98	
	Weight and Vital Signs	X	X	X
	Menstrual Cycle Assessment	X	X	
	Blood Chemistry Profile	X	3,7,9	
	Plasma Carotenoids (pre-pilot only)	X	3, 7, 9	
	Inflammationmarkers	X	3, 7, 9	
	Spirometer	X	3, 7, 9 , ,	
	Cancer Risk Calculations (pre-pilot only)	X	3, 7, 9	
Biochemical Measures of Alcohol/Nicotine Use	Carbon Monoxide Breath Test	X	X	X
	Breath Alcohol Test	X	X	X
	Urine Cotinine	X	0,11	X
	Urine EtG Level	X	0,11	X
Alcohol/Nicotine Use Measures	Smoking and Alcohol History	X		
	Timeline Followback History	X	X	X
	Fagerström Test for Nicotine Dependence		0,11	
	ADS	X		
	Nicotine Withdrawal Checklist	X	X	X
	QSU-Brief	X	X	X
	Contemplation Ladders for Smoking and Drinking	X		
	OCDS	X	X	X
	Stroop Task		0,5,11	
	AUDIT	X		
	SIP-2R	X	10	
Psychological	PANAS	X	X	X
	Cue Avoidance Coping Strategies	X	X	X
	AAQ-II	X	11	27
	AIS	X	11	27
	DAAS-21	X	X	X
	Social Network Information	X		
	PSQI	X	X (pre-pilot only)	X
	BIS-II	X		
	ERQ	X		
	B-SCS	X		
Treatment Evaluation	Client Session Report		X	
	Client Treatment Evaluation Form		Week 11	
Medication Measures	SAFTEE	X	X	X
	Pill Counts		X	

	Concurrent Medications	X	X	X

4. Genetic Testing N/A ☒

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned

ii. the plan for the collection of material or the conditions under which material will be received

iii. the types of information about the donor/individual contributors that will be entered into a database

iv. the methods to uphold confidentiality

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?

C. Is widespread sharing of materials planned?

D. When and under what conditions will materials be stripped of all identifiers?

E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?

i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

F. Describe the provisions for protection of participant privacy

G. Describe the methods for the security of storage and sharing of materials

5. Statistical Considerations: Describe the statistical analyses that support the study design.

Primary Outcomes: Smoking abstinence will be defined as self-reported non-smoking and an expired carbon monoxide level of <10 ppm. The primary smoking outcome will be point prevalence smoking abstinence (PPA) over the last 7 days at 6 months post treatment start. The primary drinking outcome will be the percentage of heavy drinking days at 6 months.

Secondary Outcomes: Secondary smoking outcomes will include continuous smoking abstinence over the entire treatment period and PPA over the last 7 days of treatment and 3 month follow-up. Secondary drinking analyses will include the number of drinks per drinking occasion and the number of abstinent days during this time period. The effects of treatments on these primary and secondary outcomes will also be explored for the treatment period. The effects of treatments on measures of sleep and depression/mood will also be examined in exploratory analyses.

RCT pilot data analyses will focus on evaluating the efficacy of CBT for SA for promoting smoking abstinence and reducing heavy alcohol use using mixed effects models because of their allowance for missing data by analyzing all available data on participants. Data will also be analyzed by imputing missing smoking data due to attrition or non-response, assuming relapse to smoking as is standard in the tobacco research field[110-112]. Sample size is not likely to be sufficient to establish statistical significance but rather a pattern of results that suggest promising effects across smoking and alcohol outcomes. RCT pilot data will be used in power calculations (to

calculate sample size) for a later, full-scale RCT of CBT for SA. Prior to assessing primary analyses, Dr. Fucito will conduct: (1) univariate analyses to verify normality assumptions and (2) bivariate analyses to evaluate baseline equivalence between groups and significant covariates. If normality is an issue, Dr. Fucito will perform non-parametric analyses.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS and BIOLOGICS

1. **Identification of Drug or Biologic:** What is (are) the **name(s)** of the drug(s) or biologic(s) being used? Identify whether FDA approval has been granted and for what indication(s).

We will be using varenicline (Chantix) 0.5 and 1 mg. The FDA has approved varenicline for smoking cessation and will be used at the approved dose of 2 mg/day for this study.

All protocols which utilize a drug or biologic **not** approved by, but regulated by, the FDA must provide the following information:

Not applicable to this project.

a. What is the Investigational New Drug (IND) **number** assigned by the FDA?

b. Who holds the IND?

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1
The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. ☐ Yes ☐ No
ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. ☐ Yes ☐ No
iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. ☐ Yes ☐ No
iv. The investigation will be conducted in compliance with the requirements for institutional (HIC)

review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☐ Yes ☐ No

v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☐ Yes ☐ No

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐ i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

- ☐ Blood grouping serum
- ☐ Reagent red blood cells
- ☐ Anti-human globulin

☐ ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐ iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

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 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, if clinically warranted, an 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.

On March 9, 2015, the FDA updated the label for varenicline to include potential alcohol interaction, rare risk of seizures, and studies of side effects on mood, behavior, or thinking. This update includes evidence of patients who drank alcohol during treatment with varenicline experiencing decreased tolerance to alcohol, including increased drunkenness, unusual or

aggressive behavior, or they had no memory of things that happened. We will warn patients about these risks and encourage participants to be careful about their alcohol intake until they know how varenicline affects them.

This new label update also includes evidence of patients experiencing seizures while taking varenicline both among individuals with no prior history and among those with a prior disorder that had been well-controlled. We will warn patients about these risks. We currently exclude individuals who have ever experienced a seizure due to alcohol withdrawal. We will extend this exclusion to anyone who has ever had a seizure as well as individuals who are currently prescribed medications known to reduce seizure threshold. Patients will be advised to discontinue varenicline and immediately seek medical care if they experience this reaction.

3. **Source:** a) Identify the source of the drug or biologic to be used.

b) Is the drug provided free of charge to subjects? ☐ Yes ☒ No
If yes, by whom?

Pfizer produces varenicline and we will purchase study medication (active) from them through the CMHC Pharmacy. The CMHC Pharmacy will package the medications into blister packs. For participants enrolled through the Yale New Haven Hospital Tobacco Treatment Service, they will pickup their medication from their local pharmacist. The medication will be dispensed in blister packs by their local pharmacist.

4. **Preparation and Use:** Describe the method of preparation, storage, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
Check applicable Investigational Drug Service utilized:

☐ **YNHH IDS**	☐ **Yale Cancer Center**
☒ **CMHC Pharmacy**	☐ **West Haven VA**
☐ **Other:**	☐ **None**

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

Varenicline will be stored at the CMHC pharmacy according to the manufacturer's instructions for participants who are not enrolled via the Yale New Haven Hospital Tobacco Treatment Service. Participants will be instructed to take them per study protocol.

5. **Use of Placebo:** ☒ **Not applicable to this research project**
If use of a placebo is planned, provide a justification which addresses the following:
a. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.
b. State the maximum total length of time a participant may receive placebo while on the study.
c. Address the greatest potential harm that may come to a participant as a result of receiving placebo.
d. Describe the procedures that are in place to safeguard participants receiving placebo.

6. **Use of Controlled Substances:**

Will this research project involve the use of controlled substances in human subjects?
☐ Yes ☒ No *See HIC Application Instructions to view controlled substance listings*.

If yes, is the use of the controlled substance considered:
☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. Continuation of Drug Therapy After Study Closure ☒ **Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☐ No If no, explain why this is acceptable.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at YNHH, e.g., YNHH Operating Room or YNHH Heart and Vascular Center? Yes ☐ No ☒
If Yes, please be aware of the following requirements:

a. A YNHH New Product/Trial Request Form must be completed;

b. Your request must be reviewed and approved by a Hospital Committee before patients may be scheduled; and

c. The notice of approval from YNHH must be submitted to the HIC for the protocol file.

Please contact Gina D'Agostino, gina.d'agostino@ynhh.org or 688-5210, to initiate the process.

2. What is the name of the device to be studied in this protocol?

Has this device been FDA approved? ☐ Yes ☐ No
If yes, state for what indication.

3. Background Information: Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

4. Source:
a) Identify the source of the device to be used.

b) Is the device provided free of charge to subjects? ☐ Yes ☐ No

5. What is the PI's assessment of risk level (significant or non-significant) associated with the use of the device?

☐ **Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

What is the **IDE number** assigned by the FDA?

Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (non-experimental/investigational)?

Who holds the IDE?

☐ **Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. *See the criteria in the HIC Application Instructions,* Section VI.B.4 at http://ycci.yale.edu/comply/Images/10605-FM.A_NewStudyRequest_tcm426-65904.pdf *to determine if these pertain to this study.*

☐ **Abbreviated IDE or Exempt IDE** – *If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.*

7. Investigational device accountability:

a. State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):

Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):

Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations:

Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:

Distributes the investigational device to subjects enrolled in the IRB-approved protocol:

SECTION VII: HUMAN SUBJECTS

1. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

   Participants will be 80 male and female volunteers, 18 years of age or older, who report smoking and heavy alcohol use and seek smoking cessation treatment (plus 4 pilot subjects not included in study analyses). 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: White (not Hispanic) 70%, Black 17%, White (Hispanic) 10%, Asian/Asian Indian 3%. Children under 18 will be excluded from participating.

2. **Subject classification:** Check off all classifications of subjects that will be <u>targeted for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☒ Females of childbearing potential	

   NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #2 for further requirements)

3. **:** What are the criteria used to determine subject inclusion or exclusion?

   <u>Participants will be eligible for *either* the focus group, pre-pilot trial or randomized, controlled pilot trial if they:</u>
   (1) are at least 18 years of age;
   (2) report smoking 100 cigarettes or more in their lifetime and currently smoke at least twice weekly on average in the past 90 days and have a urinary cotinine level of ≥30ng/mL by semi-quantitative urinalysis, and/or ≥2 on NicAlert dipstick;
   (3) are interested in quitting smoking;
   (4) understand English;
   (5) exceed NIAAA heavy drinking criteria (i.e., for men, >14 drinks/week or 5 drinks/day at least once per month over the past 12 months; for women, >7 drinks/week or >4 drinks/day at least once per month over the past 12 months.

Participants will be excluded from either study if they:
(1) meet criteria for alcohol dependence in the past 12 months that is clinically severe defined by; a) a history of seizures, delirium, or hallucinations during alcohol withdrawal;
b) a Clinical Institute Withdrawal Assessment scale (Sullivan et al., 1989) score of > 8;
c) report drinking to avoid withdrawal symptoms, or d) have had prior treatment of withdrawal;
d) have required medical treatment of alcohol withdrawal within the past 6 months;
(2) are currently enrolled in alcohol treatment;
(3) meet criteria for drug dependence in the past 12 months; with the exception of marijuana dependence
(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 suicidality (past 12 months), or report any suicide attempts within the past year, assessed with the Columbia Suicide Severity Rating Scale. Individuals with a history of any suicide attempts need to be evaluated by the study psychiatrist for inclusion in the stdy;
(6) 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;
(7) are cognitively impaired;
(8) are unable to read/understand English;
(9) 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);
(10) report new onset of psychiatric disorders or new psychotropic medications within the past 3 months, except individuals who are on a stable dose of a Selective Serotonin Reuptake Inhibitor for at least two months or who report occasional use of prescription sleep aids that they are willing to discontinue;
(11) 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)
(12) intend to donate blood or blood products during the treatment phase of the study;
(13) have a history of serious hypersensitivity reactions or skin reactions to varenicline
(14) history of seizures or use of medications known to lower seizure threshold

4. 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 advanced nurse practitioner/physician's evaluation.

5. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/Web Postings	☒ Radio
☒ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☒ Letter	☒ Departmental/Center Website	☒ Television
☒ Medical Record Review	☐ Departmental/Center Research Boards	☒ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	
☐	☒	
Other (describe):	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.quitwithyale.org, www.quitnet.com, www.google.com, www.craigslist.com, www.facebook.com) as well as direct referrals from a clinical trial recruiting a similar subject population (HIC#1106008598) (see Appendix A). Prospective participants will be screened by phone 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 screening form are attached for your review. All potential participants must contact us directly.

6. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Potential participants will primarily be identified through four mechanisms: (1) self-referral, by contacting research staff directly in response to study advertisements, (2) referral by their health care provider or other study, (3) participants referred to the Tobacco Treatment Service and meet study eligibility criteria will be offered the chance to participate in the study protocol with Dr. Fucito.

b. Describe how potential subjects are contacted.

Potential participants can contact research staff directly via phone or email. Study contact information is posted on advertisements. Potential participants who send emails or leave voicemail messages will then be contacted directly by research staff in compliance with HIPAA guidelines.

c. Who is recruiting potential subjects?

Dr. Fucito, study consultants, and study staff will be involved in the recruitment of potential participants.

7. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No

b. If yes, identify any health information and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION: Pregnancy/nursing status, treatment for any medical problem, medications or prescription drug use, allergies, seizures, history of cancer, treatment for emotional or psychiatric difficulties.

HIPAA identifiers:

☒ Names

☐ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☒ Telephone numbers

☐ Fax numbers

☒ E-mail addresses

☐ Social Security numbers

☐ Medical record numbers

☐ Health plan beneficiary numbers

☐ Account numbers

☐ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers, including license plate numbers

☐ Device identifiers and serial numbers

☐ Web Universal Resource Locators (URLs)

☐ Internet Protocol (IP) address numbers

☐ Biometric identifiers, including finger and voice prints

☐ Full face photographic images and any comparable images

☐ Any other unique identifying numbers, characteristics, or codes

8. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects

☒ Yes, some of the subjects

☐ No

If yes, describe the nature of this relationship.

Dr. Fucito, the Director of the Tobacco Treatment Service will be providing some clinical services to participants enrolled via that Service, in addition to directing the head of the research team.

9. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one: For entire study:_____For recruitment purposes only:____X___

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

The majority of potential participants first contact research staff by phone. In our experience, very few individuals present in person to inquire about the study and complete the pre-screening process. During the phone screening process, individuals provide verbal consent. The collection of PHI is limited to information that is necessary to confirm basic eligibility such as age. If an individual is not eligible, no other PHI or contact information is obtained. If an individual meets pre-screening eligibility and would like to schedule an in-person screening appointment, his/her name and phone number is then obtained. This information is obtained in order to identify the individual on the day of screening (i.e., potential participants need to provide valid identification at intake) and to provide the individual with a reminder call the day before the appointment. It would not be practical to have potential participants provide signed authorization at the time of recruitment over the phone. It presents an extra hurdle and potential waste of time for potential individuals when inquiring about the study. This system provides a more efficient method for pre-screening individuals and ensuring that the majority of individuals who are scheduled for an in-person intake appointment are likely to be eligible.

Potential participants may first contact research staff through the webscreener. During the webscreening process, participants are not permitted to advance to the screening survey until they select the "yes" option agreeing that they have read and understood the disclaimer. The collection of PHI is limited to information that is necessary to confirm basic eligibility such as age, information to contact the individual with their eligibility status such as email and phone number (the latter is optional, the former is not), and IP address. Once the participant's eligibility has been reviewed and they have been contacted, their webscreener entry will be deleted.

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

SECTION VIII: CONSENT/ ASSENT PROCEDURES

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

   Initial consent will be obtained by the research assistant at the screening appointment, however, one of the study investigators will meet with the participant to review the consent document prior to final determination of eligibility, and at the beginning of any study procedures beyond those needed for determining eligibility. Obtaining consent will be: Lisa Fucito, Susan Neveu, Denise Romano, Christine Nogueira, Tess Hanrahan, and Abedalrazaq Alkukhun.

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 first intake 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 medication at intake.

2. **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. During the consenting process, the research assistant will read and review the consent form with the prospective participant. The research assistant will then ask the potential participant various questions about the consent form and study protocol to ensure the prospective participant sufficiently understands the study and the nature of their consent to participate.

3. **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.

4. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

   This project will not enroll non-English speaking participants.

5. **Waiver of Consent:** Will you request either a waiver of consent, or a waiver of signed consent, for this study? If so, please address the following:

☒ **This section is not applicable to this research project**

Waiver of consent: (No consent form from subjects will be obtained.)

a. Does the research pose greater than minimal risk to subjects? ☐ Yes ☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

Waiver of **signed** consent: (Verbal consent from subjects will be obtained for recruitment.)

☐ **This section is not applicable to this research project**

a. Would the signed consent form be the only record linking the subject and the research? ☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects? ☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☒ Yes ☐ No **AND**
d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☒ No

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:

☒ Compound Consent and Authorization form
☐ HIPAA Research Authorization Form

SECTION IX: PROTECTION OF RESEARCH SUBJECTS

1. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, 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. A recent review of neuropsychiatric events across 17 placebo-controlled trials of varenicline for smoking cessation demonstrated that varenicline increased risk of nausea but did not increase the risk for suicidal events, depression, or aggression/agitation (141). The study concluded that varenicline has substantial benefit for smoking cessation without evidence of risk of serious psychiatric events among individuals with and without a recent psychiatric history.

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 have been reports of seizures in patients taking varenicline (Chantix) with and without a prior seizure history. We will warn patients about these risks. We currently exclude individuals who have ever experienced a seizure. Patients will be advised to discontinue varenicline and immediately seek medical care if they experience this reaction.

There have been reports of reduced tolerance to alcohol in patients taking varenicline (Chantix). In some cases, patients reported increased intoxication, unusual or aggressive behavior, or an inability to remember things that had happened. We will warn patients about these risks and encourage participants to be careful about their alcohol intake until they know how varenicline affects them.

In post-marketing, the FDA identified 48 cases of adverse events involving decreased tolerance to alcohol (n=11) or aggressive behavior (n=37) in patients taking Chantix and who also consumed alcohol that occurred since Chantix (varenicline) was approved in 2006. The Chantix label has been updated with the warning that some people have reported increased drunkenness, unusual or sometimes aggressive behavior, or memory loss of events while consuming alcohol during treatment with varenicline. As a result, we will advise participants of this potential and instruct them to decrease their drinking and contact us if they find varenicline affects their ability to tolerate alcohol.

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, if over the age of 40 or if clinically warranted, an 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 subjects. 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 4 ounces of blood over the entire course of the study; 3 ounces each at intake and Weeks 2 or 3 (pre-pilot only), between 5 and 7 and 9 or 10. 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.

2. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized. Effective screening will exclude all subjects who would be at greater risk for complications because of unstable medical or psychiatric illnesses. Subjects 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 who are over the age of 40, or who clinically warrant, 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 nicotine patch during pregnancy, the following precautions will be taken for women: 1) urine pregnancy tests will be performed at intake and pregnant or nursing women will be excluded from participation and referred to other smoking cessation 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) a urine pregnancy test will be performed again at Week 0 (before starting varenicline) and Weeks 4; if a woman becomes pregnant, she will be withdrawn from the study and referred to alternative treatments; 4) a menstrual cycle timeline will be 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 subjects' 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?

We view the use of varenicline and counseling for smoking among heavy drinking smokers to represent moderate risk to subjects.

    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

    c. Copy, paste, and then tailor an appropriate Data and Safety Monitoring Plan from http://www.yale.edu/hrpp/forms-templates/biomedical.html for
        i. Minimal risk
        ii. Greater than minimal/moderate risk
        iii. High risk

The DSM plan must designate an experienced, qualified professional (usually the PI) who can distinguish a serious adverse event (SAE) from a non-serious adverse event (AE).

Dr. Fucito is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews *quarterly.* During the review process Dr. Fucito will evaluate whether the study should continue unchanged, require modification/amendment, continue

or close to enrollment. Either Dr. Fucito, the Human Investigation Committee (HIC) or Human Subjects Committee (HSC) or the National Institutes of Health have the authority to stop or suspend the study or require modifications.

The pre-pilot and the pilot are open-label studies of an FDA-approved smoking cessation medication that is not contraindicated for this population/./As it it not a Phase III trial, the safety of the patients will be monitored by Dr Fucito, Dr. O'Malley, the study nurse practitioner Denise Romano, APRN, and the Study Physician Srinivas Muvvala, MD, during Dr. O'Malley's weekly Clinical Trials meeting in which study participants are reviewed and monitored.

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 as follows:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by Dr. Fucito according to the following categories:

a.) Definite: Adverse event is clearly related to investigational agent/participation.
b.) Probable: Adverse event is likely related to investigational agent/participation.
c.) Possible: Adverse event may be related to investigational agent/participation.
d.) Unlikely: Adverse event is likely not to be related to the investigational agent/participation.
e.) Unrelated: Adverse event is clearly not related to investigational agent/participation.

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 in 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.

In addition to grading the adverse event, the Dr. Fucito will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. is life-threatening
2. results in in-patient hospitalization or prolongation of existing hospitalization
3. results in persistent or significant disability or incapacity
4. results in a congenital anomaly or birth defect OR
5. results in death
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
7. adversely affects the risk/benefit ratio of the study

The DSM plan must indicate that serious adverse events will be reported to the local IRB and to the NIAAA project officer within 48 hours.

Subjects will be closely monitored for treatment response and safety through regular assessment sessions; these will include breath alcohol screens and assessment of psychiatric status. Although in our experience this is a very rare event in behavioral trials and trials of the nicotine transdermal patch, subjects who show significant deterioration (e.g., increased substance use or psychiatric symptoms that cannot be managed within the protocol, including significant suicidal or homicidal ideation) will be regarded as symptomatic failures, withdrawn from the treatment arm of the study, and referred for appropriate treatment (typically a more intensive level of care). The independent evaluator (study physician) will make the final determination as to whether a subject should be withdrawn from the treatment arm of the study. At the time of withdrawal, endpoint ratings will be made which include the full termination assessment battery.
Subjects in all conditions are also able to call the Substance Abuse Treatment Unit (i.e., the clinic location for the trial) on-call clinician at any time should questions or concerns arise; emergency services are available through SATU and the Connecticut Mental Health Center.

Subjects who experience a significant psychiatric or medical problem requiring an overnight hospitalization at an acute care facility will be considered to have experienced an SAE. In general, most SAEs will result in inpatient care and thus a transfer from our outpatient research clinic at SATU. Dr. Fucito is experienced with these procedures as a clinician at SATU and has worked out similar procedures to be followed for this trial.

The Principal Investigator, Dr. Fucito, will report the following types of adverse events to the Yale University Human Investigation Committee (HIC) and the NIAAA Project Office (Joanne Fertig, Ph.D.): a) serious AND unanticipated AND possibly, probably or definitely related events; b) anticipated adverse events occurring with a greater frequency than expected; and c) other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the both the Yale HIC and NIAAA within 48 hours of it becoming known to Dr. Fucito. The procedures for SAE reporting include written documentation using the clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel. Communication of recommendations and decisions from all parties (Yale Human Investigation Committee) will be made back to Dr. Fucito in a timely manner.

The DSM plan must indicate that an annual report will be submitted to the NIAAA Project Officer summarizing all adverse events.

The Yale Human Investigation Committee requires yearly reporting of all SAEs (including those that are anticipated and unrelated). This annual report will also be submitted to the NIAAA Project Officer (Joanne Fertig, Ph.D.).

The DSM plan must specify that female subjects who are pregnant, nursing, or not using effective methods of birth control will be excluded from studies involving the administration of alcohol and/or drugs.

Given the uncertain effects of varenicline use during pregnancy, the following precautions will be taken for female subjects: 1) urine pregnancy tests will be performed at intake and pregnant or nursing women will be excluded from participation and referred to other smoking cessation and alcohol treatment programs; 2) women must agree to use a reliable method of birth control while they are in the study and to alert Dr. Fucito and/or study staff if she departs from her birth control plans or if, in spite of adherence to these plans, she thinks she might be pregnant; 3) a urine pregnancy test will be performed again at the visit before starting varenicline; if a woman becomes pregnant, she will be withdrawn from the study and referred to alternative treatments; 4) a menstrual cycle timeline will be completed at each appointment during treatment, and if the woman's menses is late, a urine pregnancy test will be obtained.

If the study has a follow-up phase, there must be a specific plan for referral to treatment during follow-up of any respondent requiring additional intervention due to significantly increased alcohol consumption or serious psychiatric/medical symptoms.

The same procedures for monitoring subjects for potential serious adverse events and/or the need for additional treatment will be used during the research follow-up phase including the regular use of breath alcohol screens and assessment of psychiatric status.

Subjects who show significant deterioration (e.g., increased substance use or psychiatric symptoms including significant suicidal or homicidal ideation) will be referred for appropriate treatment (typically a more intensive level of care) in consultation with the study physician.

The DSM plan must indicate that all adverse events during follow-up will be reported (SAEs within 48 hours) to the IRB and NIAAA.

During follow-up, subjects will also able to call the Substance Abuse Treatment Unit (i.e., the clinic location for the trial) on-call clinician at any time should questions, concerns, or the need for emergency services arise.

During the follow-up period, Dr. Fucito will report the following types of adverse events to the Yale University Human Investigation Committee (HIC) and the NIAAA Project Office (Joanne Fertig, Ph.D.): a) serious AND unanticipated AND possibly, probably or definitely related events; b) anticipated adverse events occurring with a greater frequency than expected; and c) other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the both the Yale HIC and NIAAA within 48 hours of it becoming known to Dr. Fucito. The procedures for SAE reporting include written documentation using the clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel. Communication of recommendations and decisions from all parties (, Yale Human Investigation Committee) are made back to Dr. Fucito in a timely manner.

d. For multi-site studies for which the Yale PI serves as the lead investigator:
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?

ii. What provisions are in place for management of interim results?
iii. What will the multi-site process be for protocol modifications?

Not applicable

4. Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Identifiable information including participant's name, address, phone number, date of birth, social security number, and medical history will be collected and used to enroll, treat, and contact participants. It will only be used for this purpose. Given that this trial involves the administration of medication, a medical record must be generated from each participant that is separate from the research record, so that participants may be admitted to the clinic as an outpatient. The medical records will be stored in locked cabinet apart from the research records. The medical record will include some private identifiable information.

The medical records for participants enrolled and treated via the Yale New Haven Hospital Tobacco Treatment Service are in an electronic format on a secure YNHH server apart from the paper research records.

b. How will the research data be collected, recorded and stored?

Research data will be collected using in-person physical examination, laboratory testing, interviews, and self-reports. All identifiable information will be stored in a locked research cabinet. All participants will be assigned a study participant number. Subsequently, participants will be identified in the Case Report Forms (CRFs) only by that number and an encoded version of their initials (i.e., John Doe = JDO). A list of numbers and the corresponding names will be maintained by the Principal Investigator and stored in a locked research cabinet.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☒ Desktop Computer ☐ Other

Digital data with PHI will be stored on a secured server. Digital data without PHI may be stored and analyzed on a laptop or desktop computer.

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

Several steps will be taken to safeguard the confidentiality of subjects and their data. All research data that is collected will be assigned a study participant number and that number will only identify participants in digital databases. The names of participants will not be associated with this data and assessments will be maintained according to participant study number. A master list connecting participant study numbers to participant names will be kept in a locked file cabinet where it can only be accessed by senior level project staff. Any information published as a result of the study will be such that it will not permit identification of any participant.

The clinic records are maintained under the person's name, but the study number is not entered anywhere into that record. Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. The Principal Investigator will maintain a list of numbers and the corresponding names in a locked research cabinet. Consistent with mandated reporting requirements for health providers, we advise participants that in the case of child abuse or neglect, threat of injury to self or others, or intention to destroy property, that we may need to intervene and report that information to the proper authorities. Subjects will be informed of this limit to confidentiality as it is stated in the informed consent document.

All investigators and key personnel have taken the required Yale University HIPAA training. Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. A list of numbers and the corresponding names will bemaintained by the Principal Investigator in a locked research cabinet.

In addition, a Certificate of Confidentiality has been obtained from NIAAA. This certificate protects the confidentiality of all research records generated by this study. The certificate does not protect clinic records and participants will be advised of this during the consent process. However, individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 and by additional protections of substance abuse treatment records afforded under Code of Federal Regulations (CFR) Part 2, Subpart E. All research personnel will be trained on human subjects protection and HIPAA procedures.

Do all portable devices contain encryption software? ☒ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

The data will be stored in a locked room for 7 years after the final data is collected. After this point, the Data Manager and Dr. Fucito will oversee the process in which data is destroyed or de-identified.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, QUACS, SSC, etc.)? (please distinguish between PHI and de-identified data)

Organizations that have a responsibility for protecting human participants, including Yale Human Investigation Committee, may have access to subjects' medical records containing PHI. Additionally, the funding agency (NIAAA) may have access to subjects' medical records containing PHI.

g. If appropriate, has a Certificate of Confidentiality been obtained?

A Certificate of Confidentiality from the National Institute of Alcohol Abuse and Alcoholism/Department of Health and Human Services has been obtained. This certificate protects the confidentiality of all research records generated by this study. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996. All research personnel will be trained on HIC and HIPAA procedures.

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

All information collected will remain confidential except when we are legally required to disclose such information by law. These circumstances include knowledge of abuse of a child or elderly person, threats of harm to self or others, and threats of harm to property. Subjects will be informed of this limit to confidentiality as it is stated in the informed consent document.

SECTION X: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

There is a need to improve smoking cessation therapies. The purpose of this study is to determine the overall effectiveness of a combined psychotherapy intervention for smoking and alcohol for improving smoking quit rates and drinking outcomes in heavy-drinking smokers. By addressing barriers to treatment (i.e., alcohol use), this study may help to engage more smokers into treatment and reduce the enormous health care costs and loss of lives associated with cigarette smoking.

SECTION XI: 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 over the counter smoking cessation treatments such as nicotine replacement therapy. Participants may get prescriptions from their physicians for bupropion, the nicotine nasal spray, or the nicotine inhaler; however they may not use these devices while participating in this research study. Study drugs will not be available once participants complete this study. Alternative alcohol treatments include other pharmacotherapies such as naltrexone and disulfiram for which participants may get prescriptions from their physicians.

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

For Phase 1 focus groups, participants will be paid $10 for attending the intake appointment and $50 for completing the focus group session.

For Phase 2 (pre-pilot), participants will be paid $10 for attending the intake and research appointments (8 total) for a total of $90.

For Phase 3 (RCT pilot study) participants will be paid $10 for attending an intake session, $10 for each research appointment (up to 12 total), and $20 for each research follow-up sessions (2 total) for a total of up to $170 per participant.

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 experimental aspects of the treatment. Participants who are treated outside of the Tobacco Treatment Service will receive free counseling and free varenicline. Their insurance will not be billed for their treatment. For participants treated through the Tobacco Treatment Service, standard counseling and varenicline costs will be billed to their insurance. Depending upon insurance coverage, there may be a co-pay for these visits. Assistance by staff will be given to help determine coverage and/or co-pay if requested. The nicotine replacement products will be provided free of charge.

If subjects chose to continue counseling and/ or varenicline beyond the treatment portion of the study, these costs will not be covered by the study or they can choose to enroll in the Tobacco Treatment Service and have their treatment billed through their insurance.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs?
   b. Where and from whom may treatment be obtained?
   c. Are there any limits to the treatment being provided?
   d. Who will pay for this treatment?
   e. 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 the study physician or Dr. Fucito.

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