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Title: New Treatment for Alcohol and Nicotine Dependence

High and Low Dose Topiramate for the Treatment of Alcohol-Dependent Smokers

A Phase II, 18-week, double-blind clinical trial with a 3-month follow-up, in which alcohol-dependent smokers will receive brief behavioral compliance enhancement treatment (BBCET) plus a smoking self-help manual as their psychosocial treatment, and shall be randomized to get placebo, high-dose topiramate (up to 250 mg/day), or low-dose topiramate (up to 125 mg/day) to prevent relapse to heavy drinking and smoking. **IND # 56,887.**

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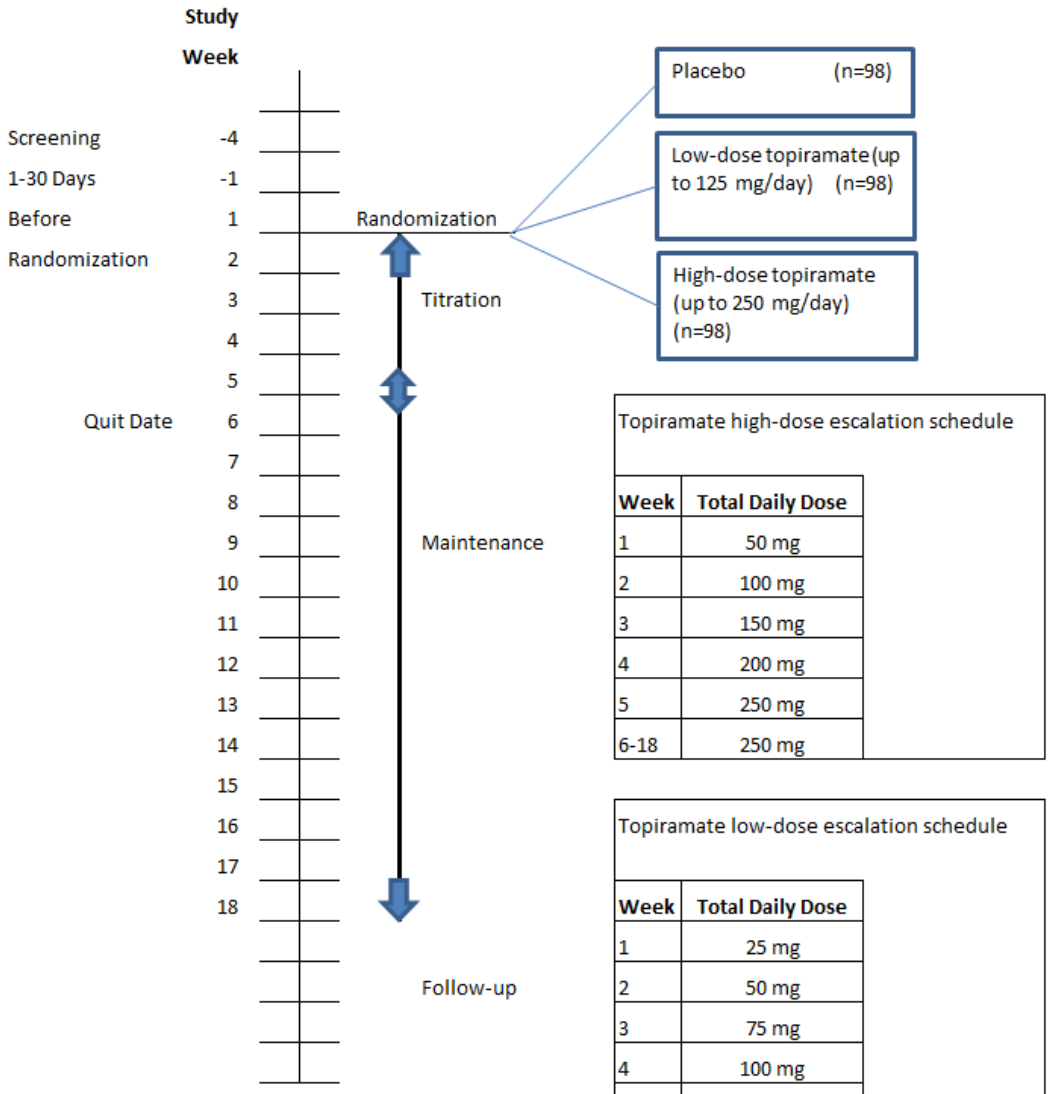
1 LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviations	Definition
AA	Alcoholics Anonymous
AE	Adverse Event
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APA	American Psychiatric Association
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorders Identification Test
BAC	Breath Alcohol Content
BBCET	Brief Behavioral Compliance Enhancement Treatment
BUN	Blood Urea Nitrogen
CBC	Complete blood count
CES-D	The Center for Epidemiologic Studies Depression Scale
CO	Carbon Monoxide
CIWA-AR	Clinical Institute Withdrawal Assessment for Alcohol-revised
CMDA	Cortico-mesolimbic dopamine
CNS	Central Nervous System
DDD	Drinks per drinking day
DrInC	Drinker Inventory of Consequences
DSMB	Data and Safety Monitoring Board
DSM-4	Diagnostic and Statistical Manual of Mental Disorders-4
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5
ECG	Electrocardiogram
ET	Early Termination
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
GABA	γ-aminobutyric acid-A
GGT	γ-glutamyl transferase
Heavy Drinking	5 or more drinks per drinking day for men, 4 or more drinks per drinking day for women
ID	Identification
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intention-to-Treat
LDH	Lactate Dehydrogenase
MD	Medical Doctor
MINI	Mini International Neuropsychiatric Interview
MOS - Sleep	Medical Outcomes Sleep Scale
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NP	Nurse Practitioner
PANAS	Positive Affect Negative Affect Schedule
PDA	Percentage of Days Abstinent
PHDD	Percentage of heavy drinking days
PI	Principal Investigator

Abbreviations	Definition
PK	Pharmacokinetics
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
SAE	Serious Adverse Event
SDU	Standard Drink Units
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
TARG	Tobacco and Alcohol Research Group
TLFB	Timeline Followback
TQD	Target Quit Date
UVa CLEAR	University of Virginia Center for Leading Edge Addiction Research
ULN	Upper Limit Of Normal
VTA	Ventral tagmental area
WSWS	Wisconsin Smoking Withdrawal Scale

2 STUDY SCHEMA



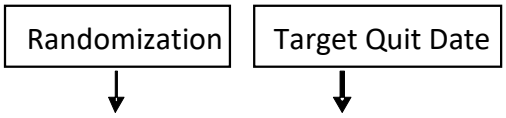
Topiramate high-dose escalation schedule

Week	Total Daily Dose
1	50 mg
2	100 mg
3	150 mg
4	200 mg
5	250 mg
6-18	250 mg

Topiramate low-dose escalation schedule

Week	Total Daily Dose
1	25 mg
2	50 mg
3	75 mg
4	100 mg
5	125 mg
6-18	125 mg

3 STUDY SCHEDULE



	Screen	Weeks 1 to 5 (-5 to -1 weeks to TQD)	Week 6 visit= TQD (0)	Weeks 6 to 10 (0 to +4 weeks from TQD)	Weeks 10 to 18 (+4 to +12 weeks from TQD)	Week 19 (+13 weeks from TQD)	Follow-Up Visit 1 month	Follow-Up Phone Call 3 months
Assessments	X	Weekly		Weekly	Biweekly	X	X	X
Psychosocial Intervention	_____	Weekly		Weekly	Biweekly	X	_____	_____
Medication Dispensation	_____	Weekly		Weekly	Biweekly	_____	_____	_____

Table 1: Time and Events Schedule

Assessment	Investigational Product Administration																	
Study Week	**-4 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**14**	**16**	**18**	**19/ ET**	**F/U 1 month**	**F/U 3 month (phone)**
Visit Number	S	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Subject characteristics																		
Informed consent	x																	
Demographics	x																	
Alcohol Use Disorders Identification Test (AUDIT)	x																	
Fagerström Test for Nicotine Dependence	x															x	x	
Tobacco Use History Questionnaire	x																	
Baseline Drug Use	x																	
MINI for DSM-4, plus supplement	x																	
Efficacy																		
Timeline follow-back*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Carbon monoxide level	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Urinary cotinine level****	x	x																
Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Alcohol Craving Visual Analog Scales	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Nicotine Craving Visual Analog Scales	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Salivary cotinine level	x															x		
Clinical Institute Withdrawal Assessment for Alcohol scale – Revised (CIWA-AR)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Wisconsin Smoking Withdrawal Scale	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Positive Affect Negative Affect Schedule (PANAS)	x	x		x		x		x		x						x	x	
The Center for Epidemiologic Studies Depression Scale (CES-D)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Medical Outcomes Sleep Scale (MOS – Sleep)	x	x				x				x		x		x		x		
Drinker Inventory of Consequences (DrInC)	x	x			x		x			x		x				x		
Psychosocial intervention																		
Brief behavioral compliance enhancement treatment (BBCET)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		

Assessment	Investigational Product Administration																	
Study Week	**-2 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**14**	**16**	**18**	**19/ ET**	**F/U 1 month**	**F/U 3 month (phone)**
Visit Number	S	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Subject characteristics																		
Clearing the Air Booklet		x																
Compliance																		
Medication compliance measures		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
BBCET session checklist		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Genotyping	x																	
Study Drug Dispensing		x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Safety																		
Other Drug Use		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Medical history	x																	
Physical exam**	x															x		
Vital signs (blood pressure, heart rate, weight)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Electrocardiogram	x															x		
Breathalyzer (BAC)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Urine pregnancy test	x	x			x			x			x			x		x		
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Blood chemistry	x															x		
Hematology	x															x		
Urine Drug Screen***	x							x						x		x		
Urinalysis	x																	
Contraceptive method	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		

Key:

S = screen is 30 days prior to visit #1 (weeks –4 to -1).

Randomization will occur before week 1 of double-blind treatment.

F/U = follow-up at months 1 and 3.

*Timeline follow-back will quantify both smoking and drinking behavior.

**Physical Exam may be done at screening or on or prior to visit 1.

***If positive at screen subject will be advised to stop using and will be allowed one repeat urine drug screen. Must provide negative results prior to randomization.

**** If subject registers a CO level of <10, a urinary cotinine will be administered. Subjects must have a cotinine level of ≥3at Screen and prior to Randomization to be eligible for study inclusion.

4 ABSTRACT

Objectives
Primary: The primary objectives of this study are to assess the efficacy of both low- and high-dose topiramate in reducing the percentage of heavy drinking days (PHDD), while also increasing the continuous abstinence rate for smoking determined by a combination of self-report and carbon monoxide (CO) monitoring after the target quit date (TQD), and in the last 4 weeks of treatment. We propose that high-dose topiramate will be more efficacious than low-dose topiramate at reducing PHDD and increasing the continuous abstinence rate for smoking determined by a combination of self-report and CO monitoring after the TQD in the last 4 weeks of treatment after TQD.

Secondary: Secondary objectives include assessing that both low- and high-dose topiramate will be more efficacious than placebo at improving quality of life and reducing alcohol and nicotine craving in the last 4 weeks of treatment after TQD; high-dose topiramate will be more efficacious than low-dose topiramate at improving quality of life and reducing craving after the TQD, and in the last 4 weeks of treatment;

Exploratory: Improvements in quality of life and craving reductions will be predictably associated with reduced PHDD, increased continuous abstinence rates for smoking, or both, irrespective of treatment group.

Study Design: Two hundred and ninety-four comorbid alcohol- and nicotine-dependent subjects who meet eligibility criteria will be randomized to 1 of 3 treatment groups — placebo, low-dose topiramate (up to 125 mg/day), or high-dose topiramate (up to 250 mg/day). Randomization will be achieved using a block randomization procedure in which treatment groups will be stratified to achieve a balance on age of onset for alcoholism (less than 26 years old or 26 years and older), gender, and drinks per drinking day (DDD) (< 8 DDD or ≥ 8 DDD) and the number of cigarettes smoked (<20 or ≥20 cigarettes/day).

Following randomization, subjects will participate in an 18-week, double-blind treatment period during which they also will receive weekly Brief Behavioral Compliance Enhancement Treatment (BBCET) and a self-help manual for smoking cessation. Topiramate and matching placebo will be titrated for the first 5 weeks of the 18-week treatment period. The TQD will be at the beginning of the 6th week of treatment. Subjects will be instructed not to attempt smoking or alcohol cessation prior to the TQD. Setting a TQD at the end of medication titration enables stability of effects, comfort with the medication prior to attempting to cease alcohol and smoking consumption, and an appreciable buildup of medication.

Study Pre-Screening Procedures: Potential subjects will call a study phone number, which will be set up for each participating site. The intake interviewer will answer queries from the subject about the nature and demands of the study. The interviewer will request permission from the potential subject to collect data that will be part of the telephone screening interview. Confirmation of consent will be completed by the subject providing his or her name and telephone number. The telephone screening interview will include demographic data, physical

status, psychiatric history, timeline follow back (TLFB) for alcohol and cigarettes, and questions to assess motivation to engage in treatment. One such question to assess motivation will read as follows: "Are you willing to quit both smoking and drinking 30 – 60 days into the study?" Subjects who answer "yes" and meet all additional eligibility criteria will be preferably scheduled for a screening visit within 30 days of the telephone screening interview.

Study Screening Procedures: At the screening visit (visit S) subjects will be provided with information about the study, its rationale, risks, and potential benefits, and the role of the Institutional Review Board. All questions pertinent to the study raised by the potential subject will be answered before consent is signed. Those who complete all screening procedures and assessments and who are eligible for the study will be scheduled for a randomization visit (visit 1). Those who complete the screening procedures, but who are not eligible for study inclusion will be provided with the address and telephone number of another treatment center or will be referred to other research studies at the research site.

Study Duration: Each subject will remain in the study for 19 weeks including a follow up visit at 1 month and a follow up phone call at 3 months. The expected ratio of intake screens to enrolled subjects is approximately 2:1. Thus, the enrollment of 294 individuals will require 588 intake sessions over approximately 54 months of recruitment. Of the enrolled 294 individuals, the expected dropout rate is 30%; therefore, 206 individuals will be expected to complete all 18 weeks of double-blind treatment.

Sample Size: Two hundred and ninety four (294) subjects will be randomized to one of 3 groups, low-dose topiramate, high-dose topiramate or placebo control.

Population: Entry into this study is open to treatment seeking men and women at least 18 years of age and to all racial and ethnic subgroups. A Diagnostic and Statistical Manual of Mental ≥Disorders-5 (DSM-5) diagnosis of mild to severe alcohol use disorder is required and subjects must smoke an average of ≥ 5 cigarettes/day in the 30 days prior to randomization.

Investigational Project: Subjects will be randomized on Study Day 1 to one of the following three groups:

1. Low-dose topiramate (up to 125 mg/day); or

2. High-dose topiramate (up to 250 mg/day); or

3. Identical matched placebo control.

To mask the intervention groups, identical matched placebo will be provided.

Dose titrations will be as follows:
The titration scheme has been devised such that this process is completed for the low- or high-dose topiramate groups, and matching placebo, at the end of week 5 (i.e., beginning of week 6). Both titration schemes are provided below.

Topiramate high-dose escalation schedule

Week	A.M. Dose	P.M. Dose	Total Daily Dose
1	-	50 mg	50 mg
2	50 mg	50 mg	100 mg
3	75 mg	75 mg	150 mg
4	100 mg	100 mg	200 mg
5	125 mg	125 mg	250 mg
6-18	125 mg	125 mg	250 mg

Topiramate low-dose escalation schedule

Week	A.M. Dose	P.M. Dose	Total Daily Dose
1	-	25 mg	25 mg
2	25 mg	25 mg	50 mg
3	37.5 mg	37.5 mg	75 mg
4	50 mg	50 mg	100 mg
5	62.5 mg	62.5 mg	125 mg
6-18	62.5 mg	62.5 mg	125 mg

Outcomes:

Primary Efficacy Outcomes: The timeline follow-back (TLFB) method of measuring alcohol and cigarette consumption will be used to construct a retrospective index of smoking behavior during the 3-month period before enrolling in the study. Thereafter, the consumption of alcohol or cigarettes between weekly visits will be recorded.[1] Days abstinent will refer to the number of days on which the subject consumes no alcohol or cigarettes. While subjects also will be provided with daily record cards as an aide-mémoire, only the TLFB data will be used in the efficacy analyses. From these data, we will determine both the PHDD and the point prevalence smoking abstinence rates. Self-reported reports of smoking cessation will be corroborated by measurement of breath CO level, and, when necessary, urinary cotinine level (see below). PHDD is calculated as days for which the number of drinks was five or greater for men and four or greater for women, divided by the number of study days. [73]

Expired carbon monoxide (CO) level will be measured using a Bedfont CO monitor, and, when necessary, Accutest NicAlert strips Self-reported abstinence will be verified by expired CO samples of <10 ppm. Individuals who report smoking at screen and visit 1, but register less than 10ppm on the CO monitor will be re-tested with a NicAlert cotinine strip. Urinary cotinine scores of 3 or higher indicate tobacco usage.

Secondary Efficacy Outcomes:

1. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)
2. The Alcohol Craving Visual Analog Scales
3. The Nicotine Craving Visual Analog Scales

Exploratory Outcomes:

Psychological Assessments:
1. Fagerström Test for Nicotine Dependence
2. Revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar),[2]
3. Wisconsin Smoking Withdrawal Scale
4. Positive Affect Negative Affect Schedule (PANAS)
5. The Center for Epidemiologic Studies Depression Scale (CES-D)
6. Medical Outcomes Sleep Scale (MOS-Sleep)
7. The Drinker Inventory of Consequences (DrInC)[3]

Study Retention and Compliance:
1. Attendance at regularly scheduled clinic visits
2. We shall assess compliance by comparing unused capsule count to dispensing logs and dosing records (number of capsules dispensed, number of capsules expected to be taken, versus the number returned).
3. Brief behavioral compliance enhancement treatment (BBCET)

Safety Assessments:
1. Medical history
2. Physical examination
3. Vital signs
4. ECG
5. Blood chemistries and hematology
6. Urine pregnancy test
7. AEs
8. Concomitant medication use
9. Contraceptive method
10. BAC

5 INTRODUCTION AND RATIONALE

5.1 General rationale for the pharmacological treatment of comorbid alcohol and smoking dependence:

Advances in the neurosciences have shown that there are important neurochemical pharmacodynamic interactions between alcohol and nicotine that might summate to increase co-dependency on both.[11] Further, there is evidence that pharmacokinetic factors associated with the absorption, distribution, and metabolism of both compounds might lead individuals to administer these compounds in such a way that the effects of one of these drugs serve to modulate the effects of the other.[12, 13] Emerging genetic evidence also shows that an earlier onset of smoking is associated with greater likelihood of problem drinking, and fetal exposure to alcohol may increase susceptibility to smoking.[14, 15] Nevertheless, despite this striking evidence for substantial neurochemical and biological overlap between alcohol and

nicotine dependence, few clinical trials have addressed the possibility of using a common pharmacological approach to treat both disorders.

Important neurochemical interactions exist between alcohol and nicotine that can serve to increase the reinforcing effects and, therefore, abuse liability of the combination.

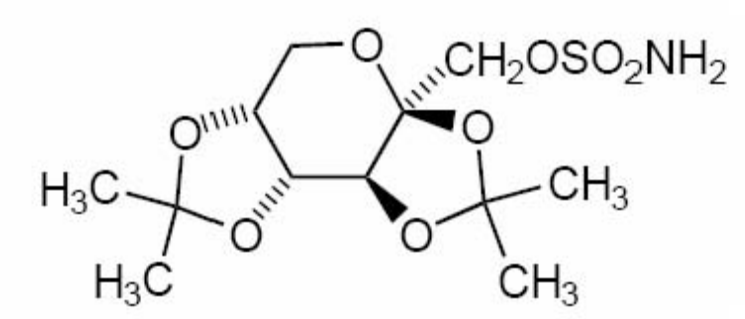
The reinforcing effects of both nicotine and alcohol are mediated through CMDA (cortico-mesolimbic dopamine) pathways.[16-18] While the primary action by which alcohol exerts its reinforcing effects is through the disinhibition of the inhibitory effects of γ-aminobutyric acid-A ($GABA_A$) neurons in the ventral tegmental area (VTA) (for a review, see Johnson[19]), there is also evidence that alcohol might excite VTA neurons through nicotinic acetylcholine receptors.[12, 20] Animal studies show that chronic nicotine intake can increase the likelihood of alcohol consumption. For instance, chronic nicotine intake up-regulates nicotinic acetylcholine receptors,[21, 22] thereby increasing the sensitization of the CMDA system to alcohol. Extended to humans, this would imply that smoking would be expected to enhance the pleasurable effects of consuming alcohol. The results of patch clamp studies have, however, been utilized to understand further the neurochemical interactions between alcohol and nicotine. The acetylcholine receptor can generate two types of current — an α-bungarotoxin-sensitive current and an α-bungarotoxin-insensitive current — that originate from the α7- and α4β2-type subunits, respectively.[23, 24] Narahashi et al.[25] have shown that alcohol potentiates the activity of the α4β2-type subunit at physiologically relevant doses and can offset nicotine's ability to desensitize this subunit. They propose that these effects of alcohol facilitate the recovery of acetylcholinergic currents from nicotine-associated desensitization, thereby serving to promote smoking behavior. Importantly, however, other authorities have suggested that the principal site of alcohol-nicotine interactions might not be the α4β2-type subunit,[26] although the nicotinic acetylcholine receptor was still implicated by demonstration that mecamylamine, a non-competitive nicotinic acetylcholine receptor antagonist, suppresses alcohol consumption.[26, 27]

In sum, whatever the exact molecular pharmacological explanation for the interaction between alcohol and nicotine, the nicotinic acetylcholine receptor appears to be principally involved. Alcohol and nicotine appear to combine such that their ability on reinforcement mechanisms is additive.[28] Thus, an important neuropharmacological approach toward simultaneous treatment of alcohol and nicotine dependence would be to administer a compound such as topiramate (see below) that has the potential to profoundly modulate CMDA function.

5.2 Topiramate

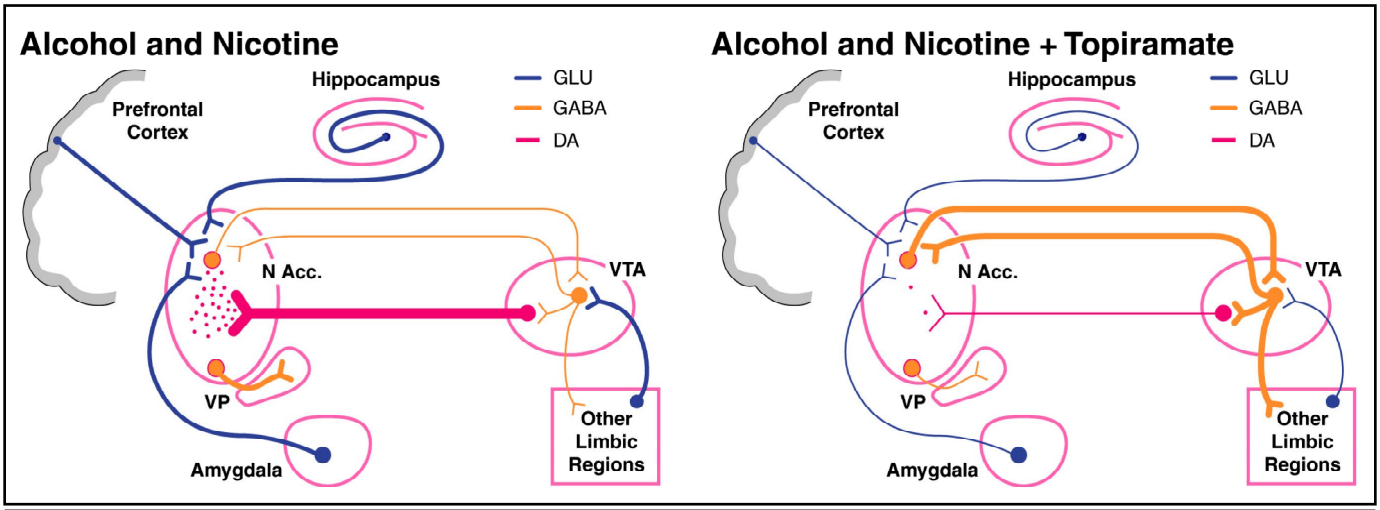
5.2.1 *Chemistry*

Topiramate has the following structural formula:



5.2.2 *Pharmacology*

Topiramate, a sulfamate-substituted fructopyranose derivative, might antagonize the reinforcing effects associated with the abuse liability of both nicotine and alcohol by modulation of CMDA function.[29] As we have conceptualized previously,[4] topiramate could, theoretically, suppress the extracellular release of dopamine by facilitating contemporaneously the actions of the inhibitory neurotransmitter, GABA, through a non-benzodiazepine receptor site[30] in the VTA and nucleus accumbens and antagonizing the excitatory effects of AMPA and kainate glutamate receptors on A10 DA neurons at these same sites[29-35] (see figure below). These effects of topiramate might be even more pronounced in the chronic compared with the acute condition because of its ability to decrease glutaminergic sensitization, thereby normalizing CMDA function. Indeed, there is evidence that topiramate can attenuate nicotine-associated rises in nucleus accumbens release of DA.[36]



Schematic illustration of the effects of topiramate on alcohol and nicotine dependence. The reinforcing effects of both alcohol and nicotine are mediated through activity at CMDA neurons. Both alcohol and nicotine enhance VTA DA neuronal function via the stimulation of nicotinic acetylcholine receptors. Alcohol also exerts an additional effect to promote increased CMDA activity by disinhibiting the inhibitory effects of GABA neurons in the VTA and nucleus accumbens (N Acc.). Topiramate antagonizes the ability of alcohol and nicotine to increase CMDA activity by facilitating GABA suppression of VTA and N Acc. neurons and antagonizing the excitatory effects of AMPA and kainate glutamate (GLU) receptors at these same receptor sites. Line weights (i.e., heavy, medium, and thin) denote relative strengths of neuronal activity. VP = ventral pallidum.

Further, there might be other effects of topiramate that may either independently or in combination serve to decrease alcohol and nicotine consumption. For instance, due to topiramate's ability to antagonize L-type calcium channel currents as well as decrease glutaminergic sensitization, it might enable individuals to withdraw more comfortably from either alcohol or nicotine. Indeed, this potential effect, when coupled with the mild anxiolytic properties of topiramate, may serve to decrease the potential for protracted withdrawal upon ceasing alcohol or nicotine consumption, or both.

Finally, topiramate might have an additional property that could make it an attractive anti-smoking aid and, among those comorbid with alcohol dependence, could enhance the drive toward sobriety. It is well recognized that the potential for weight gain upon stopping smoking is an important reason why some individuals,[37-39] particularly women,[40-44] fail to quit. While the mechanism for this effect is unknown, female smokers concerned about gaining weight upon initiating abstinence appear more likely to drop out or to fail to comply successfully with treatment compared with those without such concerns.[41] While some controversy exists in the literature about the importance of concern about weight gain as a barrier to smoking cessation, with notable discrepancies and criticisms of methodological approach, and suggestions that other factors such as self-efficacy might be equally important (for an overview, see Borrelli and Mermelstein[45]), topiramate might have utility as a putative pharmacological agent for smoking cessation, even among those with comorbid alcohol dependence, because there would be no fear of weight gain; indeed, some weight loss would be the expected result. In this respect, it is of interest that topiramate has been shown to promote weight loss in both men and

women.[46] Hence, it is reasonable for us to expect that these anti-weight-gain effects of topiramate might enhance its utility as an aid to smoking cessation even among those with comorbid alcohol dependence. Taken together, the foregoing would suggest that topiramate is a promising agent for the treatment of both nicotine and alcohol dependence.

5.2.3 *Pharmacokinetics (PK)*

The sprinkle formulation of topiramate is bioequivalent to the immediate release tablet formulation and, therefore, may be substituted as a therapeutic equivalent.

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The relative bioavailability of topiramate from the tablet formulation is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.

The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady state is thus reached in about 4 days in patients with normal renal function. Topiramate is 15-41% bound to human plasma proteins over the blood concentration range of 0.5 -250 μg/mL. The fraction bound decreased as blood concentration increased.

5.2.4 *Adverse Effects*

Topiramate at the dosage that will be prescribed in this proposal is well tolerated. The most common adverse events (AEs) that we observed in our alcohol treatment study were transient tingling, psychomotor slowing, weight loss, and dizziness. We acknowledge that other central nervous system adverse events have been reported by others, such as ataxia, speech disorders and related speech problems, cognitive slowing, mood disturbance, and nystagmus (eyes jumping), but these would appear to be more manifest at higher doses than what we have proposed. A rarer adverse event of topiramate is kidney stone, which was not seen in any of our previous studies. Topiramate has weak carbonic anhydrase properties. Thus, topiramate's concurrent use with other carbonic anhydrase inhibitors, such as acetazolamide and zonisamide, may increase the risk of kidney stone formation and should, therefore, be avoided. Topiramate may be associated with the development of metabolic acidosis.

Psychological risks can include distress and heightened sensitivity, which can occur as part of the behavioral treatments, clinical interviews, or completing self-reported ratings and questionnaires. While the possibility of such events is low, we will monitor these situations and provide an appropriate level of support. Such events will be documented fully in the case records.

5.2.5 *Withdrawal*

Antiepileptic drugs are usually withdrawn gradually to minimize the potential of increased seizure frequency. In our experience, we have not used a taper phase with topiramate. We have completed multiple trials using topiramate and have never experienced a single seizure, and carefully screen for possible seizure risk.

5.2.6 *Possible adverse events from the interaction between Topiramate and Alcohol*

In one clinical trial with alcohol-dependent adults, the following adverse events were observed with those who took topiramate: paresthesia (abnormal skin sensations), taste perversion, anorexia, and difficulty with concentration.

5.2.7 *Rationale for Study Design and Dose Regimen*

Study Design:

Two principal reasons support combining psychosocial management with pharmacotherapy for comorbid alcohol dependence and smoking. These include: 1) pharmacological agents alone are not considered to compose a comprehensive treatment program, and 2) the operative research question is whether the pharmacological agents add to the success of psychosocial management. For psychosocial management in this proposal, we plan to use a combination of brief behavioral compliance enhancement treatment (BBCET) plus a self-help manual for smoking cessation. The rationale for this choice is straightforward. In studies where psychosocial treatments have been provided for the independent treatment of alcohol dependence or smoking behavior, the general trend has been from intensive psychotherapies to briefer treatments because these are more generalizable to clinical practice. Furthermore, psychosocial treatments that promulgate the strategy of brief advice and education have been shown to be effective treatment for both alcohol dependence[4, 5] and smoking behavior.[47-53] It is, therefore, reasonable to propose the use of BBCET, which emphasizes brief advice, compliance, motivation, and education for the treatment of comorbid alcohol dependence and smoking behavior (see Appendix IV). Additionally, to ensure that there is a focus to promote smoking cessation, we will provide the self-help booklet, *Clearing the Air: Quit Smoking Today*,[54] at randomization (see Appendix V).

For this project, the educational component of BBCET will be expanded to include information about the hazards not only of excessive alcohol consumption but also of smoking. We can readily accomplish this goal as BBCET has already been adapted not only for the treatment of alcohol dependence but also for the treatment of stimulant dependence in NIH-funded studies that we have led. BBCET will be delivered in 15- to 30-minute sessions, which will emphasize that compliance with the medication and the treatment program are critical elements for reducing alcohol and nicotine intake. Whilst BBCET is a minimal intervention, it is clearly not a "no-treatment" condition, and will be combined with the self-help pamphlet to further facilitate smoking cessation. The tenets of BBCET were modeled on a development of the clinical management condition in the NIMH collaborative trial on depression — essentially a compliance management intervention that was found to be a rather significant intervention that compared well with other more sophisticated psychotherapies.[56] An added purpose of providing BBCET with the self-help pamphlet rather than a formal intensive psychotherapy is to ensure the delivery of adequate treatment while minimizing the potential for a large psychosocial treatment effect to mask our ability to detect any pharmacotherapy response in this initial proof-of-concept study. Importantly, the BBCET program has been developed into a standardized manual with well-established supervised training procedures through didactic and videotaped sessions. All BBCET practitioners will be certified to perform this intervention in the trial and will be monitored regularly.

Dose Regimen:

In patients with epilepsy, the package insert and clinical expertise recommends the dose for topiramate monotherapy in adults and children 10 years of age and older is 400 mg/day in two divided doses. Approximately 58% of patients randomized to 400 mg/day achieved this maximal dose in the monotherapy controlled trial; the mean dose achieved in the trial was 275 mg/day.

The recommended total daily dose for the treatment for prophylaxis of migraine headache is 100 mg/day administered in two divided doses.

Topiramate high-dose escalation schedule

Week	A.M. Dose	P.M. Dose	Total Daily Dose
1	-	50 mg	50 mg
2	50 mg	50 mg	100 mg
3	75 mg	75 mg	150 mg
4	100 mg	100 mg	200 mg
5	125 mg	125 mg	250 mg
6-18	125 mg	125 mg	250 mg

Topiramate low-dose escalation schedule

Week	A.M. Dose	P.M. Dose	Total Daily Dose
1	-	25 mg	25 mg
2	25 mg	25 mg	50 mg
3	37.5 mg	37.5 mg	75 mg
4	50 mg	50 mg	100 mg
5	62.5 mg	62.5 mg	125 mg
6-18	62.5 mg	62.5 mg	125 mg

Safety Considerations:
Although topiramate is generally well tolerated, its side effect profile coincides with that of alcohol. Therefore, monitoring of CNS effects, and also laboratory values (hepatic function, hematology) will be performed.

6 STUDY OBJECTIVES

6.1 Primary Objective

The primary objectives of this study will be the PHDD for the drinking outcome and the continuous abstinence rate for the smoking outcome (during the last 4 weeks of treatment, i.e., weeks 15–18 inclusive), respectively. The secondary efficacy variables will be quality of life and measures of alcohol and nicotine craving.

6.2 Exploratory Objectives

Additional objectives will include:

1. Measures of drinking severity (i.e., DDD) and abstinence (i.e., percentage of days abstinent; PDA) averaged across either the entire double-blind period or the last 4 weeks of treatment.

2. Smoking measures including the point prevalence abstinence rate and the CO level over either the entire double-blind period or the last 4 weeks of treatment.

3. Measures of nicotine and alcohol withdrawal, and negative affect as described previously.

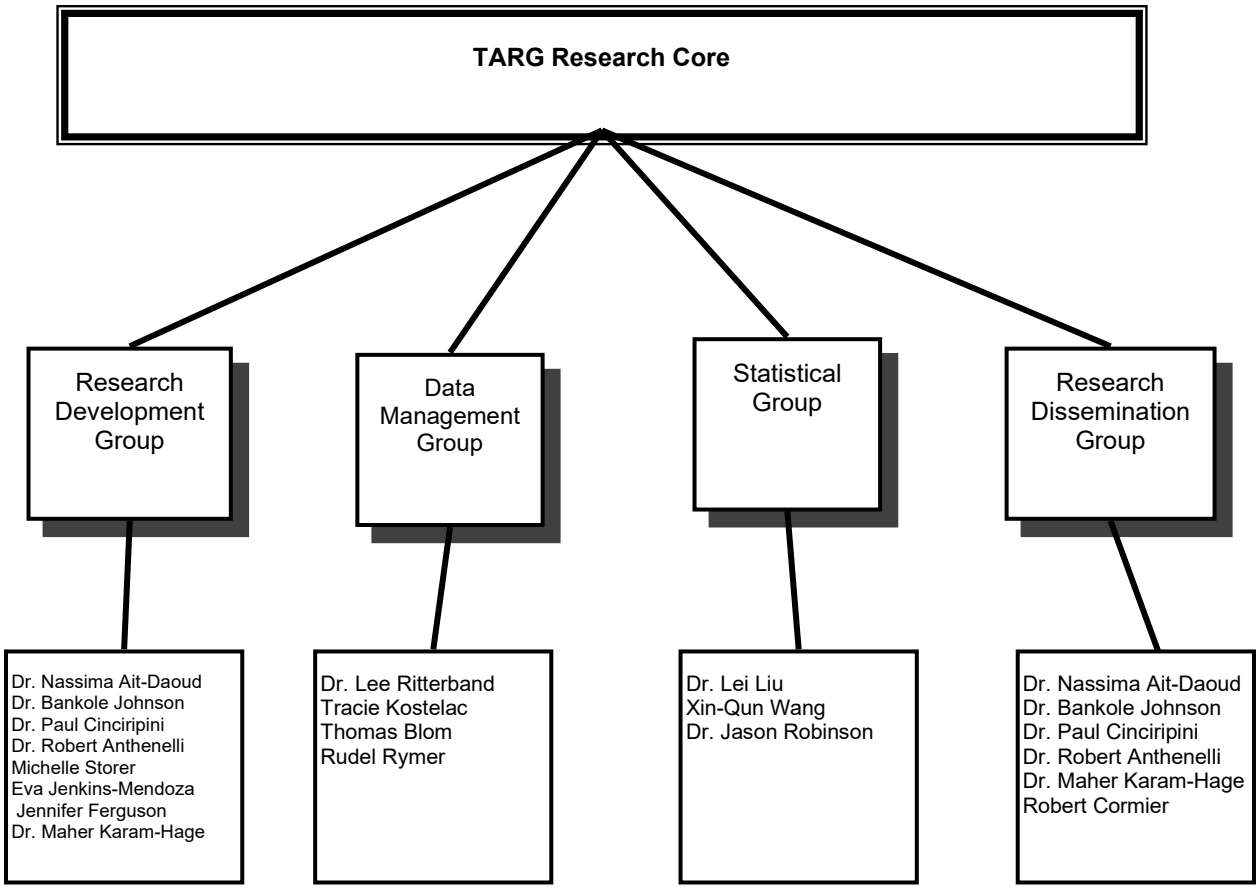
7 REGULATORY CONSIDERATIONS

We have filed for an Investigational New Drug (IND) extension as we have previously used topiramate in alcoholics, of which many were cigarette smokers as well. All investigators will obtain Institutional Review Board (IRB) approval before initiating the study at their site.

8 STUDY SITES

This project will be conducted at three different sites: the University of Virginia, the University of California, San Diego, and the University of Texas-M.D. Anderson Cancer Center. The principal investigators at each of these sites have agreed to engage in this collaborative effort, each bringing expertise in medication development for alcohol and tobacco research, and expecting to produce a synergy of creativity and productivity that will be of invaluable benefit to the research being conducted.

Dr. Nassima Ait-Daoud Tiouririne is the contact PI for this project, and the University of Virginia Center for Leading Edge Addiction Research (UVa CLEAR) will be the coordinating site. UVa CLEAR is designed to foster mutually trusting, fully collaborative, and highly productive partnerships among the different academic centers. Working together, the partnering sites will develop a system of operation that will be administered through a steering committee using a mixed matrix model. This model is exceptional for developing programs where substantial overlap and shared decision making are critical to success. Subsumed under the steering committee will be the research core with its four groups of focus: the research development group, the data management group, the statistical group, and the research and dissemination group (see figure below).



9 STUDY DESIGN

Two hundred and ninety-four comorbid nicotine-dependent subjects with mild to severe alcohol use disorder who meet eligibility criteria will be randomized to 1 of 3 treatment groups — placebo, low-dose topiramate (up to 125 mg/day), or high-dose topiramate (up to 250 mg/day). Randomization will be achieved using a block randomization procedure in which treatment groups will be stratified to achieve a balance on age of onset for alcoholism (less than 26 years old or 26 years and older), gender, and drinks per drinking day (DDD) (<8 DDD or ≧8 DDD) and the number of cigarettes smoked (<20 or ≥20 cigarettes/day).

Following randomization, subjects will participate in an 18-week, double-blind treatment period during which they also will receive weekly BBCET, and a self-help manual for smoking cessation. Topiramate and matching placebo will be titrated for the first 5 weeks of the 18-week treatment period. The TQD will be at the beginning of the 6th week of treatment. Subjects will be instructed not to attempt smoking or alcohol cessation prior to the TQD. Setting a TQD at the end of medication titration enables stability of effects, comfort with the medication prior to attempting to cease alcohol and smoking consumption, and an appreciable buildup of medication. However, in cases where individuals either quit smoking or alcohol consumption prior to the TQD, counseling will be directed at helping them maintain their abstinence and reengaging their efforts in the event of relapse. If an individual finds that he or she cannot quit

smoking and/or consuming alcohol completely following the TQD, he or she shall remain in the study and counseling will be directed at the continued setting of reduction goals, with cessation as the ultimate target.

10 SUBJECT SELECTION

10.1 Inclusion Criteria

1) Males and females who have given written informed consent
2) Subjects must be at least 18 years of age or older
3) Subjects must weigh at least 40 kg
4) Good physical health as determined by a physical examination, an electrocardiogram (ECG) within normal limits, and laboratory screening tests within acceptable parameters (see exclusion criteria below)
5) DSM-5 diagnosis of mild to severe alcohol use disorder
6) Record an expired CO level of ≥ 10 ppm or a urinary cotinine level of ≥ 3at screening and prior to randomization
7) Smoking an average of ≥ 5 cigarettes/day in the 30 days prior to randomization
8) Currently drinking at least 8 standard drink units (SDUs) per week in the 30 days prior to randomization for women and at least 15 SDUs per week in the 30 days prior to randomization for men
9) Subjects must provide evidence of stable residence in the last month prior to enrollment in the study, and have no plans to move in the next 9 months. Stable residence is a domicile in which an individual can operate as if it were his or her own homestead and does not include shelters or halfway houses
10) The pregnancy test for females of child-bearing potential at screen and prior to randomization must be negative. Additionally, women of child-bearing potential must be using an acceptable form of contraception. These include, but are not limited to: oral contraceptives, hormonal (levonorgestrel) or surgical implants, or barrier plus spermicide
11) Literate in English and able to read, understand, and complete the rating scales and questionnaires accurately, follow instructions, and make use of the behavioral treatments
15) Willing to participate in a treatment program for nicotine and alcohol dependence

10.2 Exclusion Criteria

1) Any current axis I DSM-4 psychiatric disorder (except for alcohol and nicotine addiction) that warrants treatment or would preclude safe participation in the protocol, including schizophrenia or other psychosis, bipolar disorder, major depression as assessed by the MINI, bulimia/anorexia nervosa, and dementia
2) Other neurological or psychiatric disorders, such as:
    1. Dependence on any substances except nicotine, alcohol and caffeine
3) Organic brain disease
    1. Risk of severe alcohol withdrawal as evidenced by history of alcohol withdrawal seizures, illusions/hallucinations, or delirium tremens.
4) Seizure disorders, epilepsy, severe head injury or coma
5) History of suicide attempts (5 years prior to screening) as assessed by the MINI and/or current suicidal ideation/plan as assessed by the MINI
6) Serious medical illnesses including but not limited to:
    1. Uncontrolled severe hypertension
    2. Kidney stones
    3. Significant unstable heart disease, including myocardial infarction
    4. Unstable angina
    5. Clinically significant cardiovascular abnormality (ECG)
    6. Disease of the gastrointestinal system, liver, or kidneys that could result in altered metabolism, excretion of the study agent or absorption
    7. History of major gastrointestinal tract surgery (e.g., gastrectomy, gastrostomy, bowel resections)
    8. Current or historical diagnosis of chronic disease of the gastrointestinal tract (e.g., ulcerative colitis, regional enteritis, or gastrointestinal bleeding)
    9. Serious, potentially life-threatening, or progressive medical illness other than addiction that may compromise subject safety or study conduct
7) Severe or life-threatening adverse reactions to medications (including topiramate) in the past or during this clinical trial
8) Currently on active treatment with topiramate
9) Receipt of a drug with known potential for toxicity to a major organ system within 30 days prior to study entry (e.g., isoniazid, methotrexate)

10) Female subjects who are pregnant, lactating, or not adhering to an acceptable form of contraception at any time during the study
11) Concomitant (within 2 weeks of randomization) pharmacotherapy with anticonvulsants, psychomotor stimulant-type medications, and specific anridepressants like Elavil, Endep. Wellbutrin, and MAOIs.
12) Use within 2 weeks of randomization of St. John's Wort, yohimbine, ginkgo biloba, horehound, or any other central nervous system active herbal preparations
13) Use of any opiate substitutes (such as methadone, LAAM, buprenorphine) within 1 month preceding screening
14) Exclusive use of tobacco products other than cigarettes, such as (but not limited to) cigars, chew, snuff, or pipe in the 30 days prior to screening and not agreeing to abstain from these products during the study , if concomitantly using them with smoking.
15) Nicotine replacement treatment (NRT) or participation in an NRT program or any other treatment for nicotine dependence in the last 30 days prior to screening
16) Elevation of liver enzymes serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), blood urea nitrogen (BUN), or lactate dehydrogenase (LDH) greater than four times the upper limit of the normal range
17) Electroconvulsive therapy within the 3 months preceding screening
18) Members of the same household
19) Before double-blind randomization, urine positive for opiates, THC, cocaine, amphetamines, barbiturates, benzodiazepines, methadone, methamphetamines, phencyclidine, or propoxyphene/norpropoxyphene
20) Any circumstance or condition that in the opinion of the investigator would compromise the individual's ability to adhere to the protocol and complete the study
21) Received inpatient or outpatient treatment for alcohol dependence within the last 30 days prior to screen

11 INVESTIGATIONAL PRODUCT

11.1 Topiramate and Matched Placebo Control

Greenpark Compounding Pharmacy (Houston, TX) will purchase 100-mg tablets of topiramate. They will grind the tablets into a fine powder and make capsules with the appropriate dosage strength. Placebo capsules will contain spray dried lactose, and a small amount will also be

added to the topiramate capsules. Medication will be packaged by Greenpark and distributed to the study sites.

11.2 Investigational Product Labeling

All medication will be dispensed as labeled medication in bottles. Each subject will be assigned a study number, which will be placed on his or her case records and on each of the medication bottles. The bottles also will be labeled with the subject's study treatment week number and there will be space on the label for the subject's initials and identification number as well as the date dispensed.. These procedures are designed to avoid mis-assignment of medication. Each medication bottle will be preprinted with the protocol title, the site number and name, the week number, the number of capsules the bottle contains, the dosing directions, the expiration date and bottle number.

11.3 Investigational Product Accountability

The site PI or designated study personnel will maintain a log of all investigational products dispensed to the subject, each time investigational product is dispensed. Bottles of topiramate or placebo for each subject will be inventoried and accounted for throughout the trial. The site PI or his/her staff will count the bottles returned and record the bottle count on the appropriate drug accountability form. Subject compliance with investigational product will be assessed by comparing unused tablet count to dispensing logs and dosing records. If the bottle is not returned, the subject will also be asked to report daily drug self administration.

11.4 Used/Unused Supplies

At the end of the study, all unused investigational products will be inventoried. Each site will be responsible for the destruction of any unused investigational product.

12 INTERVENTIONS

12.1 Investigational Agents

Topiramate will be self administered by subjects in a dosing regimen of one capsule in the evening beginning on Day 1, Week 1 and then moving to one capsule in the morning and one capsule in the evening beginning on Day 8, Week 2 and continuing through Day 126, of Week 18.

The titration scheme has been devised such that this process is completed for the low- or high-dose topiramate groups, and matching placebo, at the end of week 5 (i.e., beginning of week 6). Both titration schemes are provided below:

Topiramate high-dose escalation schedule

Week	A.M. Dose	P.M. Dose	Total Daily Dose
1	-	50 mg	50 mg
2	50 mg	50 mg	100 mg
3	75 mg	75 mg	150 mg
4	100 mg	100 mg	200 mg

5	125 mg	125 mg	250 mg
6-18	125 mg	125 mg	250 mg

Topiramate low-dose escalation schedule

Week	A.M. Dose	P.M. Dose	Total Daily Dose
1	-	25 mg	25 mg
2	25 mg	25 mg	50 mg
3	37.5 mg	37.5 mg	75 mg
4	50 mg	50 mg	100 mg
5	62.5 mg	62.5 mg	125 mg
6-18	62.5 mg	62.5 mg	125 mg

Missed Doses. If a subject misses a week or more of investigational products, the product may be re-introduced with the A.M. dose for two days, then only the P.M. dose for the following two nights and by day 5 both doses should be taken, if tolerated. If a subject misses up to 6 consecutive days' doses, s/he will be instructed to start taking the investigational product at the last dose that s/he was taking before stopping. If the subject realizes he/she missed the AM dose and it is after 12pm then the subject should not take missed AM dose. A missed AM dose can be taken anytime before 12pm of the same day. If the subject realizes he/she missed the PM dose and it is the next day then the subject should not take missed PM dose. A missed PM dose can be taken before 24:00 (midnight) of the same day.

Medication Management. Pills may be taken with or without food. If a subject cannot tolerate a dose, the dose will be de-escalated to the next lower tolerated dose and a new kit will be ordered from Greenpark Compounding Pharmacy. Until the new kit arrives, subjects will take only one of their two daily pills. On an as needed basis and with the judgment of the site PI, both doses can be moved to the PM to manage sedation.

Placebo Control: Subjects assigned to the placebo group will receive the same number of matched placebo capsules on the same schedule as the topiramate high-dose and low-dose groups.

In the case of drug related AEs, discontinuation of the investigational product altogether may be necessary. In such a situation, the research physician will evaluate the subject to determine whether the investigational product should be discontinued immediately, or should be dose reduced. If a woman becomes pregnant, she will be instructed to immediately stop taking investigational products without any dose tapering.

12.2 Brief Behavioral Compliance Enhancement Treatment (BBCET)

The BBCET is a brief (15 to 30 minutes per session) standardized treatment program to be used in conjunction with a pharmacological intervention for the treatment of alcohol dependence.[57] The purpose of the treatment is to increase and enhance compliance with the investigational products and other aspects of the treatment regimen. Each session addresses subject issues

related to the personal barriers of compliance, focuses on how medication can assist the subject in achieving goals related to the control of drinking and smoking, and, if necessary, addresses management of side effects. The treatment emphasizes the role of medication and setting drinking and smoking goals. Sessions will be audiotaped and 10% of tapes will be centrally reviewed by staff at University of Virginia Health System. Subjects may decline to have their sessions audiotaped.

Research staff involved in counseling the subjects will be trained to deliver BBCET and will have to pass a certification procedure ratified by Dr. Ait-Daoud (Overall PI) or a designee. Training will include didactic meetings with the therapy supervisor, reading assignments, and review of at least one training case. Dr. Ait-Daoud or a designee also will also conduct any additional training sessions, as needed. To monitor and prevent practitioner deviation from the protocol, about 10% of the recorded sessions will be selected at random for evaluation of quality and adherence to manual guidelines. Monthly conference calls to discuss issues with the BBCET will be used as another measure to monitor protocol adherence and to take necessary steps to correct any deviation from the allowed procedure. Supervision of practitioners at all sites will be coordinated through Dr. Ait-Daoud or a designee at the University of Virginia (UVa). Practitioners will remain blind to the subjects' medication condition.

A subject checklist and survey form will be designed to measure the type and amount of treatment received. This checklist, administered at the end of every session, also will serve as an index of treatment acceptability and perceived helpfulness.

Subjects who cannot tolerate the medication or who need to reduce or stop the medication for other reasons will still be allowed to take part in the BBCET and other aspects of the study.

13 STUDY PROCEDURES

13.1 Subject Recruitment

Subjects will be recruited at the research centers at UVa and in San Diego and Houston. Recruitment strategies vary across each site based on their local population, however, standard tactics will be used (i.e., flyers, newspaper advertisements, radio advertisements, internet advertisements). Local IRBs will approve all advertising materials used for subject recruitment.

Interested candidates responding to recruitment materials by telephone will be asked a standardized set of questions about their drinking and smoking behavior without revealing the entry criteria into the study and will be asked if they are seeking treatment and are available for approximately 8 months. Candidates will additionally be asked if they are willing to quit both smoking and drinking within the next 30 to 60 days.

Candidates who report drinking and smoking consistent with the entry criteria, confirm their willingness to quit smoking and drinking, and appear to be available and interested in the study will meet with the investigator or designated investigational staff within 30 days after the initial inquiry to start the informed consent process and assessment process.

13.2 Screening Assessments

At the first screening visit candidates will meet with either the Principal Investigator (PI), or a study staff member designated to obtain informed consent to receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the local site's IRB. Subjects must have a breath alcohol content (BAC) of 0.000 when signing the informed consent document. Repeat measurements of BAC are permitted at the discretion of the investigator. Subjects will be given a copy of the signed informed consent.

Interested candidates must be at least 18 years of age and have been determined during the screening process to have a DSM-5 diagnosis of mild to severe alcohol use disorder. Subjects must also report to be smoking an average of ≥5 cigarettes a day in the 30 days prior to randomization, which will be collected through the Tobacco Use History Questionnaire and the TLFB. Female subjects must be drinking 8 or more standard drink units (SDUs) per week and male subjects 15 or more SDUs per week during the 30 days prior to randomization, as assessed by the TLFB. Repeat measurements of CO at screening and visit 1 will be permitted at the discretion of site investigators. Subjects will be allowed to smoke prior to testing of CO levels. A CO level ≥10, or a urinary cotinine level of ≥3 using a NicAlert cotinine screen strips must be achieved at screening and visit 1 to be randomized into the study. Subjects will be allowed to smoke prior to testing of CO levels.

In the medical history, all female subjects will be asked about their child-bearing potential. Women of child-bearing potential must have a negative pregnancy test and must agree to use an acceptable method of birth control for the duration of the study. Medical history will be taken including the age at which the subject started drinking alcohol regularly (age of onset).

A physical exam will be performed including the subject's weight. Vital signs will be taken, an ECG will be performed, and the subject will be queried on medication use in the 90 day period prior to signing consent. Subjects will be instructed that no new prescription/non-prescription medications are to be taken between the start of screening and randomization without informing the study staff. The subject's demographics will also be collected at this visit.

A urine drug test will be performed using a point of care test strip. Blood will be collected for hematology, chemistry and optional genotyping assessments. Urine will also be collected for urinalysis. Saliva will also be collected for cotinine level.

The MINI will be performed to assess diagnoses of psychiatric disorders in accordance with DSM-4 criteria. At screening the following questionnaires will be administered: Fagerström Test for Nicotine Dependence, AUDIT, CIWA-AR, Q-LES-Q, The Alcohol Craving Visual Analog Scales, The Nicotine Craving Visual Analog Scales, Wisconsin Smoking Withdrawal Scale, PANAS, CES-D, MOS-Sleep, Baseline Drug Use, and DrInC. Screening may be completed in a single visit or over two visits (e.g., a hematology or chemistry test needs to be repeated).

Subjects will be required to provide the name, phone number, and address of up to three contact persons who are likely to know their whereabouts.

13.3 Subject Randomization

Prior to randomization, data essential for eligibility will be reassessed. Drinking and smoking requirements during the time period between the screening visit and visit 1 will be reassessed. All essential data for assignment to a treatment group will be collected by the study staff on the randomization form.

Assignment to a stratum during randomization will be based on the following: age of onset (≤25 or >25), drinks per drinking day (DDD) during the 90 days prior to screening (<8 or ≥8), average number of cigarettes smoked per day during the 90 days prior to screening, and gender. Calculations will be made using the formulas below.

$$\frac{\textbf{90 Day SDU Total}}{\textbf{\# Drinking Days}} = \textbf{Drinks per Drinking Day (DDD)}$$

$$\frac{\textbf{90 Day Cigarette Total}}{\textbf{90 Days}} = \textbf{Average \# Cigarettes per Day}$$

13.4 Intervention Phase

Subjects will be seen in person at the clinical site for 17 visits (screening, intervention phase and the one month follow-up visit) and will complete the three month follow-up visit over the phone. All subject clinic visits will be collected on source documents and entered into an electronic database, or entered directly into an electronic database and printed out and placed in the source documentation binder. Clinic visits should be scheduled on the same day of the week that the subject was randomized, if possible, but a 3-day window is allowed. In the event of a missed visit, subjects will have until the end of the same week to reschedule an appointment or if the subject is unable to visit the clinic then the visit may be conducted over the telephone.

If the subject comes to a visit outside the allowed window, assessments scheduled for this visit will be conducted and data will be recorded as if it were for that week's scheduled visit and recorded as an unscheduled visit. At each of the clinic visits during the intervention phase, subjects will receive a brief session with one or more study staff members who will systematically assess AEs since the last visit, take vital signs, measure weight, conduct a BBCET session, administer questionnaires, ask about concomitant medication use and contraceptive method, and assess drinking and smoking using the TLFB. A new supply of investigational product will be given and the medication bottle(s) from the previous period will be collected. Blood will be collected for chemistries and hematology and a physical exam and electrocardiogram will be performed at Week 19 (visit 15). Women of child bearing potential will have a repeat pregnancy test during Weeks 1, 4, 7, 10, 16 and 19. An alcohol breathalyzer will be administered at each visit to determine if the subject has a BAC ≤ 0.020 to complete the visit. A urine drug test will be performed intermittently throughout the study. If the subject misses a visit in which safety measures were collected, the safety measures should be collected at the next in-clinic visit.

The following assessments will be administered at each study visit during the intervention phase (Week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18 and 19): Q-LES-Q, Alcohol Craving Visual

Analog Scale, Nicotine Craving Visual Analog Scale, CIWA-AR, Wisconsin Smoking Withdrawal Scale, and CES-D. In addition the PANAS assessment will be administered at Week 1, 3, 5, 7, 9 and 19 and the MOS-Sleep assessment will be administered at Week 1, 5, 9, 12, 16 and 19. The DrInC will be administered at Week 1, 4, 6, 9, 12 and 19.

CO levels will be measured at each visit during the study.

Salivary cotinine level is obtained before randomization and also at visit 15. In addition, in the event that a subject is unable to attend visit 15, they may be asked to provide a cotinine sample, via mail, which will be used to verify abstinence. In such a case, a saliva collection kit and instructions will be mailed to the subject with a prepaid return address envelope.

13.5 One and three month follow-up visits

At the end of the treatment period, subjects will be scheduled to attend a follow-up assessment session at one month post-treatment and take part in a follow-up phone call at three months post-treatment.

The following assessments will be administered at the one month follow-up visit: Fagerström Test for Nicotine Dependence, Q-LES-Q, The Alcohol Craving Visual Analog Scales, The Nicotine Craving Visual Analog Scales, CIWA-AR, Wisconsin Smoking Withdrawal Scale, PANAS, and CES-D. In addition, TLFBs for smoking and alcohol consumption and BAC and CO level will be collected at this visit. During the 3 month follow-up phone call, the CIWA-AR will be administered and TLFBs for smoking and alcohol use will be performed.

13.6 Early Termination (ET)

If a subject wishes to withdraw from the study before completing all study visits during the treatment phase then the study staff will schedule an early termination visit. The early termination visit will include all procedures and assessments of visit number 15 (week 19).

13.7 Study Completion Referral to Treatment

At the last contact with a study staff member, subjects who request ongoing care will be given a referral to an alcohol treatment facility or may be given a list of alcohol treatment facilities to contact.

13.8 Management of Withdrawal

Persons drinking at the level required for study entry may experience moderate to severe withdrawal symptoms if they stop drinking abruptly or if they attempt to taper their drinking, including shakes or tremors, chills, nausea and/or vomiting, agitation, sleeplessness, seizures, and delirium (disorientation, altered sensorium, and hallucinations). In addition to being distressing to the subject, these symptoms may become severe enough to require hospitalization in order to be managed safely. If the subject requires assistance with withdrawal between the consent and randomization visit or takes any benzodiazepines during this time period, they will be given appropriate treatment referrals. Any subject who is treated for withdrawal with medication between consent and randomization is no longer eligible to participate in the study. If management of alcohol withdrawal during the study is necessary, the subject will be referred to a

health care facility. Persons who are at risk for severe alcohol withdrawal will be excluded from the study.

At every in clinic visit subjects will be assessed for the emergence of withdrawal symptoms using a modified self-report version of the CIWA-AR and will be asked about changes in their health and drinking status. If the subject is experiencing withdrawal symptoms that would be equal to or greater than a total score of 10, or if their score on any individual item exceeds predetermined thresholds specific to each item on the CIWA-AR scale, and depending upon the situation, the clinic personnel will promptly speak to the subject to further assess their status.

Continuation of the investigational products while the subject undergoes detoxification is up to the discretion of the investigator.

13.9 Concomitant Medication Use

Subjects who enter this study can be on psychotropic medication if they are deemed stable enough to participate. We also will avoid the prescription of medications with even minimal potential interactions with topiramate. It is, however, recognized that concomitant medication may be prescribed or self-administered to treat minor physical ailments during the study. Such appropriate medications will be allowed and documented in the concurrent medications section, and the physical ailment recorded in the adverse events section of the subject's study book. A list of disallowed concomitant medications will be compiled and placed in the appendix section of each case study book for easy reference (see **Appendix III, Table of Disallowed Concomitant Medications**).

13.10 Safety Monitoring Plan

In compliance with the National Institutes of Health (NIH) policy for protection of human subjects in clinical studies, a Data and Safety Monitoring Plan (DSMP) previously approved by the NIH will be implemented at each site. The Data and Safety Monitoring Board (DSMB) for this study will be at the lead site, the University of Virginia. This DSMP serves to protect the health and safety of human subjects and provide information relevant to subjects' continuation in clinical studies and will consist of the following elements:

<u>a) Responsibilities of the principal investigator (PI)</u>
These responsibilities include:

1. Reporting immediately to the Institutional Review Board (IRB) any severe adverse reaction or serious problem, whether anticipated or unanticipated;
2. Reporting immediately to the IRB the death of a subject, regardless of cause;
3. Reporting promptly to the IRB any significant findings that become known in the course of the research and that might affect the willingness of subjects to participate in the study, including such items as changes in available standard of care, any interim analyses such as DSMB reports, and results of any monitoring visits by the institution or external regulatory bodies;
4. Ensuring that only persons formally approved by the IRB enroll subjects;

5. Protecting the confidentiality of all personal identifiable information collected, and training one's staff and collaborators on policies and procedures for ensuring confidentiality of this information;
6. Submitting any change(s) to the protocol and/or consent document(s) to the IRB for review and approval prior to the implementation of the change(s);
7. Submitting a progress report: federal regulations require IRB review of ongoing projects no less than once a year;
8. Notifying the IRB when the study has been completed and submitting a final report.

b) Institutional Review Board (IRB) responsibilities

The IRB reviews all human subject research conducted by faculty, staff, and students, regardless of the location of the research activity, source of funding, and whether the research is exempt under the Code of Federal Regulations for Protection of Human Subjects (45 CFR 46).

A guarantee that all human subject research will be reviewed by the IRB has been given to the Department of Health and Human Services (DHHS) in a Multiple Project Assurance (M-1403). The Multiple Project Assurance covers the universities at each participating site. The intent of the institutional policy to review all human subject research irrespective of location, source of funding, and exempt status is to foster high ethical standards in the conduct of research and to assure that uniform criteria are applied to protect the human subjects who take part in research.

The IRB reviews research in accordance with current DHHS and FDA regulations. The main purpose of the IRB is to protect the rights and welfare of human subjects who take part in research.

c) Data and Safety Monitoring Board (DSMB)

The DSMB group will be centralized at UVa. One member from each site will be included on a yearly DSMB teleconference. The DSMB will include relevant experts with supervisory capacity and the ability to enforce such actions as may be deemed necessary. The DSMB will also have one lay member. The DSMB will meet regularly to review progress pursuant to presentation of a summary report from the principal investigator ensuring that policies on the identification and reporting of adverse events to the appropriate regulatory bodies, which can include the local IRB, the FDA, and the project officer at the NIH, have been implemented diligently and promptly. Prompt and due diligence reporting of serious adverse events (i.e., within 24 hours during the week and on the next working day following a weekend) to the regulatory bodies remains the express duty of the principal investigator. The DSMB will retain the right to make independent representation to the regulatory bodies if there has been a failure or lapse in reporting by the principal investigator. The DSMB also will have the capacity to instruct the principal investigator to pause or terminate pursuance of research if regulatory body guidelines are contravened. The DSMB will provide regular independent reports to the IRB concerning the protection of human subjects in this study. These DSMB procedures have been approved previously by the NIH for our ongoing clinical studies.

Frequency of data and safety monitoring reviews: This team has extensive experience with clinical trials using topiramate and with the recruitment and retention of alcohol- and nicotine–

dependent subjects. In the past, such trials have been conducted with minimal risks to participants. Therefore, the DSMP will include two items:

1. The research staff at each site involved in the study will meet weekly to discuss progress on the study and to address any issues with the research procedures and database.
2. Once a year thereafter, the safety data described in the above section will be reviewed by the DSMB. The executive secretary will then generate a report that is sent to the PI. The report will summarize the Board's review of cumulative serious and unexpected adverse events.

Content of data and safety monitoring report: The PI will be responsible for monitoring the safety and efficacy of this trial, executing the DSMP, providing the DSMB with the needed information, and complying with the reporting requirements. The overall PI will provide a summary of the data and safety monitoring report to the NIAAA on an annual basis as part of the progress report.

d) Confidentiality

Extensive procedures in compliance with FDA regulations on Good Clinical Practice will be implemented for this trial to protect subject confidentiality and database integrity.
Briefly, besides the consent form that contains identifiers, all other data will be coded using a code number and initials. The consent form is stored in a secure location with limited access. Security procedures are implemented to ensure that only authorized personnel can enter study data.

e) Emergency procedures

On the day of randomization, participants are given an emergency notification card. The emergency notification card has a 24-hour emergency number by which to contact a PI study staff member in case of an after-hours emergency.

f) Emergency breaking of the study blind

The decision to break the study blind for an individual subject lies with the study principal investigator (or a designated co-investigator if a PI is not available) at each site and Dr. Nassima Ait-Daoud Tiouririne. Breaking the study blind will be resorted to only in cases of a life-threatening emergency when knowledge of the treatment arm investigational agent will influence clinical management. A designated study staff member will contact Dr. Nassima Ait-Daoud Tiouririne (cell: 434-284-1709, pager: 434-924-0000, #2186) in the event that the site PI believes the blind needs to be broken. Once permission has been granted by Dr. Ait-Daoud, a designated staff member at UVa will match up the pill bottle number for the subject with the master list of dose conditions to disclose which medication the subject was assigned.

g) Subject withdrawal

An investigator may terminate a subject if he or she deems it clinically appropriate or for any of the following reasons: 1) significant side effects from the medication, 2) serious or unexpected adverse events, 3) inability to comply with the study protocol, 4) protocol violation, or 5) serious inter-current illness. A subject may withdraw from the study anytime he or she wishes. In the

event that a subject is discontinued from receiving the research medication, he or she will be allowed to continue the psychosocial interventions with the approval of the investigator.

Any subject who discontinues prematurely, regardless of the reason, will be requested to return for a final visit to perform the necessary procedures and obtain data for the end-of-study/early-termination visit.

h) Adverse event reporting

In accordance with FDA reporting requirements, all adverse events (AEs) occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators at each site. Policies established by the local IRB at each site will be followed with regard to reporting AEs.

An adverse event is any untoward, unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of the product under investigation, whether or not related to the product under investigation.

An unexpected adverse event is any adverse drug experience, the nature, specificity, or severity of which is not consistent with the investigator's brochure, package insert or the general investigational plan.

For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign, or clinically significant clinical laboratory abnormality, or a worsening of a pre-existing condition or abnormality, is considered an AE. Stable chronic conditions, such as arthritis, that are present prior to clinical trial entry and **do not worsen** are not considered AEs. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until there is a satisfactory resolution. AEs may be reported up to 4 weeks following completion of, or termination from, the study. UVa will submit all AEs to FDA.

i) Serious adverse events

Serious and unexpected adverse experiences or death occurring during the course of a research project, regardless of cause, must be reported to the IRB immediately according to institutional guidelines (i.e., within 24 hours). In addition, all sites must report all SAEs to UVa within 24 hours. Nassima Ait-Daoud Tiouririne, of UVa, is the IND holder and therefore responsible for reporting all SAEs to the FDA.

The FDA reporting requirements are similar. The FDA defines a “serious adverse experience” as any unfavorable event associated with the use of the drug, whether or not it is considered drug-related.

“Serious” means an adverse experience that is life-threatening, is permanently or severely disabling, or requires an emergency room visit or inpatient hospitalization. “Unexpected” means an adverse experience that is not listed in the current labeling or investigational use data. This includes an event that may be symptomatically and pathophysiologically related to an adverse

reaction listed in the labeling or protocol, but that differs because of greater severity or specificity. Serious and unexpected adverse experiences include:

1- Any unexpected event, injury, toxicity, or sensitivity reaction or any unexpected incidence or severity associated with clinical use, and
2- Any unusual failure of the drug to exhibit its expected pharmacological activity.

It is the responsibility of the investigator to inform UVa of the investigation and the FDA of the occurrence of unanticipated adverse reactions, death, or serious adverse experiences.

In the event that either a study subject withdraws from the study or an investigator decides to discontinue the subject from the study due to a serious adverse event, the subject will have follow-up monitoring until the problem prompting the SAE has resolved or stabilized with no further change expected, or until it is discovered to be clearly unrelated to study medication, or until it progresses to death.

13.11 Volunteer Discontinuation

The investigators will follow the protocol to identify and intervene with subjects experiencing clinical deterioration during study participation. Potential protocol discontinuations will be reported to the **overall PI, Nassima Ait-Daoud Tiouririne**.

13.12 Recommended Subject Compensation

Subjects will be compensated for travel expenses and for time contributed to this research study in the form of vouchers, retail scrip, or cash. Compensation amounts will be in accordance with each local site's IRB recommendations. Subjects will be compensated regardless of whether they continue to receive the investigational product, if they attend visits. This compensation is for time and expenses incurred for study participation (e.g., gasoline, public transportation). Compensation for all completed visits, procedures and assessments may be up to $510.

13.13 Trial Registration

This trial will be registered on the National Library of Medicine's Clinical Trials Registry on the World Wide Web at http://www.clinicaltrials.gov.

14 ASSESSMENT METHODS

Table 1 summarizes the timing of the clinical activities and assessments to be conducted over the entire study period. These include the PANAS, Q-LES-Q, The Alcohol Craving Visual Analog Scales, The Nicotine Craving Visual Analog Scales, Wisconsin Smoking Withdrawal Scale, CES-D, MOS-Sleep, DrInC, CIWA-AR, Other Drug Use, and Fagerström Questionnaires.

14.1 AEs

AEs will be assessed starting after the subject takes the first dose of investigational product. AEs assessed in the clinic will use an opened ended question: "How have you been feeling since your last visit?" If an AE is reported that requires medical attention, it should be reported to the medical team for evaluation and follow-up.

14.2 Alcohol Breathalyzer

An alcohol breathalyzer will be administered at consent, at screening, and at every in-clinic visit as a safety measure. Acceptable BAC levels at consent and screening is equal to 0.000 and less than or equal to 0.020 for in-clinic visits.

14.3 Blood Chemistries, Hematology and Urine

Blood chemistry and hematology will be performed to confirm the subjects' physical health. These tests will include: complete blood count (CBC), sodium, potassium, chloride, calcium, phosphorus, total protein, albumin, globulin, glucose, total bilirubin, alkaline phosphatase, albumin/globulin ratio, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), γ-glutamyl transferase (GGT), blood urea nitrogen (BUN), creatinine, uric acid, and lactate dehydrogenase.

Urine will be collected for routine urinalysis. Women of child-bearing potential will receive a urine pregnancy test as scheduled in Table 1. Additionally, women of child-bearing potential participating in this study will be required to use an acceptable form of contraception, which includes but is not limited to the oral contraceptive pill, barrier (diaphragm and condom) plus spermicide, or hormonal or surgical implants.

An onsite urine drug screen will be performed at the screening visit to clear each subject for randomization. This UDS must be negative for all drugs. If a patient tests positive for a drug, he or she will be permitted one repeat urine drug screen prior to randomization. At site PIs' discretion, should a patient test positive again during the repeat UDS, he or she may rescreen (including re-consenting) 30 days from the end of the original 14 day period for randomization, which began when the informed consent was signed at the first screen visit. Urine drug screens will be repeated intermittently throughout the study.

14.4 BBCET Session Compliance

The BBCET session checklist is an instrument for provider assessments of session activities that was developed by the BBCET provider in our ongoing clinical trials. The checklist contains key interventions specific to the treatment. The rationale for the use of a BBCET session checklist is to provide a reminder of the key elements of the intervention and to provide an estimate of the overall level of treatment-specific intervention to each of the subjects in the study.

14.5 Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-AR)

The CIWA-AR, a reliable and well-validated 10-item scale, will be used weekly to assess the severity of alcohol withdrawal symptoms. The CIWA-AR has been used both in clinical and research applications and has demonstrated both reliability and validity.

14.6 Wisconsin Smoking Withdrawal Scale

This questionnaire will be used weekly to assess the severity of nicotine withdrawal symptoms. It is a 28-item scale divided into 7 subscales related to smoking cessation: sadness, sleep, hunger, craving, concentration, anxiety, and anger.

14.7 Positive Affect Negative Affect Schedule (PANAS)

The 20-item PANAS is a psychometric scale developed to measure the largely independent constructs of positive and negative effect, both as states and traits.[58] Subjects will be asked to describe different feelings and emotions during the past week.

14.8 The Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D[59] was developed to measure symptoms of depression in community populations. The scale has been used in many research studies as a screen for the presence of depressive illness. When the scale was developed items were selected to represent the major components of depression on the basis of the clinical literature and factor analytic studies. Components include the following: depressed mood, feelings of hopelessness, feelings of worthlessness, loss of appetite, poor concentration, and sleep disturbance.

The measurement of mood is particularly important to both alcohol and nicotine studies. With respect to alcohol, abrupt cessation of intake in dependent individuals can be associated with mood disturbance including depression, anxiety, confusion, and irritability. Likewise, abrupt smoking cessation among those dependent on nicotine can be associated with negative affect[60] including depression and anxiety. Furthermore, because the FDA has included the monitoring of depression and suicidality for all individuals receiving an anticonvulsant (including topiramate), we have included specific measurement of those parameters using the CES-D.

14.9 Medical Outcomes Sleep Scale (MOS-Sleep)

Abrupt cessation of either alcohol or nicotine in dependent individuals can be associated with sleep disturbance, and overall improvement in clinical condition might be associated with improved sleep. Therefore, sleep behavior will be measured explicitly.

The MOS-Sleep is a self-report questionnaire consisting of 12 items to provide information across sleep dimensions.[61] The scale assesses the following sleep constructs: initiation (2 items), maintenance (2 items), respiratory problems (2 items), quantity (1 item), perceived adequacy (2 items), and somnolence (3 items). Subjects report the amount of time it took to fall asleep and the number of hours they slept each night over the past week. Subjects answer 10 additional questions on a 6-point Likert scale ranging from 1 = all of the time to 6 = none of the time.

14.10 Drinker Inventory of Consequences (DrInC)

The DrInC[3] contains 50 items assessed on a 3-point scale ranging from “never” (0 points) to “daily or almost daily” (3 points). These 50 items are further subdivided into 6 subscales: physical consequences (8 items; maximum score = 24); intrapersonal consequences (8 items; maximum score = 24); social responsibility consequences (7 items; maximum score = 21); interpersonal consequences (10 items; maximum score = 30); impulse control consequences (12 items; maximum score = 36), and control items (5 items; maximum score = 15), as well as a total consequences scale (45 items; maximum score = 135). The total consequences scale is the sum of all the subscales except for the control items subscale. A lower score indicates reduced adverse consequences of drinking as compared with a higher score. The control items subscale is the sum of 5 reverse-scored validity items.

14.11 Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence[62] will be used to assess the behaviors associated with dependence on nicotine in potential study participants. The Fagerström Test for Nicotine Dependence will be administered at screening, and will, also, be repeated at the end of the double-blind phase and during the one month follow-up to ascertain behavioral consequences associated with nicotine dependence.

14.12 Demographics

Patient demographics will be collected for all subjects who sign a consent form. The subject's date of consent, date of birth, gender, race, marital status, education, employment status, income level and ethnicity will be recorded.

14.13 Drug Accountability

Drug accountability will be performed by recording the number of capsules dispensed and the number of capsules returned at clinic visits. The amount dispensed, daily dose prescribed, and amount returned will be reconciled and recorded at each visit. If the subject reports missing capsules that were not taken, this data will also be recorded and used to calculate total drug exposure. If the bottle was not returned, then the subject's self report of drug administration will be reported.

14.14 ECG

A 12-lead ECG will be obtained during screening and at visit 15. All 12-lead ECGs will be evaluated for HR, rhythm, and QTc intervals. Any abnormalities will be noted and an assessment of clinical significance will be done by a study physician or a qualified licensed medical provider.

14.15 Eligibility Checklist

The Eligibility Checklist which includes all inclusion and exclusion criteria will be reviewed in stages as follows: 1) after screening measures are completed and before scheduling the Study Day 1 visit and 2) prior to randomization on Study Day 1. If the subject was found not to be eligible at either of these timepoints, the reason(s) will be recorded. This data will be included in the study database for all subjects who signed the informed consent.

14.16 Medical History

A medical history will be taken on all potential study subjects to assure medical fitness and will be used to supplement the physician's general inquiry and physical examination.

14.17 Concomitant Medications

All medications (prescribed and over the counter medications plus herbal remedies) taken by the subject 90 days prior to the start of screening, during the screening period, and while taking investigational products will be recorded. Medications taken after the start of screening must be pre-approved by the study physician whenever possible to avoid interactions with the

investigational products. All medications reported by the subject or prescribed by the study physician will be recorded.

14.18 Timeline Follow-Back (TLFB)

The TLFB method of measuring alcohol and cigarette consumption will be used to construct a retrospective index of smoking and drinking behavior during the 3-month period before enrolling in the study. Thereafter, the consumption of alcohol or cigarettes between weekly visits will be recorded.[1] Days abstinent will refer to the number of days on which the subject consumes no alcohol or cigarettes. While subjects also will be provided with daily record cards as an aide-mémoire, only the TLFB data collected by a designated study staff member will be used in the efficacy analyses. From these data, we will determine both the PHDD and the point prevalence and continuous smoking abstinence rates. Self-reported reports of smoking cessation will be corroborated by measurement of breath CO level (see below).

Each site will receive training from the coordinating site, UVa, on how to administer the TLFB.

14.19 Carbon Monoxide (CO) Level

Expired carbon monoxide (CO) level will be measured using a Bedfont CO monitor. Self-reported abstinence will be verified by expired CO samples of <10 ppm. This will be measured at every in-clinic visit.

14.20 Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)

The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[64] is composed of 93 items, each containing responses on a 5-point scale that can range from 1 ("not at all or never") to 5 ("frequently or all the time"). Ninety-one of these items are grouped into 8 summary scales. Five of the 8 summary scales are scored for all subjects and include: physical health/activities (13 items, maximum score = 65); subjective feelings (14 items, maximum score = 70); leisure time activities (6 items, maximum score = 30); social relationships (11 items, maximum score = 55), and general activities (14 items, maximum score = 70). The other 3 summary scales are scored when applicable, and these include: work (13 items, maximum score = 65); household duties (10 items, maximum score = 50), and school/course work (10 items, maximum score = 50). We measured satisfaction with medication and overall life satisfaction and contentment on individual item scales, each with a maximum score of 5.

14.21 Alcohol Craving Visual Analog Scales

The Alcohol Craving Visual Analog Scales will comprise 4 items on which subjects will be asked to rate themselves on how they feel "*right now*" by placing a mark along a 100-mm line anchored on the left by "*not at all*" and on the right by "*extremely*". These items include: "*Right now I crave a drink*"; "*Right now I have a strong urge to have a drink*"; "*Right now I want to have a drink*"; and "*Right now I could refuse to have a drink*". Scales of this type have been validated in a previous alcohol study by Johnson et al.[65] Whilst we are cognizant that other standardized measures of alcohol craving could have been collected (e.g., Obsessive Compulsive Drinking Scale,[66]) we chose the scale above because it also was validated and would correspond and be directly comparable to the nicotine craving measure described below.

14.22 Nicotine Craving Visual Analog Scales

The Nicotine Craving Visual Analog Scales will comprise 4 items on which subjects will be asked to rate themselves on how they feel "*right now*" by placing a mark along a 100-mm line anchored on the left by "*not at all*" and on the right by "*extremely.*" These items include: "*Right now, I crave a cigarette*"; "*Right now, I have a strong urge to have a cigarette*"; "*Right now, I want to have a cigarette*"; *and* "*Right now, I could refuse to have a cigarette*". These scales are a derivative of those used in alcohol research by Johnson et al.[65]

14.23 The Tobacco Use History Questionnaire

This will be administered at screen. This self-report instrument provides data primarily on past cessation attempts, years smoking, other tobacco use, and past methods of cessation, and will be used to describe the past smoking behavior of the participants and to determine desire to quit.

14.24 Alcohol Use Disorders Identification Test (AUDIT)[67]

The Alcohol Use Disorders Identification Test (AUDIT)[67] is a well-validated measure of ascertaining the extent of alcohol-related problems.

14.25 Mini International Neuropsychiatric Interview (MINI)

The Mini International Neuropsychiatric Interview is a short 15 minute structured clinical interview. It is used for multi-site clinical trials and epidemiological studies to determine diagnoses of psychiatric disorders according to DSM-4 or ICD-10. The MINI we use will diagnose psychiatric disorders other than alcohol use disorder based on DSM-4 criteria. However, a DSM-5 diagnosis of mild to severe alcohol use disorder is required to be eligible for the study. In order to ascertain that a subject meets this criterion, if the subject answers "yes" to question I1 on the MINI, providers will proceed to ask the subject questions in both section I2 *and* I3. In addition, a supplemental sheet with an additional DSM-5 craving question will be added to the MINI. This sheet will also contain directions for scoring: all items coded YES will receive a score of one, including questions in I2, I3, and the supplemental craving question, and excluding question I 3 c. (regarding legal consequences). The total score will then be used to determine the severity grade of the subject's alcohol use disorder. Severity grades include "no diagnosis" (a score of 0 to 1), "mild alcohol use disorder" (2 to 3), "moderate alcohol use disorder" (4 to 5), and "severe alcohol use disorder" (6 or greater).

The use of DSM-5 criteria rather than DSM-4 reflects a desire on the part of the research team to embrace the future of the Diagnostic and Statistical Manual and to be at the forefront of use of these carefully researched, revised guidelines. By including in one spectrum criteria formerly divided into two distinct, but clearly related, groups and by judging the results using a severity grade, we feel we will have a more accurate picture of a subject's disorder and his or her suitability for participation. With this change, subjects who met one or two criteria in the former dependence section and also met one or more criteria in the abuse portion—and formerly would have failed to meet study inclusion criteria—will now be judged in a more overarching manner with an eye to the various ways the disorder may express itself. As we have included minimum use levels as part of our inclusion criteria, we feel that the modifications in the DSM-5 will prevent us from excluding those who are good candidates for the treatment proposed.

14.26 Salivary Cotinine Level

Cotinine is the primary metabolite of nicotine and has a half-life of about 19 hours.[68] Salivary cotinine level will be used as an additional objective measure of tobacco exposure for those who are still smoking. We propose the use of 15 ng/ml of saliva cotinine as a cut-off level to segregate non-smokers (≤15 ng/ml) from smokers (>15 ng/ml). The SRNT Subcommittee on Biochemical Verification[69] and Seccareccia et al.[70] both recommend that a cut-off level of cotinine (15 ng/ml) be utilized for saliva, serum, or plasma samples.

Each site will collect saliva samples on all subjects before randomization and at visit 15. In the event that a subject is unable to attend visit 15, they may be asked to provide a cotinine sample, via mail, which will be used to verify abstinence. In such a case, a saliva collection kit and instructions will be mailed to the subject with a prepaid return address envelope.

Samples will be sent to a specialty lab where cotinine analysis will be performed on those who report abstinence. All sites will use the same saliva cotinine collection kits to maintain uniformity across the study.

14.27 Physical Examination

A physical examination of the oral cavity, head, eyes, ears, nose, and throat, cardiovascular system, lungs, abdomen, extremities, skin, neurological system, neck, lymph nodes, musculoskeletal system and general appearance will be performed.

14.28 Vital Signs

Vital signs to be assessed include sitting heart rate, respirations, temperature, and blood pressure. Weight will also be recorded at every visit in which vital signs are measured and height will be gathered at visits during which an ECG is performed.

14.29 Genotyping

It has been proposed recently that a single nucleotide polymorphism (SNP) variant of the glutamate receptor GluR5 gene (GRIK1) might predict adverse events to topiramate. Specifically, the SNP in intron 9 of the GRIK1 gene (rs2832407) appears to be particularly associated with adverse events.[71] Whilst it would not be reasonable to exclude participants from the study based upon the findings of a single unconfirmed report, because of the need to increase the generalizability of topiramate use, should this study demonstrate efficacy, we propose to type this SNP. Collecting DNA also will provide us with genetic samples that may be utilizable as science advances to understand further the neurobiology of excessive alcohol intake or smoking, and related behaviors.

Each site will collect blood samples for DNA extraction and genotyping. Samples will be collected for genotyping from subjects who consented to genetic testing. Samples will be shipped to University of Texas-MDACC where the DNA extraction and genotyping procedures will take place. **The blood collection for genotyping protocol can be found in Appendix VI.**

14.30 Baseline Drug Use and Other Drug Use

The Baseline Drug Use form will be used at screen to assess current and lifetime drug use. The Other Drug Use form will be used at visits 1-15 and at the one month follow-up visit to record any new drug use since the participant's last visit.

14.31 Contraceptive Method

The Contraceptive Method form will be used at screen and during visits 1-15. The form will record contraceptive method for females of childbearing potential or why the participant cannot bear children. For male participants, the form will be marked "Not Applicable" at the screening visit.

15 ANALYTICAL PLAN

15.1 Outcome Measures

The primary efficacy variables will be the PHDD for the drinking outcome and the continuous abstinence rate for the smoking outcome (during the last 4 weeks of treatment, i.e., weeks 15–18 inclusive), respectively. The secondary efficacy variables will be quality of life and measures of alcohol and nicotine craving. Exploratory outcomes include measures of dependence, and measures of nicotine and alcohol withdrawal including negative effect, as noted below:

1. Fagerström Test for Nicotine Dependence
2. Revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) [2]
3. Wisconsin Smoking Withdrawal Scale
4. Positive Affect Negative Affect Schedule (PANAS)
5. The Center for Epidemiologic Studies Depression Scale (CES-D)
6. Medical Outcomes Sleep Scale (MOS-Sleep)
7. The Drinker Inventory of Consequences (DrInC)[3]

Additional exploratory outcome variables will include other: 1) measures of drinking severity (i.e., DDD) and abstinence (i.e., percentage of days abstinent; PDA) averaged across either the entire double-blind period or the last 4 weeks of treatment, and 2) smoking measures including the point prevalence abstinence rate and the CO level over either the entire double-blind period or the last 4 weeks of treatment.

15.2 Standard Drink and Drinking Day Definitions

Drinking days are defined as the number of days in which the subject reported consumption of at least one standard drink. The data given by the subjects on amount and type of alcoholic beverage(s) consumed will be converted to SDUs (standard drink units). The following SDU formulas and conversions will be used:

$$\textbf{(\# of Drinks) x (oz drink) x (\% alcohol) x 2 = Daily SDU}$$

$$\frac{\textbf{30 Day SDU Total}}{\textbf{30}} \textbf{ x 7 = Weekly SDU}$$

15.3 Statistical Hypotheses

Primary Outcomes:

1. Both low- and high-dose topiramate will be more efficacious than placebo at reducing the percentage of heavy drinking days (PHDD) and increasing the continuous abstinence rate for smoking determined by a combination of self-report and CO monitoring after the TQD, and in the last 4 weeks of treatment.
2. High-dose topiramate will be more efficacious than low-dose topiramate at reducing PHDD and increasing the continuous abstinence rate for smoking determined by a combination of self-report and CO monitoring after the TQD, and in the last 4 weeks of treatment.

Secondary Outcomes:

3. Both low- and high-dose topiramate will be more efficacious than placebo at improving quality of life and reducing craving, after the TQD, and in the last 4 weeks of treatment.
4. High-dose topiramate will be more efficacious than low-dose topiramate at improving quality of life and reducing craving, nicotine and alcohol withdrawal symptoms and negative affect after the TQD, and in the last 4 weeks of treatment.

5. **Exploratory Outcomes:**Both low- and high-dose topiramate will be more efficacious than placebo at improving nicotine and alcohol withdrawal symptoms and negative affect in the last 4 weeks of treatment after the TQD.
6. Improvements in quality of life and craving reductions will be predictably associated with reduced PHDD, increased continuous abstinence rates for smoking, or both, irrespective of treatment group.

15.4 Subject Populations

The ITT population will be used for the primary analysis and is defined as the subjects who are randomized into the study. The evaluable population is defined as those subjects randomized to the study who completed at least 6 consecutive weeks of maintenance investigational product administration with a dose of at least 50 mg per day for at least 5 days of each 7-day weekly period. The safety population includes all subjects who received at least one dose of investigational product.

Analysis: Data will be summarized with respect to the primary and secondary outcome measures, demographics, and baseline characteristics. In general, quantitative variables will be summarized with standard descriptive statistics (e.g., range, quartiles, means, standard deviations), while frequency tables will summarize categorical variables. Group comparison for quantitative variables will be performed using standard two-sample t-tests or analysis of variance as appropriate. Highly skewed variables may be transformed prior to inferential comparison, or non-parametric methods may be used if needed. Group comparison for categorical variables will be analyzed with two-sample comparisons of proportions, or chi-square tests as appropriate.

The primary efficacy variables will be the PHDD for the drinking outcome and the continuous abstinence rate for the smoking outcome (during the last 4 weeks of treatment, i.e., weeks 15–18 inclusive), respectively. The secondary efficacy variables will be quality of life and measures of alcohol and nicotine craving.

Exploratory outcome variables will include other: 1) measures of drinking severity (i.e., DDD) and abstinence (i.e., percentage of days abstinent; PDA) averaged across either the entire double-blind period or the last 4 weeks of treatment, and 2) smoking measures including the point prevalence abstinence rate and the CO level over either the entire double-blind period or the last 4 weeks of treatment; 3) psychological assessments including measures of nicotine and alcohol withdrawal (WSWS, MOS-Sleep, CIWA-Ar), negative affect (PANAS, CES-D), dependence (FTND), drinking behavior (DrInC) and compliance (BBCET).

The general approach to statistical analyses will be the same as what we utilized in our previous studies.[4, 5] All randomized subjects will be included in the analysis using the intent-to-treat principle. Statistical analyses will be conducted using SAS 9.1 (SAS Institute Inc., Cary, NC).[6]

Primary Outcomes Analytical Models:

We will use generalized linear models (GLM) to estimate treatment effects on PHDD and logistic regression for abstinence. We will adjust for baseline covariates on the same drinking or smoking variables. For the drinking and smoking variables, that baseline is the averaged value for the 90-day period prior to the screening visit. Other potential covariates shall include age, gender, and ethnicity. We also will consider the treatment period up to the TQD as an additional set of covariates for analyses that focus on the last 4 weeks of treatment. The residuals from our analyses will be checked for normality by computing their skewness and kurtosis and will be checked for homogeneity of variance by plotting them in a histogram and against predicted outcomes. Standard transformations will be employed to improve the distributions when required (i.e., square root or log transformation).

If, however, there is a differential attrition rate (i.e., if dropout is informative), we shall consider other approaches to handle repeated-measures data that can be adopted to obtain valid results.[7, 8]

Exploratory Analytical Models:

We also will use the more advanced two-part random-effects model[9, 10] to analyze the daily drinking and smoking record. Such a model can simultaneously characterize the frequency (odds of daily drinking or smoking being zero) and quantity (number of drinks on a drinking day or number of cigarettes smoked on a smoking day) of drinking and smoking outcomes, respectively. It is more efficient and can tackle non-normality in the drinking or smoking level. We also are interested in trajectory analysis of different treatments over time to capture differences in these outcomes. Such analysis is more clinically intuitive and could be more powerful than the analysis based on endpoint.

The Kaplan-Meier survival method will be used to compare time to achieve continuous abstinence between the treatment groups. Homogeneity between different arms will be tested with the log-rank test. Additionally, we will use the Cox proportional-hazards model to estimate the relative likelihood (i.e., magnitude of the treatment response) between the treatment groups for achieving continuous periods of abstinence. For the Cox regression model, potential confounding variables such as age of onset for alcoholism (less than 26 years old or 26 years and

older), gender, weight, and baseline smoking level will be considered as potential covariates for inclusion in the final analytic model.

If the saliva cotinine level satisfactorily achieves criteria for normality as longitudinal data, we will compare the groups using a mixed-effects linear model, accounting for a three-group design as well as the repeated measure of weeks (when appropriate). Otherwise, salivary cotinine level will be dichotomized as negative if ≤15 ng/ml and positive if >15 ng/ml and analyzed using the generalized linear mixed models.

Logistic regression analysis will be used to compare point prevalence abstinence rates for the topiramate vs. placebo groups. We will determine point prevalence abstinence rates by a report of not smoking (0 cigarettes/day) for the entire period prior to a particular visit and an expiratory CO of <10 ppm at the present visit.

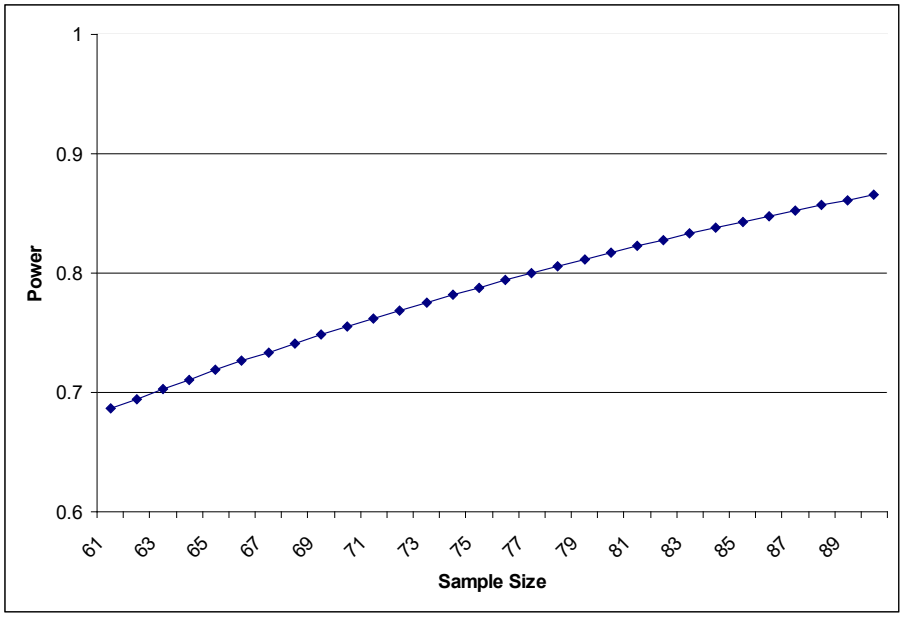
15.5 Sample Size Calculation

We did two sets of power analysis to account for the drinking and smoking endpoints in our proposed study. Importantly, because smoking outcomes are based mostly on dichotomous variables, power estimates for these outcomes drive the numbers needed for this comorbid alcohol- and nicotine-dependent cohort. Hence, it is important to have adequate power for the smoking outcomes even though this will result in a superfluous level of power for the drinking outcomes.

First, for the smoking outcomes, we did a power analysis by comparing the two-sample difference in nicotine abstinence using SAS Proc POWER. We have estimated power based upon our ability to detect a difference in the percentage of smoking abstinence between the treatment groups. Because the comparisons of the topiramate groups with one another (i.e., high vs. low) and with placebo are experimental, we chose to calculate power to detect the effect size of therapeutic treatments typical of the smoking cessation literature. We chose to calculate power based on our estimates of the percentage of smoking abstinence in the pivotal study by Jorenby et al.,[72] where bupropion was compared with placebo in a 9-week randomized, controlled clinical trial. In that study, the TQD occurred at the end of the first week of double-blind treatment. As a conservative measure, we have accepted the subject numbers for these two groups for the present study to represent the comparison of the low-dose topiramate vs. placebo or the high-dose vs. low-dose topiramate. Thus, we have assumed that the difference between low-dose topiramate and placebo would be similar to that between high- and low-dose topiramate. Since there are 3 pairwise comparisons between the three arms, we will adopt Bonferroni's adjustment and take alpha level as 0.05/3 = 0.017.

From Figure 1 in Jorenby et al.,[72] the continuous prevalence rate of smoking abstinence at 18 weeks is approximately 10% for placebo and 28% for bupropion. Using these numbers, we find that 98 subjects in each arm (294 in total) are needed to achieve a power of 0.80. If we observe a similar effect to that in the preliminary study we will be operating under even increased power.

For the drinking outcome, we based the power calculation from data obtained in a previous multi-site randomized controlled trial of topiramate for the treatment of alcohol dependence.[5] We observed that the slope of PHDD for the topiramate group declined faster than that for the placebo group by 0.014 per week, with a standard error of 0.003. We anticipate that the weekly PHDD will have this similar variability in the proposed trial. We have assumed that the low and high doses of topiramate will have a similar trajectory but with the high dose being more efficacious.



The null hypothesis is that there is no difference in the declining rate in weekly PHDD between low-dose topiramate, high-dose topiramate, and the placebo group. Power was then obtained by the probability that the non-centrality parameter is greater than the critical value in the F-distribution with the numerator and denominator degrees of freedom from the mixed-model results. Since there are 3 pairwise comparisons between the three arms, we will use Bonferroni's adjustment and take alpha level as 0.05/3 = 0.017. We find that 76 subjects in each of the treatment arms (a total of 228 subjects in 3 arms) will yield a power of 80%. Hence, this study will be operating under increased power for the primary efficacy variable on drinking outcome. The technical details of the power calculations for mixed models can be found in Littell et al.[73] (Chapter 12). The figure above shows the power curve for different sample sizes.

Since we already accounted for dropout in the mixed model for the multi-site study, no additional measure to address the attrition rate is necessary as long as the weekly dropout rate (i.e., not the total dropout) in the present study is similar to that in the previous trial.

After considering both sample sizes, we chose the larger value, 98 subjects in each group, as our final sample size. It can fulfill our need to test our primary hypothesis.

15.6 Additional Exploratory Analyses

Data will be collected in this study for scientific use and not as primary or secondary outcome measures. Additional *post hoc* analysis may be performed to evaluate other confounding factors on outcomes such as depression or patterns of alcohol use at baseline prior to randomization (visit 1) and after interventions.

16 DATA MANAGEMENT

16.1 Data Collection

Database and statistical functions for this project will be managed at each center by an experienced core group. Collected pen-and-paper-completed data will be entered into an electronic web-based database in a timely manner The database group at each site will follow compliance with all FDA database and statistical procedures. The database and statistical procedures will be supervised by the statistical team at UVa.

16.2 Data Editing, Monitoring and Control

Data collected for this study will be entered into a secure web-based database provided by DatStat (Seattle, WA). DatStat ensures the privacy of data by utilizing industry best practices for security such as password protection, data encryption, and secure networks. The transfer of survey data is accomplished using the internet with a secure connection via the secure sockets layer (SSL). All surveys hosted with DatStat are encrypted using 128-bit SSL Technology (Secure Socket Layer) that is equivalent to the industry standard for securely transmitting credit card information over the Internet. This technology encrypts participant responses. Thus, all responses are instantly encrypted and remain so until they are received at the DatStat database.

All data will be stored at DatStat and will be backed up on a daily basis and held in a tightly secured facility. All DatStat servers that are used for data collection are highly fault tolerant and, to this end, are equipped with redundant, hot-pluggable power supplies, redundant network interfaces, and RAID 1/5 hot-pluggable disk storage. Most customer applications are deployed under the Linux operating system using Apache server technology. Servers are stored in a locked, well-ventilated room in locked server cabinet/racks. The server room is in a building with 24/7 alarm security. Any building compromise will sound the alarm and generate a call to the building supervisor and police, who will subsequently notify DatStat personnel of the intrusion. All primary servers are plugged into a monitored uninterruptible power supply (UPS) offering a minimum of 30 minutes of battery power in the event of a power outage. At least one additional server is available at all times to handle the off-chance of a major server crash.

The overall study coordinator will be in charge of monitoring data entry at all study sites. This includes coordinating trainings, and completing monitoring visits with audits.

16.3 Study Documentation and Records Retention

Study documentation includes all data correction forms, workbooks, source documents, monitoring logs and appointment schedules, Sponsor and investigator correspondence and regulatory documents (e.g., signed protocol and amendments and IRB correspondence and approved consent form and signed informed consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be retained for the length of time that the IND is open and for an additional 2 years after the IND is closed.

The likelihood of information from our clinic being disseminated without the subject's consent to an outside source is remote. No information about a subject is disclosed without his or her written authority. At each site, source documents are kept at a secure location in locked files. Access to these files is restricted to known personnel.

16.4 Confidentiality

16.4.1 *Confidentiality of Data*

Particular attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and IRB.

By signing this protocol the investigator affirms to UVa that information furnished to the investigator by UVa will be maintained in confidence and such information will be divulged to the IRB or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

16.4.2 *Confidentiality of Subject Records*

To maintain subject confidentiality, all laboratory specimens, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by representatives of UVa. Upon approval of the study by an IRB, an application will be filed with UVa for a Certificate of Confidentiality.

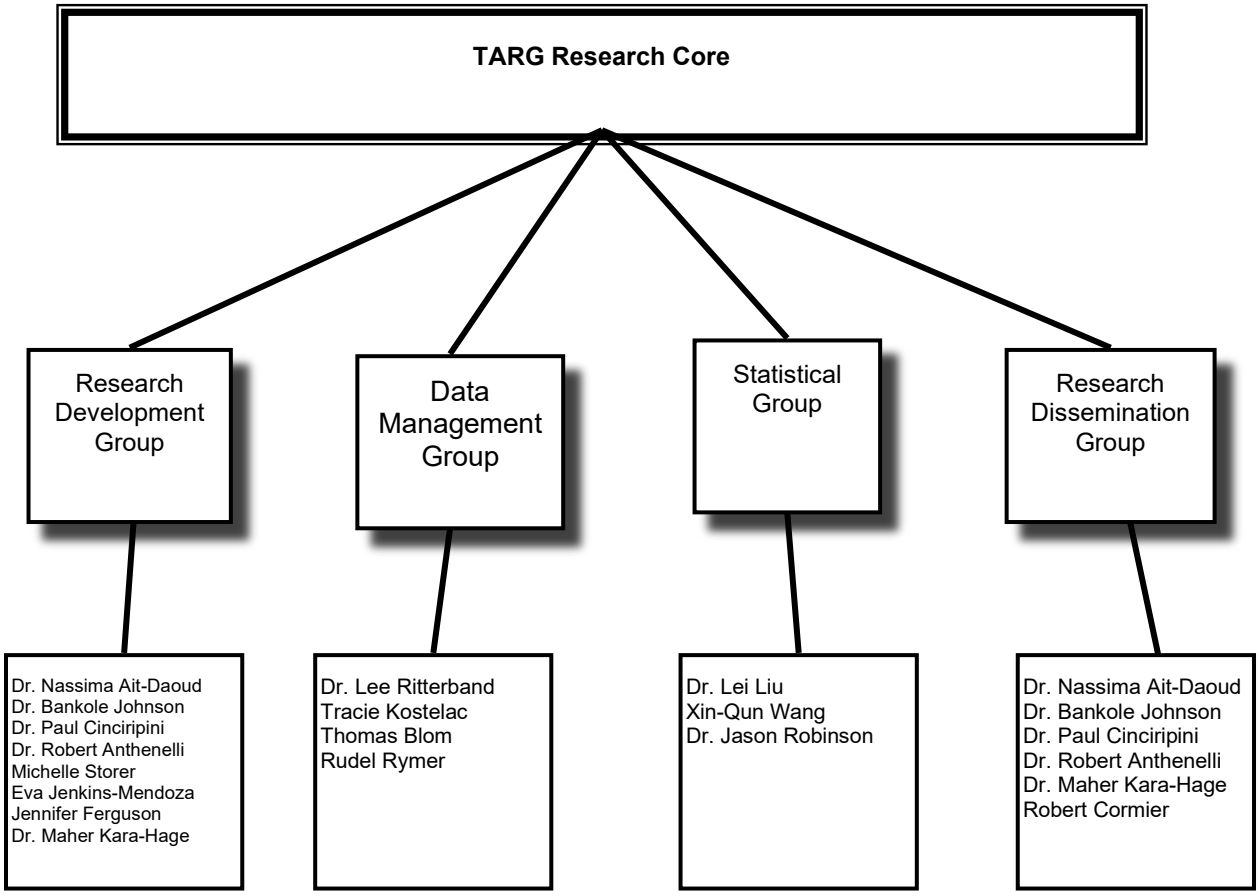
The use and procedure for applying for a Certificate of Confidentiality are provided in **Appendix II**.

17 PUBLICATIONS OF THE STUDY RESULTS

The role of Tobacco and Alcohol Research Group (TARG) (diagram below) is to assist the PI and co-investigators in data dissemination and manuscript preparation and publication. This group will create a database of measures and possible manuscripts, identify the authors to be involved in each manuscript, and review manuscripts before submission.

The statistical group will provide ongoing statistical support to carry out the research project and to develop and apply innovative methods in study design and statistical analysis. Thus, the group will provide statistical support to investigators in statistical analysis and interpretation, and in the preparation of abstracts, presentations, and manuscripts. The group consists of biostatisticians who are members of the Division of Biostatistics and Epidemiology in the

Department of Public Health Sciences at the University of Virginia, and who have established expertise in a wide range of statistical areas. Their areas of strength include experimental designs, dose finding, clinical trials, longitudinal analysis, and survival analysis (particularly in dealing with non-classical analyses such as those involving dependent censoring).



18 SIGNATURES

INVESTIGATORS

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 13.10 i and Appendix I of this protocol.

Typed Name	**Signature**	**Date**
Nassima Ait-Daoud Tiouririne, M.D Site Principal Investigator	_____	_____
Robert M. Anthenelli, M.D Site Principal Investigator	_____	_____
Paul M. Cinciripini, Ph.D. Site Principal Investigator	_____	_____

19 APPENDIX I

Instructions for Evaluating and Reporting AEs and SAEs

A. GENERAL INSTRUCTIONS

1. Record AEs beginning the day of randomization (subject will take the first dose of investigational product that evening).

2. Report the severity of the event following the guidance in section B below.

3. Report the relatedness of the event to the investigational product administration according to the guidance in section C.

B. DEFINITIONS – ADVERSE EVENT, UNEXPECTED ADVERSE EVENT AND SEVERITY OF EVENTS

Adverse event (AE): An adverse event is any untoward, unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of the product under investigation, whether or not related to the product under investigation.

Unexpected adverse event: Any adverse drug experience, the nature, specificity, or severity of which is not consistent with the investigator's brochure, package insert or the general investigational plan.

Mild:	Awareness of symptom, but easily tolerated.
Moderate:	Discomfort enough to cause interference with usual activity.
Severe:	Incapacitating with inability to work or do usual activity.
Life-threatening:	At imminent risk of death without intervention.

C. DEFINITIONS – RELATEDNESS OF EVENTS

The study physician is responsible for defining, in his/her best judgment, the relationship of the AE/SAE to the investigational products. The degree of certainty for which the AE/SAE is attributed to the investigational product or alternative causes (e.g., natural history of the underlying disease, concomitant therapies, etc.) should be determined by how well the experience can be understood in terms of one or more of the following:

- ***Exposure:*** Is there evidence that the subject was actually exposed to the investigational product?

- ***Timing of the study drug/placebo:*** Did the AE/SAE follow in a reasonable temporal sequence from administration of the investigational product?

- ***Consistency with study drug profile:*** Known pharmacology and toxicology of the study drug in animals and man; reaction of similar nature having been previously described with the investigational product.

- ***Alternative explanations*** for the AE such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.

- ***Response to discontinuation*** of the study investigational product.
  Terms and definitions to be used in assessing the investigational product relationship to the AE/SAE are:

- ***Unknown:***
  Use this category only if the cause of the AE/SAE is not possible to determine

- ***Not Related:***
  The subject did not receive the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is not reasonable, or there is another obvious cause of the AE/SAE.

- ***Remotely (Unlikely) Related:***
  There is evidence of exposure to the investigational product or there is another more likely cause of the AE/SAE.

- ***Possibly Related:***
  There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, but the AE/SAE could have been due to another equally likely cause.

- ***Probably Related:***
  There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, and the AE/SAE is more likely explained by the investigational product than by any other cause.

- ***Definitely Related:***
  There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, the AE/SAE is more likely explained by the investigational product than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the investigational product or investigational product class.

D. DEFINITIONS FOR ADVERSE EVENT REPORTS

A serious adverse event is defined as one that satisfies any of the following criteria:

- results in death,
- is immediately life-threatening,

- requires in-patient hospitalization, or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital abnormality or birth defect, or
- is an important medical event that may jeopardize the subject, or may require medical intervention to prevent one of the outcomes listed above.

SAEs are further explained as follows:

- any death resulting from an AE occurring during the trial period or within 14 days after the last dose of the trial drug.
- the subject must have been at an immediate risk of dying from the AE as it occurred. This does not include events that might have caused death if they had occurred in a more serious form (e.g., drug-induced hepatitis that resolves without hepatic failure).
- any AE resulting in hospital admission and usually an overnight stay. Prolongs hospitalization means delayed planned or anticipated discharge date (again usually by at least one overnight stay). This does not include hospitalization for elective surgery for a condition that was present prior to trial entry and whose clinical course has not changed after exposure to the trial drug.
- any AE resulting in impairment, damage or disruption in the subject's body function, structure or both, physical activities or quality of life.
- any AE resulting in a condition which requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure of the subject. Examples of this can include procedures such as blood transfusion or catheterization. However, discontinuation of the trial drug, or routine administration of prescription medications or changes in their dosages, should not be considered as medical intervention.
- if there are suspicions that exposure of either parent to the trial drug resulted in an adverse outcome in the offspring.

Guide to Interpreting the Causality Question

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug?
- Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacologic properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Life threatening

"Life-threatening" means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

E. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

A laboratory or ECG AE is any clinically significant worsening in a test variable that occurs during the course of the study, whether or not considered to be investigational product related. For each such change, provide the information requested on date of test, severity, likelihood of a relationship to investigational product, change in investigational product dosage due to the AE, and treatment required.

All laboratory AEs should be specified as an increased or decreased test result (e.g. "increased glucose", "decreased potassium") or as a term that implies an abnormality (e.g., hypercalcemia, azotemia, hypokalemia, or bradycardia). Any abnormal laboratory value that is considered clinically significant will be recorded as such on the clinical laboratory form in the source document along with a comment providing justification for that determination.

F. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Serious and unexpected adverse experiences or death occurring during the course of a research project, regardless of cause, must be reported to the IRB immediately according to institutional guidelines (i.e., within 24 hours). In addition, all sites must report all SAEs to UVa within 24 hours. Nassima Ait-Daoud Tiouririne, of UVa, is the IND holder and therefore responsible for reporting all SAEs to the FDA.

Upon receipt of a report of adverse experience or report of death, the IRB will decide whether further investigation of the event is required. In some cases, an investigator may be required to suspend a study pending the outcome of IRB review. It is the responsibility of the investigator to inform the sponsor of the investigation and the FDA of the occurrence of unanticipated adverse reactions, death, or serious adverse experiences.

In the event that either a study subject withdraws from the study or an investigator decides to discontinue the subject from the study due to a serious adverse event, the subject must have appropriate follow-up medical monitoring. If the subject is hospitalized, medical monitoring will consist of not less than daily evaluation by physical examination, vital signs, laboratory evaluations, and, if applicable, ECG monitoring for significant treatment emergent abnormalities. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized

with no further change expected, or until it is discovered to be clearly unrelated to study medication, or until it progresses to death.

The following information with the initial report of an SAE or unexpected AE must be provided to the IND holder, Nassima Ait-Daoud Tiouririne:

- Name of person reporting the SAE/unexpected AE
- Subject's I.D. number
- Name of the PI and institution
- Date the subject signed informed consent
- Date first dose of investigational product was ingested
- Description of the SAE/unexpected AE
- Date and time of Onset
- Date/time of administration of last dose of investigational product prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- Investigator's assessment of the relationship of the SAE/unexpected AE to investigational product (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the investigational product, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

Follow-Up of All AEs/SAEs

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended hospitalization period or a change in status from outpatient to inpatient.

All AEs must be recorded on the adverse event log. Anticipated adverse experiences are AEs that have been anticipated in the protocol, such as reactions to drugs, and do not have to be reported to the IRB unless they are unexpectedly serious, life-threatening, or fatal.

Each week, each site PI must review the adverse event log completed for the previous week for any events that were reported as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until there is a satisfactory resolution. AEs may be reported up to 4 weeks following completion of, or termination from, the study.

20 APPENDIX II: Certificate of Confidentiality

The only people who will know the identity of the subjects are members of the research team and, if appropriate, the physicians and nurses. No information about the subjects, or provided by the subjects during the research, will be disclosed to others without the subjects' written permission, except if necessary to protect subjects' rights or welfare.

When the results of the research are published or discussed in conferences, no information will be included that would reveal subjects' identity. Authorized representatives of the FDA and NIAAA study monitors may need to review records of individual subjects. As a result, they may know subjects' names, but they are bound by rules of confidentiality not to reveal their identity to others. The results of this study including laboratory results and clinical information collected during this study will be submitted to the FDA and may be used for research purposes. The results of this study may be published but will not personally identify any subjects. All records will be kept in locked storage locations that will be accessible only to authorized study personnel.

UVa will apply for a Certificate of Confidentiality for all participating sites.

This Certificate of Confidentiality helps researchers protect the privacy of subjects in health research projects against compulsory legal demands (e.g., court orders and subpoenas) that seek the names or other identifying characteristics of research subjects. The certificate was developed to protect against the involuntary release of personally identified research information of a sensitive nature sought through any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. This authority was granted under the Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law No. 91-513, Section 3(a).

This certificate is necessary for investigators to avoid being required to involuntarily disclose personally identifiable research information about individual study subjects. Under this statute:

"The Secretary [of the Department of Health and Human Services] may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, and on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals" (Public Health Service Act 301 (d), 42 U. S. C. 241 (d), as amended by Public Law No. 100-607, Section 163 (November 4, 1988)).”

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic investigation, designed to develop or contribute to generalizable knowledge). It is granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

The study subjects should be informed that a Certificate is in effect, and be given a fair and clear explanation of the protection it affords, including the limitations and exceptions. This information will be included in the informed consent. Please see below some suggested wording:

"We have received a Certificate of Confidentiality from the NIAAA, which will help us protect your privacy. The Certificate protects against the involuntary release of information about your participation in this study. The researchers involved in this project cannot be forced to disclose your identity or your participation in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, you or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests disclosure of your participation, the researchers will provide research data. The Certificate does not protect against that voluntary disclosure.

Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or a Food and Drug Administration request under the Food, Drug and Cosmetics Act."

"A Certificate of Confidentiality has been obtained from the Federal Government for this study to help insure your privacy. This Certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. If we see [learn] something that would immediately endanger you, your child, or others, we may discuss it with you, if possible, or seek help."

Study subjects will be notified that a Certificate has expired if they are recruited to the study after the expiration date of the Certificate and an extension of the Certificate's coverage has not been granted.

If the research scope of a project covered by a Certificate should change substantially, the PI will request an amendment to the Certificate; however, the NIAAA Certificate Coordinator may require a new Certificate depending on the extent of the change in scope. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate, as research information collected after the expiration of a Certificate is not protected from compelled release.

A Certificate of Confidentiality is a legal defense against a subpoena or court order, and is to be used by the researcher to resist disclosure. The researcher should seek legal counsel from his or her institution if legal action is brought to release personally identifying information protected by a certificate. The Office of General Counsel for DHHS is willing to discuss the regulations with the researcher's attorney.

21 APPENDIX III: Table of Disallowed Concomitant Medications*

Drug Class

- Opioid Analgesics (1)
-
- Psychomotor stimulant-type medications (e.g. Adderall®, Ritalin®)
- Opiate substitutes (e.g. methadone, LAAM, buprenorphine)
- Drugs with known potential for toxicity to a major organ system (e.g. isoniazid, methotrexate)
- Anticonvulsants
-
-
- Anti-dependence (e.g., Chantix®, Wellbutrin® NRT, acamprosate, or naltrexone, antabuse)
- Carbonic anhydrase inhibitors
- Dietary supplements and Herbal remedies (2)
- Nicotine replacement
- The medication being studied

Definitions

Chronic use: 4/7 days per week or more, for a month or more. Additionally, the medication must have been started and stabilized for at least 2 weeks prior to study enrollment. **Periodic or episodic use:** 3/7 days per week or less, or more frequent use for less than a month's duration.

*This table is to be used as a guideline. The physician at each site may use their clinical judgment based on each drugs individual profile to allow or disallow medications listed or not listed specifically in this table.

Key

1. Episodic use of narcotic pain relievers are allowable.
2. Supplements with CNS action including pro-metabolic supplements/anorexics, and those having an effect on mood (e.g. St. John's Wort, yohimbine, ginkgo biloba, horehound) are not allowed. Vitamins at therapeutic doses will be permitted.

Note:

- Specific antidepressant like Elavil, Endep, Wellbutrin, and other MAOIs will not be allowed.
- Antipsychotics will be allowed as precautionary medications as long as they are prescribed for sleep, anxiety, or mood stabilization.
- Anxiolytics and withdrawal agents will be allowed if they are prescribed short term by a provider for anxiety.

22 APPENDIX IV

BBCET Manual
(Attached as separate document)

23 APPENDIX V

Clearing the Air Booklet
(Attached as separate document)

24 APPENDIX VI: Blood Collection for Genotyping*

1. PROCEDURES

A. Blood Collection:

- Collect 2 yellow top tubes (BD vaccutainer tubes containing ACD buffer) from each subject that consented to genetic testing, using standard phlebotomy techniques.
- Label each tube with subject ID#, date, visit#, and study ID.
- The 2 tubes should contain 8-10ml of whole blood.
- After collection, invert the tubes 5-10 times to mix blood with the ACD buffer that was in the tube.

B. Storage

- Within two hours of blood collection, transfer blood from yellow top tubes (2) to cryovials (2) using a pipette (Prior to transfer, invert the tubes to mix the contents).
- Label each cryovial with subject ID#, date, visit#, and study ID.
- Store each cryovial in separate cryovial boxes at -80^0C until shipment (i.e. Subject A has two cryovials, cryovial 1 placed in cryovial box 'A' and cryovial 2 placed in cryovial box 'B').

C. Shipping

- Shipments to University of Texas-MDACC should be made every 6 months or when cryovial boxes reach full capacity.
    - Cryoival box 'A' and cryovial box 'B' should be in separate shipments in case of any lost or damaged boxes.
- Shipments should be overnight and on a Monday, Tuesday, Wednesday or Thursday.
- Each site will follow their local IRB's rules and regulations regarding the shipment of biological materials (i.e. the use of dry ice).
- University of Texas-MDACC study coordinator should be notified when shipments are en route.

*** DNA Extraction and Genotyping will be done at University of Texas-MDACC.**

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