NCT02371889 Unique Protocol ID: 821035 Secondary IDs: 821035, R01AA023192

# Study Title: A Randomized, Double-blind Placebo-Controlled Pharmacogenetic Study of Topiramate in European-American Heavy Drinkers (TOPG) Protocol with Statistical Analysis Plan

Feburary 19, 2019

Penn Medicine
University of Pennsylvania School of Medicine

CLINICAL RESEARCH PROTOCOL

# A Randomized, Double-blind Placebo-Controlled Pharmacogenetic Study of Topiramate in European-American Heavy Drinkers

**Regulatory Sponsor:** *Henry Kranzler, M.D.*
*Psychiatry*
*3535 Market St., Fifth Floor, Suite 500*
*Philadelphia, PA 19104*
*(215) 386-6662*

**Funding Sponsor:** *National Institute on Alcohol Abuse and Alcoholism*
*National Institutes of Health*

**Study Product:** *Topiramate*

**Protocol Number:** *821035*

**IND Number:** *NA*

**Version 18: February 19, 2019**

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## List of Abbreviations

AD: Alcohol dependence
AUD: Alcohol use disorder
CDT: carbohydrate-deficient transferrin
%dCDT: percent disialotransferrin
DSM: Diagnostic and Statistical Manual of Mental Disorders
GGTP*:* gamma glutamyl transpeptidase
HDD: Heavy drinking day
SNP: single nucleotide polymorphism
TLFB: Timeline Follow-back Method

## Study Summary

| | |
|---|---|
| Title | A randomized, double-blind placebo-controlled pharmacogenetic study of topiramate in European-American heavy drinkers |
| Short Title | Topiramate by Genotype (TOP-G) |
| Protocol Number | |
| Phase | 2 |
| Methodology | Randomized, double-blind, placebo-controlled, parallel-groups |
| Study Duration | 5 years |
| Study Center(s) | University of Pennsylvania and Corporal Michael J. Crescenz VA Medical Center (CMCVAMC) |
| Objectives | 1) To examine the moderating effect of rs2832407 in *GRIK1* on the efficacy of topiramate 200 mg/day in reducing the frequency of heavy drinking; 2) To examine daily processes, including expectancies regarding the positive effects of drinking and confidence in resisting heavy drinking, and their interaction with genotype and medication group to predict nighttime drinking; 3) To conduct 3- and 6-month post-treatment follow-up assessments to examine the persistence of treatment effects; 4) To conduct an optional sub-study to examine the effects of topiramate on resting baseline cerebral blood flow and alcohol cue reactivity using functional magnetic resonance imaging. |
| Number of Subjects | A total of 200 subjects will be randomized (up to 100 at the CMCVAMC site) |
| Diagnosis and Main Inclusion Criteria | Heavy drinkers who self-identify as European-American and who have an average weekly ethanol consumption of $\geq$24 standard drinks for men or $\geq$18 standard drinks for women, with a weekly average of $\geq$ 2 heavy drinking days (HDDs) during the month before screening |
| Study Product, Dose, Route, Regimen | Topiramate 200 mg/day for 12 weeks. Dosage will be 200 mg/day, initiated at 25 mg/day and gradually increased such that the maximal dosage will be reached in the sixth week of treatment. The dosage will be altered to minimize adverse effects and after 12 weeks will be tapered off completely. |
| Duration of administration | 12 weeks (plus a one-week taper) |
| Reference therapy | Placebo |
| Statistical Methodology | The four medication by genotype groups will be compared on weekly number of HDDs using mixed effects models for count responses. Estimates of effects over the final six weeks of treatment, with associated standard errors and confidence intervals, will be used to test the primary hypothesis. Similar models will be used to examine data from 3- and 6-month follow-up visits to evaluate the persistence of treatment effects. Regression analyses will also examine the effects of topiramate and rs2832407 and their interaction on resting baseline cerebral blood flow and alcohol cue reactivity. |

# 1 Introduction

This document is a protocol for a human research study. The study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and institutional research policies and procedures.

## *1.1 Background*

In the United States, the estimated 12-month prevalence of a DSM-IV alcohol use disorder (AUD) is 8.5%; this includes 4.7% of individuals with alcohol abuse and 3.8% with alcohol dependence (AD) (Grant, Dawson et al. 2004). Although AUDs are associated with a range of problems and are a leading cause of preventable death in the United States (Mokdad, Marks et al. 2004), their treatment is generally not evidence based (McGlynn, Asch et al. 2003). Thus, despite the fact that, since 2005, NIAAA has recommended that medications with demonstrated efficacy be considered as a first-line treatment for AD, in practice, few people receive such treatment (Mark, Kranzler et al. 2003; Mark, Kranzler et al. 2003; Mark, Kassed et al. 2009). In part, the reluctance of physicians to prescribe alcohol treatment medications and of patients to take them stems from their limited efficacy (Mark, Kranzler et al. 2003; Mark, Kranzler et al. 2003). Further, although some studies have included subjects who are heavy drinkers, without necessarily meeting a diagnosis of AD (Kranzler, Armeli et al. 2003; Karhuvaara, Simojoki et al. 2007; Kranzler, Tennen et al. 2009), most medication trials have been limited to individuals with AD, reducing their applicability to heavy drinkers and others who want to reduce their drinking. Recently, DSM-5 replaced the abuse/dependence distinction with the diagnosis of AUD, which requires that only two of 11 criteria be met for the diagnosis. This will increase the identification of individuals needing an intervention (Agrawal, Heath et al. 2011; Peer, Rennert et al. 2013). This study will help to address that need by testing topiramate in individuals with DSM-5 AUD who are regular heavy drinkers.

Currently, three medications are FDA-approved to treat AUD: naltrexone, acamprosate, and disulfiram (Harris, Kivlahan et al. 2010). Empirical evidence suggests that naltrexone reduces the reward properties of and cravings for alcohol (Sinclair 2001) and acamprosate supports abstinence (Mason, Goodman et al. 2006); however, their effect sizes compared to placebo are small (Mark, Kranzler et al. 2003; Rosner, Hackl-Herrwerth et al. 2010; Oliva, Maisel et al. 2011). Disulfiram differs from naltrexone and acamprosate in that it blocks the metabolism of alcohol's primary metabolite, acetylaldehyde, which accumulates in the blood causing unpleasant effects when alcohol is ingested (Franck and Jayaram-Lindstrom 2013). There is limited evidence of the efficacy of disulfiram, and its potential for toxicity limits it use (2009). These concerns about safety and limited efficacy likely contribute to the fact that FDA-approved medications for AUD are not widely prescribed (Mark, Kranzler et al. 2003; Mark, Kranzler et al. 2003). Indeed, only 2.8% of patients treated in the Veterans Health Administration who were diagnosed with an AUD received pharmacotherapy (Oliva, Maisel et al. 2011). Given these issues and concerns, several medications, other than the currently approved medications for AUD, have been prescribed off label and have shown promise in reducing alcohol consumption.

The anticonvulsant topiramate, though not approved to treat AD, substantially reduced the frequency of heavy drinking in four placebo-controlled trials and two open-label studies. Based on these findings, topiramate is increasingly being prescribed off-label to treat AD (e.g., in the VA Healthcare System). Recently, we found that the ability of topiramate to reduce heavy drinking was limited to individuals with the CC genotype of rs2832407, a single nucleotide polymorphism (SNP) in *GRIK1*, the gene encoding the kainate receptor GluK1 subunit. This finding for topiramate adds to similar pharmacogenetic findings for two other medications to

treat AD, the beneficial effects of which are substantially enhanced by genetic moderators: naltrexone (which is moderated by a SNP in the mu-opioid receptor gene, *OPRM1*) and ondansetron (which is moderated by two genotypes in *SLC6A4*, the serotonin transporter gene). Consistent with the goal of personalized treatment for AD, these findings would allow clinicians to identify, in advance, which patients are likely to respond to each of these medications and which should be spared the unnecessary adverse effects that may accompany treatment in a likely non-responder. Of note, together, these three pharmacogenetic findings would make it possible to select the best medication to reduce heavy drinking in ~75% of European Americans.

### *1.1.1 Personalized Treatment of AUD Using Pharmacogenetics*

*Topiramate Pharmacogenetics:* Topiramate's effects, as mentioned above, are moderated by kainate receptors, tetrameric assemblies that respond to glutamate. The GluK1 and GluK2 kainate subunits (encoded by *GRIK1 and GRIK2*, respectively) are the ones for which topiramate's effects on AMPA/kainate receptors are most potent and selective (Gryder and Rogawski 2003; Kaminski, Banerjee et al. 2004). Kranzler, Gelernter et al. (2009) examined variation in *GRIK1*, on the hypothesis that evidence of association to AD could identify a moderator of the effects of topiramate in individuals with AD. The study focused on variation in the 3'-half of the gene, including the differentially spliced exons 9, 17, and 18. The C allele of rs2832407 in intron 9 was significantly overrepresented in AD (Kranzler, Gelernter et al. 2009). *GRIK1* was also nominally associated with successful attempts to quit smoking in pooled genomewide association analyses (Uhl, Liu et al. 2008), suggesting that it may serve more generally as a moderator of treatment response in addictive disorders. Ray et al. (Ray, Miranda Jr et al. 2009) examined the moderating effect of rs2832407 on topiramate treatment outcome in 51 individuals from a placebo-controlled study of topiramate in heavy drinkers (Miranda Jr, MacKillop et al. 2008). Although they found that the SNP did not moderate the therapeutic effects of topiramate, carriers of the A allele reported more severe topiramate-induced adverse events. In our recently completed topiramate study (Kranzler, Covault et al. 2014) we did not find a moderating effect of rs2832407 on adverse events. However, we found that the SNP robustly moderated the therapeutic response to topiramate. Further, in that trial, use of a micro-longitudinal approach, which previously supported the pharmacogenetics of naltrexone response (Kranzler, Armeli et al. 2013), helped to clarify the associated subjective effects of topiramate, rs2832407, and their interaction. Although there are no known coding SNPs in *GRIK1*, rs2832407 is in a region of differential splicing and is upstream of a *GRIK1* antisense RNA. Thus, rs2832407 or other SNPs with which it is in linkage disequilibrium may act by influencing RNA processing or the regulation of gene expression. We are currently examining the SNP's functional effects using expression assays in neural cultures derived from induced pluripotent stem cells (Lieberman, Levine et al. 2012).

### *1.1.2 Innovative Aspects*

This is the first prospective study of a genetic moderator of topiramate with adequate statistical power to guide the personalized treatment of AD. Currently, approximately 10% of FDA-approved medications contain pharmacogenetic labeling, which allows the prescriber to personalize treatment based on a genetic test, representing a paradigm shift in medical care (Hamburg and Collins 2010). The public health implications of tailoring treatments to those with an AUD based on likely treatment response are considerable. Pharmacogenetics offers the potential to do that with topiramate. Additionally, topiramate is a generic medication for which there is no incentive for further commercial development. However, combining a genetic marker with the medication offers the potential to develop a commercially viable entity that could lead a company to develop topiramate specifically to treat AUD.

The dosage of topiramate used in this study is lower than that used in most previous studies. In our recently completed trial (Kranzler, Covault et al. 2014), use of a 200 mg/day dosage enhanced treatment retention and provided additional information on the optimal dosage of topiramate to be used in clinical care (i.e., taking into account both its efficacy and tolerability). Subject selection is also an important aspect of this study, and will be more inclusive than in previous studies. It will include both individuals whose goal is to reduce drinking and individuals whose goal is to become abstinent, allowing us to generalize the findings regarding the utility of topiramate and the moderating effects of rs2832407 to a more diverse population than prior studies, which were limited to people with a goal of abstinence (Johnson, Ait-Daoud et al. 2003; Johnson, Rosenthal et al. 2007) or a goal of reducing drinking (Kranzler, Covault et al. 2014). This will increase the external validity of the study. Selected subjects will also include individuals with DSM-5 AUD, a more inclusive diagnostic group than DSM-IV AD. Given the shift to DSM-5, this will increase the external validity and applicability of the study's findings. Our use of daily data collection (i.e., a micro-longitudinal study design) to monitor daily processes and drinking behavior will provide insight into the subjective dimension of topiramate's effects in reducing heavy drinking, both overall and as a function of genotype. Finally, the use of functional magnetic resonance imaging to examine the effects of topiramate and its moderation by rs2832407 has not previously been done, and it may provide insights into the mechanism of the pharmacogenetic effect.

## *1.2 Investigational Agent*

Topiramate is an anticonvulsant medication for oral administration approved in the United States for the treatment of seizures, the prevention of migraine headaches, and for the promotion of weight loss (in combination with phentermine). Topiramate absorption is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The bioavailability of topiramate from the tablet formulation is about 80% compared to a solution and is not affected by food. The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady state is reached in about 4 days.

According to the FDA-approved labeling, topiramate has been found to be safe at dosages of 200 mg and 400 mg per day in adults.

## *1.3 Preclinical Data*

Topiramate is a sulfate-substituted monosaccharide with multiple pharmacological effects. It facilitates GABAergic function by interacting with a non-benzodiazepine site on the $GABA_A$ receptor (White, Brown et al. 2000), antagonizes glutamate activity at AMPA and kainate receptors (Gibbs, Sombati et al. 2000; Skradski and White 2000), modifies effects at NMDA receptors without directly blocking them (McDonald and Rogawski 2006), blocks voltage-dependent $Na^+$ and L-type voltage-gated $Ca^{++}$ channels, and inhibits carbonic anhydrase, and enhances $K^+$ conductance (McDonald and Rogawski 2006). The drug's effects on AMPA/kainate receptors are most potent and selective for those containing the GluK1 (previously known as GluR5) and GluK2 (previously GluR6) subunits (Gryder and Rogawski 2003; Kaminski, Banerjee et al. 2004).

## *1.4. Clinical Data*

Topiramate is approved by the FDA to: 1) treat seizure disorder, 2) prevent migraine, and 3) promote weight loss (in combination with phentermine). It is associated with mild-to-moderate adverse effects and is best tolerated when initiated at a low dosage that is gradually increased over a period of weeks.

Two randomized controlled trials of topiramate 300 mg/day, including a single-center study (Johnson, Ait-Daoud et al. 2003) and a multicenter study in subjects with AD (Johnson, Rosenthal et al. 2007), showed it to have a medium-sized effect in reducing HD. In the first study (Johnson, Ait-Daoud et al. 2003), 150 subjects received an escalating dosage of topiramate (beginning with 25 mg/day) or matching placebo for 12 weeks. The medication was well tolerated and topiramate-treated subjects reduced the percentage of HD days significantly more than those receiving placebo, with the groups beginning to separate significantly after the first month of treatment. In the 14-week, double-blind, placebo-controlled, multicenter trial of 371 subjects (Johnson, Rosenthal et al. 2007), topiramate was also significantly more efficacious than placebo at reducing the percentage of HDDs. Miranda et al. (Miranda Jr, MacKillop et al. 2008) randomly assigned 61 non-treatment seeking heavy drinkers to receive topiramate 200 mg/day, topiramate 300 mg/day, or placebo. The medication was titrated to the target dosage over a 32-day period and maintained there for one week. During the titration period, the frequency of HD was significantly lower in both topiramate groups than with placebo.

In a 12-week, open-label trial (Rubio, Ponce et al. 2004), topiramate (up to 400 mg/day) was well tolerated and associated with reduced drinking and craving by week 2 and decreased carbohydrate-deficient transferrin (CDT) levels beginning at week 6. In a second open-label study (Paparrigopoulos, Tzavellas et al. 2011), subjects completing inpatient alcohol detoxification were assigned to receive either topiramate (up to 75 mg per day) plus psychotherapy (n = 30) or psychotherapy alone (n = 60). During a 4-month follow-up period, significantly fewer (66.7%) of the topiramate-treated subjects than the psychotherapy-only subjects (85.5%) relapsed, with topiramate subjects' median time to relapse being 10 weeks compared with four weeks for those in the psychotherapy-only group, a significant difference. A placebo-controlled study failed to show a significant advantage for topiramate in reducing drinking (Likhitsathian, Uttawichai et al. 2013). However, in that study, only 53% of the topiramate group and 47% of the placebo group completed treatment and adherence to the prescribed regimen was not evaluated, both of which seriously limit the interpretation of the results.

Our recently published placebo-controlled trial of topiramate 200 mg/day in heavy drinkers (Kranzler, Covault et al. 2014) showed a robust treatment effect. We randomly assigned 138 heavy drinkers (62.3% male, 92% with DSM-IV AD) to receive 12 weeks of treatment with topiramate 200 mg/day (n=67, 48.6%) or matching placebo (n=71, 51.4%), with medical management (MM, see section 6.7.2, below). The only demographic or clinical variable on which the groups differed was age: placebo subjects were ~3.5 yr older than topiramate subjects. Using the Timeline Follow-back Method (TLFB; see section 6.10, below) to measure drinking during the 90-day pre-treatment period, both groups drank heavily (men: $\geq$ 5 drinks; women: $\geq$ 4 drinks) on ~5 days/week and had 1 abstinent day/ week. Fifty-six topiramate subjects (83.6%) and 61 placebo subjects (85.9%) completed the 12-week treatment period ($p=0.70$). There was a main effect of medication group ($p<0.001$) and an interaction with treatment week ($p<0.0001$). Topiramate subjects had fewer heavy drinking days (HDDs) and decreased the number of HDDs/week more rapidly than placebo subjects. During week 12, the odds that the placebo group would have at least one HDD was 5.32 (95%CI=1.68-7.30) times that of the topiramate group ($p<0.001$). There was twice the number of treatment responders (i.e., those with no HDDs during the last four weeks of treatment) in the topiramate group (n=24, 35.8%) as in the placebo group (n=12, 16.9%) with (OR=2.75, 95%CI=1.24-6.10). There was a main effect of medication group ($p=0.032$) and an interaction with treatment week ($p=0.013$). Topiramate subjects had more abstinent days and increased the number of abstinent days/week more rapidly than the placebo group. During week 12, the odds of an abstinent day in the topiramate group was 2.57 (95%CI=1.13-5.84) times that of the placebo group.

## *1.5 Dosage Rationale and Risk/Benefits*

**Dosage Rationale**

The dosage used in the only large prior study of topiramate was 300 mg/day, which resulted in a differential dropout between active and placebo treatments (Johnson, Rosenthal et al. 2007). The dosage of topiramate selected for this study (200 mg/day) is based on previous research indicating that 200 mg/day is the dosage at which heavy drinkers begin to show therapeutic effects (Johnson, Ait-Daoud et al. 2003; Johnson, Rosenthal et al. 2007; Miranda, MacKillop et al. 2008). Further, our previous study of 138 heavy drinkers who sought to reduce their drinking received a 12-week treatment with topiramate 200 mg/day (N=67) or matching placebo and showed that topiramate was well tolerated, with no serious side effects, and was efficacious at reducing heavy drinking days and increasing abstinent days (Kranzler, Covault et al. 2014). As recommended in the package insert, we will reduce the dosage of topiramate by one-half (i.e., a maximum of 100 mg/day) for anyone with a creatinine clearance <70 mL/min/1.73 $m^2$.

**Potential Risks**

Topiramate is not reinforcing and is therefore not a drug of abuse. There are few serious adverse effects associated with topiramate treatment and none were seen in our recently completed study of topiramate. The most common adverse effects of topiramate compared to placebo are numbness and tingling (49% vs. 6%). The other most common side effects (experienced by 10-31% of subjects) in clinical trials include: change in sense of taste, tiredness/sleepiness, fatigue, dizziness, loss of appetite, nausea, diarrhea, weight decrease, difficulty concentrating and difficulty with memory. Cognitive adverse effects (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties) that were reported during 6-month migraine prophylaxis studies (28% vs. 10% for placebo) were of mild-to-moderate severity.

Other adverse effects (experienced by 5-9% of subjects) in some clinical trials include: nervousness, slow thinking, abnormal vision, confusion, decreased sensitivity (hypesthesia), anxiety, abdominal pain, dry mouth, involuntary muscle contractions, and language problems. Depression and mood problems have also been reported (experienced by 5-9% of subjects). Some individuals have had suicidal thoughts or actions (experienced by about 1% of subjects). Although these adverse effects have not been reported in alcohol-dependent subjects, study participants will be informed that, should they feel a change in their mood, feel depressed, or feel they may harm themselves, they should contact the study doctor.

An adverse effect of topiramate, which is less common but potentially serious is renal calculi (experienced by about 2% of subjects). Drinking an adequate volume of fluids is recommended while taking topiramate, and may reduce the risk of renal calculi. Subjects will be counseled to drink water frequently throughout the day.

Severe metabolic acidosis (increased bicarbonate levels) is associated with topiramate treatment in 3-7% of individuals taking the medication. We will repeat bicarbonate levels at the visit six of the study to identify anyone with severe acidosis. Further, individuals taking carbonic anhydrase inhibitors will be excluded from this study, due to the added risk of metabolic acidosis. Treatment with topiramate may cause oligohidrosis (decreased sweating), which has primarily been reported in children.

Acute secondary glaucoma has been described in some people taking topiramate, usually occurring at the beginning of treatment (less than 1%). Individuals with a history of narrow angle glaucoma will be excluded from this study. Subjects will be informed that should they have sudden, significant worsening of vision, blurred vision, or eye pain to contact the study doctor immediately. This adverse event is very rare. Overdoses of topiramate have been associated with convulsions, drowsiness, speech disturbance, blurred vision, diplopia (double

vision), impaired mental activity, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. Deaths have been reported in overdoses.

Rare and isolated cases of liver failure/hepatitis and blistering skin rashes (bullous skin eruptions) have been reported with topiramate (less than 1% for both). Careful instructions on the use of topiramate and dispensing of limited quantities of the medication will serve to reduce the risk of accidental overdose. Careful screening using module 2 of the MINI International Neuropsychiatric Interview 6.0 (MINI) will exclude individuals with significant suicidal risk and ongoing monitoring throughout the study will serve to reduce the risk of intentional overdose or other suicidal behavior. Suicidal risks will be assessed using the MINI Suicidality section (B) at each study visit, and if rated equal to or greater than 9 (i.e., clinically significant suicidal ideation), the physician will be consulted to decide the appropriate clinical management.

It is possible that some hormonal contraceptives (birth control pills, hormonal implants or hormonal injections) may be made less effective by topiramate. If appropriate, the study doctor will discuss alternatives or additional non-hormonal methods of birth control to be used during participation in the study. Women of childbearing potential who are using hormonal contraceptives will be instructed to inform the study nurse about any changes in menstrual bleeding patterns. Further, at the time of randomization, for women using hormonal contraceptives, the study physician will discuss with the participant non-hormonal methods of birth control to be used during her participation in the study.

Topiramate is labeled by the Food and Drug Administration as a category D medication. This means that there are data in humans from investigational or marketing experience showing that topiramate can cause harm to the fetus, but potential benefits may warrant the use of the medication in pregnant women despite risk to the potential risks. Data from pregnancy registries show that infants exposed to topiramate *in utero* have an increased risk for cleft lip and or cleft palate (oral clefts). Pregnancy testing of women of childbearing potential prior to study randomization (Screening and Informed Consent visit) and at visits 1 (week 1), 5 (week 5), 7 (week 8), and 9 (week 11) will minimize the risk of fetal exposure to study medication.

Topiramate does not produce clinically significant additive CNS depressant effects in combination with ethanol. In placebo-controlled clinical trials of topiramate treatment of AD, individuals who consume alcohol have not reported ill effects of the combination. This was the case in the recently completed study of topiramate in heavy drinkers, who were drinking from the outset of the study. The medication was well tolerated in that study and there was no evidence of differential attrition in the topiramate group.

### Potential Benefits

Benefits to subjects include careful evaluation of their medical and psychiatric status and alcohol use and potential reduction in or discontinuation of their alcohol consumption, which may improve their health and wellbeing. Benefits to society include a potential improvement in the effectiveness of treatment for problem drinking, which may reduce the personal and societal costs associated with the problem. In addition, clinicians and scientists may better understand the effects of topiramate treatment of AUD. An improved understanding of the genetic and other moderators of response to these medications will enhance their clinical utility and the process of medications development for alcohol treatment.

### Risk/Benefit Ratio

Although treatment with topiramate presents some risks, it has been shown to be safe when administered for the 12 weeks of treatment to reduce heavy drinking for which it will be used in this study. Problems with tolerability that have been observed in some studies have been

transient or have resolved upon discontinuation of the medication. The potential risks of these treatments are minor compared to the risk incurred by individuals who continue to drink heavily. The risk/benefit ratio thus appears favorable to the proposed treatment.

# 2 Study Objectives

***2.1. Primary Objective:*** To examine the moderating effect of rs2832407 in *GRIK1* on the efficacy of topiramate 200 mg/day in reducing the frequency of heavy drinking in the last six weeks of the treatment trial. We expect that subjects treated with topiramate will report significantly fewer heavy drinking days (HDDs) than those receiving placebo.

Our primary hypothesis is that the effect will be significantly larger in rs2832407 C-allele homozygotes than in A-allele carriers. We will also examine the SNP's moderating effects on the efficacy of topiramate in improving other self-reported drinking measures (e.g., abstinent days), adverse consequences of drinking (e.g., the Short Index of Problems score: SIP; see section 6.8.3 below), and biological measures of heavy drinking (e.g., %dCDT, an improved assay for carbohydrate deficient transferrin). Finally, we will conduct 3- and 6-month post-treatment assessments on the hypothesis that rs2832407 C-allele homozygotes will show greater reduction in primary and secondary outcomes after the medication is discontinued.

**The primary outcome** for the study is the frequency of heavy drinking (defined as 4 or more drinks in a day for women and five or more drinks in a day for men).

**Secondary outcomes** include the number of abstinent days, absence of any heavy drinking days during the last month of treatment, mean daily alcohol consumption, drinks/drinking day, %dCDT and gamma glutamyl transpeptidase (GGTP) levels, and severity of alcohol-related problems (i.e., SIP score), using models similar to those described below for the primary outcome.

***2.2. Secondary Objective:*** To examine daily processes, including expectancies regarding the positive effects of drinking and confidence in resisting heavy drinking and their interaction with genotype and medication group to predict the intensity of nighttime drinking. We expect that evening reports of a high level of positive expectations regarding alcohol's effects and a low level of confidence in resisting heavy drinking will be associated with heavier drinking later that night.

Our secondary hypotheses are that topiramate treatment will significantly reduce both positive alcohol-outcome expectancies and confidence in resisting heavy drinking across the weeks of the study and nighttime drinking measured daily in rs2832407 C-allele homozygotes, but not A-allele carriers.

***2.3 Optional MRI Sub-Study Objective:*** Conduct an optional sub-study to examine the effects of topiramate on resting baseline (RB) cerebral blood flow and alcohol cue reactivity using functional magnetic resonance imaging (fMRI). The goals, rationale, background and study methods for this objective are described in Appendix I: "Brain Mechanisms of Topiramate's Effects on Heavy Drinking."

# 3 Study Design

## *3.1 General Design*

This is a 12-week, prospective, randomized clinical trial of the moderating effect of rs2832407 on the efficacy of topiramate in reducing HD in 200 individuals of European descent with DSM-5

AUD. We will stratify the randomization on genotype and oversample rs2832407*C homozygotes, the most topiramate-responsive genotype, to ensure comparable numbers of subjects in the four medication x genotype groups. We will compare the efficacy of topiramate to placebo in reducing the frequency of HDDs in subjects with AUD using a two-arm, parallel-groups design. Subjects will either have a goal to reduce their drinking to safe levels or to stop drinking entirely. We will use daily data collection to examine changes in relevant process variables and their interaction with genotype and medication group as predictors of HD. This study will be registered on clinicaltrials.gov.

At each visit, all subjects will receive MM (Pettinati, Weiss et al. 2004) (see section 6.7.2), which was developed for the COMBINE Trial and which we modified to be relevant for both reducing heavy drinking and promoting abstinence. Random assignment to treatment group and double-blind conditions will be maintained throughout the study. Raters will be trained in the reliable use of all assessments. We will use serum GGTP and percent disialotransferrin (%dCDT), an improved assay for carbohydrate deficient transferrin (Helander, Wielders et al. 2010), to validate subject reports. Following a one-week pre-treatment assessment period, subjects will receive 12 weeks of treatment. There will be a 6-day taper period, during which subjects will reduce their dosage of topiramate gradually and then discontinue it completely. Daily reports during the treatment period will be obtained using interactive voice response (IVR) to identify subjective correlates of medication effects and to monitor medication use. Following the 12-week treatment period, subjects will be asked to return to the clinic for 3-month and 6-month post-treatment follow-up visits to evaluate the durability of treatment effects.

**Two hundred men and women of European descent** will be recruited using referrals from treatment programs throughout Philadelphia; IRB-approved advertisements on mass transit, on local radio and television stations and in newspapers, social media, and broadcast email messages at institutions (e.g., the University of Pennsylvania Health System) that offer such a service and by posting/distributing recruitment materials in community and college settings. To ensure adequate representation of Hispanics of European descent, we will conduct outreach via English-language advertisements in Spanish-language media in the greater Philadelphia area. Respondents will initially be evaluated by telephone prior to an in-person visit to the Treatment Research Center of the University of Pennsylvania Perelman School of Medicine.

**Up to 100 men and women veterans of European descent will be recruited from the CMCVAMC**. Recruitment at the CMCVAMC site will be focused on patients identified in primary care settings. The Behavioral Health Laboratory (BHL) conducts clinical assessments on all patients referred from primary care. At the completion of the clinical assessment, all patients potentially eligible to participate in this research, which has been approved by the CMCVAMC IRB and the Mental Illness Research, Education and Clinical Center (MIRECC), will be informed of the project and asked if they may be contacted by appropriate study personnel to discuss the study in accordance with that protocol's procedures. Additionally, the study will seek referrals from the Mental Health Clinic (MHC) and Addictions Recovery Unit (ARU) within the CMCVAMC. An investigator and study staff will meet with the staff of the BHL, the MHC and ARU to explain the goals of the research study and ask for assistance with patient referrals. The PI and study staff will have ongoing in-service meetings with the providers to facilitate engagement in the recruitment process. Recruitment flyers and informational brochures will be available for potential participants in the Primary Care Clinic, MHC, and ARU.

At both the UPenn and CMCVAMC sites, we will stratify subjects based on their genotype to ensure comparable numbers of individuals who are rs2832407 C-allele homozygotes and A-allele carriers in each of the treatment groups. We will also stratify by site and block randomize subjects to balance the groups on treatment goal (i.e., reduced drinking or abstinence).

### *3.2 Primary Study Endpoints*

***3.2.1 To examine the moderating effects of the GRIK1 SNP rs2832407 on the response to topiramate:*** The primary outcome measure will be the frequency of HDDs (≥5 standard drinks in a day for men and ≥4 in a day for women). We chose this outcome because it is a sensitive, clinically relevant measure in alcohol treatment trials (Falk, Wang et al. 2010). Subjects will be followed irrespective of whether they continue to receive treatment, so that the analysis of all outcomes will be based on all of the data available for all randomized subjects. Drinking data for this aim will come from the TLFB (see section 6.10 below).

***3.2.2 To examine the relations among daily process measures, medication use, and drinking level:*** We will use multilevel models to evaluate the associations of alcohol expectancies and self-efficacy (confidence in resisting drinking and heavy drinking) with daily drinking and how these associations vary as a function of medication group and rs2832407 genotype. Similar to Kranzler, Armeli et al. (2013), we will focus on predicting nighttime drinking (i.e., drinks consumed after the early evening report), but here we will use alcohol-related expectancies reported during the early evening in the daily survey. Nighttime drinking levels will be determined by subtracting the number of drinks consumed during the current day from the total number of drinks consumed for that day (reported the following day).

### *3.3 Secondary Study Endpoints*

*Secondary endpoints* include: the number of abstinent days, absence of any heavy drinking days [the FDA-recommended outcome measure (Anton, Litten et al. 2012)], mean daily alcohol consumption, drinks/drinking day, %dCDT and GGTP levels, and severity of alcohol-related problems (i.e., SIP score), using models similar to those described below for the primary outcome. All outcomes (primary and secondary) will also be evaluated at 3- and 6-month post-treatment assessments.

### *3.4 Primary Safety Endpoints*

Subjects will be monitored carefully for adverse events including the development of renal calculi or metabolic acidosis. At each study visit, participants will provide subjective reports of side effects using the adverse events checklist developed from prior studies of topiramate for alcohol treatment. Using data from that periodic inquiry, we will compare the medication groups on the overall frequency of adverse events during treatment, the frequency of severe adverse events during treatment, and the frequency of adverse events during treatment that are rated moderate or severe.

## 4 Subject Selection and Withdrawal

### *4.1 Inclusion Criteria*

1) Determined to be physically healthy, based on medical history and physical examination and approval of the study physician
2) Age 18 to 70 years, inclusive
3) Self-identified European ancestry
4) Meets DSM-5 criteria for AUD
5) Average weekly ethanol consumption of ≥24 standard drinks for men and ≥18 standard drinks for women, with a weekly average of ≥ 2 HDDs during the month before screening
6) Stated goal to reduce drinking to safe levels or to stop drinking
7) Able to read English at an 8th grade or higher level and no gross cognitive impairment

8) Willingness to nominate an individual who will know the subject's whereabouts to facilitate follow up during the study
9) Women of child-bearing potential (i.e., who have not had a hysterectomy, bilateral oophorectomy, tubal ligation or is less than two years postmenopausal): must be non-lactating and practicing a reliable method of birth control, and have a negative urine pregnancy test prior to the initiation of treatment. Examples of medically acceptable methods for this protocol include: the birth control pill, intrauterine device, injection of Depo-Provera, Norplant, contraceptive patch, contraceptive ring, double-barrier methods (such as condoms and diaphragm/spermicide), male partner sterilization, abstinence (and agreement to continue abstinence or to use an acceptable method of contraception, as listed above, should sexual activity commence), and tubal ligation.
10) Willingness to provide signed, informed consent and commit to completing the procedures in the study

#### *4.1.1. Inclusion of Women, Children and Minorities*

1) Based on prior treatment studies for AUD, we estimate that approximately 32% of participants in this study will be women. This approximates the proportion of the population with AUD that is female, so no specific outreach will be required to ensure adequate representation of women in the study sample.
2) Children between the ages of 18 and 20 will be included in the study. Because we will be recruiting on college campuses in Philadelphia, we anticipate that up to 10% of the sample will be in that age range. We will limit children to those who are at least 18 years of age because data are insufficient to support the use of topiramate to reduce heavy drinking in younger children.
3) The primary hypothesis to be tested in this study is genetic moderation of the response to topiramate by the single nucleotide polymorphism rs2832407. Preliminary results in a sample of 8,051 individuals that were recruited to participate in genetic studies of alcohol and drug dependence showed that the prevalence of the rs2832407 C allele was 65.1% in European Americans, with 43.1% of individuals being C-allele homozygotes. In contrast, among African Americans, the C allele was the minor allele, with a frequency of 17.9% and a C-allele homozygote frequency of 3.5%. Based on the low prevalence of the CC genotype (which is hypothesized to moderate the beneficial effects of topiramate), it is not feasible to recruit an adequate number of African American subjects to test the hypothesis in that population. Thus, for scientific reasons, this study will enroll only subjects who self-identify as being of European ancestry. Of this number, about 15% of the subjects will be Hispanic. To ensure adequate representation of Hispanic subjects (~15% of the total), we will conduct outreach via English advertisements in Spanish-language newspapers, radio, and television in the greater Philadelphia area.

### *4.2 Exclusion Criteria*

1) A current, clinically significant physical disease or abnormality on the basis of medical history, physical examination, or routine laboratory evaluation, including direct bilirubin elevations of >110% or a transaminase elevation >300% of normal
2) A history of nephrolithiasis
3) A history of glaucoma
4) Current treatment with carbonic anhydrase inhibitors, due to the added risk of metabolic acidosis.

5) Current, serious psychiatric illness (i.e., schizophrenia, bipolar disorder, severe or psychotic major depression, panic disorder, borderline or antisocial personality disorder, organic mood or mental disorders, eating disorder, or imminent suicide or violence risk)
6) Current DSM-IV diagnosis of dependence on a drug other than alcohol or nicotine
7) A history of hypersensitivity to topiramate
8) Current regular treatment with a psychotropic medication (e.g., benzodiazepines, antidepressants), which affect neurotransmitter systems, or a medication to treat alcohol dependence
9) Currently taking any tricyclic antidepressant (e.g., Adapin (doxepin), Anafranil (clomipramine), Elavil (amitryptyline), Pamelor (nortryptyline), Tofranil (imipramine), Sinequan (doxepin)
10) Urine drug screen positive for recent use of opioids, cocaine, or amphetamines (may be repeated once and if the result is negative on repeat it is not exclusionary)
11) Because co-administration of topiramate with dolutegravir reduced plasma concentrations of the antiretroviral through induction of CYP3A, the use of dolutegravir is exclusionary.
12) Judged by the principal investigator or his designee to be an unsuitable candidate for receipt of an investigational drug

### *4.3 Subject Recruitment and Screening*

Subjects at the UPenn site will be recruited using the following methods: referrals from treatment programs throughout Philadelphia; advertisements on mass transit, on local radio stations and in newspapers; social media; and broadcast email messages at institutions (including the University of Pennsylvania Health System, Craigslist, community agencies, local college campuses) that offer such a service; and by posting/distributing recruitment materials in community settings with public posting areas or other means of providing community access to materials (such as hospitals, town halls, public libraries, YMCAs, health fairs). We will obtain permission at selected locations before distributing or posting the approved recruitment materials (ensuring compliance with other institutions' guidelines, including seeking IRB approval as needed to conduct recruitment activities). We will use the Penn Data Store to obtain patient demographics, medical diagnosis codes related to AUD, individual names and addresses, and provider names. We will request permission of providers to contact the individuals with an IRB-approved letter and recruitment materials (i.e., the study brochure, outreach letter). We will also use Research Match (Vanderbilt University), iConnect (UPenn) and the Treatment Research Center (UPenn) website for Internet recruitment.

To ensure adequate representation of Hispanics (~15% of the total), we will conduct outreach via English-language advertisements in Latino newspapers, radio, and television in the greater Philadelphia area. We will also invite individuals with Spanish surnames identified through the University of Pennsylvania Health System electronic medical record that appear to qualify for study participation to contact our screening line. The study sample will include children (i.e., individuals who are 18-20 years old).

We will request a partial waiver of consent and HIPAA Authorization from the IRB to allow for preliminary phone screening for calls initiated by potential subjects. Individuals deemed eligible for in-person screening will sign a HIPAA Authorization and study consent form at their first visit. During the in-person screening visit (once telephone screening shows preliminary eligibility), each subject will receive an explanation of the study protocol and 2), its risks, potential benefits, and alternative treatments by a study staff member. Following resolution of any questions, individuals who appear to understand the nature of the study and consent will be asked to sign the study consent form. An entire copy of the informed consent form will be

given to each subject. Based on our experience with this method of recruitment, we anticipate that about 30% of subjects eligible and willing to participate will be female. Because of the genetic moderator analysis, in which European Americans (EAs) have a higher prevalence of the C allele of rs2832407 than other population groups in the Philadelphia area (e.g., African Americans), we will limit study participation to self-identified EAs. Because we will be enrolling individuals as young as 18 years old, and recruiting on college campuses where there are substantial rates of heavy drinking, children will be included in the study sample.

Subject recruitment at the CMCVAMC site will be focused on patients identified in the primary care settings. The BHL conducts clinical assessments on all patients referred from primary care. At the completion of the clinical assessment, all patients potentially eligible for this IRB-approved and MIRECC-approved project will be informed of the project and asked if they may be contacted by appropriate study personnel to discuss the study in accordance with the protocol. Additionally, the study will seek referrals from the Mental Health Clinic (MHC) and Addictions Recovery Unit (ARU) at the CMCVAMC. The PI and study staff will meet with the BHL, MHC, and ARU providers to explain the goals of the research study and ask for assistance with patient referrals. An investigator and study staff will have ongoing in-service meetings with the providers to facilitate engagement in the recruitment process. Recruitment flyers and informational brochures will be available for potential participants in the Primary Care Clinic, MHC, and ARU

Subjects who are referred or who express interest by responding to recruitment flyers will be contacted by phone to participate in a telephone screening interview. We will describe the nature of the study, including the number of visits, subject protections and confidentiality. If the caller is interested in participating, we will obtain verbal consent to perform a phone screening interview. As part of the verbal consent process, callers will be told that if they are ineligible to participate in the study, the only information collected during the interview that will be retained is their name, phone number, and the reason that they were deemed ineligible. They will not be told why they were excluded. Only individuals who give verbal consent will be asked to complete the phone screen interview. If we determine the applicant to be eligible based on this screening, s/he will be asked whether s/he is interested in participating. If the caller is still interested, s/he will be scheduled for an initial informed consent and screening visit. The information collected during the phone interview will be retained only if the subject is eligible to participate and signs a study ICF at the screening visit. The phone interview will be stored in the research record once the participant has signed the ICF. We will maintain a log of subjects contacted, which will include their name, phone number, date of call, study status, eligible or not eligible, and, for those excluded, the reason the participant was not eligible to ensure that we don't call the same person multiple times.

## *4.4 Early Withdrawal of Subjects*

### *4.4.1 When and How to Withdraw Subjects*

Subjects with severe psychological symptoms (e.g., suicidal thoughts), those who fail to adhere to protocol requirements, and those who withdraw consent will be withdrawn from the study and if applicable, referred for appropriate clinical care. Suicidal risks will be assessed using the MINI Suicidality section (B) at each study visit, and if rated equal to or greater than 9 (i.e., clinically significant suicidal ideation), the physician will be consulted to decide the appropriate clinical management. If a subject is found to be pregnant during screening or during study, she will immediately be withdrawn from the study, referred for obstetric evaluation, and advised to

discontinue all drinking. Any subject experiencing a serious adverse event felt to be related to study drug will be withdrawn from the study.

### *4.4.2 Data Collection and Follow-up for Withdrawn Subjects*

For subjects that leave treatment prematurely, the study nurse or research coordinator will complete the Early Termination Form, indicating the subject's level of functioning at termination. The form is used to identify the reasons for early termination (e.g., symptomatic failure, adverse effects) and other relevant circumstances. Additionally, we will make a strong effort (via phone calls and alternative contact information) to obtain follow-up information on all subjects who are prematurely withdrawn from the project. We will invite subjects to return to the clinic for assessment at the time of their discontinuation from treatment and again at the scheduled end of treatment, as well as all post-treatment follow-up visits. The following efforts will be made to contact subjects who discontinue treatment prior to the twelfth week: 2 telephone calls by the research coordinator or technician resulting in contact (either with the subject or by leaving a message on voicemail or a person answering the subject's telephone, followed by 2 telephone calls by a study physician, followed by a letter. Only if all of these efforts are unsuccessful in obtaining follow-up information (either during an in-person visit or a telephone interview), the subject will be considered to be lost to follow-up.

# 5 Study Drug

## *5.1 Description*

Topiramate is an anticonvulsant medication for oral administration approved in the United States for the treatment of seizures, the prevention of migraine headache, and for weight loss (in combination with phentermine). The molecular formula of this sulfate-substituted monosaccharide is C12H21NO8S and the molecular weight is 339.35. It is designated chemically as 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate. According to the FDA-approved labeling, topiramate has been found to be safe at doses of 200 mg and 400 mg per day in adults. For more detailed information, see section 1.2 (Investigational Agent).

## *5.2 Treatment Regimen*

The maximal dosage of topiramate in this study will be 200 mg/day orally in two divided doses, based on prior evidence of the efficacy and greater tolerability of this dosage (Kranzler, Covault et al. 2014). Although a 300-mg dosage of topiramate has been used most commonly to treat AD, we will use a lower dosage to reduce adverse effects. We will use a six-week titration period (see Table 1 below), which we found in our completed topiramate study to be well tolerated. We will reduce the dosage of topiramate by one-half for anyone with a creatinine clearance <70 mL/min/1.73 $m^2$.

Table 1. Topiramate or Placebo Dose Titration/Taper Schedule

| | **Medication Dispensed** | **Morning Dose** | **Evening Dose** | **Total Daily Dose** |
|---|---|---|---|---|
| Screening Visit | Week 0 | No medication | No medication | 0 mg |
| Visit 1 Baseline | Week 1 | No medication | 25 mg | 25 mg |
| Visit 2 | Week 2 | 25 mg | 25 mg | 50 mg |
| Visit 3 | Week 3 | 25 mg | 50 mg | 75 mg |
| Visit 4 | Week 4 | 50 mg | 50 mg | 100 mg |
| Visit 5 | Week 5 | 50 mg | 100 mg | 150 mg |
| Visit 6 | Weeks 6 and 7 | 100 mg | 100 mg | 200 mg |
| Visit 7 | Weeks 8 and 9 | 100 mg | 100 mg | 200 mg |
| Visit 8 | Weeks 10 and 11 | 100 mg | 100 mg | 200 mg |

| | | | | |
|---|---|---|---|---|
| Visit 9 | Week 12 and 6- day Taper | 100 mg | 100 mg | 200 mg |
| | | Reduce dose by 50 mg every 2 days over 6 days: 150 mg for 2 days, 100 mg for 2 days, 50 mg for 2 days, then D/C | | |
| Visit 10 | Week 14 | No medication | No medication | 0 mg |
| Visit 11 (3-Month Follow-up) | Week 24 | No medication | No medication | 0 mg |
| Visit 12 (6-Month Follow-up) | Week 36 | No medication | No medication | 0 mg |

The dosage of medication will be increased only as tolerated and subjects experiencing intolerable adverse effects will have their dosage decreased gradually to the highest tolerated dosage, which will be determined by the study physician. Upward titration following a dose reduction will be allowed at the discretion of the study physician during the trial. Dose titration will be carefully documented in the study chart along with the clinical rationale. The study nurse, in consultation with the study physician, will provide guidance for subjects as they increase their medication dosage, per the titration schedule (Table 1 in section 5.2). At the end of the 12-week treatment period, subjects will be titrated off study medication over a period of 6 days (i.e., 150 mg/day for 2 days, 100 mg/day for 2 days, and 50 mg/day for 2 days). The titration schedule for subjects on a reduced dosage (less than 200 mg/day of topiramate or placebo equivalent) will be determined by the study physician

## *5.3 Method for Assigning Subjects to Treatment Groups*

Subjects will be randomly assigned to one of two treatment conditions using a block randomization scheme: topiramate 200 mg/day (n = 100) or placebo (n = 100). A designated randomization staff member who is not otherwise involved in the conduct of the study will work with the Investigational Drug Service (IDS) staff to implement the randomization. The process for randomization is: 1) a study coordinator will complete a “block randomization form,” which includes the variables to be entered into the block randomization program [i.e., sex, genotype (i.e., C-allele homozygote vs A-allele carrier), number of heavy drinking days in the past month (trichotomized)]; 2) the randomization staff member will enter the variables into the block randomization program; 3) the randomization staff member will fax the randomization group to IDS, who will assign a kit number to subject and fax kit assignment to research coordinator; 4) the research nurse or physician will dispense medication to the subject and complete and sign the IDS prescription form included in the starter kit; 5) the research coordinator will fax the completed form to IDS.

Study drug for subsequent visits will be ordered by the research coordinator using the “Research Pharmacy Schedule” form (following the schedule in Table 1), a copy of which will be retained in the subject’s research file. At each visit, the research nurse will dispense a supply of study medication. In the event that scheduled visits change or the subject’s dosage is adjusted by the study physician, medication will be mailed via a UPS or Fedex to the subject, to ensure that they have enough medication to get them to their next scheduled visit. The study physician will approve all medication mailed to subjects and the study nurse or physician will document the medication dispensed via mail and call to ensure and instruct the patient on how the medication should be taken and to document all AEs. Study staff will also document whether the mailed medication was received by the subject.

Subjects with severe psychological symptoms or determined to be inappropriate for the study by an investigator will be withdrawn from the study. Subjects who are withdrawn completely will be referred for appropriate clinical care.

## *5.4 Preparation and Administration of Study Drug*

Topiramate will be purchased commercially and formulated by the IDS in opaque capsules. Placebo capsules will be formulated to match the active medication, so that inspection of the capsules cannot allow them to be differentiated. The IDS will be responsible for blinding study medication according to the protocol outlined by the study statistician. The UPenn IDS will supply medication to both the UPenn and CMCVAMC study sites.

## *5.5 Subject Compliance Monitoring and Enhancement*

We will use three methods to monitor medication adherence:

1*) IVR technology*. At home, subjects will use IVR daily to report their medication use.

2) *Pill counts*. We will ask subjects to return any unused medication at each visit, conduct pill counts and record medication taken.

3) *Medical Management*. Subjects in both medication groups will receive Medical Management (MM; section 6.8.2 below). MM supports the subject's efforts to reduce his/her drinking and improve medication adherence, with the study nurse making direct recommendations for positive behavior changes.

## *5.6 Prior and Concomitant Therapy*

Individuals who have completed prior alcohol treatment studies and meet study criteria will be invited to participate if subject participation ended at least 30 days before the current study starts (i.e., no pharmacotherapy or empirically supported treatment for 30 days). Subjects currently in a treatment program for alcohol use disorders may not participate. Self-help group participation will not be disqualifying and attendance will be monitored to provide a measure of participation. Concomitant treatment with a psychotropic medication or a medication to treat AD is not permitted during the 12-week course of the study. See exclusion criteria, section 4.2.

## *5.7 Packaging*

The UPenn Investigational Drug Service (IDS) will package bulk drug on-site. The child-safe prescription bottles will contain 8 days of medication. Subjects will be provided with an extra day of medication to ensure that they have enough medication if a weekly visit needs to be rescheduled.

## *5.8 Blinding of Study Drug*

All subjects and research staff will be blinded as to whether the subject is in the topiramate or placebo group until the decision to break the study blind is determined at the end of the study (after study database lock). Codes linking randomization number for each subject to actual treatment will be secured in a sealed, opaque envelope and maintained in a locked drawer in the research pharmacy and the hospital pharmacy. Research subjects will be given the emergency contact number for the study during the consenting process. See section 8.4 (Unblinding Procedures) for a description of the process for unblinding a study subject.

## *5.9 Receiving, Storage, Dispensing and Return*

### *5.9.1 Receipt of Drug Supplies*

There is no industry sponsor for this study. The UPenn IDS will compound the study medication using commercially available product. IDS will periodically dispense coded, blinded study drug kits to the research coordinator for both the UPenn and CMCVAMC sites. IDS will supply the study drug kits coded in such a way that the UPenn site study medication can be easily

distinguished from the CMCVAMC site study medication. The study medication will be stored at the TRC medication storage room, which is temperature controlled and monitored daily for temperature excursions. The room is locked and the medication will be stored in a locked file cabinet that only study staff will have access to. The research coordinator will maintain 100% drug accountability at the clinic for the duration of the study. The research coordinator will document all medication using a drug accountability log to track the study medication from time it leaves IDS to the time it is returned to IDS for reconciliation and disposal. For the CMCVAMC site, the UPenn IDS will send a monthly report to the VA investigational pharmacy with a list of all subjects randomized to study medication.

### *5.9.2 Storage*

Study drug will be stored at the IDS at controlled room temperature (59-86 degrees F). Study drug kits dispensed from the pharmacy to the clinic will be stored in a locked cabinet under control room temperature until dispensed. Any returned study medication will also be kept under locked condition until returned to the pharmacy for disposal.

### *5.9.3 Dispensing of Study Drug*

The study nurse and study coordinator will maintain a dispensing record, documenting the amount of medication dispensed to the subject, the amount returned, and the amount taken. The dispensing record will also document the amount of study drug returned to the pharmacy and the date returned.

### *5.9.4 Return or Destruction of Study Drug*

A final reconciliation of all remaining study medication will be made at the end of the study. All unused kits and medications dispensed and later returned by the subjects will be returned to the IDS. The IDS will be responsible for the disposal/destruction of all unused study medication. The study coordinator will return each subject's unused study medication and empty medication bottles to IDS for reconciliation as each subject completes the treatment phase of the study. All attempts will be made to collect the study medication and bottles from subjects at the end of the study and during follow-up sessions as needed.

## *6.1 Initial Telephone Screen (***approximately 20 minutes)**

Subjects will be recruited through local advertisements. Subjects who express interest by responding to advertising will be contacted by phone to participate in a telephone screening interview. We will describe the nature of the study, including the number of visits to the center, subject protections and confidentiality. If the caller is still interested, we will obtain verbal consent for the phone screening. Screening questions cover general health, psychiatric history and alcohol consumption. If we determine the applicant eligible based on this screening, s/he will be asked whether they accept or decline to participate. If the caller is still interested, s/he will be scheduled for an initial consenting appointment.

## *6.2 Informed Consent and Screening Visit (Week 0)*

Upon arriving to the Informed Consent and Screening Visit, which will be conducted at the Treatment Research Center at 3535 Market Street, Philadelphia, PA, subjects will be asked to show legal photo identification and undergo a breathalyzer test to ensure a breath alcohol concentration (BrAC) of 0.00% to ensure that the subject is able to provide informed consent. Reading ability will be evaluated (Slosson Oral Reading Test-Revised (SORT-R; Shaw, 1998) to verify reading ability at an eighth grade level and the capacity to understand the informed consent form. Subjects will then be given the informed consent form to read, which a study staff

member will review with the subject, providing an explanation of the study protocol, its risks, potential benefits, and alternative treatments. Following resolution of any questions, subjects will be asked to sign the study informed consent form. An entire copy of the informed consent form will be given to the subject, who will be reminded that the consent addresses his or her willingness to participate but that the subsequent screening process will determine his or her eligibility to do so. Further, the subject will be reminded that participation is voluntary, and at any time, he or she may withdraw from the study.

The subject will then meet with the study nurse who will obtain a medical history, conduct a physical examination, and obtain weight and vital signs (blood pressure and heart rate). Baseline laboratory measures will include:

- CBC
- Blood chemistries (i.e., standard blood work and lipids)
- Serum bicarbonate (which can be reduced by topiramate)
- GGTP (to assess the validity of self-reported drinking)
- %dCDT (to assess the validity of self-reported drinking)
- DNA extraction (followed by immediate genotyping)
- Urinalysis
- Urine toxicology (presence of psychoactive drugs)
- Urine pregnancy test for women of childbearing potential
- Oral HIV test (only if agreeable and otherwise eligible to participate in the MRI sub-study)

A total of approximately 3 tablespoons of blood will be drawn by study staff trained in phlebotomy. A portion (approximately 1.75 tablespoons) of this blood sample will be used to extract DNA for genotyping. In cases where blood samples are drawn and potential lab errors or abnormal findings occur, subjects will be asked to provide an additional blood sample to

# 6 Study Procedures

## Table 2. Schedule of Study Assessments and Procedures

| Assessment or Procedure | Visit 0 Screen Wk 0 | | Visit 1 Baseline Wk 1 | Visits 2-5 Wks 2-5 | Visit 6 Wk 6 | | Visits 7 & 8 Wks 8 & 10 | Visit 9 (Wk 12) & Taper | Visit 10 Endpoint Wk 13 | Visits 11&12 Follow-up Wks 24 & 36 |
|---|---|---|---|---|---|---|---|---|---|---|
| **ALL VISITS** | | | | | | | | | | |
| Breathalyzer, weight & vitals | X | | X | X | X | | X | X | X | X |
| **SCREENING** | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | |
| Med Hx & Physical Exam | X | | | | | | | | | |
| | | | | | | | | | | |
| **LABORATORY TESTS** | | | | | | | | | | |
| Chemistry Panel, CBC, DNA | X | | | | | | | | | |
| GGTP, %dCDT | X | | | | X | | | | X | X |
| Bicarbonate | X | | | | X | | | | | |
| Urinalysis & urine toxicology | X | | | | | | | | | |
| Urine pregnancy test for women of childbearing potential | X | | X | X (Visit 5 only) | | | X (Visit 7 only) | X | | |
| **ASSESSMENTS** | | | | | | | | | | |
| SORT | X | | | | | | | | | |
| Demographic Interview | X | | | | | | | | | |
| Locator information | X | | | | | | | | | |
| SCID (with DSM-5 AUD) | X | | | | | | | | | |
| SCID (only DSM-5 AUD) | | | | | | | | | X | X |
| FHAM | X | | | | | | | | | |
| TLFB | X | | X | X | X | | X | X | X | X |
| SIP | | | X | | | | | | X | X |
| PHQ-9 | | | X | X | X | | X | X | X | X |
| Digit Span | X | | | | | | | | X | X |
| FTND | X | | | | | | | | X | X |
| COWA | X | | | | | | | | X | X |
| SF-12 | | | X | | | | | | X | X |
| MINI 6.0 (Section B only) | X | | X | X | X | | X | X | X | X |
| CIWA-AR | X | | X | X | X | | X | X | X | |
| AUQ | | | X | | | | | | X | X |
| CSM | | | X | | | | | | | |
| ISI | | | X | X | X | | X | X | X | X |

GGTP=gamma-glutamyltranspeptidase, %dCDT=% disialotransferrin, SORT= Slosson Oral Reading Test, SCID=Structured Clinical Interview for DSM-IV, AUD=Alcohol Use Disorder, FHAM=Family History Assessment Module, TLFB=Timeline Follow-back Interview, SIP=Short Index of Problems, PHQ-9=Patient's Health Questionnaire, FTND=Fagerstrom Test for Nicotine Dependence, COWA= Controlled Oral Word Association Test, SF-12=Short Form Health Survey, MINI=Mini International Neuropsychiatric Interview, CIWA-Ar=Clinical Institute Withdrawal Assessment for Alcohol-revised, AUQ=Alcohol Urge Questionnaire, CSM= Composite Scale of Morningness, ISI=Insomnia Severity Index, **Performed only if sub-study visit is not done on same day as main study visit, when these assessments are routinely done.

| Assessment or Procedure | Visit 0 Screen Wk 0 | | Visit 1 Baseline Wk 1 | Visits 2-5 Wks 2 through 5 | Visit 6 Wk 6 | | Visits 7 & 8 Wks 8 & 10 | Visit 9 (Wk 12) & taper | Visit 10 Endpoint Wk 13 | Visits 11&12 Follow-up Wks 24 & 36 |
|---|---|---|---|---|---|---|---|---|---|---|
| **CLINICAL TREATMENT** | | | | | | | | | | |
| Dispense Study Medication | | | X | X | X | | X | X | | |
| Return Study Medication | | | | X | X | | X | X | X | |
| Adverse Events Checklist | | | X | X | X | | X | X | X | X |
| Measures of Treatment Received | | | X | X | X | | X | X | X | X |
| Medical Management | | | X | X | X | | X | X | X | |
| IVR Reports/Daily Diary | | | X | X | X | | X | X | | |
| Medication Questionnaire | | | | | | | | | X | |
| Early Termination Form*** | | | | | | | | | | |
| | | | | | | | | | | |
| **MRI SUB-STUDY ONLY** | **(Visits or tests will only be completed only for subjects enrolled in the sub-study.)** | | | | | | | | | |
| | **Sub-study Screening Visit** | **Scan 1** | | | | **Scan 2** | | | | |
| Breathalyzer | X** | X** | | | | X** | | | | |
| Informed Consent | X | | | | | | | | | |
| Urine toxicology | X** | X | | | | X | | | | |
| Urine pregnancy | X** | X** | | | | X | | | | |
| Rapid HIV test (Oral) | X | | | | | | | | | |
| Electrocardiogram | X | | | | | | | | | |
| Blood sample (Hormone concentrations; women only) | | X | | | | X | | | | |
| CIWA | | X** | | | | X** | | | | |
| AUQ | | X | | | | X | | | | |
| WASI | X | | | | | | | | | |
| MCQ | X | | | | | | | | | |
| MRI Scan | | X | | | | X | | | | |
| MRI video | X | | | | | | | | | |
| MRI Safety Sheet (Metal) | X | X | | | | X | | | | |
| Within-session rating scale | | X | | | | X | | | | |
| CogBias Tasks | | X | | | | X | | | | |
| CogState Battery | X | X | | | | X | | | | |

IVR=interactive Voice Response, HIV=human immunodeficiency virus, WASI= Wechsler Abbreviated Scale of Intelligence; MCQ=Menstrual Cycle Questionnarie; MRI=magnetic resonance imaging ***Performed only if subject discontinues treatment prematurely

repeat the test(s). For subjects who are otherwise eligible and interested in participating in the MRI sub-study, an oral HIV test will be administered. If the oral HIV test is positive, the nurse will inform the subject of the results, counsel the subject regarding the need to confirm the finding with a blood test and to avoid potential exposure of others to HIV, and draw an additional tablespoon (i.e., a total of 4 tablespoons) of blood to conduct a confirmatory HIV blood test. If the blood test is positive for HIV, the subject will be referred for medical care and given a copy of the test to provide to the doctor for the follow-up visit.

Study staff with complete the following assessments with subjects:

- *Sociodemographic/general subject information:* An assessment of medical history, personal and family history of alcoholism, marital status, educational and occupational information and substance abuse treatment history will be obtained, along with the individual's self-identified ancestry.
- *Slosson Oral Reading Test*: A standardized assessment used to determine reading level.
- *Locator information:* The research coordinator will select subject locators on the basis of relationship to the subject, duration and current status of relationship, frequency of contact with the subject, and willingness to participate. Locators are contacted when efforts to reach a subject are unsuccessful, which enhances retention of subjects in treatment and data collection.
- *The Structured Clinical Interview for DSM-4 (SCID)* will be used to classify subjects according to the presence or absence of standard psychiatric disorders according to DSM-criteria. The alcohol use disorder criteria will be modified to permit a DSM-5 diagnosis as well.
- *The International Neuropsychiatric Interview 6.0 (Mini 6)*: Suicidal risk will be assessed using the MINI Suicidality section (B) at each study visit and, if rated greater or equal to 9 (i.e., clinically significant suicidal ideation), the physician will be consulted to decide on the appropriate clinical management.
- *The Family History Assessment Module* (Rice, Reich et al. 1995) systematically queries the subject about the presence of an alcohol use disorder (AUD) in relatives. The subject will provide information concerning parents' and siblings' history of alcohol use without their being identified.
- *The Timeline Follow-back (TLFB)* (Sobell and Sobell 1992) will be used to estimate past 90-day drinking at intake and at every treatment visit going back in time from the last assessment. This interview procedure will provide quantity/frequency of alcohol consumption data for each day during the period prior to the interview. The TLFB is reliable and valid when used by trained interviewers. However, it is less useful than daily measures for detecting patterns of alcohol consumption that vary on a day-to-day basis (Carney, Tennen et al. 1998; Searles, Helzer et al. 2000).
- *Controlled Oral Word Association Test (COWA)* is a verbal fluency test that takes approximately 5 minutes to administer and measures spontaneous production of words beginning with a designated letter (Ruff, Light et al. 1996). This measure will be used to examine the effects of topiramate on verbal fluency.
- *Wechsler Adult Intelligence Scale-Third Edition Digit Span subtest* (Wechsler 1997) will be used to assess verbal working memory and explore the potential effects of topiramate on verbal working memory.

- *Fagerstrom Test for Nicotine Dependence (FTND)* (Fagerstrom and Schneider 1989) is a 6-item, self-report measure of nicotine dependence derived from the Fagerstrom Tolerance Questionnaire.
- *The Clinical Institute Withdrawal Assessment for Alcohol Scale–revised (CIWA-Ar)* (Sullivan, Sykora et al. 1989) is a 10-item scale for clinical quantification of the severity of alcohol withdrawal.

### *6.3 Visit 1 (Week 1; Baseline and First Treatment Visits)*

Subjects will be informed of their eligibility status within 5 days and scheduled for a baseline assessment within 30 days of the screening visit. All subjects not eligible for the study will be referred to the appropriate treatment center or other research study. Eligible subjects will undergo a **baseline** research evaluation (lasting up to 2 hours) within 30 days of completing the screening visit.

Subjects will be asked to complete a breathalyzer test. If a subject's breath alcohol concentration is ≥ 0.02%, an investigator will evaluate whether the subject is too impaired to complete the study assessments. The study visit may be completed at the discretion of the investigator. If the subject is deemed to be unable to complete assessments, the investigator may ask the subject to wait until his or her blood alcohol level decreases or if that is not feasible to return the next day after having consumed no alcohol. Prior to discharge from the TRC, a clinician will assess the subject to ensure that it is safe for the subject to leave. Study staff will complete the following assessments with all subjects (the exception being that only for women of childbearing potential, will study staff obtain a urine sample for a pregnancy test).

- *The Patient Health Questionnaire (PHQ-9)*, a validated 9-item self-report measure of depressive symptoms that yields a total score of 0-27 (Kroenke, Spitzer et al. 2001), will be administered at each visit.
- *The International Neuropsychiatric Interview 6.0 (Mini 6)*: Suicidal risk will be assessed using the MINI Suicidality section (B) at each study visit and, if rated greater or equal to 9 (i.e., clinically significant suicidal ideation), the physician will be consulted to decide on the appropriate clinical management.
- *Daily Interactive Voice Response (IVR) Telephone Call (daily for 12 weeks, beginning with the initiation of treatment)*
    a. *Drinking diary:* Every evening, as part of the daily IVR diary report, subjects will record their alcohol consumption by reporting the number of standard drinks of beer, wine, liquor and "other" category. The daily assessment will also include the number of cigarettes smoked that day. To capture all drinking during the preceding 24-hour period, subjects are asked to report separately drinking from yesterday (in total), and any drinking during the current day, up until the time of the IVR report. This will allow us to examine lagged associations (Kranzler, Armeli et al. 2013) The time of the calls (5-8 PM) was chosen to minimize the potential for subjects to have begun drinking heavily prior to making the calls. Subjects are taught to complete the telephone interview, which requires less than 5 minutes/day. Daily measures of alcohol consumption obtained via IVR will enable us to examine co-variation of alcohol-related subjective reports and drinking behavior to test for moderator effects.
    b. *Daily medication usage:* Subjects will use Interactive Voice Response (IVR) daily to report whether they took their medication as prescribed. We previously found that subjects used the IVR system to report their use of medication that day,

which correlates highly (r=0.91) with electronic monitoring (i.e., MEMS cap) (Feinn, Tennen et al. 2003).

c. *Subjective Reports*

i. *Daily mood:* Patients will be asked to rate their overall mood daily during the 12 weeks of active treatment using an adjective checklist. The checklist consists of 4 mood adjectives, each of which will be rated on a 5-point scale (0 = "not at all" to 4 = "extremely"). The items will measure unpleasant (*sad, angry, nervous*) and pleasant (*happy*) mood.

ii. *Expectancies of the effects of alcohol:* These will include 4 items assessing anticipated positive (n=3) and negative (n=1) outcomes for drinking later that day. The positive expectancy items, adapted from existing expectancy scales (Rohsenow 1983; Fromme, Stroot et al. 1993; Leigh and Stacy 1993), correspond to the commonly identified expectancy domains of general pleasure, tension reduction, and social expressiveness. Specifically, subjects will be asked “If you were to drink tonight how likely is it that you” (a) “would have a good time?”, (b) “would feel less tense/more relaxed?”, and (c) would be more outgoing/friendly? The negative expectancy item will be “would you get sick or have a hangover later?” Responses will be made on a 5-point.

iii. *Thoughts about drinking:* Based on anecdotal reports by subjects that topiramate substantially reduced the extent to which they thought about drinking (which they differentiated from desire to drink), they will be asked to rate this measure daily on a 5-point scale.

iv. *Self-efficacy:* We will measure both confidence to avoid drinking and confidence to resist heavy drinking on a 5-point scale.

v. *Desire to drink:* We will measure desire to drink using three items from the Alcohol Urge Questionnaire (Bohn, Krahn et al. 1995), which will be rated on a 5-point scale

vi. *Experience of an alcohol-induced blackout*: We will ascertain whether the subject experienced an alcohol-induced blackout using the following yes/no questions: (a) “Since your last call, after or while you were drinking alcohol, did you experience a period of time that you could not remember things you said or did? (b) (Follow-up question if the person responds yes): “When you experienced difficulty remembering something you said or did while drinking, did you later remember when given cues or reminders about it?”

- *Medication Adverse Effects Checklist:* Subjects will be interviewed by the study nurse and asked to report adverse effects at each study visit using a checklist of adverse medication effects derived from completed studies of topiramate for alcohol treatment. This method worked well in our completed trial using the 200-mg/day dosage (Kranzler, Covault et al. 2014).

- *Measures of treatment received:* Records of medication taken will be kept and subjects will be asked to return the unused portion of study medication at each visit. The nurse will also record the number of contact hours subjects have been exposed to any alcohol treatment outside of the study.

- *The Short Index of Problems (SIP).* The SIP, a 15-item instrument subset of the 50-item DrInC (Miller, 1995), measures alcohol dependence symptoms and medical, psychological,

social, occupational, and legal problems. This shorter questionnaire reduces respondent burden (Feinn, Tennen et al., 2003b).

- *The RAND 12-Item Health Survey (SF-12)* (Ware Jr, Kosinski et al. 1996), a self-report measure of life functioning in various domains, will be completed at study baseline and endpoint. We will focus on the mental health component of the SF-12.
- *Alcohol Urge Questionnaire (AUQ)* (Bohn, Krahn et al. 1995) is an 8-item, self-administered state measure assessing the urge for an alcoholic drink at the time the questionnaire is completed and provides an index of acute craving. The AUQ contains four items pertaining to the desire to drink: two items regarding expectations of positive effects from drinking, and two items relating to the inability to avoid drinking if alcohol were present. This measure has strong correlations with measures of alcohol dependence and severity.
- *The Clinical Institute Withdrawal Assessment for Alcohol Scale–revised (CIWA-Ar)* (Sullivan, Sykora et al. 1989) is a 10-item scale for clinical quantification of the severity of alcohol withdrawal.
- *Composite Scale of Morningness (CSM)* is a 13-item survey that assesses whether the participant is most alert in the morning or later in the day, e.g. an “owl” or a “lark.” (Smith, Reilly et al. 1989)
- *Insomnia Severity Index (ISI)* is a five-item questionnaire that assesses the quality of sleep and its effect on activities of daily living. (Bastien, Vallieres et al. 2001)

Study staff will train subjects to use the IVR phone system. Subjects will be instructed on when to call in each day and how to use the phone system to complete the daily assessment. They will receive a written copy of the directions with all of the questions and responses. Study staff will program subjects’ study identification number into the IVR phone system after they have been randomized to study medication.

Subjects will receive the first counseling session and study medication (topiramate or placebo) during the **first treatment session** scheduled on the same day as the baseline assessment (after all assessments have been completed). At this visit, the subject will also meet with the physician. At this (and every) visit, the study nurse experienced in the use of Medical Management in alcohol pharmacotherapy trials will use the method to counsel the subject. This provides a basic clinical intervention that was designed to be used in conjunction with prescribed medication, and to be easily implemented by medically trained practitioners in non-specialty settings. The treatment will support subjects’ efforts to stop or reduce their drinking, with the study nurse making direct recommendations for reducing drinking to sensible levels.

The first counseling session (which will last approximately 30 minutes) will consist of a review of the results of the initial evaluation, identifying any concerns the subject may have. The subject is then provided with a rationale and information about pharmacotherapy and the importance of adherence. Subsequent treatment sessions (approximately 20 minutes) will be conducted at each treatment visit. During these sessions, the study nurse will obtain the subjects’ vital signs and weight, ask about medication side effects and concurrent medications, perform a brief assessment of the subjects’ drinking and medication adherence, and in some cases, make recommendations on strategies for the subject to follow until the next visit. Men will be advised to consume no more than 3 standard drinks per day and 12 standard drinks per week and women will be advised to consume no more than 2 drinks per day and 8 drinks per week. Because subjects will not be physically dependent on alcohol, reduction of heavy drinking is a safe and ethical goal.

The physician will meet with the subject at the beginning of treatment and discuss clinical management with the study staff weekly. The physician will evaluate the subject for any severe or persistent adverse effects.

### *6.4 Visits 2-8 (Weeks 2-11; Treatment Visits)*

At each visit, the study nurse will dispense study medications as shown in Table 1. In the event that scheduled visits change or the subject's dosage is adjusted by the study physician, medication will be mailed via a UPS or Fedex to the subject, to ensure that they have enough medication to get them to their next scheduled visit. The study physician will approve all medication mailed to subjects and the study nurse or physician will document the medication dispensed via mail and call to instruct the subject on how the medication should be taken and to document all AEs. Study staff will also document whether the mailed medication was received by the subject.

The dosage of medication will be increased only as tolerated and subjects experiencing intolerable adverse effects will have their dosage decreased gradually to the highest tolerated dosage, which will be determined by the study physician. Upward titration following a dose reduction will be allowed during the trial to minimize adverse effects while maximizing potential efficacy. Dose titration will be carefully documented in the study chart along with the clinical rationale. The study nurse, in consultation with the study physician, will provide guidance for subjects as they increase their medication dosage, per the titration schedule. Subjects will be given study medication consisting of topiramate or matching placebo and titrated up to a maximum of 200 mg/day of topiramate or the placebo equivalent (see Table 1).

During the 12-week treatment period, subjects will return to the clinic weekly (+/- 4 days) for the first 6 weeks and every other week (+/- 4 days) for weeks 7-12. At each visit, the subject's BrAC, weight, and vital signs will be measured. Subjects will be asked not to drink before coming to the scheduled visits. Subjects will be asked to complete a breathalyzer test. If a subject's breath alcohol concentration is $\geq$ 0.02%, an investigator will evaluate whether the subject is too impaired to complete the study assessments. The study visit may be completed at the discretion of the investigator. If the subject is deemed to be unable to complete assessments, the investigator may ask the subject to wait until his or her blood alcohol level decreases or if that is not feasible to return the next day after having consumed no alcohol. Prior to discharge from the TRC, a clinician will assess the subject to ensure that it is safe for the subject to leave. Study staff will complete the following assessments with all subjects (the exception being that only for women of childbearing potential, will study staff obtain a urine sample for a pregnancy test).

Subjects who are deemed suitable for assessment will complete questionnaires and be interviewed by the study nurse about their concomitant medications, adverse events, and protocol compliance. At every treatment visit (i.e., for a total of 10 sessions), the study nurse will deliver the MM intervention. Study staff will also administer the following assessments, as described above:

- *The Timeline Follow-back (TLFB)*: To collect data on daily drinking, cigarette use, and medication taken.
- *The Patient Health Questionnaire (PHQ-9)*: To measure depressive symptoms.
- *The International Neuropsychiatric Interview 6.0 (Mini 6)*: Suicidal risk will be assessed using the MINI Suicidality section (B) at each study visit and, if rated greater or equal to 9 (i.e., clinically significant suicidal ideation), the physician will be consulted to decide on the appropriate clinical management.

- *The Clinical Institute Withdrawal Assessment for Alcohol Scale–revised (CIWA-Ar)* (Sullivan, Sykora et al. 1989) is a 10-item scale for clinical quantification of the severity of alcohol withdrawal.
- *Medication Adverse Effects Checklist*
- *Measures of treatment received*
- *Daily Interactive Voice Response Telephone Call (daily for 12 weeks, beginning with the initiation of treatment)*
- *ISI*

Also, at the **week six visit**, the study staff will obtain a blood sample to measure bicarbonate levels, as topiramate can cause metabolic acidosis, and GGTP and %dCDT concentrations to corroborate self-reported alcohol consumption. At visits 5 (week 5) and 7 (week 8)**,** study staff will obtain a urine sample for a pregnancy test for subjects who are women of childbearing potential. If a subject reports being pregnant or tests positive, she will immediately be withdrawn from treatment with study medication, referred for obstetric evaluation, and advised to discontinue all drinking.

### *6.4.1 Visit 9 (Week 12 and taper)*

The study nurse will dispense study medications as shown in Table 1. At this visit (+/- 4 days), the subject will receive 1 more week of 100 mg BID (enough study medication to complete a total of 84 days on study medication) and the 6-day study medication taper (to reduce the dose by 50 mg every 2 days over 6 days: 150 mg for 2 days, 100 mg for 2 days, 50 mg for 2 days, then discontinue it). In the event that scheduled visits change or the subject's dosage is adjusted by the study physician, medication will be mailed via a UPS or Fedex to the subject, to ensure that they have enough medication to get them to their next scheduled visit. The study physician will approve all medication mailed to subjects and the study nurse or physician will document the medication dispensed via mail and call to instruct the subject on how the medication should be taken and to document all AEs. Study staff will also document whether mailed medication was received by the subject.

At this visit, the subject's BrAC, weight, and vital signs will be measured. Subjects will be asked not to drink before coming to the scheduled visits. Subjects will be asked to complete a breathalyzer test. If a subject's breath alcohol concentration is $\geq$ 0.02%, an investigator will evaluate whether the subject is too impaired to complete the study assessments. The study visit may be completed at the discretion of the investigator. If the subject is deemed to be unable to complete assessments, the investigator may ask the subject to wait until his or her blood alcohol level decreases or if that is not feasible to return the next day after having consumed no alcohol. Prior to discharge from the TRC, a clinician will assess the subject to ensure that it is safe for the subject to leave. Study staff will complete the following assessments with all subjects (the exception being that only for women of childbearing potential, will study staff obtain a urine sample for a pregnancy test). Subjects who are deemed suitable for assessment will then complete questionnaires and be interviewed by the study nurse about their concomitant medications, adverse events, protocol compliance, and MM intervention. For women of childbearing potential, study staff will obtain a urine sample for a pregnancy test.

Study staff will also administer the following assessments, as described above:

- *The Timeline Follow-back (TLFB)*: To collect data on daily drinking, cigarette use, and medication taken.

- *The Patient Health Questionnaire (PHQ-9)*: To measure depressive symptoms.
- *The International Neuropsychiatric Interview 6.0 (Mini 6)*: Suicidal risk will be assessed using the MINI Suicidality section (B) and, if rated greater or equal to 9 (i.e., clinically significant suicidal ideation), the physician will be consulted to decide on the appropriate clinical management.
- *The Clinical Institute Withdrawal Assessment for Alcohol Scale–revised (CIWA-Ar)* (Sullivan, Sykora et al. 1989) is a 10-item scale for clinical quantification of the severity of alcohol withdrawal.
- *Medication Adverse Effects Checklist*
- *Measures of treatment received*
- *Daily Interactive Voice Response Telephone Call (daily for 12 weeks, beginning with the initiation of treatment)*
- *ISI*

## *6.5 Visit 10 (Week 13; Endpoint Visit)*

At the end of treatment, week 13 (+/- 4 days) we will repeat the research assessments and will query the subject as to his or her belief regarding their treatment condition using the Medication Questionnaire (MED-Q). Blood samples for measurement of serum GGTP and %dCDT will be obtained to assess the validity of self-reported drinking. Subjects will be asked not to drink before coming to the scheduled visits. Subjects will be asked to complete a breathalyzer test. If a subject's breath alcohol concentration is $\geq$ 0.02%, an investigator will evaluate whether the subject is too impaired to complete the study assessments. The study visit may be completed at the discretion of the investigator. If the subject is deemed to be unable to complete assessments, the investigator may ask the subject to wait until his or her blood alcohol level decreases or if that is not feasible to return the next day after having consumed no alcohol. Prior to discharge from the TRC, a clinician will assess the subject to ensure that it is safe for the subject to leave. Study staff will complete the following assessments with all subjects (the exception being that only for women of childbearing potential, will study staff obtain a urine sample for a pregnancy test). Subjects who are suitable for assessment will then complete questionnaires and be interviewed by the study nurse.

All subjects will be asked to complete an end-of-treatment evaluation and to complete all scheduled assessments to facilitate intent-to-treat (ITT) analyses. All subjects will be informed of these procedures prior to study enrollment. Subjects will be compensated $50 for completing the end-of-treatment visit. Subjects who decide to terminate the study prior to visit 10 will also receive payment upon completion of the end-of-treatment procedures and 3- & 6-month follow-up visits. For subjects who withdraw early and do not wish to continue with study visits/procedures, all end-of-treatment procedures will be administered at the time of withdrawal. These subjects will also be asked to undergo in-person or telephone follow-up at the end-of-treatment for collection of the remaining treatment-phase Timeline Follow-back data.

If the subject cannot be reached by phone after three attempts, a final outreach letter will be mailed. The study nurse and physician will follow continuing adverse events to their conclusion, as feasible. Subjects requesting (or clearly needing) additional treatment for alcohol problems will be referred to local treatment centers.

- *Breathalyzer, weight, and vital signs*
- *Timeline Follow-back (TLFB) interview*
- *The International Neuropsychiatric Interview 6.0 (Mini 6)*: Suicidal risk will be assessed using the MINI Suicidality section (B) at each study visit and, if rated greater or equal to 9 (i.e., clinically significant suicidal ideation), the physician will be consulted to decide on the appropriate clinical management.
- *The Clinical Institute Withdrawal Assessment for Alcohol Scale–revised (CIWA-Ar)*
- *The Patient Health Questionnaire (PHQ-9)*
- *Word Association Test (COWA)*
- *Wechsler Adult Intelligence Scale-Third Edition Digit Span subtest*
- *Alcohol Urge Questionnaire (AUQ)*
- *Fagerstrom Test for Nicotine Dependence (FTND)*
- *Medical Management*
- *Medication Adverse Effects Checklist*
- *Measures of Treatment Received*
- *Medication Questionnaire (MED-Q)*
- *Short Index of Problems (SIP)*
- *RAND 12-Item Health Survey (SF-12)*
- *DSM-5 AUD Diagnosis (using the SCID for DSM-IV adapted for this purpose)*
- *Early Termination Form* (for early withdrawal from the study) indicates the subject's level of functioning at termination, and will be completed by the study staff or study nurse for any subjects that leave treatment prematurely. The form is used to identify the reasons for early termination (e.g., symptomatic failure, adverse effects) and other relevant circumstances.
- *ISI*

### *6.6 Missed Visit*

Subjects will receive study medication from the study nurse or physician at each study visit. During the first 6 weeks they will receive 8 days of study medication, which is enough medication to get them to their next scheduled study visit, plus 1 extra day. Once the subject reaches the 200 mg daily dose, they will receive 16 days of study medication, which is enough to get them to their next scheduled study visit plus 2 extra days. The study coordinator will work with the study nurse to ensure that the treatment phase of the study is not extended beyond 12 weeks. At visit 9, the study nurse will dispense the exact amount of study medication required for the subject to complete 84 days of study medication before starting the taper. These procedures will ensure that no subject is on study medication for more than 84 days before tapering off the study medication.

If a subject anticipates missing a study visit (e.g., due to a vacation), the study nurse will provide the subject with enough study medication to ensure that the maintenance of the daily dosage of study medication until the next scheduled visit. In the event that study medication is not ready to be dispensed at the time of the study visit (e.g., nurse and/or physician determine at the time of

the study visit that the subject requires a reduced dosage), study staff will mail the study medication to the subject via UPS or Fedex, to ensure that they have enough medication to get them to their next scheduled visit. The study physician will approve all medication mailed to subjects and the study nurse or physician will document the medication dispensed via mail. The study nurse will call the subject to document that all mailed study medication was received by subjects, to provide instructions on how to take the study medication as per the dosing schedule, and to collect information on any AEs. Subjects will be instructed to call the Treatment Research Center (TRC) at any time to discuss problems or concerns they may have while participating in the study. They will be provided phone numbers to contact the study staff during office hours and a pager number for off-hours contact. Subjects will be asked to come in for their next study visit as soon as possible.

If a subject anticipates missing a study visit (e.g., due to vacation), the study staff and study nurse will attempt to schedule a day and time to conduct the study visit over the phone for safety monitoring and data collection purposes. Self-report assessments, completed by subjects at study visits, will be administered by study staff over the phone. Breathalyzer, weight, and vital signs will not be obtained for phone visits. Subjects will be compensated for completing phone visits at their next study visit. If a subject is traveling out of the range of telephone access (e.g., internationally), he or she will be provided with paper copies of the daily IVR diary report to complete each evening instead of calling in to the system. The subject will be compensated for completing the IVR report on paper at their next study visit.

If a subject calls to cancel a scheduled study visit due to an unforeseen event, the study visit will be rescheduled for as soon thereafter as possible. Study staff will mail study medication to the subject via UPS or Fedex, under the supervision of a study nurse to avoid having the subject run out of study medication. Subjects will be given only enough study medication to ensure that they maintain their daily dosage of study medication until their next scheduled visit. The physician or nurse will instruct the subject by phone regarding how to take the study medication per the dosing schedule and will record any adverse events that have occurred since the last study visit. Study nurses will instruct subjects to call the TRC at any time to discuss any problems or concerns they may have while taking the study medication. Study staff will also document whether the mailed medication was received by the subject. Study staff will make efforts to reschedule missed study visits as soon as possible. The study physician will approve all medication mailed to subjects and determine how many additional weeks of study medication a subject will be allowed to receive without attending a study visit.

## *6.8 Visits 11 and 12 (Weeks 24 and 36; Post-treatment Follow-up Visits)*

- At the 3-month and 6-month follow-up visits, we will repeat the research assessment, focusing principally on alcohol consumption and alcohol-related problems over the preceding 12 weeks (or for individuals for whom data are missing, we will attempt to have them reconstruct their drinking history since the last assessment was completed). We will also obtain a blood sample for measurement of serum GGTP and %dCDT to assess the validity of self-reported drinking.

- Subjects will be asked not to drink before coming to the scheduled visits. Subjects will be asked to complete a breathalyzer test. If a subject's breath alcohol concentration is $\geq$ 0.02%, an investigator will evaluate whether the subject is too impaired to complete the study assessments. The study visit may be completed at the discretion of the investigator. If the subject is deemed to be unable to complete assessments, the investigator may ask the subject to wait until his or her blood alcohol level decreases or if that is not feasible to return the next day after having consumed no alcohol. Prior to

discharge from the TRC, a clinician will assess the subject to ensure that it is safe for the subject to leave.

- After the six-month follow-up visit, subjects who wish to learn whether they received treatment with topiramate or placebo will receive a "de-briefing letter" from IDS. Subjects will have the option to receive the "de-briefing letter" at the screening visit by initialing yes on the ICF. Study staff will provide IDS with an envelope that has the patient's address along with the "de-briefing letter," which notes the patient's name and ID number. The pharmacy technician will complete the letter indicating the medication assignment, and mail it to the subject. Study staff (physicians, nurses, and coordinators) will remain blinded to study medication assignment.
- *Breathalyzer, weight and vital signs*
- *Medication Adverse Effects Checklist (Follow-up with any unresolved AEs)*
- *Timeline Follow Back (TLFB)*
- *The International Neuropsychiatric Interview 6.0 (Mini 6)*: Suicidal risk will be assessed using the MINI Suicidality section (B) at each study visit and, if rated greater or equal to 9 (i.e., clinically significant suicidal ideation), the physician will be consulted to decide on the appropriate clinical management.
- *Word Association Test (COWA)*
- *Wechsler Adult Intelligence Scale-Third Edition Digit Span subtest*
- *Alcohol Urge Questionnaire (AUQ)* *Fagerstrom Test for Nicotine Dependence (FTND)*
- *SCID module for the AUD diagnosis (adapted from DSM-IV to yield a DSM-5 AUD Diagnosis)*
- *Short Index of Problems (SIP)*
- *The Patient Health Questionnaire (PHQ-9)*
- *RAND 12-Item Health Survey (SF-12)*
- *Measure of treatment received*
- *ISI*

## *6.9 Description of Study Treatments*

### 6.9.1 Pharmacotherapy:

The maximal dosage of topiramate to be used in the present study is 200 mg/day in two divided doses. We will use a six-week titration period, which was well tolerated in our completed topiramate study. The dosage of medication (active or placebo) will be increased only as tolerated and subjects experiencing intolerable adverse effects will have their dosage decreased gradually to the highest tolerated dosage, which will be determined by the study physician. The study nurse, in consultation with the study physician, will provide guidance for subjects as they increase their medication dosage, per the titration schedule.

### 6.9.2 Medical Management Counseling:

At each treatment visit, all subjects will receive medical management (MM), a standard, widely used, medically oriented intervention that supports the use of pharmacotherapy and enhances medication adherence in the treatment of AUD (Pettinati, Weiss et al. 2004). Clinicians with minimal specialty training but who are knowledgeable about AUD can deliver this brief and effective intervention, which has been widely used. In MM, the clinician highlights the individual's AUD symptoms and need for treatment. The subject is advised to reduce or stop drinking, is educated about AUD, is provided a rationale to take medication for its treatment, and is instructed on the importance of daily medication adherence. The clinician and subject jointly develop an individualized medication adherence plan and the subject is given information on the medications. MM enhances adherence and provides treatment that is feasible in most medical settings, but unlikely to obscure a medication effect on drinking outcomes.

Subjects will receive MM at each of the treatment visits. The first MM session will last 30 minutes and subsequent sessions 20 minutes. During all sessions, the study nurse will check the subject's vital signs and weight, adverse effects, medication adherence, and concurrent medications; and make recommendations for the subject to follow until the next visit. Individuals with severe psychological symptoms (e.g., suicidal thoughts) will be withdrawn from treatment and referred for appropriate clinical care. Suicidal risks will be assessed using the MINI Suicidality section (B) at each study visit, and if rated equal to or greater than 9 (i.e., clinically significant suicidal ideation), the physician will be consulted to decide the appropriate clinical management.

Ensuring Adherence to MM Content and Procedures: Gail Kaempf, MSN, CRNP, nurse practitioner, has more than 10 years of experience with MM (Pettinati, Weiss et al. 2004), including in the completed topiramate trial (Kranzler, Covault et al. 2014). She will train the other nurses in its administration, which will entail a review of the protocol and MM manual, role-play, practice of initial and follow-up sessions, and review of taped practice sessions until adequate performance is achieved. To assure the quality and uniformity of all sessions, audiotapes (with the consent of the participant) will be used to monitor the MM sessions for this study. The audiotapes will be reviewed by a trained clinician not involved in the counseling process. S/he will listen to 10% of recorded visits and will evaluate adherence to MM principles, record the total time in the treatment session, assess the therapeutic relationship, review the achievement of reduced drinking goals and clinical improvement during treatment, and provide individual feedback. One session from each subject will be reviewed with equal frequency for each of the nine different MM sessions. Weekly protocol adherence meetings will be held with the study nurses to assure protocol adherence. Audiotapes will be destroyed after review.

## *6.10 Description of Laboratory/Medical Assessments:*

These assessments serve to: 1) screen subjects for medical exclusion criteria, 2) assess potential adverse effects of topiramate, and 3) corroborate self-reported drinking. Prior to entrance into the study, each subject will receive a physical exam, urinalysis and urine toxicology, CBC, a chemistry panel [which includes electrolytes, liver enzymes (ASAT, ALAT, GGTP), bilirubin, uric acid, BUN, and creatinine], %dCDT, and pregnancy testing for women of childbearing potential. Bicarbonate levels will be repeated at the week six visit because topiramate can cause metabolic acidosis. Pregnancy testing for women of childbearing potential will also be repeated at visits 1 (week 1), 5 (week 5), 7 (week 8), and 9 (week 11). If a subject reports being pregnant or tests positive, she will immediately be excluded or withdrawn from treatment with medication, referred for obstetric evaluation, and advised to discontinue all drinking. At the week six visit and endpoint, GGTP and %dCDT will be repeated to corroborate self-reported alcohol consumption. %dCDT will be measured in the laboratory of Dr. Raymond

Anton, using the HPLC reference assay method, recommended for the measurement of %dCDT, the new standard analyte for measurement of CDT. This method corrects for total transferrin concentration and increases the utility of CDT to evaluate heavy drinking in women (Helander, Wielders et al. 2010).

### *6.11 Study Timeline:*

**Table 3: Timeline of Performance Goals**

| Activity | Year 1 | | | | Year 2 | | | | Year 3 | | | | Year 4 | | | | Year 5 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Staff training & study preparation | ■ | | | | | | | | | | | | | | | | | | | |
| Subject enrollment | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | | |
| Endpoint assessments | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | |
| Data entry & cleaning | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| Data analysis | | | | | | | | | | | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Report writing | | | | | | | | | | | | | | | | ■ | ■ | ■ | ■ | ■ |

# 7 Statistical Plan

### *7.1 Sample Size Determination*

Power for the analysis for **Specific Aim 1**, as described below, will be determined by the patterns of outcomes in the final six weeks, so power estimates are based on weeks 7 through 12 as a 6-week trial, with adjustments for loss to attrition between baseline and week 6. Based on our prior study (Kranzler, Covault et al. 2014), we anticipate that, through the first six weeks, 94% of subjects (i.e., n=47 per group) will provide data, despite up to 10% discontinuing medication. We anticipate an additional 6% loss due to dropout from research during the final six weeks, also with 10% discontinuing treatment. In these power estimates, we use a square root transform to approximate the Poisson distributions by Normal distributions, on which we base our estimates using the methods of Hedeker et al. (1995) and Stroup (1999). Our primary comparison is the interaction effect of *GRIK1* with TOP. In our previous study, for the square root Poisson scale, we observed a standardized effect (Cohen 1988) of d=0.27 for TOP relative to PLA in the AA/AC group and a standardized effect of d=0.93 for TOP relative to PLA in the CC group. We have a single primary hypothesis, so we consider power for a two-sided test at $\alpha$=0.05, with a total of 4 x 47=188 subjects, with 6% research loss to attrition across six weeks. Finally, we assume a within-subject correlation of 0.35 for the repeated measures. With these assumptions, we have 81% power for the effects observed in our prior study. For **Specific Aim 2**, we used simulation studies (Kreft and De Leeuw 1998) to evaluate the adequacy of our sample size in relation to moderation by the CC genotype of TOP's effects on the contingent relation between early evening outcome expectancies and nighttime drinking (Kranzler, Armeli, et al. 2013). These show that designs having at least 30 level-2 units with 30 observations each (i.e., 900 total person days) will provide power of 80% to detect small effect sizes. Assuming a rate of missing data of about 20% (Kranzler, Armeli, et al. 2013), we will have approximately 15,000 person days for the comparison of TOP and PLA, which will provide high power to detect a small effect.

### *7.2 Statistical Methods*

**To examine the moderating effects of the *GRIK1* SNP rs2832407 on the response to TOP (Specific Aim 1.)**

The four medication (Topiramate/Placebo) by *GRIK1* genotype (CC vs. AA/AC) groups will be compared on the weekly number of heavy drinking days using mixed effects models for count responses (83, 84), fitted using PROC GLIMMIX in SAS and the HGLM module of the HLM7 program. Estimates of effects over the final six weeks from the models, with associated standard errors and confidence intervals, will be used to test the primary hypothesis, i.e., medication group by genotype contrasts within the final six weeks will directly address the significance and pattern of differences in distributions of HDDs among the four medication by genotype groups.

The fixed effects for the primary models will include binary factors for intervention group (Topiramate/ Placebo) and *GRIK1* genotype (CC or AA/AC), and their interaction, with covariates for linear and quadratic time trends and further terms for group by time, genotype by time, etc., as appropriate for model fit. The random effects will include a random intercept and, if necessary, residual autocorrelations, random slopes, or other specifications will be used (Molenberghs, Verbeke et al. 2005, McCulloch, Searle et al. 2008). Although the primary contrasts will concentrate on the final six weeks, these models utilize all available data from all subjects, so the analyses follow the intent-to-treat principle. If the polynomial time trends described above do not capture the range of individual trajectories observed in the trial, then more flexible non-linear time trends can also be fitted. Additional covariates can also be included in the models, allowing for sensitivity analyses for effects of covariate imbalances, and to examine moderation effects (see below) and group by goal of treatment (reduced drinking or abstinence) interactions. For example, we will also include the proportion of European ancestry as a covariate, to adjust for admixture. Here, AIMs genotype data will be used to calculate ancestry proportions using a principal components method implemented in EIGENSTRAT (Price, Patterson et al. 2006) or PLINK (Purcell, Neale et al. 2007), and the proportion will be included in the model as a covariate. The models can also be extended to allow for zero inflation, where weekly patterns of abstinence may yield more zero counts of heavy drinking days than can be accommodated by a Poisson model.

**To examine the relations among daily process measures of expectancies, medication use, and drinking level (Specific Aim 2.)**

Multilevel models similar to those described above will be used to evaluate the associations between alcohol expectancies and daily drinking and how these associations vary as a function of medication group and rs2832407 genotype. Similar to Kranzler et al. (2013), we will focus on predicting nighttime drinking (i.e., drinks consumed after the early evening report), but here we will use alcohol-related expectancies reported during the early evening in the daily survey. Nighttime drinking levels will be determined by subtracting the number of drinks consumed during the current day from the total number of drinks consumed for that day (reported the following day). We will follow the general analysis scheme used by Kranzler, Armeli et al (2013), but will use mixed effects/multilevel models, rather than generalized estimating equations (GEE) models (Walls, Jung et al. 2006,Schafer 2006). We will examine the number of drinks consumed (using a Poisson model). We will use the HGLM module of the HLM7 program, as it is more flexible for some of our models than PROC GLIMMIX in SAS. Analysis will focus on the last six weeks of treatment, consistent with the analyses of the primary outcome in Specific Aim 1.

Predictors in these models will include 6 day-of-the-week contrasts in the level-1 model (i.e., including responses that change over days within person), to control for day of the week trending in the outcomes [e.g., greater propensity to drink on weekends (Armeli, Carney et al. 2000, Armeli, Tennen et al. 2000)], along with linear and quadratic study time contrasts and daytime drinking. The day-level predictor of interest (i.e., expectation of positive effects of drinking) will also be included in the level-1 portion of the model. The outcome expectancy

predictor will be person-mean centered (91). The level-2 portion of the model (i.e., measures that do not change over days) will include treatment group, binary factors for rs2832407 genotype (i.e., CC vs. A-carrier) and associated interaction terms. This analysis will test the hypothesis that TOP will significantly reduce positive alcohol expectancies relative to PLA, but only in C-allele homozygotes, similar to the analysis of the primary outcome in Specific Aim 1.

### *7.3 Subject Population for Analysis*

The study will be conducted using a modified intent-to-treat approach in which all randomized subjects who have received at least one dose of study medication and provided at least 10 days of data on drinking after initiating treatment will be used in the efficacy analyses. All randomized subjects who received at least one dose of study medication will comprise the safety population.

### *7.4 Genetic Analyses*

Genotyping will be performed by Dr. Richard Crist in the Department of Psychiatry at the University of Pennsylvania Perelman School of Medicine. Whole blood will be coded and shipped to Dr. Crist's lab. Samples will be hand-delivered or transported via courier without identifiers, following University of Pennsylvania shipping procedures. Staff will send the blood sample after collection at screening visits. Staff will keep a log of all samples sent to Dr. Crist's lab, maintaining tracking logs of all samples sent verified with results received within 5 days to determine inclusion criteria. DNA will be purified from whole blood standard methods. TaqMan allelic discrimination assays will be used to genotype rs2832407 using kits provided by Applied Biosystems Inc. Genotyping will be performed using the 5'-nuclease TaqMan closed-tube fluorescence method and an ABI Sequence Detector System for post-PCR plate reads. Dr. Crist's lab will send genotype information to study staff designated as the randomization staff member who is not otherwise involved in the conduct of the study. That individual will maintain a log of all subjects' genotype results and inform study staff if the subject is eligible for randomization to study medication due to genotype, keeping the study staff member blinded to the subject's genotype.

If necessary to ensure the timeliness of the genotyping, we will send a blood sample to the University of Pennsylvania's Molecular Profiling Facility as an alternative to Dr. Crist's laboratory. Under those circumstances, procedures similar to those described above will be used to ensure privacy and maintenance of the blind.

## 8 Safety and Adverse Events

### *8.1 Definitions*

**Unanticipated Problems Involving Risk to Subjects or Others**

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

**Adverse Event**

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

**Serious Adverse Event**
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

**Adverse Event Reporting Period**
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

**Pre-existing Condition**
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

**General Physical Examination Findings**
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

**Post-study Adverse Event**
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or

adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

**Abnormal Laboratory Values**
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

**Hospitalization, Prolonged Hospitalization or Surgery**
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

## *8.2 Recording of Adverse Events*

At each contact with the subject, study staff must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

## *8.3 Reporting of Serious Adverse Events and Unanticipated Problems*

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study center
- Subject number
- Current status
- Whether study treatment was discontinued
- The reason the event is classified as serious
- A description of the event
- Date of onset
- Investigator assessment of the association between the event and study treatment

### *8.3.1 Data and Safety Monitoring Plan (DSMP)*

The DSMP is intended to ensure the safety of research participants and the integrity of the study data. Dr. Henry Kranzler, M.D., the principal investigator of this study, or one of the other study physicians, will be charged with determining the severity rating of all adverse events. The study staff (P.I., co-investigators, clinical research coordinator) is responsible for collecting and recording all clinical data. As these results are collected, all toxicities and adverse events will be identified, graded for severity and assigned causality, reported to the required entities, and compiled for periodic review. After assigning causality, the P.I. will decide the course of action for the study participant. The P.I. will evaluate every adverse event and determine whether it affects the risk/benefit ratio of the study and whether modifications to the protocol or informed consent form are required. The principal investigator (and, in his absence, physician co-investigators) will differentiate serious from non-serious adverse events. Serious adverse events will be reported to the Penn IRB and the NIAAA project officer within 48 hours and an annual report summarizing all adverse events will be prepared and reported to the UPenn IRB, CMCVAMC IRB, and NIAAA. The following information will be considered in the periodic safety report to the Data and Safety Monitoring Board (DSMB), which will be empanelled prior to initiation of the trial:

- Summary of adverse events.
- Dropout rates and reasons for the dropouts.
- Number of patients who have completed the study.
- Any other relevant information

The DSMB, a full description of which is provided below, will follow guidelines established for monitoring clinical trials in the Center for Studies of Addiction. It should be noted that, at no time will a DSMB member participate in the review of a study in which he or she is a co-investigator or otherwise actively involved.

Any patients thought to be at risk from drinking or psychiatric or medical disorders during treatment will be referred to appropriate clinical services. Given the anticipated moderate effect sizes, we will not conduct interim analyses, nor have we elaborated stopping rules for

the study in relation to efficacy. An adequate evaluation of efficacy will require a sample size larger than what will be available before the study is completed as designed. However, if it has been determined, for any reason, that the study should be suspended, we will discontinue enrollment of new patients, while continuing the treatment and monitoring of patients already enrolled in the study, unless to do so would create a risk that is not justified by any potential benefit to patients.

Women of Reproductive Age: As noted above, precautions for pregnant or reproductive age women are in accordance with NIAAA requirements and this will be monitored as part of the DSMP. Women who are pregnant, nursing or of reproductive age and not using effective methods of birth control will be excluded from the study. The study inclusion and exclusion criteria, in total and as specified in the protocol, will be the basis for determining study eligibility. As mentioned above, it is possible that some hormonal contraceptives (e.g., birth control pills, hormonal implants or hormonal injections) may be made less effective by topiramate. If appropriate, the study doctor will discuss with patients alternatives or additional non-hormonal methods of birth control to be used during participation in the study.

Data and Record Safety/Confidentiality: Records, filed in the IRB office, verify that all research project personnel have completed training in the protection of human research subjects in accordance with the guidelines of the U.S. Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP). The study staff (PI, clinical research coordinator, etc.) will keep all study medical records (including any codes to de-identified data) under lock and key in a secure location, as required by law. All electronic data and files (e.g., database, spreadsheet, etc.) containing identifiable patient information shall be password protected. Any computer hosting such files shall have a BIOS password to prevent access by unauthorized users. If patient data are to be exchanged with others, the data will be coded. If identification is necessary, then the data will be encrypted while en-route to the recipient with strong encryption levels (≥128 bits for symmetric encryption (DES) and ≥1024 bits for asymmetric encryption (RSA).

All data and blood specimens will be stored without direct identifiable information, but will be identifiable via a linking code. Blood will not be used for the purpose of establishing cell lines. Any hard copy records associated with the study will be kept in locked offices at the clinical site. The secured research records are labeled with code numbers only (names and other identifying information are kept separate from research records). Access to hard copy data is only given to staff members working on the study. Only staff members designated to handle or analyze study samples will have access to the samples and their storage. Coded blood samples are stored in clinic-specific refrigerators and freezers, which are located in secure rooms. As per routine in the Treatment Research Center, all electronic files (e.g., database, spreadsheet) will be password protected. Any computer hosting such files will have a BIOS password to prevent access by un-authorized users.

Data used for safety monitoring will include serious adverse events, dropout rates and reasons for dropout, enrollment numbers, patient interviews, medication compliance, review of symptoms or performance status, review of clinical/diagnostic test results, review of physical examination, review of vital signs, review of evaluation performed, protocol deviations, and blinded data. If it has been determined, for any reason, that there will be a suspension of this study, the PI will suspend enrollment of new patients but continue intervention/monitoring of previously enrolled patients if it is in the best interest of those patients. We have determined that this study involves more than minimal risk to patients, but that potential benefits outweigh potential risks of treatment.

Blood will be collected for DNA analysis. The information derived from analysis of the patients' DNA will not be provided to the patient, since at the present time the existing preliminary genetic data to predict the response to topiramate treatment do not provide a basis for genetic counseling. Should that situation change over the course of the treatment trial, procedures will be developed in conjunction with the Penn IRB to provide patients with relevant information on genotype and to counsel them in relation to that information. While the study is open, DNA samples will be coded with a number that provides an indirect link to the patient's identity (samples will be accessible only by the researchers and staff involved with this study). Upon completion of the study the sample will be kept in storage indefinitely. However, the sample will forever be separated from all identifiers. These de-identified samples may be shared with other researchers and used in other projects. The lab procedures for storage include a passcode-protected locked room, and secure storage freezers. All samples will be retained securely as per lab protocols.

### *8.3.2 University of Pennsylvania School of Medicine, Center for Studies of Addiction, Data and Safety Monitoring Board*

Introduction: The Center for the Studies of Addiction, here after referred to as the Center, has identified the need to assist investigators with meeting their ethical responsibility for ongoing study monitoring of treatment outcomes and safety monitoring. Furthermore, NIH Guidelines (1998) specify that all clinical trials should have a system in place for appropriate oversight and monitoring to ensure the safety of participants and the validity of the data. In order to help meet these needs the Center is establishing a committee called a Data and Safety Monitoring Board (DSMB).

Purpose: The purpose of the DSMB is to assure that the safety of study subjects is protected while the scientific goals of the ongoing studies are being met. Specifically, the DSMB is charged with monitoring the safety of participants and the quality of the data, as well as the appropriate termination of studies either when significant benefits or risks have been uncovered or when it appears that a clinical trial cannot be concluded successfully.

Objectives:

A. To determine which studies conducted at the Center require a Data and Safety Monitoring Board.

B. To review initial protocols for studies to ensure the following (see Appendix 1):

• Each protocol captures the information necessary to evaluate the safety and efficacy of the study when it is ongoing and completed and to provide recommendations that may improve the protocol.

• Each protocol includes a detailed Data Safety and Monitoring Plan (DSMP). This plan, in turn, also references this DSMB plan as well as specifying modifications to the Board plan that are necessary. The DSMP should also include stopping rules that specify the outcome differences detected between groups during an interim analysis that can stop a clinical trial. In general, stopping rules will reflect one of the following conditions:

1. There is clear evidence of harm or harmful side-effects of the treatment; 2. There is no likelihood of demonstrating treatment benefit; or 3. There is overwhelming evidence of the benefit of the treatment.

C. To monitor ongoing protocols to evaluate the following (see Appendix 2):

• The safety of the subjects as pre-specified in the DSMP of each protocol and independently the DSMB will make recommendations to researchers to continue, to

amend, or to terminate a clinical trial based on the interim analysis of the safety data (e.g., terminate a clinical trial because of high incidence of an SAE).

• The efficacy of the treatments being tested as pre-specified in the interim monitoring plan of each protocol and independently make recommendations to researchers to continue, to amend or to terminate a clinical trial based on the interim analysis for efficacy (e.g., terminate a clinical trial because the analyses indicate the study is having a negative effect, the intervention is not adequately implemented or there is no evidence of a treatment effect after the prescribed level of power is reached).

• The presence of early unanticipated therapeutic results, side effects or adverse consequences for each protocol, and independently make recommendations to continue, to amend or to terminate a clinical trial based on the interim analysis for efficacy (e.g., terminate a clinical trial because it would be unethical to continue the non-treatment compared to the treatment-as-usual arm).

• The performance of each trial (e.g., protocol violations, improper entry criteria, slow accrual rate, low participation rate, failure of randomization, inadequate treatment adherence, inadequate follow-up rate, severely compromised validity), and to independently make recommendations for improvement or termination if the trial would be unable to prove anything meaningful, regardless of modifications.

### *8.3.3. Studies Requiring a DSMP and DSMB*

All clinical trials involving human subjects require study-specific IRB approval and a detailed DSMP, and will be reviewed by the Center's DSMB. The DSMB will make a determination regarding studies that require ongoing DSMB review. The National Institutes of Health policy on data and safety monitoring will serve as a guide to the DSMB in making decisions regarding trials that require DSMB oversight and monitoring. As such, all phase III clinical trials are required to have data safety and monitoring in the form of a DSMB. Phase I or II trials will be required to have DSMB oversight for the following reasons: if the investigator is the investigational new drug (IND) holder, if the study has multiple clinical sites, is blinded, or employs a particularly high-risk intervention or vulnerable population. Additionally, a DSMB may be indicated when there are special concerns regarding subject safety, a study investigator is inexperienced or where study integrity could be enhanced by the independence of the DSMB. The DSMB's role is oversight above and beyond that of the Institutional Review Board. The intent of the board is not to place an onerous burden on investigators. If a trial has the oversight of an external DSMB there does not need to be duplication of effort.

### *8.3.4. Scope of Data Monitoring*

The precise nature of the data to be monitored and the analyses used per protocol will be determined by the DSMB. The primary source of the data will be the Case Report Form developed for each protocol. The study investigators, as requested by the DSMB, will provide additional detailed information regarding serious adverse events.

A. Study Admission Data: The DSMB will assess the sites' performance with respect to subject recruitment. Monitoring of admission data will include the number of subjects calling for treatment for substance use/abuse problems, number of subjects scheduled for an intake appointment, number of subjects who attended an intake appointment, and number of subjects admitted to the study. The DSMB may request a report of the reason why subjects were disqualified from participating in the study. For subjects admitted to the study, the

DSMB will review eligibility criteria for admitted subjects, any protocol violations, and the demographic distribution of the subjects (by group if required) (see Appendix 2).

B. Protocol Compliance: The DSMB will monitor the data per protocol to assess compliance with the protocol including adherence to protocol participation rules for safety or administrative adherence. Examples of participation rules might include, for example, stopping participation or withholding treatment for elevations of liver function tests, severe neuropsychiatric disturbances or changes in vital signs. The DSMB will also monitor the quality and completeness of the data being collected. For data collected at specified times the Board should monitor the frequency of missing or erroneous data, and presence and frequency of outliers.

C. Safety Data: Monitoring of safety data will include per protocol a review of Adverse Events (AE's) and Serious Adverse Events (SAE's), and data commonly accepted to reflect differences in safety between treatment groups such as clinical laboratory data, treatment retention, and reason for drop out. Safety information for all studies will be reported to the Board in a blinded manner. The Board may determine if a review of unblinded data is indicated. Unblinded information will only be discussed during closed meeting sessions. Furthermore, the Board may request formal statistical analyses of the safety data.

For non-serious AE's, data may be summarized by treatment groups, with data on individual subjects available for DSMB review as needed and if the study blind is not compromised. For SAE's, data will include all of the adverse event data that meet the FDA definition of serious adverse events. In the assessment of SAE's, the DSMB will review each individual case including treatment group assignment.

After each meeting of the DSMB, the executive secretary will forward a summary report of all serious and unexpected adverse experiences to each investigator per protocol. The report will document that a review of data and outcomes took place on the date of the meeting. It will summarize the Board's review of cumulative serious and unexpected adverse events reported without specific disclosure by treatment arm. Furthermore, the report will inform investigators of the Board's recommendations with respect to progress or need for modification of the protocol. The principal investigator is required to transmit the report to the local IRBs.

The DSMB will follow up on the outcome of AE's and SAE's, and that all appropriate AE's and/or SAE's are reported to the UPenn IRB, CMCVAMC IRB, FDA, NIH or other pertinent regulatory agency.

D. Efficacy Data: Efficacy data determined by the protocol are based on the primary and secondary outcome variables detailed in the DSMP for each component which will be required to have been reviewed and accepted by the DSMB. The data may be presented for all treatment groups combined or by treatment groups. Data by treatment groups can be presented to the DSMB blinded and then the DSMB may request to unblind the data. In the event that a safety concern arises that requires an interim analysis of efficacy data, an analysis may be made on a for-cause basis. Any for-cause interim analysis requested by the DSMB should specify in advance the efficacy outcome of interest, the number of comparisons to be made for purposes of the analysis, the statistical method to be employed in the analysis, the significance required to reach a decision, and the new p value necessary to reject the null hypothesis should the study run to completion (such that the probability of a Type 1 error is maintained at $<0.05$ for all primary analyses that would be conducted).

For studies that are conducted in a blinded manner, the presentation of data relating specifically to outcome measures should be presented to the DSMB in the manner and timing described in the DSMP for that study. Additionally, the Board will determine whether interim analyses of efficacy data are required. Studies that include interim analysis of efficacy data should provide the proposed number of interim analyses to be made, the specific comparisons to be made at each such analysis, the stopping rules on the basis of efficacy findings, including both standards for the determination of 'overwhelming efficacy' and an 'inevitable failed trial', and the methods of statistical correction to be used to control the final overall Type 1 error. When defining this interim review in the protocol, consideration should be given to whether the data can be prepared for the DSMB review in a sufficiently timely manner so that any resulting decision can in fact impact on the study if the study is largely completed before the conclusions are made, the interim review may be unnecessary.

E. Establishing a DSMB

• Board membership: The DSMB will consist of at least four members. Three members will constitute a quorum. The Center's Executive Committee will approve the composition of the DSMB, and appoint the members. The term of membership for the DSMB will be for three years.

• The DSMB members will include James McKay, Ph.D. (Chair), Kyle Kampman, M.D., Daniel Weintraub, M.D., Deborah Dunbar, MSN, CRNP, ANP-BC, David Metzger, Ph.D., Reagan Wetherill, Ph.D., Cynthia Clark, Ph.D., CRNP, Kevin Lynch, Ph.D. (biostatistician) and Richard Feinn, Ph.D. (alternate biostatistician).

• Because board members should be free of financial interest that could be substantially affected by the outcome of the trial, conflict of interest disclosure documentation is necessary to avoid real or apparent conflict of interest of the DSMB members. Individuals invited to serve on the DSMB should disclose in writing to the sponsor any potential conflicts of interest, actual or implied by appearance. Should an unanticipated situation arise that the Board member feels represents a conflict of interest, the Board member should recuse themselves from deliberations. At the start of each new member's term, the individual will sign a confidentiality statement promising not to disclose any proprietary and nonproprietary data. Furthermore, no disclosure should be made of the deliberations of the Board.

• The DSMB may identify the need for inclusion of scientists or non-scientists that may provide unique insights to a particular study or aspect of a study. These individuals could be a clinical pharmacologist, a medical ethicist or an individual that could bring the perspectives of the population under study. Whenever a project is reviewed that directly involves one of the board members, alternate members will be chosen to review the study or studies in question. At no time will a board member be involved in the review of his or her own study.

F. Board meeting schedule: The DSMB meetings will be held annually. The Board has the option of expedited meetings to review unexpected SAEs or other urgent issues that may arise during the course of the trials. Unscheduled meetings may be recommended and initiated by the Chair of the DSMB or the sponsor (or the principal investigator) of the study. The data and any other relevant materials to be reviewed by the DSMB will be made available to the Board members at least two weeks before the meeting. Investigators will be informed that their protocol is scheduled for on-going review by the DSMB at least two months before

the meeting. Should an investigator wish to have a non-emergent item placed on the agenda of an upcoming DSMB meeting, the investigator should place their request in writing to the Chair of the DSMB. The investigator will be notified of the outcome regarding their request at least two weeks before the scheduled meeting.

G. Conduct of the Meetings: The DSMB meetings will be divided into three sessions: open, closed and executive. The Principal Investigator and other study staff per protocol will attend the open session and will present relevant information to the Board about general aspects of the trial. The open session may focus on the background of the study, the protocol, status of the study, problems with accrual and follow-up, baseline demographic data, compliance issues, frequency of adverse events, documentation of endpoints, data quality issues, flow of forms, data based protocol modification issues, and any other issue regarding the studies under review that can be discussed without reference to interim comparative results.

Following the open session, a closed session will be held. During the closed session, the DSMB chair or representative will conduct the review of all issues and put each issue to a vote. A quorum for the DSMB is (4) voting members. This session will be attended by the DSMB members, the DSMB executive secretary, and if necessary the principal investigator. During the closed session, the discussions will focus on the treatment safety, efficacy data, whether the primary study question has been answered, the interim results by treatment arm (usually masked), determining when study data may be released and reviewing requests for access to the results of the interim analysis, and updating the Board on actions taken related to their actions and recommendations of the previous meeting.

Following the closed session, an executive meeting may be held. The executive meeting is restricted to DSMB members (voting and non-voting members). During these sessions, the Board may discuss any unmasked analysis of a blind clinical trial and any sensitive issues surrounding the clinical trials under review.

H. Report Format: Reports to the DSMB may include reports from the Data Management Center that reflects the status of the study, progress or findings to date, and any relevant issues. Additionally, data are presented that describe the administrative status of the study including recruitment. Reports should also provide a safety assessment and may include copies of monitoring reports. Recommendations related to clinical trials will be made in writing by the Board's Chairperson to the principal investigator of the trial. Normally, results of the interim analysis will not be disseminated. Only under certain conditions should the results be released. The Board should make the final decision related to the release of this information.

The Board Chairperson will prepare the draft report of the meeting, with the assistance of the Executive Secretary. The Executive Secretary will be responsible for the preparation of meeting minutes for inclusion in the DSMB report. The report will outline and summarize all discussions during the open and closed sessions of the meeting. Recommendations and action items will be clearly marked within the body of the report. If the DSMB decides to conduct an executive session, a statement will be included in the Minutes of the Meeting stating an executive session was conducted, but should not disclose the contents of the discussions. Minutes for the executive session will be recorded separately and not distributed beyond the DSMB members. The draft report will be reviewed and edited by all Board members prior to issuance of the final report. The Principal Investigators will ensure that their reports are sent to the UPenn IRB, CMCVAMC IRB, NIH or others, as indicated.

### 8.3.1 Investigator reporting: Notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  **AND**

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

**Reporting Process**
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

**Reporting Deaths: more rapid reporting requirements**
Deaths that occur during the course of a research study and that are:

- Unexpected; AND
- Related to the research study; AND
- When other participants are believed to be at an increased risk of harm

Must be reported to the IRB within 3 days from the time the investigator becomes aware of the death.

**Other Reportable events:**
For clinical drug trials, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.

- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

### 8.3.2 Sponsor reporting: Notifying the FDA

N.B. This protocol is being submitted to the FDA as suggested by the agency to determine whether an IND is required. The following information will only be relevant if an IND is required.

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days***
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening, and

- ***Within 15 calendar days***
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:

– suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

**Additional reporting requirements**
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

**Reporting Process**
Adverse events may be submitted on FDA Form 3500A or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
301-796-3980

### *8.4 Unblinding Procedures*

In the event that subjects are prematurely discontinued from participation in treatment, it will be necessary to avoid breaking the blind whenever possible, in order to protect the integrity of the study. If an emergency necessitates that the blind be broken, only the pharmacist will have access to the unblinding codes and will be given the names of the staff with authority to request that the blind be broken. If the IDS or hospital pharmacy is contacted by other persons requesting that the study blind be broken for a subject, and Dr. Kranzler or another study physician is not reachable via pager, the pharmacist will act according to his/her best judgment in deciding whether to break the study blind for that subject. The hospital pharmacist can be reached 24 hours a day by beeper to rapidly access subject unblinding codes. Dr. Kranzler should be notified of the need to unblind the subject as soon as is feasible by the individual making that decision.

### *8.5 Medical Monitoring*

The Principal Investigator will oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, and the construction and implementation of a site data and safety-monitoring plan (see section 10: Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

## 9 Data Handling and Record Keeping

### *9.1 Confidentiality*

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject

authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Separate Certificates of Confidentiality from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) will be obtained for both the main study and the sub-study described in this protocol. As per the NIAAA's website: Certificates of Confidentiality are issued by NIH Institutes pursuant to Section 301 (d) of the Public Health Service U.S.C. Section 241 (d) to afford special privacy protection to subjects enrolled in biomedical, behavioral, clinical, or other research within NIH mission areas. A Certificate helps the researcher avoid compelled 'involuntary disclosure' (e.g., subpoenas) of identifying information about a research subject. It does not prevent voluntary disclosures such as disclosure to protect the subject or others from serious harm, as in cases of child abuse. Also, a researcher may not rely on a Certificate to withhold data if the subject consents to the disclosure. When a researcher obtains a Certificate of Confidentiality, the subjects must be told about the protections afforded by the Certificate, and any exceptions to that protection. This information is usually included in an 'informed consent'.

All subjects will be informed about the protections afforded by the Certificate in the Informed Consent Form for both the main and sub-study using the language inserted below:

"To further help us protect your privacy, we have obtained a Certificate of Confidentiality from the United States Department of Health and Human Services (DHHS).

With this Certificate, we cannot be forced (for example by court order or subpoena) to disclose information that may identify you in any federal, state, local, civil, criminal, legislative, administrative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except to prevent serious harm to you or others, and as explained below.

You should understand that a Certificate of Confidentiality does not prevent you, or a member of your family, from voluntarily releasing information about yourself, or your involvement in this study.

If an insurer or employer learns about your participation, and obtains your consent to receive research information, then we may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy.

You should understand that we will in all cases, take the necessary action, including reporting to authorities, to prevent serious harm to yourself, children, or others (for example, in the case of child abuse or neglect)."

This language is located in the section of both of the Informed Consent Forms titled "Who can see or use my information? How will my personal information be protected?"

Records, filed in the IRB office, verify that all research project personnel have completed training in the protection of human research subjects in accordance with the guidelines of the U.S. Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP). The study staff (PI, Clinical research coordinator, etc.) will keep all study medical records (including any codes to de-identified data) under lock and key in a secure location, as required by law. Only date and time of the research visit and lab specimen data will be placed in the client's existing electronic medical record. All electronic data and files (e.g., database, spreadsheet, etc.) containing identifiable subject information shall be password protected. Any computer hosting such files shall have a BIOS password to prevent access by un-authorized users. If subject data are to be exchanged with others, the data will be coded. If identification is necessary, then the data will be encrypted while en route to the recipient with

strong encryption levels (≥ 128 bits for symmetric encryption (DES) and ≥ 1024 bits for asymmetric encryption (RSA).

All data and blood specimens will be stored without direct identifiable information, but will be identifiable via a linking code. The secured research records are labeled with code numbers only (names and other identifying information are kept separate from research records). Access to hard copy data is only given to staff members working on the study. Only staff members designated to handle or analyze study samples will have access to the samples and their storage. Coded blood samples are stored in clinic-specific refrigerators and freezers, which are located in secure rooms. As per routine in the TRC, all electronic files (e.g., database, spreadsheet) will be password protected. Any computer hosting such files will have a BIOS password to prevent access by un-authorized users.

Blood will be collected for DNA analysis. The information derived from analysis of the subjects' DNA will not be provided to the subject, since at the present time the existing preliminary genetic data for predicting response to topiramate do not provide a basis for genetic counseling. Should that situation change over the course of the study, procedures will be developed in conjunction with the UPenn IRB, to provide subjects with relevant information on genotype and to counsel them in relation to that information. While the study is open, DNA samples will be coded with a number that provides an indirect link to the subject's identity (samples will be accessible only by the researchers and staff involved with this study). Upon completion of the study, the sample will be kept in storage indefinitely. However, the sample will forever be separated from all identifiers. These de-identified samples may be shared with other researchers and used in other projects. The lab procedures for storage include a passcode-protected locked room, and secure storage freezers. All samples will be retained securely as per lab protocols.

Data used to process subject payments with the Greenphire Clincard program are entered electronically using secure web-based interfaces. Greenphire Clincard is HIPAA compliant. Please see document titled, "ClinCard Data Security and Privacy Statement," located in the appendix. The Greenphire system requires that we complete a W9 for each subject, entering the subject's name, address and social security number.

## *9.2 Source Documents*

Source data include all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

## *9.3 Case Report Forms*

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For

clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

### *9.4 Records Retention*

It is the investigator's responsibility to retain study essential documents for at least 3 years after the closure of the study with the IRB.

# 10 Study Monitoring, Auditing, and Inspecting

### *10.1 Study Monitoring Plan*

This study will be monitored according to the monitoring plan described below. The Principal Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g., diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

The Principal Investigator and research staff will monitor the study. Written monitoring procedures for monitoring clinical investigations, proposed by the OHR and previously established at the TRC will be implemented to assure the quality of the study and to assure that each person involved in the monitoring process carries out his or her duties.
The Principal Investigator will maintain a record of the findings, conclusions, and action taken to correct errors noted by the monitor for each visit.

Monitoring Responsibilities: The monitor, in accordance with local and NIH requirements, should ensure that the study is conducted and documented properly by carrying out the following activities:

a. Verifying that the investigator has adequate qualification and resources and these remain adequate throughout the study period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the study and these remain adequate throughout the study period.
b. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
c. Verifying that written informed consent was obtained before each subject's participation in the study.
d. Verifying that the investigator is enrolling only eligible subjects.
e. Reporting the subject recruitment rate.
f. Verifying that source data/documents and other study records are accurate, complete, kept up to date, and maintained.
g. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated and identify the study.
h. Checking the accuracy and completeness of the CRF entries, source data/documents, and other study related records against each other.
i. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained, and initialed by the investigator or by a member of the study staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.
j. Determining whether all adverse events (AE's) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the applicable regulatory requirement(s).

k. Determining whether the investigator is maintaining the essential documents.
l. Communicating deviations from the protocol, SOP's, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.
m. Follow the University SOP's, GCP, and the applicable regulatory requirements.

**Study Monitoring**
The study Principal Investigator and research staff have prepared a case record form (CRF) that is designed to reduce coding errors and promote data quality. Each page of the CRF will contain a header that includes the title of the protocol, the protocol number, the subject randomization number, subject screening number, and visit number. The technicians are responsible for data entry. The research charts will be maintained separately from the CRF and will contain subject information that is not entered in the study CRF database.

Regulatory Binder: A detailed Regulatory Binder will be assembled. Any changes to procedures are documented in this section. This binder is the backbone of quality assurance. We use this binder to train any new study personnel and for reference so that our policies and procedures are standard throughout all phases of the protocol. The 'Measures' section of the binder addresses, specifically all forms and instruments that comprise the CRF. A Table of Contents has been prepared that contains all the forms used in the study.
The study manual will include

- study protocol research team names, titles, roles and responsibilities, work and home phone numbers
- purpose of study, study intent and rationale
- all study procedures for each team member (PIs, technicians, study coordinator, pharmacists, nurses, physicians, etc.)
- recruitment and screening procedures
- intake procedures
- study phase procedures
- completion/discontinuation procedures

**Data Collection Training**
The TRC provides comprehensive data collection training for all research technicians (RTs). RTs receive training on how to proceed with problematic subjects. RTs are trained to follow the general data collection guidelines listed below.

- RTs should be present when subject is completing instruments.
- Research interviews and evaluations should be administered in a private, quiet office or area.
- Instruments are introduced and explained the same way each time to each subject.
- Order of research assessments should be maintained, as much as possible.
- Order of specimens obtained should be maintained as much as possible.
- RTs should show an interested, polite, appropriate, and helpful demeanor.

**Quality assurance (QA) procedures**
Changes to the CRF and the study database are strictly monitored. After a single line is drawn through the corrected data point, the RT documents the change by placing his or her initials and the date of the change adjacent to the correction. Typical QA responsibilities of the RT include:

- Checking all data during or immediately after study visits.
- Checking charts at predetermined points during the study (initials and date of checker are required on each form checked).
- Performing the initial data check after a few charts have been entered.
- Performing a 10% data check when all data have been entered.

**Typical responsibilities of the PI include:**

- Monitoring and reporting on RT interviewing and data collection proficiency at subject study visits.
- Checking charts at predetermined points during the study (initials and date of PI are required on each form checked).
- Supervising study database checks.
- When databases, in Filemaker Pro or other applications, are developed by the research staff, only the data checked by the RT are entered. Data sets are double checked in pairs by technicians. The PI supervises any corrections to the data set and reviews the completed database before the information is used in any reports or analyses.
- The PI holds meetings with the RTs to report and review the project and data entry status.
- PI reviews lab results and screening information for potential subjects.
- PI reviews adverse events on at least a weekly basis.

Monitoring activities include:

- Oversight of Investigator conduct, including supervision of study site staff and data reporting
- Review of the study site's processes and procedures (e.g., process for investigational product administration)
- Review of site records for completeness and accuracy
- Ongoing evaluation of safety data and the emerging benefit-risk profile of an investigational product
- Review of recruitment rates
- Review of protocol deviations and non-compliance
- Review of subjects who dropped out
- Review of the timeliness of data collection and submissions
- Verification that informed consent was obtained appropriately
- Verification of adherence to the protocol, including eligibility criteria, study test and procedures, investigational product accountability
- Verification of the disposition of the investigational product
- Review of evaluation, assessment, documentation and reporting of Adverse Events
- 100% source data verification will be performed for all subjects.
- 100% review of all off-site tracking logs and the source documents that confirm the data and samples transferred were received.

Enrollment will take place at the Treatment Resarch Center. For all subjects consented, the Monitor will:

- Review the informed consent form (ICF) and informed consent process
- Verify eligibility (i.e., review of inclusion/exclusion criteria)
- Assess treatment compliance
- Review subject evaluations, testing and follow-up per the protocol
- Assess and follow-up safety issues
- Review and compare source documents and CRFs for completion and accuracy
- Review investigational agent accountability and adherence to product labels

- Review any regulatory documents for amendments/modifications/updates

Timing and Frequency of Monitoring Visits:

Monitoring visits will be done twice each year that the study is active.
  - The first monitoring visit will be held no later than four weeks (and no earlier than two weeks) after the baseline visit of the first subject in any new site added. Subsequent monitoring visits will take place twice each year.
  - A study closeout visit at each active site will be conducted no later than 1 month after the final subject has completed the study at that site.
- Review of the Informed Consent Form
- Review the ICFs to verify that consent was obtained in accordance with regulations and guidelines.
- Regulatory Document Review
- The site regulatory documents will be maintained in the site regulatory binder. The regulatory binder will be reviewed by the Monitor at each monitoring visit. The Monitor will review the binder to ensure its completeness and that study documents are filed appropriately in a timely manner.
- Adverse Event (AE) and Serious Adverse Event (SAE) Reporting

AEs: The Monitor will confirm during review of the collected data and source data/documentation that SAEs, AEs, and protocol deviations have been reported as required by the IRB, FDA, and otr regulatory agencies.

**Study Logs and Reports**
Study logs are routinely maintained in order to keep computerized back up records of identifying and socio-demographic characteristics and experimental group status. The study subject log usually includes subjects' initials, study number, CRF number, date of birth, race, medication start dates, subject status (active, drop-out, completer, follow-up) and relevant dates and comments.

**Data Storage on Site**
The CRFs and research charts are stored in file rooms specifically designed for data storage. All study data are housed in locked file cabinets. Only designated members of the research team have access to the file cabinets containing research data. Data are kept on site for not less than three years after the subject has completed the final assessment. Data are then eligible for archiving.

## *10.2 Auditing and Inspecting*

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

# 11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The Subject Informed Consent Form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

# 12 Study Finances

## *12.1 Funding Source*

This study is financed through a grant from the US National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health.

## *12.2 Conflict of Interest*

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

## *12.3 Subject Stipends or Payments*

Subjects will receive $1.00 for each phone call they make or $10 for each week they complete all 7 phone calls (up to $120 for all calls across the 12-week monitoring period). They will receive $3 for returning medication bottles at each study visit, $4 to cover the cost of mass transit for roundtrip travel, $25 for completing the week visit 6 and $50 for completing the endpoint visit. They will receive $50 for each of the two follow-up visits. The total amount that subjects can receive for full participation in the research study is $374. Subjects will be paid at the visits shown in Table 3 based on their daily phone calls, medication bottles returned, and assessment visits completed. Payments will be made at each study visit for which a payment is due, as shown in Table 3. Payments will be made with a GreenPhire ClinCard. Clincards are reloadable prepaid cards that may be used for in-store purchases (by selecting either the “credit” or “debit” option), online purchases, at an ATM to get cash, or for cash advances at a bank.

**Table 3. Schedule for Study Payments**

| Visit | Returned Medication Bottle | Travel Cost | Completed Visit | Daily Phone call: $1/day or $10 for all 7 days/week | Maximum Payment |
|---|---|---|---|---|---|
| Screening Visit -0 | N/A | $4 | $0 | N/A | $4 |
| Visit 1 Baseline | N/A | $4 | $0 | N/A | $4 |
| Visit 2 | $3 | $4 | $0 | 0 | $7 |
| Visit 3 | $3 | $4 | $0 | 0 | $7 |
| Visit 4 | $3 | $4 | $0 | 0 | $7 |
| Visit 5 | $3 | $4 | $0 | 0 | $7 |
| Visit 6 | $3 | $4 | $25 | $50 | $82 |
| Visit 7 | $3 | $4 | $0 | $20 (2 wks) | $27 |
| Visit 8 | $3 | $4 | $0 | $20 (2 wks) | $27 |
| Visit 9 | $3 | $4 | $0 | $20 (2 wks) | $27 |
| Visit 10 Endpoint visit | $3 | $4 | $50 | $10 | $67 |
| Visit 11 (3-Month) | N/A | $4 | $50 | N/A | $54 |
| Visit 12 (6-Month) | N/A | $4 | $50 | N/A | $54 |
| Totals | $27 | $52 | $175 | $120 | $374 |

Note: Subjects will receive a portion of the payment based on completion of study visits, daily phone calls and returning both medication containers (i.e., $1.50 for returning only one of the 2 bottles). Payments will be deferred if they fail a Breathalyzer test. Payments for phone calls made during the first five weeks will occur at Visit 6 and then as shown above.

# 13 Appendix I: (Sub-study) Brain Mechanisms of Topiramate's Effects on Heavy Drinking

## *13.1 Background*

Alcohol is the third leading risk factor for premature death and disability (Alcoholism 2013), as well as a leading cause of preventable cancers (Nelson, Jarman et al. 2013). Alcohol dependence affects 18-20 million Americans (i.e. 1 in 12), and alcohol problems cost our society nearly $225 billion annually (Alcoholism 2013). Alcohol dependence is a chronic disorder marked by high rates of relapse. Relapses to drinking are often preceded by a strong desire or craving for alcohol when exposed to alcohol-related stimuli. Knowledge of the mechanisms underlying stimuli- or alcohol cue-induced craving may aid in the search for additional viable pharmacotherapies to help alcohol dependent individuals remain abstinent for life.

Currently, there are three FDA-approved medications to treat alcohol use disorders (AUD): naltrexone, acamprosate, and disulfiram (Harris, Kivlahan et al. 2010). Empirical evidence suggests that naltrexone reduces the reward properties of and cravings for alcohol (Sinclair 2001) and acamprosate supports abstinence (Mason, Goodman et al. 2006); however, their effect sizes compared to placebo are small (Mark, Kranzler et al. 2003; Rosner, Hackl-Herrwerth et al. 2010; Oliva, Maisel et al. 2011). Disulfiram differs from naltrexone and acamprosate in that it blocks the metabolism of alcohol's primary metabolite, acetylaldehyde, which accumulates in the blood causing unpleasant effects when alcohol is ingested (Franck and Jayaram-Lindstrom 2013). There is limited evidence of the efficacy of disulfiram, and its potential for toxicity limits it use (2009). These concerns about safety and limited efficacy likely contribute to the fact that FDA-approved medications for AUD are not widely prescribed (Mark, Kranzler et al. 2003; Mark, Kranzler et al. 2003). Indeed, only 2.8% of patients treated in the Veterans Health Administration who were diagnosed with an AUD received pharmacotherapy (Oliva, Maisel et al. 2011). Given these issues and concerns, several medications, other than

the currently approved medications for AUD, have been prescribed off label and have shown promise in reducing alcohol consumption.

One promising medication for the treatment of AUD is the GABA/glutamate modulator, topiramate. Although topiramate is FDA-approved as an anticonvulsant, prophylactic treatment for migraine, and for weight loss, both preclinical (Hargreaves and McGregor 2007; Breslin, Johnson et al. 2010) and clinical studies (Johnson, Ait-Daoud et al. 2003; Rubio, Ponce et al. 2004; Johnson, Rosenthal et al. 2007; Miranda, MacKillop et al. 2008) show that topiramate is effective in reducing heavy drinking. Specifically, topiramate reduced alcohol craving (Rubio, Ponce et al. 2004); had a moderate treatment effect in reducing heavy drinking in three published placebo-controlled trials (Johnson, Ait-Daoud et al. 2003; Johnson, Rosenthal et al. 2007; Miranda, MacKillop et al. 2008), and appears to have a larger effect size than naltrexone (Baltieri, Daro et al. 2008; Florez, Saiz et al. 2011) and acamprosate (Kenna, Lomastro et al. 2009). Kranzler, Covault et al. (2014 found that 200 mg/day of topiramate was well tolerated, reduced the number of heavy drinking days and increased the number of abstinent days more than placebo. In fact, during the last week of the 12-week study, the odds of the placebo group having at least one heavy drinking day was 5.33 times that of the topiramate group. Although these robust findings support the use of topiramate to reduce heavy drinking, the mechanisms underlying its therapeutic effects are not well understood. Thus, the present study aims to elucidate the brain and behavioral mechanisms that mediate topiramate's reduction of heavy drinking.

Functional neuroimaging provides a powerful, non-invasive method to study addictive processes. For example, we, and others, have identified a consistent neural substrate for reactivity to cocaine-, heroin-, cigarette-, marijuana- and alcohol-related cues using a variety of imaging modalities (Childress, Mozley et al. 1999; Grusser, Wrase et al. 2004; Hutchison, Rutter et al. 2004; Franklin, Wang et al. 2007; Langleben, Ruparel et al. 2008; Goldman, Szucs-Reed et al. 2013). In general, chronic, heavy substance users show greater neural activity in reward-related brain regions, such as the orbitofrontal cortex (OFC), striatum, and anterior cingulate cortex, during drug cue exposure than during non-drug cues. Neuroimaging techniques have also been used to determine how some pharmacotherapies influence factors contributing to substance use. For example, naltrexone has been shown to reduce alcohol cue-induced activation in the ventral striatum (VS) and OFC in non-treatment-seeking alcoholics (Myrick, Anton et al. 2008), suggesting that naltrexone's effects are mediated through its reduction of reward-related cue reactivity. To date, there are no published studies examining the effects of topiramate on neural activity or how such effects could be associated with changes in heavy drinking. Based on our own recent finding that topiramate decreased heavy drinking days and increased abstinent days and other research indicating that topiramate reduces heavy drinking days (Johnson, Ait-Daoud et al. 2003; Johnson, Rosenthal et al. 2007; Miranda, MacKillop et al. 2008) and self-reported craving (Rubio, Ponce et al. 2004), we hypothesize that topiramate may be an effective tool in reducing the reward-related neural activity commonly associated with heavy drinking (i.e., alcohol cue reactivity). Further, our longitudinal, quantitative perfusion fMRI approach, which provides for the acquisition of resting brain cerebral blood flow (CBF: ml of blood/100 g of tissue/minute) will provide invaluable information on the mechanisms underlying the ability of a GABA/glutamate modulator to blunt alcohol cue reactivity and heavy drinking.

Neurogenetics is a promising and novel addition to neuroimaging studies. Twin, family and adoption studies indicate that vulnerability to substance abuse is partially inherited. Individual response to medications will most likely be related to genetic phenotypes. Genetics studies, on their own, require huge sample sizes and are expensive; however, when combined with neuroimaging, which offers a 'picture' of individual brains, we can learn why some individuals are vulnerable to alcohol and substance use disorders and why others do not. For example,

evidence suggests that the rewarding properties of alcohol involve GABA-ergic, glutamatergic, opiodergic, and dopaminergic neurotransmitter systems. As such, we will focus on genes associated with these systems, such as *DRD4* (D4 dopamine receptor gene), *GABRA2* ($GABA_A$ receptor alpha-2 subunit gene), *OPRM1* (mu-opioid receptor gene), and *GRIK1* (glutamate receptor, ionotropic, kainate 1 gene) (Kranzler and Edenberg 2010). Further, based on our previous research showing that the C-to-A single nucleotide polymorphism (SNP), rs2832407, in intron 9 of the *GRIK1* gene is associated with alcohol dependence (Kranzler, Gelernter et al. 2009), this variant in *GRIK1* will be our primary focus. Thus, those who have the A allele will likely show the strongest alcohol cue responses.

In summary, the data reviewed above provide strong support for the need to identify the brain and behavioral mechanisms underlying the effects of one of the most prescribed (Del Re, Gordon et al. 2013), yet poorly understood, medications to treat AUD, topiramate, on key factors contributing to heavy drinking. Given that topiramate 1) has been shown to be effective in reducing heavy drinking (Johnson, Ait-Daoud et al. 2003; Rubio, Ponce et al. 2004; Johnson, Rosenthal et al. 2007; Miranda, MacKillop et al. 2008), 2) appears to have a larger effect size than naltrexone (Baltieri, Daro et al. 2008; Florez, Saiz et al. 2011) and acamprosate (Kenna, Lomastro et al. 2009), and 3) has dual $GABA_A$-mediated inhibitory impulses and AMPA and kainate antagonist effects (Johnson and Ait-Daoud 2010) that likely suppress reward-related mesocorticolimbic dopamine release, we hypothesize that topiramate ameliorates neurophysiological vulnerabilities to heavy drinking by dampening neural activity in the brain at rest *and* during alcohol cue exposure in reward-related brain regions. The current study will elucidate the brain and behavioral mechanisms underlying topiramate's effects and test our hypotheses using a randomized, double-blind placebo-controlled design, pseudo-continuous arterial spin labeling (pCASL) perfusion functional magnetic resonance imaging (fMRI), and other relevant assessments described below. This project will yield novel findings on brain and behavioral responses to alcohol cues, the neuromodulatory effects of topiramate on alcohol cue reactivity, and the mechanisms [resting baseline (RB) modulation] underlying the ability of this GABA/glutamate modulator to blunt alcohol cue reactivity and heavy drinking. Thus, the proposed research, although not a treatment trial, will examine the effects of topiramate on brain and behavior and thereby contribute to medications development and the treatment of AUD.

### *13.2 Risk/Benefits*

**Potential Risks**
The potential risks of this study include the small risk incurred by venipuncture

**Potential Benefits**
Subjects will receive close psychiatric and medical attention, including careful evaluation of their medical and psychiatric status. The potential benefits to society include a potential improvement in the effectiveness of treatment for problem drinking, which may reduce the personal and societal costs associated with the problem.

**Risk Benefit Ratio**
The potential benefits of this study far outweigh the potential risks. Alcohol use disorders are serious disorders with mildly effective pharmacotherapy. Even in the best programs, relapse rates are high. Individuals accepted into this study will receive close medical and psychiatric monitoring. Subjects will be screened prior to admission into the study and those at risk for adverse reactions will be excluded.

## 14 Sub-Study Objectives

**Objective 1:** Demonstrate neuromodulatory effects of a GABA/glutamate modulator, topiramate, on RB and alcohol cue reactivity

**Hypothesis 1:** We hypothesize that topiramate will ameliorate neurophysiological vulnerabilities by dampening neural activity in the brain 'at rest' *and* during alcohol cue exposure in reward-related regions, such as the amygdala, mOFC, VS, and the insula. In contrast, neural activity in placebo-treated individuals at rest and in alcohol cue reactivity will not differ from pre- to post-treatment.

**Objective 2:** Examine the mechanism underlying topiramate's ability to blunt alcohol cue reactivity and reduce heavy drinking days

**Hypothesis 2:** We hypothesize that there will be a direct relationship between RB in the VS and mOFC and its effects on alcohol cue reactivity. Although overall effects are expected, reductions in heavy drinking days will correlate with topiramate's ability to modulate reward circuitry responses.

**Exploratory Objective:** Examine the moderating effects of rs2832407 on topiramate's effects on brain and behavioral responses

**Exploratory hypothesis:** C-allele homozygotes at this locus will show the most robust effects of topiramate.

# 15 Sub-Study Design

## *15.1 General Design*

- ***Phase II Study -*** This is a phase 2 research study aimed at identifying the brain and behavioral mechanisms underlying the GABA/glutamate modulator, topiramate.
- ***Design –*** One hundred heavy drinkers who meet DSM-5 criteria for AUD and express an interest in reducing or stopping drinking will be recruited from the main study, screened, consented, and if eligible, receive 2 MRI scans. Scan 1 will occur before Topiramate or placebo is administered in the main study. Scan 2 will occur after subjects have received at least six weeks of medication in the main study (i.e., 6-8 weeks from the first dose of study medication). We will use perfusion and blood oxygen-level dependent (BOLD) fMRI during resting state and alcohol cue exposure to acquire brain and behavioral responses when the brain is "at rest" and during exposure to alcohol cues. The goals of this study are to pilot test the validity of our alcohol cues and to identify brain and behavioral mechanisms of topiramate in reducing heavy drinking in alcohol dependent individuals.

## *15.2 Primary Study Endpoints*

The primary endpoints to be measured include:

- Self-report ratings of cues, subjective ratings of craving during/following cue exposure, and neuroimaging data on cerebral blood flow when the brain is at rest and when exposed to alcohol cues.

## *15.3 Secondary Study Endpoints*

The effects of rs2832407 on topiramate's neural mechanisms

# 16 Sub-Study Subject Selection and Withdrawal

## *16.1 Inclusion Criteria*

1) Subjects have consented to main study protocol and are eligible to randomize to study medication

2) Age 18 to 60 years, Inclusive
3) Provide voluntary informed consent
4) Intelligence quotient of ≥ 80, as estimated by the 2-subtest score of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999)
5) Agree to complete the first MRI visit before being randomized to study medication in the main study and agree to complete the second MRI after taking 6 weeks of study medication and before 8 weeks on study medication.

## *16.2 Exclusion Criteria*

1) History of head trauma or injury causing loss of consciousness, lasting more than five (5) minutes or associated with skull fracture or intracranial bleeding or abnormal MRI
2) History of seizures
3) Presence of magnetically active irremovable prosthetics, plates, pins, permanent retainer, bullets, *etc*. (unless a radiologist confirms that it's presence is unproblematic). An x-ray may be obtained to determine eligibility given the possibility of a foreign body
4) Claustrophobia or other medical condition preventing subject from lying in the MRI for approximately one (1) hour
5) Vision problems that cannot be corrected with glasses
6) Body Mass Index (BMI) greater than or equal to 34, body girth greater than 52 inches and a head girth greater than 25 inches [Imaging data acquisition is impaired with high weight individuals]
7) Individuals suffering from or with a history of stroke and/or stroke related spasticity
8) Individuals who are HIV positive, as the human immunodeficiency virus affects neurocognitive function, even in otherwise asymptomatic individuals (Woods et al. 2009), which can confound the results of fMRI testing.
9) Individuals who have taken topiramate for alcohol use disorder and report no treatment response
10) Urine drug screen positive for recent use of opioids, cocaine, or amphetamines.
11) Positive urine pregnancy test for females.

## *16.3 Subject Recruitment and Screening*

Subjects will be recruited from among those who have completed the main study phone screen and are deemed eligible for a screening visit for the main study. Subjects will first be given information about this optional study over the phone when the study staff schedules the subject for the main study Informed Consent and Screening visit. If the subjects are interested, they will be provided with an overview of the study and asked a few more questions related to the Sub-study, to assess eligibility. All potential subjects will be informed that participation in the optional sub-study will in no way affect their opportunity to participate in the main study. Additionally, they will be informed that they must be eligible for randomization into the main study to participate in this sub-study. If the individual satisfies preliminary criteria and shows continued interest in participating in the optional sub-study, he or she can choose either to schedule their screening visit for the sub-study on the same day as the screening visit for the main study or to schedule the visits separately. In all cases, the subject will be consented to the main study and complete all procedures for the main study screening visit and be deemed eligible, before being consented to the sub-study and completing the sub-study screening visit.

At the sub-study screening visit, subjects who otherwise meet inclusion/exclusion criteria for the MRI sub-study and express an interest in participating in the sub-study will undergo oral HIV

testing, as HIV seropositivity is an exclusion criterion for the sub-study. If the oral HIV test is positive, the nurse will inform the subject of the results, counsel the subject regarding the need to confirm the finding with a blood test and to avoid potential exposure of others to HIV, and draw 1 tablespoon of blood to conduct a confirmatory HIV blood test. If the blood test is positive for HIV, the subject will be referred for medical care and given a copy of the test results to provide to the doctor of his or her choice for the follow-up visit.

If the individual satisfies study inclusion/exclusion criteria and shows continued interest in participating in the sub-study, an appointment will be made for the Laboratory/MRI Scanning Session 1. This visit can be scheduled in conjunction with the subjects' main study baseline visit or separately depending on the subject's availability and MRI scan times. This will help to ensure that the subject completes the screening visit and the MRI visit prior to beginning the study medication (i.e. before or at the baseline visit). The initial screening process will be described and the individual will also be informed that s/he must be available for at least one more scan visit to be scheduled after the completion of 6 weeks of study medication (to achieve a maximal dosage of topiramate 200 mg/day or placebo equivalent). The second scan will be scheduled before the 8-week treatment visit (i.e., 6-8 weeks from the first dose of the study medication).

## *16.4 Early Withdrawal of Subjects*

### *16.4.1 When and How to Withdraw Subjects*

Subjects with severe psychological symptoms (e.g., suicidal thoughts), those who fail to adhere to protocol requirements, and those withdraw consent will be withdrawn from the study and if applicable, referred for appropriate clinical care. Suicidal risks will be assessed using the MINI Suicidality section (B) at each of the Main study visits, and if rated equal to or greater than 9 (i.e., clinically significant suicidal ideation), the physician will be consulted to decide the appropriate clinical management. If a subject is found to be pregnant during screening or during study, she will immediately be withdrawn from the study, referred for obstetric evaluation, and advised to discontinue all drinking. Subjects that withdraw from the Main study will be withdrawn from this sub-study.

The PI, Dr. Wetherill, will determine whether a subject who experiences a serious adverse event judged to be related to the study drug will be withdrawn from the sub-study.

### *16.4.2 Data Collection and Follow-up for Withdrawn Subjects*

We will make a strong effort (via phone calls and alternative contact information) to obtain follow-up information on all subjects who are prematurely withdrawn from the project.

## Study Procedures

There are 3 main parts to this study. Depending on the subject's availability, the parts may be combined with visits for the Main Study. Thus, it is possible that one, two or all three of the MRI study visits (i.e., screening and the two MRI scan visits) will be combined with regular study visits.

## *16.5 Screening and Informed Consent* (approximately1.5 hours)

Upon arriving to the Informed Consent and Screening Visit, subjects will be asked to complete a breathalyzer test to ensure a breath alcohol concentration (BrAC) of 0.00 g%. Subjects will then undergo the informed consent process. Specifically, subjects will be provided a standard HIPAA form that contains privacy laws, and a study staff member will review the consent form with the

subject, including an explanation of the study protocol, its risks, potential benefits, and alternative treatment. Following resolution of any questions, subjects who appear to understand the nature of the study and consent will be asked to sign the study consent form. An entire copy of the informed consent form will be given to each subject. S/he is also reminded that the consent expresses willingness to participate but that the subsequent screening process will determine final eligibility. Further, s/he is reminded that participation is voluntary, and at any time, s/he may withdraw from the study.

Following consent, subjects will watch an fMRI video that simulates the experience of undergoing an MRI and meet with study staff to complete study assessments. They will also be asked to complete an MRI safety sheet. Baseline laboratory measures include: 1) urine drug screen (to determine the presence of psychoactive drugs); 2) electrocardiogram; 3) oral swab rapid HIV test (If the test is positive, study staff will draw a tablespoon of blood to conduct a confirmatory HIV blood test); and 4) for all females: a urine pregnancy test. In cases where blood samples are drawn and potential lab errors or abnormal findings occur, subjects will be asked to provide an additional blood sample to repeat the test(s).

*Measures obtained (in addition to those obtained routinely for the Main Study):*

**a. Menstrual Cycle Questionnaire (MCQ)** is a questionnaire administered by the Nursing Staff to all prospective female subjects that elicits information on menses status, menstrual cycle length, and premenstrual symptoms (PMS). This measure is acquired because hormone levels vary and cortical GABA levels decline from follicular to luteal phase of the menstrual cycle (Epperson, O'Malley et al. 2005), and these changes influence CBF (Krejza, Rudzinski et al. 2013) and behavior (Silveri, Sneider et al. 2013). Thus, this questionnaire (and progesterone/estrogen levels) will help us determine if females are pre-, peri- or post-menopausal.

**b. Wechsler Abbreviated Scale of Intelligence (WASI)** (Wechsler 1999) is a brief and reliable measure of intelligence that provides an estimate of an individual's IQ scores. We will use the two-subtest form (vocabulary and matrix reasoning) that offers an estimate of an individual's cognitive functioning. Individuals with an intelligence quotient of ≤ 80 are excluded because they do not have the cognitive skills necessary to participate in several of the study components.

All screening assessments will be performed to determine subject eligibility, and the results will be documented. The PI or study physician will confirm and sign off on the inclusion and exclusion criteria on a case report form prior to the subject being formally included in the study. Subjects will be called within 5 days of the screening visit to be informed of their eligibility for the sub-study. Eligible subjects will be booked for the Laboratory/MRI Scanning visit either before or on the day of the Main Study baseline visit based on their and the MRI scanner's availability. Subjects must complete MRI Scanning Visit 1 before starting to take the study medication.

**c. CogState computerized battery** is a 20-minute assessment of the cognitive effects of changes in drinking behavior and of topiramate treatment. A practice session of the CogState will be administered at the Screening and Informed Consent visit. Subsequent sessions of the CogState will be administered at the Laboratory/MRI session 1 and 2 visits. It consists of:

- Detection Task (Psychomotor Speed) [2 minutes]. For this test, subjects must press a response key as soon as they detect an event. The software measures the response time to detect each event.
- Identification Task (Attention) [3 minutes]. In this task an event occurs in the center of the computer screen and the subject must decide whether the event meets a predefined and unchanging criterion. The software measures the speed and accuracy of each response.

- One Card Learning Task (Visual Learning) [5 minutes]. In this task a pre-determined set of six cards is shown repeatedly four times. Each time the set of six cards is presented the six cards are intermixed with eight distracter stimuli. Each distracter stimulus is shown only once in a task. Each time subjects see a stimulus presented in the center of the computer monitor they must decide whether they have seen this card in the task before. The software measures the speed and accuracy of each response.
- One Back Memory Task (Working Memory) [1 minute]: On this task the subject is shown a single stimulus in the centre of the computer screen (a card turns face up). They must decide whether the current card matches the card they had seen on the immediately previous trial. The software measures the speed and accuracy of each response.
- Shopping List Task (Verbal Learning and Memory) [5 minutes]: The test administrator reads the subject a brief list of words at the rate of one word every 2 seconds. After the list is complete, the subject is asked to recall as many of the words as possible. This process is repeated for a second and a third trial. After a delay, the subject is asked again to recall as many words as possible, without being read the list again. The total number of words recalled at initial recall and delayed recall are the outcome scores for this task.
- Groton Maze Learning Test (GMLT) (Reasoning and Problem Solving) [5 minutes]: The task begins with a chase task to familiarize the subject with the task context. The subject is shown a 10 x 10 grid of tiles on a computer touch screen and is instructed to "chase" a moving tile around the grid. This is followed by the timed chase test, where they must chase the target for 30 sec. The subject is then shown the same 10 x 10 grid of tiles on a computer touch screen. A 28-step pathway is hidden among the 100 possible locations, with the start and finish locations in the top left and bottom right of the grid, respectively. The subject is instructed to move one step from the start location and to continue, one tile at a time, toward the end. The subject moves by touching a tile next to the current location with the stylus. After each move, the computer indicates whether it is correct or incorrect. If a choice is incorrect, the subject must touch the last correct location and then make a different tile choice to advance toward the end. While moving through the hidden maze, the subject is required to adhere to two rules: no diagonal moves or touching the same tile twice in succession and no moving backwards along the pathway. The subject learns the 28-step pathway though the maze on the basis of this trial and error feedback. Once completed, the subject is returned to the start location and repeats the task, usually 4 more times, trying to remember the pathway just completed. There are 20 well-matched alternate forms for this task, and these are selected in pseudo-random order to ensure that no subject completes the same hidden path until all 20 have been completed. The software measures the total number of errors.

## 16.6 Laboratory/MRI Scanning Visit 1 (approximately 3 hours)

Upon arriving to the Laboratory/MRI Scanning visit, subjects will be asked to complete a breathalyzer test to ensure a breath alcohol concentration (BrAC) of 0.00 g%.

- Baseline laboratory measures include:
  - 1) urine drug screen (to determine the presence of psychoactive drugs);
  - 2) in all females: a urine pregnancy test and an additional blood sample for biochemical measurement of progesterone and estradiol levels to determine their menstrual cycle phase. A total of approximately 1 tablespoon of blood will be taken.

In cases where blood samples are drawn and potential lab errors or abnormal findings occur, subjects will be asked to provide an additional blood sample to repeat the test(s).

*Measures obtained (in addition to those obtained routinely for the Main Study):*

**a. CogState Computerized Battery:** Described above.

**b. Cognitive Bias Computer Tasks:** Individuals with emotional or dependence disorders exhibit biased attention toward stimuli associated with their disorder. This bias appears to diminish following successful treatment. Several tasks will be administered: the dot-probe attention task, the primed attention task, the implicit association task, and a go/nogo inhibition task. Generally, subjects will be told that the purpose of the task is to see how quickly and accurately they can detect targets presented on a display terminal. During the tasks, the subject will be seated in front of an eye level computer screen. Alcohol, nonalcohol, pleasant and unpleasant pictures will be presented on the screen. Subjects will be given specific instructions for each task and will be asked to respond appropriately by pressing a button.

**c. Within Session Rating Scale (WSRS):** This scale is used to assess a person's desire to consume alcohol and their thoughts about the audio/visual images viewed during the scanning session.

Prior to the scan session, subjects will complete the CIWA-Ar and the AUQ to assess withdrawal symptoms and alcohol craving. Study staff will walk or take a taxi with the subject to the 3.0 Tesla scanner to complete the MRI scan. Prior to entering the scanner, subjects will be asked to drink to satiety to avoid potential confounding effects of thirst on neural responses to cues. During the scanning session, subjects will be asked to lie still with their eyes open for a 5 minute resting baseline scan, followed by two 10-minute audio-visual clips consisting of either alcohol-related cues: individuals differing in race, age and sex who are drinking alcohol and using explicit language designed to induce appetitive desire for alcohol; or non-alcohol-related cues that are similar in content, but individuals relate interesting short stories that do not portray alcohol consumption or alcohol reminders. Subjects will also be asked their level of alcohol craving (on a scale from 0-10) before and after each audio-video clip.

MRI scanning will be conducted on a Siemens 3.0 Tesla whole-body scanner (Siemens AG, Erlangen, Germany), using a standard Transmit/Receive head coil. A 30-second localizer scan and a 5-minute T1-weighted high-resolution scan are acquired before the functional scanning. These scans are used for subsequent normalization and anatomical co-registration of the images, and they provide subjects with a habituation period to the MRI environment. The 3-plane localizer scan (sagittal, axial and coronal) is acquired with FOV = 280 mm, TR/TE = 20/5ms, 192x144 matrix, and slice thickness 5mm. Acquisition parameters for the 3D High-Resolution MPRAGE structural in the axial plane are: FOV = 250 mm, TR/TE = 1620/3ms, 192x256 matrix, slice thickness 1 mm. The CASL technique will be used to acquire images during functional MRI (RB and SC exposure). Interleaved images with and without labeling will be acquired using a gradient echo echo-planar imaging sequence. A delay of 1000 ms will be inserted between the end of the labeling pulse and image acquisition to reduce transit artifact. Acquisition parameters are: FOV=22cm, matrix=64x64, TR/TE = 3000/17ms, flip angle=90°. Fourteen slices (8mm thickness with 1.5mm gap) will be acquired from inferior to superior in a sequential order. Each cue CASL scan with 200 acquisitions will be 10 minutes in length. The RB CASL scan will be 5 minutes with 100 acquisitions.

### *16.7 Laboratory/MRI Scanning Visit 2 (approximately 3 hours)*

After the subject has completed 6 weeks of medication in the main study, they will complete the second scanning session. Upon arriving at the TRC, subjects will be asked to complete a breathalyzer test to ensure a breath alcohol concentration (BrAC) of 0.00 g%. Procedures for the Laboratory/MRI Session 2 visit are identical to those for the first Laboratory/MRI Session.

## 17 Sub-Study Statistical Plan

### *17.1 Sample Size Determination*

The current sample size is based on our previous research examining drug cue reactivity using audio-visual videos both on- and off-magnet through computerized tasks and during fMRI scanning.

### *17.2 Statistical Methods*

#### *17.2.1 Imaging Data Processing*

Prior to performing analyses, brain data are examined for gross movement and full image acquisition. A Statistical Parametric Mapping (SPM)-based ASL data processing toolbox is used for data analyses. ASL image pairs are realigned to the mean of all control images and spatially smoothed with a 3D isotropic Gaussian kernel with full width at half maximum of 10mm. CBF image series are generated using a simplified two-compartment model with the sinc interpolation method for CBF calculations. The mean control image of each subject's data is co-registered to a high-resolution 3D T1 structural image using the mutual information based co-registration algorithm provided by SPM8. The same co-registration parameters are used to co-register the CBF maps to the structural image. The structural image is then spatially normalized to the Montreal Neurological Institute (MNI) standard brain. The same parameters are used to normalize the CBF images to the MNI standard space. Each subject's normalized mean control images are segmented using SPM8. The segmented gray matter masks are averaged and the overlap of subject's gray matter is extracted. This final mask is used for calculating global CBF for each session.

#### *17.2.2 Imaging Data Analyses*

Global CBF time course will be included in the model as a covariate to examine the effects of topiramate on regional CBF. No temporal smoothing will be applied. Contrasts between conditions (alcohol cue vs non-alcohol cue; scan 1 vs scan 2) will be defined in the general linear model to assess the voxel by voxel CBF difference. Using the corresponding parametric maps of this contrast ($\beta$ maps), random effects analysis will be employed to test for a significant main effect of condition with a statistical parametric map of the T statistic at each voxel for population inference for each session for the placebo and topiramate groups (second-level analysis). A 2x2 factorial design matrix will be used to assess the effects of the pharmacological manipulation by including the group (topiramate vs placebo) and condition (scan 1 vs scan 2) as the two factors. An associated contrast will be defined in this model to examine administration effects. This two-stage analysis is theoretically equivalent to a 2-way analysis of variance (ANOVA). Simple regression analyses will be conducted on CBF with the change in craving scores [post-alcohol cue minus pre-alcohol cue craving scores, number of heavy drinking days during the past 30 days, and age] as covariates of interest to test for prognostic brain/behavioral correlations. For the exploratory aim, subjects will be grouped by genotype (CC vs A-allele carrier) to examine the moderating effects of rs2832407 in *GRIK1* on topiramate effects using the same simple regression analyses described above. We will limit this analysis to European

Americans, as that is the population in which the preliminary findings were obtained and allele frequencies differ significantly by population.

### *17.2.3 Behavioral Analyses*

Statistical significance tests use an alpha of .05 unless otherwise noted. Continuous demographic variables (e.g., age, education, quantity/frequency of alcohol use) are checked for normality, transformed if necessary, and summarized by calculating means, standard deviations and ranges. Scores on each factor will be included as covariates of interest with respect to perfusion fMRI data and genetic variance. Analysis of variance will be used to assess demographic differences across groups. Nominal demographic variables (e.g., race, sex, genotype) are summarized by calculating proportions and compared across groups using chi square analyses. Demographic (age, years education, monthly income) and clinical (depression, anxiety) will also be summarized.

### *17.3 Subject Stipends or Payments*

Subjects will be paid $50 to complete the Screening and Informed Consent visit. They will also be paid $150 to complete the initial MRI session visit, and $200 to complete the second MRI visit. The total amount that subjects can receive for full participation in the sub-study is $400. Payments will be made with a GreenPhire ClinCard. Clincards are reloadable prepaid cards that may be used for in-store purchases (by selecting either the “credit” or “debit” option), online purchases, at an ATM to get cash, or for cash advances at a bank.

**Schedule for Sub-Study Payments**

| Visit | Payment | | Total |
|---|---|---|---|
| Screening and Informed Consent | $50 | | $50 |
| MRI Scanning Visit 1 | $150 | | $150 |
| MRI Scanning Visit 2 | $200 | | $200 |
| Totals | Up to $400 | | $400 |

*Subjects will receive a pro-rated portion of the payment based on the extent to which they complete the study visit.

***ALL REMAINING ASPECTS OF THE SUB-STUDY ARE DESCRIBED ABOVE IN SECTIONS 8-12.**

# 18 Confidentiality

A Certificate of Confidentiality from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) that is separate from the one for the main study will be obtained for the sub-study described in this protocol. As per the NIAAA’s website: Confidentiality Certificates are issued by NIH Institutes pursuant to Section 301 (d) of the Public Health Service U.S.C. Section 241 (d) to afford special privacy protection to subjects enrolled in biomedical, behavioral, clinical, or other research within NIH mission areas. A Certificate helps the researcher avoid compelled 'involuntary disclosure' (e.g., subpoenas) of identifying information about a research subject. It does not prevent voluntary disclosures such as disclosure to protect the subject or others from serious harm, as in cases of child abuse. Also, a researcher may not rely on a Certificate to withhold data if the subject consents to the disclosure. When a researcher obtains a Certificate of Confidentiality, the subjects must be told about the protections afforded by the Certificate, and any exceptions to that protection. This information is usually included in an 'informed consent'.

All subjects will be informed about the protections afforded by the Certificate in the Informed Consent Form for both the main and sub-study using the language inserted below:

“To further help us protect your privacy, we have obtained a Certificate of Confidentiality from the United States Department of Health and Human Services (DHHS).

With this Certificate, we cannot be forced (for example by court order or subpoena) to disclose information that may identify you in any federal, state, local, civil, criminal, legislative, administrative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except to prevent serious harm to you or others, and as explained below.

You should understand that a Certificate of Confidentiality does not prevent you, or a member of your family, from voluntarily releasing information about yourself, or your involvement in this study.

If an insurer or employer learns about your participation, and obtains your consent to receive research information, then we may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy.

You should understand that we will in all cases, take the necessary action, including reporting to authorities, to prevent serious harm to yourself, children, or others (for example, in the case of child abuse or neglect).”

This language is located in the section of both of the Informed Consent Forms titled “Who can see or use my information? How will my personal information be protected?”

# 19 APPENDIX II: CLINCARD PROGRAM: DATA SECURITY & PRIVACY STATEMENT

***ClinCard Program: Data Security & Privacy Statement***
Updated 14 January 2016

***Confidentiality of Protected Health Information (PHI)***
All clinical trial participant information is stored securely. Greenphire does not sell, use or distribute clinical trial participant information for any purpose other than those needed to execute, service and maintain the ClinCard program (including ClinCard Direct Deposit and Travel Reimbursement methods). Greenphire protects the privacy of Electronic Protected Health Information (“EPHI”), disclosed or provided to us in compliance with the Security Standards for the Protection of Electronic Protected Health Information at 45 CFR Sections 160 and 164 (the “Security Rules”). Towards that end, Greenphire has implemented administrative, physical, and technical safeguards (detailed below) that reasonably and appropriately protect the confidentiality, integrity, and availability of EPHI; ensures that any agent or subcontractor to whom we provide EPHI agrees to implement reasonable and appropriate safeguards to protect it; and will report any Security Incident involving EPHI of which it becomes aware within five (5) days of learning of the Security Incident.

***Data Information Security***
As a matter of policy and commitment to clients and clinical trial participants, Greenphire takes great strides to protect all information relating to cardholders. Greenphire has deliberately designed its payments and communication platform including all of Greenphire’s externally facing web toolsto actively protect all data transfers and data stored with Greenphire’s infrastructure:

**Database and Encryption**– All passwords within our database are protected using the one-way SHA1 algorithm to encrypt passwords, which are then encrypted by the one-way MD5 algorithm. Where

necessary, Greenphire's platform makes use of encryption using the 256 bit Advanced Encryption Standard (AES or otherwise known as Rijndael), which is one of the most popular algorithms used in symmetric key cryptography. AES is approved by the US National Intelligence Agency (NSA) for top secret information.

**Web Tools** – All of Greenphire's web tools that are involved in transferring data between an end-user's web browser and Greenphire's platform (and vice versa) are secured by 256 bit Secured Socket Layer (SSL) with TLS 1.2 encryption. Greenphire is able to track the activities performed on accounts by site administrators through a system of unique logins which allow users access to the clincard.com web tool. In addition, all user activities in the Greenphire Platform are auditable.

**Financial Data Transfer** - Communications between the Greenphire platform and financial networks are executed via Web Service (API) or sFTP transport.

**Physical Protection** – Greenphire houses its internal database on servers that are located in a highly secure, off-site facility. Access to the physical servers at the facility is limited to Network Operations Center (NOC) Engineers and Technicians. The facility is secured with a bio-metric security system that can track access to the facility and is monitored by digital security video surveillance, includes multiple suppliers for network connectivity and redundant power supplies including on-site power generation in the event of emergency.

**Authorized Access** – Greenphire restricts access to sensitive data to only a limited number of essential internal personnel. Authorized individuals are only permitted to access data if it is required to service our client, their authorized users or the clinical trial participant. The number of authorized individuals remains limited to protect against internal threats to the security of sensitive data.

**Proactive Design** - Greenphire's internal technology platform has been intentionally designed to exclude the requirement of certain sensitive information that other similar companies require to be stored in their systems, such as PIN numbers. If new types of sensitive data must be introduced and stored, per the design of a specific protocol, Greenphire will protect the data using the encryption methods described previously.

**Customer Service** - Greenphire provides all of its cardholders with 24/7/365 customer service. Customer service is handled by both an automated IVR system and a call center where live customer service representatives may provide financial assistance to cardholders. Customer service functionality is intentionally kept separate from implementation and client support and, consequently, no information is shared with customer service representatives related to the protocol, sponsor, structure of the trial, medical indication or other potentially sensitive information.

**Quality Control Process** - Greenphire's Quality Control (QC) Department performs system testing in an isolated environment to test and ensure that the software is functioning properly. Each new piece of functionality is thoroughly tested individually. In addition, QC conducts integration and regression testing before new code is approved for movement into production. When a change to the system necessitates a change to the database, the required changes and process to make the changes are documented and tested prior to being performed on production. No code is pushed to production until it has passed QC testing. Data used in QC is test data and does not include data that is, or ever was, production data.

### *Safe Harbor*

Greenphire has voluntarily obligated itself to the jurisdiction of the U.S. Department of Commerce by selfcertifying to the Safe Harbor framework necessary to receive personal data from companies doing business in the European Union and Switzerland. Further information regarding the U.S. – EU and U.S. - Swiss Safe Harbor Frameworks is available at export.gov/safeharbor/index.asp

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