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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

# UNIVERSITY OF PENNSYLVANIA
# RESEARCH SUBJECT
# INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

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| **Protocol Title:** | *A Randomized, Double-blind Placebo-controlled Pharmacogenetic Study of Topiramate in European-American Heavy Drinkers* |
| **Protocol Number:** | *821035* |
| **Principal Investigator** | *Henry Kranzler, M.D.*<br>*Professor of Psychiatry*<br>*Center for Studies of Addiction*<br>*3535 Market St., Fifth Floor, Suite 500 Philadelphia. PA 19104*<br>*(215) 746-1943* |
| **Study Contact:** | *Study Coordinator*<br>*(215) 746-1902 or Press 0 for the Operator* |
| **Emergency Contact:** | *24 - Hour Emergency Pager #: 215-505-3799* |

## Why am I being asked to volunteer?

You are being invited to participate in a research study because you are a regular drinker and expressed an interest in trying to reduce or stop your drinking. Your participation is voluntary, which means that you can choose whether you want to participate. If you choose not to be in the study, you will not lose any benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do as a participant in this study. We will give you this consent form to read and a copy to keep for future reference. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form or about any other aspects of the study. If you decide to participate, you will be asked to sign this form.

## What is the purpose of this research study?

This is a research study involving 12 weeks of study medication, topiramate or a placebo (a harmless, inactive substance) and brief counseling to reduce or stop drinking. Topiramate is approved by the U.S. Food and Drug Administration to treat epilepsy, prevent migraine headaches and, combined with another medication (phentermine), for weight loss. Its use in the treatment of alcohol dependence is experimental. An earlier study by this research team showed that topiramate was more effective than placebo in people with a certain genotype (a person's unique DNA makeup) than in other people. This genotype is more common in people of European descent than in other groups. The purpose of this study is to evaluate the safety and effectiveness of

topiramate compared to placebo in reducing the number of drinking days among European-Americans who want to stop or reduce their drinking.

We will draw a blood sample from you to extract your DNA to determine your genotype. Because we will select people to participate based on their genotype, we may not be able to include you. Based on your genotype, we will evaluate you to determine whether you are otherwise eligible to participate in this study. We will also use your genotype (DNA) to test it with your response to the study medication. We will examine a number of genes thought to be involved in the effects of topiramate, including the one that we identified in our last study. Because the DNA analysis is a key part of the study, if you choose not to provide blood for a DNA sample, you will not be able to participate in the study.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

*MRI Sub-study*: You may also have the opportunity to enroll in a separate sub-study that uses magnetic resonance imaging (MRI) to compare the effects of topiramate with placebo on your brain's response to certain visual reminders of alcohol use. If you are eligible to enroll in the MRI sub-study, we will contact you to provide you with more detailed information about it. You will then be given a separate consent form to review and sign prior to participating in that study. You are not required to participate in the MRI sub-study in order to participate in this research study.

## How long will I be in the study? How many other people will be in this study?

The total duration of your involvement in this study is approximately 9 months. There is a 12-week period during which you will receive topiramate or placebo and brief counseling and a 6-day period at the end to taper and discontinue the study medication. There will also be 2 follow-up visits at 3 and 6 months after completion of the study medication. The entire study will last for 5 years and will include up to 200 people, up to 100 of whom will be recruited from the Corporal Michael J. Crescenz Philadelphia VA Medical Center (CMCVAMC).

## What am I being asked to do?

Before you enter the study, your eligibility to participate will be determined at a screening evaluation. You will be asked not to drink before this and all other visits. At all visits, the study nurse will check your breath alcohol level using a Breathalyzer. If your breath alcohol level is greater than 0.02%, you may not be able to complete the visit.

1. **Screening Visit**: The screening visit will determine whether the study is a good fit for you. The entire visit should take about three hours.
    - First, we will ask you to show us a legal photo ID and then undergo a breathalyzer test to ensure that you are able to make a well-reasoned decision about whether or not to participate in the study. You must have a 0.00 breath alcohol level to complete this visit. Your reading ability will also be evaluated, so that we know that you can understand the consent form and study assessment questionnaires.
    - Once you have read this informed consent form and all of your questions have been answered, you will be asked to sign this form. An entire copy of the informed consent form will be given to you. You will be reminded that your participation is voluntary, and at any time, you may withdraw from the study. Signing the consent form does not automatically enroll you in the study since the screening process might show the study is not a good match for you.

- The study staff will ask you to provide information on your medical history and family history of alcoholism. We will not ask you for your family members' names or any other identifying information.
- The study nurse will ask you questions about your medical history and perform a physical examination. Study staff trained in drawing blood will draw a total of approximately 3 tablespoons of blood for standard laboratory tests and to test your DNA. Your DNA will be studied to identify specific genetic markers that might influence risk of alcohol dependence (and related behaviors and disorders) and response to the study drug. It is possible that your bloodwork will need to be repeated due to unforeseen events (abnormal findings or potential lab errors). Study staff will also ask you to provide a urine sample to conduct a urinalysis, drug screen, and for women of childbearing potential (i.e., who have not had a hysterectomy, bilateral removal of the ovaries, or a tubal ligation or is less than two years postmenopausal), a urine pregnancy test. If you are pregnant, breast-feeding, or if you test positive for certain illegal drugs, you will not be eligible for the study.
- If you are eligible and decide to participate in the study you will be required to provide the names and contact information of one or two people (trusted friends or family members) who may serve as additional contacts if we cannot locate you for safety or other study-related reasons. We will only tell them that you are in a study and that you gave us their names to help us contact you, if we are unable to reach you during the study.
- Study staff will then ask you to complete 6 assessments about your psychological health, alcohol and drug use history. You will also be asked to perform 2 tasks that will test your working memory.

2. **First Study Drug Visit (Week 1):** We will contact you within 5 days after your screening visit to tell you whether you are eligible to participate in the study and to set up your next study visit.
   - This visit will take approximately one and one-half hours to complete and will occur no longer than 30 days after the screening visit.
   - You will be asked to complete a breathalyzer test and study staff will measure your weight and vital signs (blood pressure and heart rate).
   - If you are a woman of childbearing potential, study staff will obtain a urine sample from you for a pregnancy test.
   - You will be asked to complete 11 assessments about your psychological health and your alcohol and drug use history.
   - We will instruct you how to use the interactive voice response (IVR) system: Once you have started taking the study medication you will be asked to call a toll-free phone number each day, between 5:00 and 8:00 p.m. to connect you to an IVR system. The system uses your study ID and a password, which we will give you. You can access the system from a touch-tone phone. The IVR system will prompt you to answer questions about your feelings, whether you used medication, and your use of alcohol each day and the preceding day. Once you become familiar with the system, the time required for completion of this interview is less than 5 minutes per day. If you do not call the IVR system by 8:15 p.m., you will receive a reminder call from the system at a phone number that you provide; the reminder prompt will not relay any details of the study or its purpose. You will then have until 9:00 p.m. to call the number for that day.
   - You will have your first brief counseling session, which will last about 30 minutes. The study nurse will discuss with you your goal with respect to your drinking and encourage you to take your medication regularly. The nurse will also encourage you to consider ways to reduce or stop your drinking, depending upon whether your goal is to drink less or become completely abstinent.

- With your permission, we will make an audiotape of this and all other counseling sessions that you receive during the study. These tapes will be destroyed after they have been reviewed to ensure that the study nurse has followed correct counseling procedures.
- You will be assigned to receive study medication, which will be either topiramate or placebo (a harmless, inactive substance) and will receive your first week's supply of study medication. The decision on which medication you will receive is random, like a flip of a coin. The topiramate or placebo will look the same. Neither you nor any of the study personnel will know which medication you will receive. In an emergency, though, the pharmacist in charge of the study medication can be contacted.

  The study nurse will provide you with detailed dosing instructions and will adjust your study medication dose as necessary during the 12-week period. Study medication will be provided in capsules and will be packaged in child-resistant bottles. It is important that you follow your study nurse's instructions on when and how to take the study medication. At each visit, study staff will ask you about any side effects or other adverse events that you may have experienced.

3. **Weekly Visits (Weeks 2-6)**: At each weekly visit:
   - Your breath alcohol concentration (Breathalyzer), weight, and vital signs will be checked and you will be asked about any side effects or other adverse events that you may have experienced.
   - The study staff will ask you to complete 6 assessments about your psychological health and your alcohol and drug use history. These should take about 20 minutes to answer.
   - You will receive brief counseling from the study nurse, which will last about 15 minutes.
   - The study nurse will collect your study medication bottles with any remaining capsules and dispense another week's supply of study medication. In the event that study medication is not ready to be given to you at the time of the study visit (because for example, the nurse and/or physician determine at the time of the study visit that you require a reduced dosage), study staff will mail you the study medication via UPS or FedEx to prevent you running out of study medication. You will be asked to sign for the delivery and the study nurse will call you to ensure that you received the study medication, to provide you with instructions on how to take the study medication, and to ask you about any side effects you may have experienced.
   - You will continue to call the IVR toll-free number nightly.
   - **At week 5**, if you are a woman of childbearing potential, you will have another urine pregnancy test. If the test is positive, showing that you are pregnant, we will discontinue the medication and you will be referred to an obstetrician for care.
   - Every week, for the first 6 weeks, the dose of the medication will be gradually increased.
4. **Week 6 Visit**: At this visit:
   - Your breath alcohol concentration (Breathalyzer), weight, and vital signs will be checked and you will be asked about any side effects or other adverse events that you may have experienced.
   - The study staff will ask you to complete 6 assessments about your psychological health and your alcohol and drug use history. These should take about 20 minutes to answer.
   - Study staff will draw 1 tablespoonful of blood for lab tests.
   - If you are a woman of childbearing potential, you will have another urine pregnancy test. If the test is positive, you will be referred to an obstetrician and you will not be allowed to continue in the study.
   - You will receive brief counseling from the study nurse, which will last about 15 minutes.
   - The nurse will collect your study medication bottles with any remaining capsules and dispense another week's supply of study medication

- In the event that study medication is not ready to be given to you at the time of the study visit (because for example, the nurse and/or physician determine at the time of the study visit that you require a reduced dosage), study staff will mail you the study medication via UPS or FedEx to prevent you running out of study medication. You will be asked to sign for the delivery and the study nurse will call you to ensure that you received the study medication, to provide you with instructions on how to take the study medication, and to ask you about any side effects that you may have experienced.
- You will continue to call the IVR toll-free number nightly.

**5. Biweekly Visits (Weeks 8 and 10)**: At each biweekly (every other week) visit:

- Your breath alcohol concentration (Breathalyzer), weight, and vital signs will be checked and you will be asked about any side effects or other adverse events that you may have experienced.
- The study staff will ask you to complete 6 assessments about your psychological health and your alcohol and drug use history. These should take about 20 minutes to answer.
- You will receive brief counseling from the study nurse, which will last about 15 minutes.
- The nurse will collect your study medication bottles with any remaining capsules and dispense another week's supply of study medication.
- In the event that study medication is not ready to be given to you at the time of the study visit (because for example, the nurse and/or physician determine at the time of the study visit that you require a reduced dosage), study staff will mail you the study medication via UPS or FedEx to prevent you running out of study medication. You will be asked to sign for the delivery and the study nurse will call you to ensure that you received the study medication, to provide you with instructions on how to take the study medication, and to ask you about any side effects that you may have experienced.
- **At week 8**, if you are a woman of childbearing potential, you will have another urine pregnancy test.
- You will continue to call the IVR toll-free number nightly.

**6. Week 12 Visit and Taper**:

- Your breath alcohol concentration (Breathalyzer), weight, and vital signs will be checked and you will be asked about any side effects or other adverse events that you may have experienced.
- The study staff will ask you to complete 6 assessments about your psychological health and your alcohol and drug use history. These should take about 20 minutes to complete.
- You will receive brief counseling from the study nurse, which will last about 15 minutes.
- If you are a woman of childbearing potential, you will have another urine pregnancy test.
- The study nurse will collect your study medication bottles with any remaining capsules and dispense the final supply of medication.
- In the event that study medication is not ready to be given to you at the time of the study visit (because for example, the nurse and/or physician determine at the time of the study visit that you require a reduced dosage), study staff will mail you the study medication via UPS or FedEx to prevent you running out of study medication. You will be asked to sign for the delivery and the study nurse will call you to ensure that you received the study medication, to provide you with instructions on how to take the study medication, and to ask you about any side effects that you may have experienced.
- At this visit, you will be instructed on how to safely taper the medication dose over 6 days.
- You will continue to call the IVR toll-free number nightly to complete 12 weeks of phone calls.

**7. Endpoint Visit (Week 13):**

- Your breath alcohol concentration (Breathalyzer), weight, and vital signs will be checked and you will be asked about any side effects or other adverse events that you may have experienced.
- The study staff will ask you to complete 11 assessments about your psychological health and your alcohol and drug use history. These should take about 45 minutes to complete. You will also be asked to perform 2 tasks that will test your working memory.
- Study staff will draw 1 tablespoonful of blood for lab tests.
- You will receive brief counseling from the study nurse, which will last about 15 minutes.
- The nurse will collect your study medication bottles with any remaining capsules.

**8. Follow-up Visits (Months 3 and 6)**: At the two follow-up visits (one hour each):

- The study staff will check your breath alcohol concentration (Breathalyzer), weight and vital signs.
- Study staff will draw 1 tablespoonful of blood for lab tests.
- Study staff will ask you to complete 9 assessments about your psychological health and your alcohol and drug use history. You will also be asked to perform 2 tasks that will test your working memory.
- Once you have completed this study visit you will have the option of receiving a letter from the UPenn Investigational Pharmacy to tell you whether you received topiramate or placebo.

### Early Termination Visit

- If you choose to withdraw from the study early, we will ask you to return to the research center for a visit to allow these procedures to be done and the study nurse to instruct you on how to decrease and stop taking the study medication.

## What are the possible risks or discomforts?

### Risks and Side Effects Associated with Topiramate

The most common adverse effect of topiramate compared to placebo is numbness and tingling (49%of patients). The other most commonly reported side effects (experienced by 10-31% of patients) include: change in sense of taste, tiredness/sleepiness, fatigue, dizziness, loss of appetite, nausea, diarrhea, weight decrease, difficulty concentrating and difficulty with memory.

Other side effects (experienced by 5-9% of participants) in some clinical trials include: nervousness, slow thinking, abnormal vision, confusion, decreased sensitivity, anxiety, abdominal pain, dry mouth, involuntary muscle contractions, and language problems.

Depression and mood problems have also been reported (by 5-9% of participants). Some participants (about 1%) have had suicidal thoughts or actions. If you feel a change in your mood or if you feel depressed, or that you may harm yourself, please contact study staff, or if that is not possible, seek emergency care.

Other side effects that are less likely to occur with topiramate treatment but that are potentially serious include kidney stones (experienced by about 1% of participants). Drinking an adequate amount of fluids is recommended while taking topiramate. This may reduce the risk of kidney stones.

Psychosis was reported in trials with seizure disorder patients (less than 1%) but was likely related to the underlying epilepsy, since it was not identified as being related to topiramate treatment in trials for other disorders (including trials of alcohol dependence and studies of topiramate for treatment of migraine headache).

*Metabolic acidosis* (a severe increase in the level of acidity in the blood) may be associated with topiramate treatment. This effect was experienced by about 3 to 7% of participants in other studies of topiramate. Metabolic acidosis can cause symptoms such as tiredness and loss of appetite, or more serious conditions including irregular heartbeat (arrhythmia) or coma. **IF YOU EXPERIENCE ANY SIGNS OR SYMPTOMS LIKE THIS THAT CONCERN YOU, CALL A DOCTOR IMMEDIATELY.** Long-term metabolic acidosis can result in thinning of the bones (osteoporosis) with an increased risk for fractures. Metabolic acidosis may increase the risk for kidney stones.

Participants on carbonic anhydrase inhibitor medications, commonly used to treat glaucoma, should not participate in this study, due to the increased chance of metabolic acidosis from combining these medications with topiramate. These medications include Diamox (acetazolamide), Neptazane (methazolamide), or Trusopt (dorzolamide).

Treatment with topiramate may rarely (in less than 1% of cases) cause decreased sweating, which has primarily been reported in children treated with topiramate. Activities such as exercise or exposure to warm temperatures while using topiramate may increase the risk of heat-related side effects, such as heat stroke. We recommend that you drink plenty of fluids while participating in this study.

Patients with a history of narrow angle glaucoma should not participate in this study. A medical condition consisting of sudden worsening of vision and an elevation of fluid pressure in the eyes (acute secondary glaucoma) has been described in a few cases (less than 1%) of patients taking topiramate, usually occurring in the beginning of treatment. If you have sudden, significant worsening of vision, blurred vision, or eye pain you should contact study staff immediately, or if that is not possible, you should seek emergency care.

Rare and isolated cases of hepatitis/liver failure (experienced by less than 1% of patients) and blistering skin rashes (experienced by about 1% of patients) have been reported with topiramate. Signs and symptoms of hepatitis include: dark urine and pale or clay colored stools, loss of appetite, fatigue, stomach pain, general itching, yellowing of the skin or whites of the eyes, nausea and vomiting, fever, weight loss, and breast development in males. If you experience any of these symptoms, you should contact study staff immediately, or if that is not possible, you should seek emergency care.

Overdoses of topiramate have been associated with convulsions, drowsiness, speech disturbance, blurred vision, double vision, impaired mental activity, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. Deaths have been reported in overdoses.

Topiramate may cause a change (increase or decrease) in the effect of some other medications. If you are taking other medications during your participation in this study, your doctor will explain whether topiramate may have an effect and if necessary, may adjust your study drug dose.

There may be risks to topiramate that are not now known. You will be notified of any new significant findings that might affect your willingness to continue in the study.

Due to the possibility of dizziness or drowsiness, you must be cautious when operating a vehicle or heavy equipment while in this study, until you have experience using topiramate.

### *What Safeguards Should I Take?*

You should drink a minimum of three, 8 oz. glasses of water daily. We will ask about any side effects or other adverse events that you may experience. If you experience any side effects, please contact our study staff immediately. You can call our 24-hour pager at (215) 505-3799 during non-office hours or Dr. Henry Kranzler at (215) 746-1943.

Topiramate or placebo capsules will be given to you only during the study drug portion trial and not during the 3- and 6- month follow-up periods.

### What Other Types of Risk Are Involved If I Choose To Participate?

The study assessments will address potentially sensitive matters, including your drinking, drug use, psychiatric symptoms, and possible health, legal, family, and other problems. The counseling you receive will not differ much from standard medical counseling for drinking problems, and should pose no particular risk to you. However, it is possible that the counseling, even when accompanied by topiramate, may not adequately help you to reduce your drinking to non-hazardous levels.

There is a chance that people outside of the research team may learn of your study participation. If this happens, you may be unable to obtain health, disability or life insurance. This may also result in other types of financial or emotional problems. For example, you might be refused employment or you might lose your current job.

## Risks Associated with Blood Draws

There will most likely be some mild discomfort from the blood draw. Some people develop a bruise at the needle site; some people report dizziness after the blood is drawn; and, some people develop minor infections. Other risks of blood drawing include possibly fainting.

### *Safeguards To Be Taken*

Only study staff trained to perform venipuncture will perform the blood draws. The area where the needle is to be inserted will be wiped with a disinfectant before the needle is inserted. Only sterile needles will be used. The puncture site will be covered with a bandage. You will be seated at the time blood is drawn and will be permitted to lie down if you feel faint.

## Risks for Women of Childbearing Potential:

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). Therefore, participation in this study could possibly have an adverse effect on a developing fetus. You must inform the study physician/study nurse if you are pregnant/possibly pregnant. As part of the screening process and before you take the first dose of study drug, a urine pregnancy test will be done if you are able to become pregnant or are less than two years post-menopausal. You will also have urine pregnancy tests at visits 1 (week 1), 5 (week 5), 7 (week 8), and 9 (week 11). If you have had a hysterectomy, then a pregnancy test will not be required. While you are participating in this study, you must continue to use an effective method of birth control.

Acceptable methods of birth control 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.

It is possible that some hormonal contraceptives (e.g., birth control pills, implants or injections) may be made less effective by topiramate. If you are using a hormonal contraceptive, your study doctor will discuss with you non-hormonal methods of birth control to be used during your participation in the study.

If you are using hormonal contraceptives, you should report to the study nurse any change in your bleeding patterns.

If you become pregnant during this study, you must tell the investigator and consult an obstetrician or maternal-fetal specialist. You will be discontinued from the study and the study medication will be stopped immediately.

### *Confidentiality*

Every attempt will be made by the investigators to maintain all information collected in this study strictly confidential. However, authorized representatives of the University of Pennsylvania will have access to and may copy, both your medical records and records from your participation in this study. This access is necessary to insure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this research, you will not be identified by name. The data are kept in secure, locked areas and access to these areas is possible only through the investigator or research technician.

If we learn that you or someone else is in serious danger of harm (such as in cases of child or elder abuse) we may make disclosures to protect you and/or the other persons.

### Risks related to Genetic (DNA) Testing:

The principal risk of genetic testing is breach of confidentiality, with sensitive information concerning your genetic risk for disease becoming known. Such information, if available to you, could cause distress and if available to health or life insurers could adversely affect your access to insurance or its benefits.

Differences in some genes are known to be directly related to risk for certain illnesses, and other genes that we may study using your DNA may be shown at some point in the future to be related to illness. Certain genetic research may reveal that you are at risk for certain diseases or that you are a carrier of a genetic disorder. This could mean that you or members of your extended family may have an increased likelihood of developing the disorder, or may be carriers.

Some states have laws that help to protect against genetic discrimination. A recent federal law (Genetic Information Non-Discrimination Act, GINA) helps reduce the risk from health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. If you want to learn more about the GINA Law, you can find information about it on the Internet or ask the study staff. Study staff will provide you with a GINA handout for your information.

Variation in some genes is known to be directly related to risk for certain illnesses, and other genes we may study in your DNA may be shown at some point in the future to be related to illness. Certain genetic research may reveal that you are at risk for certain diseases or that you are a carrier of a genetic disorder. This could mean that you or members of your extended family may have an increased likelihood of developing the disorder, or may be carriers.

### *Risks associated with providing personal information*

You will have to take the time to come to the clinic for regular visits each week. Some of the questions about your personal and sexual habits, lifestyle, and drug and alcohol use may make you feel uncomfortable.

### *Safety*

The study drug must be kept out of the reach of children**.** Please do not share your study drug with others as the study drug (or dose level) you are receiving in the research study may have unpredicted negative side effects in other individuals. You have been screened for safely taking the research study drug, but others have not undergone this screening.

***Who can I contact in case of an emergency?*** If at any time you have a question regarding your participation in this study, you may call Dr Kranzler at **(215) 746-1943**. You may also call the ***24-hour research emergency line at HUP (215)-349-5412.*** If assistance is not available by either of these methods, you are instructed to go to the emergency room of the Hospital of the University of Pennsylvania. You will receive a copy of this consent form containing these instructions for managing any complications, which may occur after leaving the hospital.

## What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

## What are the possible benefits of the study?

You are not expected to get any benefit from being in this research study. You may benefit from the screenings and medical examinations and medical management counseling provided during the study. You may have a good response to the study medication and successfully reduce drinking. However, it is possible that you will receive no direct health benefit from being in this study. Other people who have alcohol problems may benefit from the information learned from the study in the future. We might find a better way to treat them. Societal benefits may include a better understanding within the medical community of how best to treat heavy drinking. However, there is also the possibility that no benefit will come from this study.

You will not directly benefit from the genetic testing. Potential societal benefits may include a greater understanding of the genetic basis of alcohol use disorders and related psychiatric conditions, and potentially an understanding of the genetic moderators of the response to treatment with topiramate.

## What other choices do I have if I do not participate?

Your participation in this trial is entirely voluntary and you may choose not to participate. If you choose not to participate in the study, alternative options are available to you .Topiramate (study medication) is being prescribed off-label to treat alcohol dependence in this study. As an alternative to study participation, you may obtain treatment with other medications (including three that are approved for the treatment of alcohol dependence: acamprosate, disulfiram and naltrexone), and standard counseling, including individual and group therapy. You could also request that your medical provider prescribe topiramate “off-label” to treat your alcohol problem.

## Will I be paid for being in this study?

You will be paid for completion of different parts of the study. Payments will be made to you with a GreenPhire ClinCard. A Greenphire ClinCard is a reloadable prepaid card that may be used for in-store purchases (by selecting either the "credit" or “debit" option), online purchases, ATMs to get cash, and cash advances at a bank (though there are fees associated with ATM withdrawals or bank cash advances). The study doctor or other study staff member will tell you more about when you will get paid and provide you with an information sheet about how to use the Greenphire ClinCard. Funds added to the card should be available immediately, however in some cases it may take up to 1 business day. If you lose the card, please contact our study staff immediately. The study coordinator and cancel the original card and reissue a new card to you.

The total amount will be between **$4 and $374,** depending on the parts of the study that you complete:

- $1.00 for each IVR phone call OR a total of $10 for completing all 7 calls in each week for a maximum payment of $120 for all calls during the 12-week study drug period
- $3 for returning study medication bottles at each visit
- $4 to cover the cost of mass transit for roundtrip travel to each visit
- $25 for completing Visit 6
- $50 for completing the Endpoint Visit
- $50 for completing each of the two Follow-up Visits

**Study Payment Schedule**

| 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 |

Payments will be deferred if you fail a breathalyzer test, so please avoid drinking before coming in for a visit. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

## What information about me may be collected, used, or shared with others?

- Name
- Address
- Telephone number
- Email address
- Date of Birth
- Social Security Number
- You will be asked to show your driver's license or another form of photo identification at the screening visit for study staff to confirm your identity. Study staff will not copy your identification or record any specific information from the license or other identification.
- Allergies
- Current and past medications or therapies
- Medical Record Number
- Full face photographic images and any comparable images
- Audio-recordings, if you agree to have your counseling sessions taped. These will be destroyed as soon as they are checked to ensure that the session is completed properly.
- Information from a psychiatric examination, which includes a series of interviews and questionnaires that obtain information on your substance abuse, family/social, legal, and psychiatric histories
- Information from a physical examination that includes routine labs (urine and blood work), blood pressure reading, heart rate, breathing rate and temperature, electrocardiogram

## Why is my information being used?

- Your information will be used by the research team to contact you during the study. Your information and results of tests and procedures are used to:
- do the research

- oversee the research
- to see if the research was done right.

## Who may use and share information about me?

- The following individuals may use or share your information for this research study:
- The Principal Investigator and the Investigator's study team (other University staff associated with the study)
- The University of Pennsylvania Institutional Review Boards (the committees charged with overseeing research on human subjects) and University of Pennsylvania Office of Regulatory Affairs
- The University of Pennsylvania Office of Human Research (the office which monitors research studies)
- Authorized members of the University of Pennsylvania and the University of Pennsylvania Health System and School of Medicine workforce who may need to access your information in the performance of their duties (for example: to provide treatment, to ensure integrity of the research, accounting or billing matters, etc.).
- The Principal Investigator and study team at the Corporal Michael J. Crescenz Philadelphia VA Medical Center (CMCVAMC) (the coded study data from both sites will be merged and a copy will be stored at the CMCVAMC).
- The Corporal Michael J. Crescenz Philadelphia VA Medical Center Institutional Boards (the committees charged with overseeing research on human subjects there).
- Greenphire ClinCard for processing study payments.

## Oversight organizations

- The Food and Drug Administration
- The Office of Human Research Protections
- The study data and safety monitoring board

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations. In all disclosures outside of the University of Pennsylvania Health System and School of Medicine, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

## How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of the information we collect about you for this specific study does not expire. Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

## Can I change my mind about giving permission for use of my information?

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study. We will de-identify all of your study information and retain your information for study reporting purposes.

**What if I decide not to give permission to use and give out my health information?**
You will not be able to be in this research study.

## Will I have to pay for anything?

There is no charge for participating in this research study. You may have to take time away from work to come to the appointments. You may be responsible for some of your travel expenses to attend study visits. Study medication (topiramate or placebo), laboratory testing, and all clinic visits will be provided to you free of charge for the duration of your participation in the study.

## What happens if I am injured from being in the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed above in this form.

## When is the Study over? Can I leave the Study before it ends?

You are free to stop taking part in this study at any time. If you choose to stop before the end of the study, the principal investigator may ask you to continue to take the study medication for a little while on a reduced schedule. A reduced schedule will lessen your symptoms of withdrawal from the study medication. Symptoms of withdrawal may include headaches, mood swings and/or nausea.

If you decide to withdraw your participation, we ask that you let us know by calling the study Staff at (215) 746-1987. We will ask that you return to the clinic to complete all final study procedures. We will also call you at the planned end of the study to collect some final information.

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by the principal investigator or the Food and Drug Administration without your consent because: 1) the principal investigator believes that your medical care could be improved with another therapy, 2) you become pregnant, 3) you experience a significant illness or unacceptable side effects from the study drug, or 4) you fail to follow the study schedule (i.e., do not come to the clinic when scheduled, or do not take your study medication). The study principal investigator or the Food and Drug Administration may also decide to stop the study. There may also be other reasons that are not specified here. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for the decision.

If your participation in the study is stopped for any reason, you may be asked to come back to the clinic to be interviewed and to have final tests of your blood. At that time you will be asked to return all unused medication or empty medication bottles. You will no longer receive free study medication.

If you decide to participate in the study, you are free to leave the study at any time. Withdrawal will not interfere with your future care.

## Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal

information may be given out under certain circumstances described below. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the Food and Drug Administration, they may review your research records.

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).

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).

## The following procedures will be used to protect the confidentiality of your data:

The study staff (principal investigator, research coordinator, co-investigators, etc.) will keep all study records (including any codes to your data) locked in a secure location. Research records will be labeled with a code. The code will be derived from a 3-digit number identifying the study, followed by a 3-digit number that is a sequential indicator of the number of patients that have been enrolled in the study. A master key that links names and codes will be maintained in a separate and secure location. All electronic files (e.g., database, spreadsheet, etc.) containing identifiable information will be password protected. Any computer hosting such files will also have password protection to prevent access by unauthorized users. Data that will be shared with others will be coded as described above to help protect your identity. Any lab results will be stored in your research record only.

All information related to your participation in this study will be kept in a research record, apart from your medical record. The research record will be labeled with a code and kept locked in a file cabinet in one of the study offices. Only researchers officially appointed to work on this project and agencies or departments with responsibility for research compliance will have access to your information while it is stored in an identifiable format.

We intend to run tests on your DNA sample in order to examine the genetic moderators of response to treatment with topiramate. Once the sample is taken it will become the property of the University of Pennsylvania. It will be stored in the laboratory of Dr. Kranzler or a study co-investigator. During the study, the sample will be stored under a code that only the principal investigator can link to your name.

Upon completion of the study, the DNA blood sample will be kept in storage for up to 20 years to permit complete analysis of the sample. However, the sample will forever be separated from your identity. There will be no way, not even through codes, to link the sample back to you. These “de-identified” samples may be shared with other researchers and used in other projects.

If you choose to withdraw from the study after your DNA sample has been obtained, we will destroy all records in our research files connecting your identity with your sample(s). In this way, the samples could only be studied anonymously from this point forward. We will not destroy the de-identified sample.

You will not be told during the study whether you are taking topiramate or placebo. However, when you complete the 6-month follow-up visit for the study, you will be eligible to receive that information. If you choose (after completing the 6-month follow-up), the research pharmacy will mail you a letter telling you which medication you were taking (topiramate or inactive placebo). Study staff (study physicians, nurses, and research assistants) will remain blinded.

You will not be told the results of the genetic testing. If you would like a copy of the overall results of the study once it is completed, you may request from the principal investigator a copy of the article that the researchers write describing the study.

In addition to the research we intend to do, it is possible that unexpected and/or unrelated information will be discovered that is not the focus of this study. This information will not be disclosed to you.

## *Electronic Medical Records and Research Results*

### What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record. This study does not use an EMR and will not enroll you into the University of Pennsylvania Health System.

In the event of your needing medical care within the University of Pennsylvania Health System either as a result of participating in this study or at the recommendation of the study team, the fact that you are a research study participant may be identified in an Electronic Medical Record created and maintained by UPHS.

Once placed in your EMR, the fact that you have participated in research (with the only details of your participation being those needed to care for you medically) will be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc)."

## Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

Agreeing to be audio taped is not a requirement to participate in the study. Please initial your decision:

Yes, you agree that we can tape record your counseling sessions: _____

No, you do not agree that we can tape record your counseling sessions: _____

Agreeing to receive a debriefing letter for the UPenn investigational pharmacy is not a requirement to participate in the study. Please initial your decision:

Yes, you wish to receive the de-briefing letter from the UPenn Pharmacy: _____

No, you do not wish to receive the de-briefing letter from the UPenn Pharmacy: _____

| _____ | _____ | _____ |
|---|---|---|
| Name of Subject (Please Print) | Signature of Subject | Date |
| _____ | _____ | _____ |
| Name of Person Obtaining Consent (Please Print) | Signature | Date |