University of Pittsburgh

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

Study Title: Limbic pallidum DBS for the treatment of severe alcohol use disorder

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You can contact the study investigator if you have any questions about the study, concerns, or complaints.

ABBREVIATIONS AND ACRONYMS

AUD	Alcohol Use Disorder
CT	Computed Tomography
CMS	Center for Medicare and Medicaid services
DBS	Deep Brain Stimulation
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
UPMC	University of Pittsburgh Medical Center

1. Research Consent Summary – Key Information

a. You are being asked to take part in a research study. This study includes only people who choose to take part. The study team members will explain the study to you and will answer any questions you might have. You should take your time to read through this consent form and to make your decision, paying special attention to the time commitment and risks involved.

b. The purpose of this study is to determine if the use of deep brain stimulation (referred to as DBS throughout the rest of this form) can improve symptoms of alcohol use disorder. To do this, we will need to place a very small needle called an electrode in a specific part of the brain, called the limbic pallidum, which we believe contributes to your symptoms. This area is deep within the brain.

c. If you decide to join the study, you can change your mind later, at any time.

d. If you enroll, you will be in this study for about 13 months. There will be 28 visits, with the last visit taking place 12 months after brain stimulation has been started.

e. We will ask you to undergo several tests as part of baseline and follow-up evaluations, including:

- urine and blood tests,

- brain imaging,
- behavioral tasks,
- questionnaires, and
- clinical evaluations.

The deep brain stimulation uses a surgical procedure to implant the electrode and the stimulator that controls the stimulation electrode in your brain.

f. Risks and side effects related to DBS and surgery include those which are:
- Likely: e.g., pain or discomfort related to surgery or brain stimulation
- Less Likely: e.g., new or exacerbation of neurological symptoms, such as changes in vision, coordination, sensation, muscle contraction (twitching), and changes in feelings, thinking, and behavior.
- Rare but serious: e.g., stroke (blood clot in the brain), paralysis (or lack of movement in the arms and/or legs), infection, hardware complications, heart attack, allergic reaction, and death.
- Unknown but serious: e.g., bleeding; patients with severe alcohol use disorder and/or liver disease may be more prone to fatal intracranial bleeding than other individuals who previously participated in DBS studies.

g. The study may reduce your alcohol use but this benefit is not guaranteed to you from being in this study.

2. Introduction: why is this research being done?

This study is being done to better understand whether DBS of the limbic pallidum can prevent use of alcohol after one decided to stop drinking, known as relapse, and address the symptoms of alcohol use disorder (known as alcoholism) that have not responded to currently available treatments. There is some research from people who have strokes in this brain area that suggest it may contribute to alcohol craving in individuals with alcohol use disorder (AUD). Research in humans is limited and has not yet provided any conclusions about the role of DBS in the treatment of patients with alcohol use disorder. However, there is strong research from animal studies connecting the limbic pallidum to alcohol-seeking (relapse) behavior.

DBS is currently approved by the Food and Drug Administration (FDA) for treatment of Parkinson's disease, essential tremor, and epilepsy. The FDA has not approved DBS for use in people with AUD. The device manufacturer (Medtronic) has not conducted testing for the device in AUD. Therefore, the use of DBS in this study is investigational and we do not know if you will benefit.

The DBS system being used in this study is manufactured by Medtronic, and includes an electrode, the SenSight DBS Directional Leads, and a stimulator, the Percept PC Neurostimulator.

You are being asked to participate in this study because you are between the ages of 21 and 75 years, and have been diagnosed with severe alcohol use disorder and advanced liver disease. This is a phase 1 study which means the researchers are trying to find out if this therapy is safe and whether it is feasible.

How many people will be in this study?

A total of three people will be implanted with DBS in this study.

Population studied

Male and female subjects between 21 and 75 years old who have severe alcohol use disorder and liver disease.

Why DBS?
DBS allows targeting areas deep in the brain to modify their activity, which is not otherwise possible with other non-invasive tools like transcranial magnetic stimulation.

Summary of inclusion and exclusion criteria
Inclusion criteria are the specific characteristics of the subjects that will be enrolled in the study; these include being between 21 and 75 years old, having history of heavy alcohol use and wanting treatment for it, have tried available treatments and failed, having liver disease (this can be without any symptoms and not previously detected), be willing to follow the study protocol, having social support (family, friends), and if you are a female of reproductive age, be willing to use contraception.

Exclusion criteria are the specific criteria that disqualify someone from participating in the study. These include not speaking English, being on blood thinners, having a major medical or neurologic condition, being pregnant, being suicidal, have metal in your body, having major psychiatric illness other than alcohol use, having severe liver disease (with clinical symptoms from the liver disease), and having a history of liver transplant.

3. Research Activities

If you decide to sign this consent form and agree to participate in this study, you will be scheduled next to complete a screening and eligibility assessment visit, where we will determine if you fulfill all the criteria for enrollment in the study. If all the inclusion criteria are fulfilled and you don't meet any of the exclusion criteria, we will schedule you for a baseline evaluation visit in order to collect comprehensive preliminary measurements. We will ask you to undergo detox and abstain from alcohol for at least 7 days prior to the DBS surgery to minimize complication risks during the surgery.

You will then be scheduled for two surgical visits: the first to place the electrodes, the second to place the stimulator. You will be seen in follow-up visits to ensure you are doing well and to optimize the stimulation settings. In the 12 months following the start of stimulation, you will make monthly visits to submit blood and urine tests and complete assessments, with the 6-month and 12-month visits consisting of more comprehensive evaluations, resembling the baseline evaluation.

Because some of the study activities include exposure to radiation (described in detail later) which can be harmful to a developing fetus, we require female participants of childbearing potential who are, or might be, heterosexually active to use a medically acceptable, highly effective contraceptive method (≤ 1% pregnancy rate if used under perfect conditions*), in the opinion of the investigator (examples include: tubal ligation, vasectomized partner, IUD or IUS (intrauterine device or system), and long-acting reversible contraceptives (LARC)).

<u>Prescreening</u>

Insight questionnaire

We will ask you questions as part of pre-screening to determine your awareness of your alcohol use disorder and how it is affecting you.

Screening and Baseline evaluation

The screening and baseline visits will occur over approximately a 4-24 day period. Depending on the resource and personnel availability, some procedures or assessment may occur on a different day than described below.

Screening visit – Day 1

If you consent to the study, we will proceed with your screening visit, where we will assess whether you fulfill the eligibility criteria to be enrolled in this study. You will be asked to give a breathalyzer test (this will be asked of you on most study days). You will provide blood samples and undergo imaging and clinical evaluations. The imaging will include magnetic resonance imaging (MRI) of your brain, with contrast, and a liver ultrasound to assess for the degree of liver disease. Clinical evaluations will consist of medical, neurologic, and psychiatric components. The medical evaluation will include an electrocardiogram, which will help us assess whether you will be a good candidate for the surgical procedures in this study.

MRI:

The MRI exam will take approximately 30-60 minutes. The MRI exam of the brain is being done to ensure that, in the medical opinion of the PI, there is no evidence of a lesion in the brain (e.g., tumor, cyst, infection) that may increase your risks of study participation, prevent you from completing the requirements of the study according to the study protocol, or is likely to impact the integrity of the data or the validity of the study results. Prior to your exam, you will be asked to complete a standard questionnaire. The purpose of this questionnaire is to ensure that you can safely enter the MRI area. If you have a history of metal in your head or eyes, you cannot take part in this study.

To start your MRI test, you will lie on a padded table. The table on which you are lying will be moved to the center of an MRI magnet, which looks like a long narrow tube. Even though the tube is open, some people feel confined in small places. If this bothers you, please notify the MRI staff. We can give you a medication to help with the anxious feeling. You may end your participation in this study at any time by telling the MRI staff. When MRI pictures are taken, radio-signals and magnetic fields are used. When this happens, it is normal for the MRI machine to make loud, banging, and clicking noises. You will be asked to wear earplugs or headphones for your comfort during the exam.

During the exam, the MRI staff will be monitoring you from a separate room and they can see and hear you from the scanner. You will be able to communicate with the MRI staff via intercom. The MRI staff will be talking to you throughout your MRI exam and may issue simple instructions regarding holding your breath, maintaining position, etc. You will be requested to lie perfectly still throughout the exam. Pillows or a head cradle may be used to avoid blurring of the images.

Part of the MRI scan will be with contrast, which involves an agent called gadolinium being injected into your arm. This enables the physician to review and decipher your brain images with greater clarity.

If you're unsure about metal in your body, we will perform an x-ray. You will sign a separate consent form for that procedure.

Liver ultrasound

The ultrasound will take approximately 30 minutes. This is to measure how much the liver is affected by the alcohol use. At the beginning of the exam, a warm gel will be lathered on your abdomen and an examiner will move a transducer around over the skin of your abdomen and ribcage. You may be asked to perform some different breathing techniques to get the best images, and to lay in different positions. If you are scheduled for liver ultrasound in the morning you are asked to stop eating and drinking (except water, medications) from midnight the night before the ultrasound. If you are scheduled for later in the day you are asked to stop eating and drinking (except water, medications) for at least 4 hours prior to the ultrasound.

Clinical evaluations

During these evaluations – medical, neurologic, and psychiatric – you will be interviewed and examined by board-certified clinicians in their respective specialties. You will be asked questions about your current state of health and your past medical history. The clinician may also obtain a physical exam. These evaluations allow the study team to determine whether you meet eligibility criteria, and in later visits allows screening for any DBS-related symptoms or adverse events.

Electrocardiogram

The electrocardiogram will take approximately 15 minutes. The electrocardiogram (ECG) is to determine whether your heart rate and rhythm are normal. This is a common and painless test which consists of up to 12 sensors, which look like sticky patches, being attached to your chest and limbs. If you have hair on the parts of your body where the patches will be placed, this may be shaved to allow the patches to adhere properly. You will be asked to lie still for a few minutes while the sensors record electrical signals from your heart.

Blood Work

Bloodwork is being performed to check your blood counts, liver and kidney function, and clotting ability. It is also being used to look for indicators of liver damage and an alcohol biomarker (not a genetic biomarker). We may also draw blood to diagnose liver fibrosis in some cases where the liver ultrasound was inconclusive or unable to be done.

This visit may last up to a full day.

<u>Baseline evaluation – Day 7</u>

If the results of the screening visit deem you an appropriate candidate for this study, you will be formally enrolled and scheduled for your pre-DBS baseline evaluation. This evaluation will take place over 2-3 days. On Day 1 of this evaluation, you will complete further clinical evaluations, including medical, neurologic, psychiatric, and neurosurgical. You will provide blood and urine samples (for a drug screen), and female patients may be asked to provide a pregnancy test. You will also be asked to give a breathalyzer test. You will have an MRI (if not completed on Day 1), without contrast this time, and a head computed tomography (CT) scan. Lastly, you will undergo an AUD assessment and a couple of cognitive and behavioral tasks.

Neurosurgical evaluation

You will be interviewed and examined by a clinician in the field of neurosurgery. During this baseline visit, they will evaluate your general health and readiness for surgery, as well as identify any potential contraindications. You will also be consented for the neurosurgical procedure to implant the electrodes and stimulator. Neurosurgical evaluations during later visits will be primarily screening for adverse events or DBS-related symptoms.

AUD assessment

This will consist of 4 different scales or questionnaires which you will answer, pertaining to your patterns of alcohol consumption and symptoms of AUD. These will take around 5-15 minutes each, and we estimate around 30-60 minutes total.

Cognitive and behavioral tasks

These tasks are intended to measure the cognitive and behavioral processes that are associated with vulnerability to relapse to alcohol. You will complete them using a computer screen and you will press a button or fill out a paper questionnaire after you are presented with a cue on the screen. Each task takes about 15-30 minutes to complete, and overall around 1.5-2 hours total on Day 1. These will be repeated during follow up evaluation visits after the DBS system is implanted.

Questionnaires

These will ask questions about your overall functioning, mood, and any tendencies to hurt yourself over the past month or so. Each questionnaire will take an average of 10 minutes.

This visit may last up to a full day.

<u>Baseline evaluation – Day 8</u>

On Day 3, we will ask you to complete further cognitive and behavioral tasks (1-2 hours) as well as a series of questionnaires. Some of the cognitive and behavioral tasks will be done while recording brain activity using electrodes placed on your scalp (electroencephalogram). You will also complete a Positron Emission Tomography (PET) scan.

Questionnaires

These will ask questions about your sleep quality, mood, and feelings over the past month or so. Each questionnaire will take an average of 10 minutes, and around 1-2 hours total to complete all of them.

PET

The PET scan will take approximately 2 hours to complete. This will help measure brain activity. If you are scheduled for PET scan in the morning you are asked to stop eating and drinking (except water, medications) from midnight the night before the scan. If you are scheduled for later in the day you are asked to stop eating and drinking (except water, medications) for at least 4 hours prior to the scan. Upon arrival to the imaging center your blood glucose level will be checked. Blood glucose level should be less than 175 mg/dL (7.8 mmol/L). If blood glucose level is greater than 175 mg/dL, we may reschedule you if possible. You will have a radiotracer drug injected into your arm, which will take around 30 minutes to be absorbed. Then you will lie on a padded table which will slide into the scanner. You will be asked to lie still while the images

are taken. The scan itself will take about 30 minutes. If you are a woman of childbearing potential, we will collect a urine sample from you for a pregnancy test.

The machine will make buzzing and clicking sounds and the scanner itself may feel like an enclosed space. The technologist will be monitoring you and you will be able to communicate via intercom. After completion of the scan, you will be provided with a snack or a meal.

This visit may last up to a full day.

Baseline evaluation – Day 9

On Day 4, you will complete a neuropsychological evaluation. Based on your past medical history and ongoing clinical status during study participation, the investigator may recommend additional blood tests. Subjects will be informed as to which blood tests are recommended and the associated reasons.

Neuropsychological exam

This is a standard evaluation which will ask you to complete questions and short tasks which will assess various cognitive domains like memory, planning, and language. You will use a pencil and paper to complete the evaluation.

This visit may last up to a half day.

Pre-operative Visit

CT scan

The CT scan will take approximately 20 minutes. Similar to an MRI scan, you will be asked to lie on a padded table which will slide into an opening in the scanner. While the table moves into the scanner, detectors will rotate around you and you may hear buzzing and whirring noises.

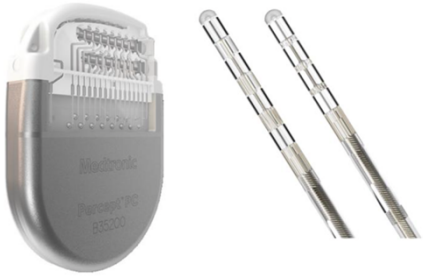
A technologist will be monitoring you from a separate room, and they will be able to see and hear you from the scanner. You will be able to communicate via intercom. You will be asked to lie still during the scan, and pillows or a head cradle may be used to avoid blurring of the images.

This may need to be performed on a different evaluation day depending on availability of resources.

DBS implantation

Once baseline measurements have been taken, we will schedule you for DBS placement. You will be asked to sign a separate consent form for the surgical procedure.

The first phase of this will require a neurosurgical procedure to place the electrodes, and for you to stay in the hospital for 2-3 days. The second phase will be scheduled for 7-10 days after electrode placement, which will consist of an outpatient procedure to place the neurostimulator,



DBS neurostimulator (left) and electrodes (right)

and you will be discharged the same day.

Phase 1 visit: you will be admitted by the neurosurgical team for 2-3 days. Based on your past medical history and ongoing clinical status during study participation, the investigator may recommend additional blood tests in the morning of the surgery to make sure the bleeding risk is still low. Subjects will be informed as to which blood tests are recommended and the associated reasons. You will have surgery to place electrodes in the brain. The surgery itself will be performed with intravenous sedation only. An anesthesiologist will always be present in the operating room in the event of an emergency. You will also be asked to complete a cognitive task during the procedure.

CT scan

You will undergo 2 CT scans during phase 1 admission; one prior to placing the electrodes in your brain (pre-op) and one afterwards (post-op). The first CT will help with the surgical planning to target the electrodes properly. The second CT is to verify the proper electrode location in the brain. CT scan will take approximately 20 minutes. Similar to an MRI scan, you will lie on a table which will slide into an opening in the scanner. While the table moves into the scanner, detectors will rotate around you and you may hear buzzing and whirring noises.

You will be monitored at all time and staff will be able to see and hear you from the scanner. You will be able to communicate with staff during the CT. You will be asked to lie still during the scan, and pillows or a head cradle may be used to avoid blurring of the images.

Phase 2 visit: you will return for implantation of the neurostimulator (the "battery") under the chest wall. The electrode will be connected to the stimulator which supplies power to the electrode. The DBS lead cables are tunneled behind the ears and connected to the lead extension cables. The lead extension cables are tunneled under the skin to the collarbone pocket housing the stimulator. The stimulator itself is attached to the underlying tissue that covers the muscle (pectoralis fascia) with stitches to avoid it flipping in the pocket.

The study neurologist will set the initial stimulation parameters. You will also be provided with a patient controller device that will allow you to turn the device on or off at home if needed.

Deep brain stimulation pulse generators typically have a battery lifetime of between 3-5 years, this may become shorter for your case if the current required to control your symptoms is relatively high. Exchanging the pulse generator for a new one requires a brief operative procedure, typically performed with local anesthesia and sedation.

Surgical follow-up

About 2 weeks after stimulator placement, you will be evaluated by the neurosurgical team to assess for any surgical complications and ensure appropriate recovery. This visit may last up to 30 min.

DBS optimization day 1

DBS optimization means setting the ideal stimulation parameters. Your next visit will be 2-3 weeks after the neurostimulator has been placed. The stimulation settings will be changed according to any side-effects you might be experiencing and your levels of alcohol craving; this will be assessed by your completion of a few questionnaires and cognitive tasks. You will also answer questions about mood and emotional health. You will additionally undergo a PET scan and assessment of your alcohol use with questionnaires and blood work like during the baseline evaluation. We will also consider obtaining an MRI of your brain to visualize the placement of the electrodes if the CT scans did not allow proper visualization of the DBS electrodes. If you are a woman of childbearing potential, we will collect a urine sample from you for a pregnancy test.

The DBS electrodes deliver electricity to the area where they are implanted. This will change the neural activity of neurons in that area. It is most likely that you will not feel anything when the electrodes are activated but you may notice reduced alcohol cravings. Sometimes people may feel flashes of light, changes in emotion, or changes in ability to think or focus; in those instances we will adjust the stimulation parameters.

This visit may last up to a full day.

DBS optimization day 2

If optimization is not completed on day 1, you will come back for a second optimization visit the next day.

This visit may last up to a full day.

Follow-up visits during the study (11)

These visits (total of 11 visits over 12 months) will be scheduled every month following optimization of the DBS stimulation, except at 6-months and 12-months, which will consist of more comprehensive evaluations (explained below). During these monthly visits, you will again provide blood and urine samples, a breathalyzer test, psychiatric evaluation, and AUD assessment.

Reprogramming of the device will be implemented as needed based on the development of adverse events (i.e., infections) or your clinical condition at the time of the visit (worsening of your symptoms, lack of tolerability for the device).

These visits may last up to a half day.

Follow-up phone calls: after your DBS device is turned on, we will call you every day or every other day to check on you until your next in-person follow-up visit 2 weeks later; between in-person follow-up visits, we will call you every week to check on you and ask you questions about your mood and possibly your alcohol use. These phone calls may take up to 15 min.

6- and 12-month evaluations

These comprehensive evaluations will be nearly identical to the pre-DBS baseline evaluation.

- *Day 1:* you will complete further clinical evaluations, including medical, neurologic, and psychiatric. You will provide blood and urine samples, and female patients may be asked to provide a pregnancy test. You will also be asked to give a breathalyzer test. You will have an AUD assessment, and complete some questionnaires and a couple of cognitive and behavioral tasks.
- *Day 2:* we will ask you to complete further cognitive and behavioral tasks as well as a series of questionnaires. You will also complete a PET scan.
- *Day 3:* you will complete a neuropsychological evaluation.

Study completion visit

This study completion visit serves to close out the study. After the 12-month evaluation, you will have completed the study. If you have experienced a significant benefit from the DBS stimulation, you will have the option to 1) keep the DBS system implanted with stimulation turned ON, 2) keep the DBS system implanted but with stimulation turned OFF, or 3) have the DBS electrodes and neurostimulator removed.

For options 1 and 2, the study team will continue to follow-up with you on a yearly basis (or more frequently if needed) for 5 years, and possibly longer. These follow-ups will involve standard of care clinical evaluations in the Neurology and Psychiatry clinics of the study investigators. During these visits, we will continue to screen for potential adverse effects, and you will undergo neurological and psychiatric evaluations. If the DBS did not provide benefit, or if you choose to have the device removed, we will remove the DBS electrodes and neurostimulator. Removal will require a neurosurgical procedure similar to that of DBS placement. We will again check your blood for bleeding risk few days before and on the day of surgery to remove the DBS. You will be asked to abstain from alcohol for 7 days prior to surgery. You will be admitted to the hospital and will be monitored overnight following the procedure. You will then receive a post-operative CT scan to ensure there are no complications from the surgery. You will be referred to the outpatient psychiatry clinic for standard of care follow ups.

If you wish the device to be removed at any time, the study doctor will arrange for this to take place.

This visit may last up to 60 min.

Follow-up visits after study completion (3)

These visits (total of 3 visits over 3 months) will be scheduled every month following the completion of the study. These will help assess for sustained clinical effect of DBS. During these monthly visits, you will undergo a psychiatric evaluation and AUD assessment.

These visits may last up to a half day.

4. Study Risks

DBS implantation, titration, and stimulation

The risks of this study are the same as for brain surgery in general: bleeding, suffering a stroke, paralysis (or lack of movement in the arms and/or legs), death, infection, and risks of anesthesia such as heart attack or allergic reaction. The post-operative pain from the chest or head incisions could increase your risk of poor sleep and could cause you to drink more alcohol post-operatively. You are also at risk of alcohol withdrawal after your surgery, while in the hospital, or when the DBS device is turned on.

The risks associated with DBS stimulation and optimization are failure of therapy, neurologic symptoms including muscle contractions, flashing lights, electric jolting sensations, emotional lability, and altered ability to think or remember. However, most of these can be reversed by adjusting the pattern of stimulation.

There is a small but serious risk of intracranial hemorrhage (bleeding in the brain) with implantation of the electrode. The rates of symptomatic and asymptomatic intracranial hemorrhage in DBS are ~ 2% and 1.2%, respectively and infection occurs in ~ 2% of cases. The mortality rate for the procedure is below 1% and is mostly due to intracranial hemorrhage. In a review of DBS studies including 8983 patients, no deaths were reported. You are at higher risk of complications due to the history of alcohol use and liver disease. Some people with severe liver disease and alcohol use disorder who underwent DBS surgery have suffered unanticipated complications due to head bleeds which were fatal.

From the device brochure, Medtronic DBS therapy has a risk of adverse events related to the therapy, device. These include: “intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications (including pain, infection, dehiscence, skin erosion, seroma, and hematoma), meningitis, encephalitis, brain abscess, cerebral edema, aseptic cyst formation, device/hardware complications (including lead fracture, lead/device migration, lead failure, neurostimulator malfunction) that may require revision or explant, extension fibrosis (tightening or bowstringing), new or exacerbation of neurological symptoms (including vision disorders, speech and swallowing disorders, motor coordination and balance disorders, sensory disturbances, cognitive impairment, and sleep disorders), psychiatric and behavioral disorders (including psychosis and abnormal thinking), cough, shocking or jolting sensation, ineffective therapy, and weight gain or loss.” Post-surgical pain may cause you to drink more until the surgical wounds heal.

The DBS System may be affected by or adversely affect medical equipment such as cardiac pacemakers or therapies, cardioverter/ defibrillators, external defibrillators, ultrasonic equipment, electrocautery, or radiation therapy.

Risks related to DBS removal are similar but less severe than implantation surgery risks and include risks of hemorrhage, infection, and hardware complications.

These risks will be minimized by close and frequent monitoring of any side-effects or symptoms you experience. You will receive a copy of the Medtronic Patient Therapy Guide prior to surgery and you will be given a patient controller, which will allow you to turn off stimulation if you experience severe

side-effects. You will also have the phone numbers of members of the study team to be reached at any time.

DBS removal

These risks are similar to DBS implantation but much less likely since there will be no hardware in the brain. You are at higher risk of complications due to the history of alcohol use and liver disease. Some people with severe liver disease and alcohol use disorder who underwent DBS surgery have suffered unanticipated complications due to head bleeds which were fatal.

PET scans and CT head scans

Participation in this research study involves exposure to radiation from *PET and CT scans*. The amount of radiation exposure that you will receive from *these* procedures is equivalent to a uniform whole body dose of 1.42 rem (a “rem” is a unit of radiation dose), which is approximately 28% the annual radiation dose (5 rem) permitted to radiation workers by federal regulations. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that you will receive from this study is considered to be low and comparable to everyday risks

Additionally, radiation from CT and PET scans can be harmful to a developing fetus, which is why we require female participants of childbearing age to use a method of contraception and to provide negative pregnancy tests. The injected compound, FDG, is considered generally safe by the University of Pittsburgh’s Radioactive Drug Research Committee and IRB in accordance with FDA approval.

Fasting before the PET scan/liver Ultrasound

You may feel hungry or thirsty because of fasting prior to the PET scan or liver ultrasound. You are allowed to drink water and take your medications. Some people may feel lightheaded if their blood sugar levels drop because of fasting. If you feel lightheaded, we will check your blood sugar level, and if it is low, you will be allowed to eat or drink to raise the blood sugar level. You will be provided with a snack or a meal after the scan.

MRI scans with contrast

The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. You will be asked to wear earplugs or earphones while in the magnet. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to tell the MRI staff if you have had brain surgery for a cerebral aneurysm or have a metal clip in your brain, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye. If you have a history of metal in your head or eyes, you cannot participate in this study.

During the scan, we will be using Gadolinium contrast, which is injected intravenously. This is associated with a very low risk of rare vision problems in fetuses. Symptoms from the contrast infusion are usually mild and may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number of patients, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. Contrast may cause

dangerous reactions for people with kidney disease, so you will not receive contrast if your kidney function is abnormal.

Liver ultrasound

You may experience some discomfort from the pressure of the ultrasound probe on your abdomen.

Detox

You may experience alcohol withdrawal symptoms which include restlessness, sweating, loss of appetite, nausea, vomiting, agitation, irritability, anxiety, fast heart rate, tremor, disorientation, headache, insomnia, and seizures.

Electrocardiogram

You may experience some skin irritation from the location of the leads.

Blood tests

Taking blood may cause discomfort, bleeding or bruising where the needle enters the body. In rare cases, it may result in fainting. There is a small risk of infection.

Female contraception

Any side-effects you may experience will depend on the type of contraception method used. Symptoms span a wide variety, including nausea, headache, spotting between periods, breast tenderness, and mood changes.

Cognitive and behavioral tasks and questionnaires

You may experience discomfort from the nature of the questions or discomfort from the length of time required to complete the questionnaires. Specifically, questions related to thoughts of suicide or self-harm may trigger emotions that msy cause you some distress. Additionally, exposure to alcohol cues may cause craving, anxiety and discomfort. Electroencephalogram

You may experience some discomfort and some scalp/skin irritation from the location of the leads.

Incidental findings

There is a possibility that while reviewing your evaluations (e.g., MRI, ultrasound, blood tests) we may see an abnormality that we did not expect to see in this study. This is what is called an “incidental finding.”

We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by mail or by phone. In the case of a potential serious emergency, someone may go to your home. A qualified person (usually a member of the research team) will talk to you if there is an incidental finding. You do not have an option to decline information about an incidental finding.

If you want, we will give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

- An incidental finding may cause you to feel anxious.
- Since an incidental finding will be part of your medical record, you could face greater difficulty in getting health or life insurance.

- The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

Neuropsychological evaluation

This evaluation may make you uncomfortable psychologically due to the nature of the questions about your thinking abilities, memory, etc. or physically because of the duration of the evaluation.

Loss of confidentiality

It is possible that your identity as a participant in this trial may become known. This can occur in any of the study activities.

Unknown risks

As with any experimental procedure, there may be adverse events or side effects that are currently unknown and some of these unknown risks could be permanent, severe or life-threatening.

Financial risks

If you benefit significantly from the DBS (reduced alcohol use and improved quality of life) and decide to keep the DBS system implanted, you might incur some financial risks due to the need for yearly follow-ups (once a year or more) in the neurology and psychiatry clinics for standard of care assessments as well as screening for delayed adverse events. This cost will not be covered by the study. In addition, the battery of the DBS stimulator might need to be replace when depleted (after several years). This cost will not be covered by the study. In addition, if you initially choose to keep the DBS system implanted but decide to have it electively explanted later, after the study has ended, we will help arrange for that, but this cost will not be covered by the study. Therefore, if you decide to keep the device implanted after the study ends, you could end up paying out of pocket for some expenses related to battery replacement, complications or explantation.
We cannot guarantee any financial assistance, but we will do our best to ensure that the financial risks are minimized to the greatest extent possible. However, in all of these cases, we will work with your insurance company or the Center for Medicare and Medicaid services (CMS) to cover the costs of follow up visits and battery replacement if needed given the clinical benefit you will have experienced from DBS. Non-financial risks of keeping the DBS implanted for longer time periods include infection, bleeding, headaches, device malfunction, and miscellaneous neurological symptoms.
We will also work with your insurance company or CMS if after opting to keep the DBS system in, you decide to have it explanted after the study has ended, especially if it was deemed to be no longer necessary and you have achieved sustained remission.

5. Study Benefits

There may or may not be a direct benefit to you from being in this study. If you take part in this study, you may help others in the future.

6. What are your options if you do not want to be in the study?

You do not have to join this study. If you do not join, your care at UPMC will not be affected. The alternative to the type of treatment we are proposing is for you to continue with all of your current treatments for AUD including non-pharmacological treatments.

7. Confidentiality/HIPAA

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings; if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects).

By signing this form, you provide your permission, called your “authorization,” for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records.

As part of this study, a statement will be added to your medical record that you are in this research study.

Some test results, especially those related to admission for DBS surgery, will be placed into your medical records held at UPMC. These tests include the brain MRI, results of blood, urine, and pregnancy tests (for women of childbearing potential), and as well as the results of imaging and clinical evaluations. This medical record information, which includes your name, is available to members of the research team for an indefinite period.

Confidentiality of patient information will always be maintained. All members of the study team will have the required training in maintaining data integrity and security. Confidentiality will be guarded using established procedures such as storing data in locked cabinets within locked offices or locked data rooms. Report forms are de-identified to avoid revealing your identity. All data will be encrypted prior to any electronic transfer. Electronic records will be kept in computer files that are password-protected and housed on the UPMC network behind the UPMC firewall. Only study personnel will have access to the data sets on protected servers.

The research team will know your identity and that you are in the research study. Other people at UPMC, particularly your doctors, may also see your information. We make this information available to your doctors for your safety.

Authorized representatives of the University of Pittsburgh Office of Research Protections and the FDA may review your identifiable research information for the purpose of ensuring the appropriate conduct of this research study. Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical

information) related to your participation in this research study for the purpose of (1) fulfilling orders made by the investigators for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

At some point, your identifiers might be removed from the private information and/or biospecimens. This de-identified information and/or biospecimens may be used by other researchers for future research studies. If this happens, we will not contact you for additional consent.

If the investigators learn that you or someone with whom you are involved is in danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies. If you test positive for certain diseases, we are required to report to the Pennsylvania Department of Health.

We cannot do this study without your authorization to use and give out your information. You do not have to give us this authorization. If you do not, then you may not join this study.

Your data and specimens used in this research study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or their agents may realize.

Per the University of Pittsburgh's policy, all research records must be maintained for at least 7 years following reporting or publication of the study

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing (Dr. Moussawi, contact info on first page of this form). If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

8. Subject Access to Research Results

Results of some testing performed under this research study will be included in your medical record. You have the right to access information that is in your medical record. However, results from testing done purely for research purposes will not be included in your medical record and will not be provided to you because of their investigational nature.

9. Are there benefits to being in the study?

There may or may not be a direct benefit to you from being in this study. If you take part in this study, you may help others in the future.

10. FDA Clinical Trial Registry

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

11. Costs

Neither you nor your insurance provider will be charged for any of the research activities (e.g., DBS surgery, MRI scans, PET scans) that are administered to you during this study. If you believe you have received a bill for a research related procedure, contact the study team and the UPMC office that sent the bill.

12. Payments

If you participate in this study, you will be compensated for each visit. Parking and food expenses during each visit will be covered, and you will additionally receive compensation for time spent on research activities. You will receive $200 for every full day evaluation visit (e.g., screening visit, baseline, 6-, and 12-month assessments), $100 for every follow up visit, and $200/day for every admission day to the hospital (during electrode placement or removal). You will also receive up to $70 for cognitive tasks, $20/day for parking and $30/day for food. Upon completion of the study, you will receive a sum of $750.

Payment to study participants is considered taxable income regardless of the amount. If you receive $600 or more in a calendar year from one organization, that organization is required by law to file a "Form 1099 – Miscellaneous" with the IRS and provide a copy to the taxpayer. We are required to give your name and social security number to the Accounting Office. Participants who do not provide a social security number may still participate in the research, but the IRS requires that 24% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 76% of the expected payment.

13. Will the study require any of your other health care providers to share your health information with the researchers of this study?

As a part of this study, the researchers may ask to see your health care records from your other health care providers.

- You will be asked to give us a list of other health care providers that you use.

14. Compensation for Injury

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury

requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You do not waive any rights by signing this form.

15. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, the University of Pittsburgh/UPMC may use or give out any identifiable research information obtained as part of this study prior to the date that you withdrew your consent will continue to be used by the investigators for the purposes described above. If you want to withdraw, notify the study team. Your decision to withdraw will have no effect on your current or future relationship with the University of Pittsburgh or UPMC.

If you withdraw from study participation after the DBS system has been implanted, the device will be removed. You will be monitored overnight after the procedure, receive a post-operative CT scan to ensure there are no complications, and be evaluated by the neurology/neurosurgery team at a follow-up visit 2 weeks later. You will also be referred to outpatient psychiatry clinic for standard of care follow-ups.

16. Why might we take you out of the study early?

It is possible that you may be removed from the research study by the researchers if, for example, serious or unexpected events occur that make your continued participation unsafe (e.g., if you start taking chemotherapy or experimental medication, or if you start blood thinners before the DBS is implanted), or if you are having difficulty fulfilling the requirements of the study. If you start taking chemotherapy or other experimental drugs during the study

There may be other reasons to take you out of the study that we do not know at this time

If you leave the study early, the University of Pittsburgh/UPMC may use or give out any identifiable research information obtained as part of this study prior to the date that you withdrew your consent will continue to be used by the investigators for the purposes described above. If you want to withdraw, notify the study team. Your decision to withdraw will have no effect on your current or future relationship with the University of Pittsburgh or UPMC.

If you withdraw from study participation after the DBS system has been implanted, the device will be removed. You will be monitored overnight after the procedure, receive a post-operative CT scan to ensure there are no complications, and be evaluated by the neurology/neurosurgery team at a follow-up visit 2 weeks later. You will also be referred to outpatient psychiatry clinic for standard of care follow-ups.

17. What other things should you know about this research study?

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 1-866-212-2668. You may also call this number for other questions, concerns or complaints about the research.

a. What do you do if you have questions about the study?
Call the principal investigator, Dr. Moussawi at 412-383-3084. If you wish, you may contact the principal investigator by letter, email, or by fax. The address, email and fax number are on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 1-866-212-2668.

b. What should you do if you are injured or ill as a result of being in this study?
If you think you are injured or ill because of this study, call Dr. Moussawi at 412-383-3084 during regular office hours.

If you have an urgent medical problem related to your taking part in this study, call Dr. Moussawi at 412-383-3084 during regular office hours and at 215-609-7680 after hours and on weekends.

c. What happens to Data and Biospecimens that are collected in the study?
UPMC and our research partners work to understand and cure diseases. The biospecimens and/or data you provide are important to this effort.

If you join this study, you should understand that you will not own your biospecimens or data, and should researchers use them to create a new product or idea, you will not benefit financially.

With appropriate protections for privacy, the University of Pittsburgh and UPMC may share your information with our research sponsors and partners. At some point, your de-identified research information may be used by other researchers for future research studies. If this happens, we will not contact you for additional consent.

d. Will the study be overseen by the FDA?
Yes; the FDA approves the study before it starts and may inspect the records at any point during the study.

e. A medical record for you will be created at the Clincal and Translational Research Center where you will be undergoing most of your assessments.

f. Your doctor may be involved as an investigator in this research study. Before agreeing to participate, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not obligated to be a part of any research study offered by your doctor.

18. Signature Section

What does your signature on this consent form mean?

Your signature on this form means that: You understand the information given to you in this form; you accept the provisions in the form and you agree to join the study. You will not give up any legal rights by signing this consent form.

Consent to Participate

The above information has been explained to me and all my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any part of this research study during this study. Any future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the Human Research Protection office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that occurred during my participation. By signing this form, I consent to participate in this research study and provide authorization to use and share my medical records. A copy of this consent form will be given to me.

Printed Name of Participant

Date

Signature of Participant

Investigator Certification

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions, concerns or complaints as they arise. I further certify that no research component of this protocol was started until after this consent form was signed.

Printed Name of Person Obtaining Consent

Role in Research Study

Signature of Person Obtaining Consent

Date/Time