Limbic pallidum DBS for the treatment of severe alcohol use disorder

Protocol Number:	STUDY22030036
Version Date:	1/31/2024
Version Number:	8
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IDE Number:	G220077
NCT Number:	05522751
Source of Funding:	National Institutes of Health (NIH)

History of Protocol Versions:

Version	Date	Sections Changed	Rationale for the Change
1.0	Mar 01, 2022	N/A	N/A
2.0	Mar 25, 2022	8.1	Added potential LP DBS risks
3.0	Apr 04, 2022	11.2	Clarified discontinuation criteria
4.1	July22, 2022	9.2, 12.4, Schedule of Activities	Removed 12-month PET scan (HUSC)
4.2	July 28, 2022	7.1, Schedule of Activities	Clarified screening/baseline procedures may occur over 4 days, footnote for CT scan (IIS)
4.3	9/13/2022	5.4	Added NCT #; changed compensation bonus
4.4	12/01/2022	5.4, 7.1, 7.4, 13.1	Miscellaneous clarifications
5.0	1/17/2023		Added fasting before PET scan
6.0	3/26/2023	5.1, 5.2, 5.4, 7.1, 8.2, 9.1, 9.2 Schedule of Activities	Added blood test to determine liver fibrosis stage, extended study visit windows, clarified number of implanted vs. consented subjects
7.1	6/21/2023	5.3, 7.1, 8.1, 9.1	Blood tests for platelet and fibrinogen function; exclusion criteria

Contents

ABBREIVATIONS AND ACRONYMS

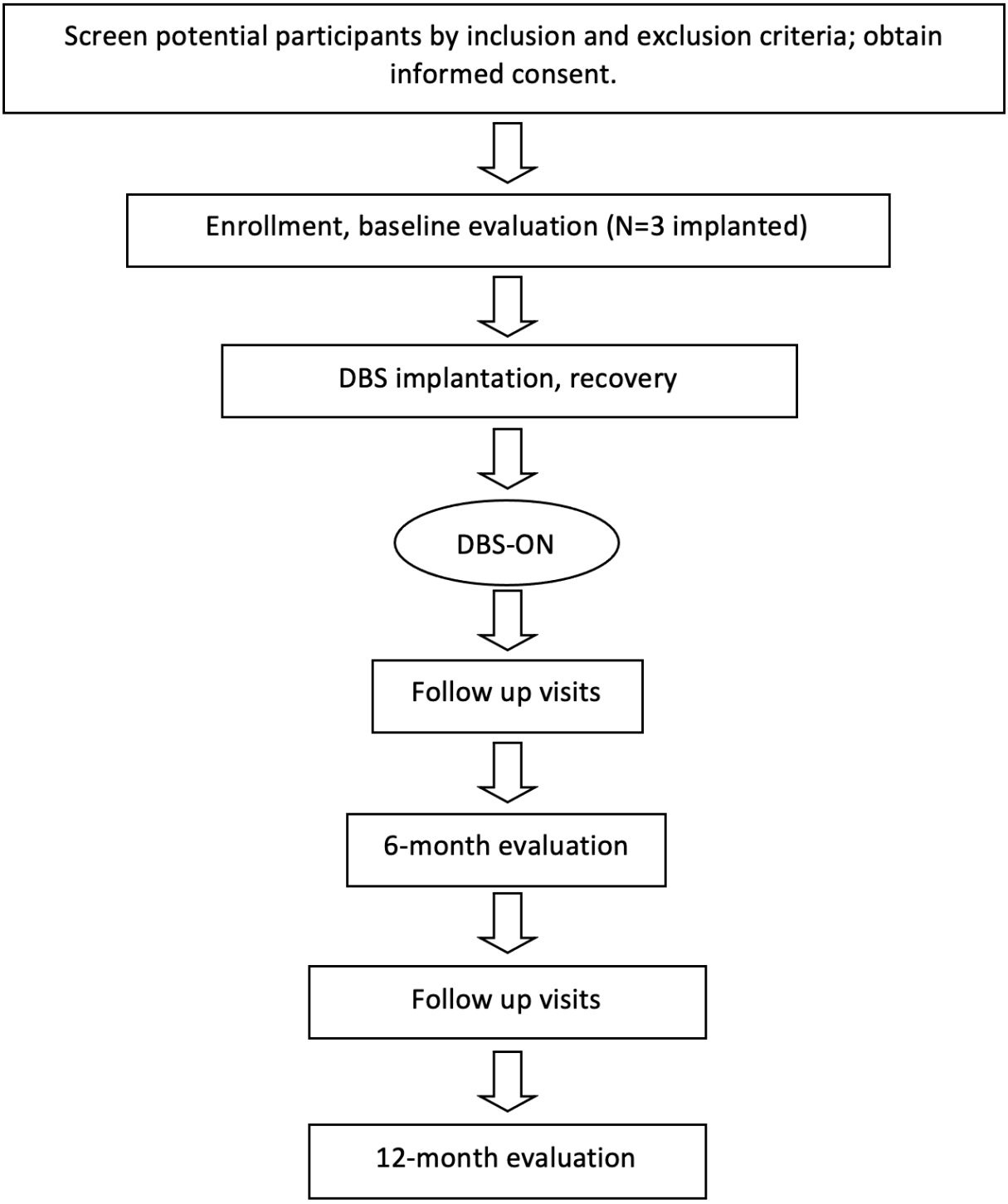
ACQ-SF-R	Alcohol Craving Questionnaire-Short Form
ADS-25	Alcohol Dependence Scale
AE	Adverse Effect
AES	Apathy Evaluation Scale
ADL	Activities of Daily Living
ALD	Advanced Liver Disease
ANOVA	Analysis of Variance
AUD	Alcohol Use Disorder
BART	Balloon Analog Risk Task
BAS	Behavioral Activation System
BIS	Behavioral Inhibition System
CBC	Complete Blood Count
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CGM	Cerebral Glucose Metabolism
CGT	Card Guessing Task
CIWA	Clinical Institute Withdrawal Assessment
CMP	Complete Metabolic Panel
C-SSRS	Columbia -Suicide Severity Rating Scale
CR	Cue Reactivity
CRF	Case Report Form
CT	Computed Tomography
DBS	Deep Brain Stimulation
DD	Delay Discounting
DDD	Drinks per Drinking Day
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG/EKG	Electrocardiogram
EEG	Electroencephalogram
EHR	Electronic Health Record
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HARS	Hamilton Anxiety Rating Scale
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-To-Treat
LP	Limbic Pallidum

MADRAS	Montgomery Asberg Depression Rating Scale
Mini-MASQ	Mood and Anxiety Sympton Questionnaire
MPI	Multiple Principal Investigator
MRI	Magnetic Resonance Imaging
NCT	National Clinical Trial
NIH	National Institutes of Health
OCDS	Obsessive Compulsive Drinking Scale
PD	Parkinson's Disease
PDA	Percent Days Abstinent
PET	Positron Emission Tomography
PEth	Phosphatidylethanol
PI	Principal Investigator
PSQI	Pittsburgh Sleep Quality Index
PT	Prothrombin Time
aPTT	activated Partial Thromboplastin Time
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SAE	Serious Adverse Event
SCID-R	Structured Clinical Interview for the DSM-V for Research
SSRT	Stop Signal Reaction Time Task
SUD	Substance Use Disorder
TLFB	Timeline Followback
UPMC	University of Pittsburgh Medical Center
UPPS-P	Urgency, Premeditation, Perserverance, Sensation seeking, Positive urgency, Impulsive Behavior Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WHODAS 2.0	World Health Organization Disability Assessment Schedule 2.0
WTAR	Wechsler Test of Adult Reading
YMRS	Youth Mania Rating Scale

1 Protocol Overview

Study Description	This is a pilot open label clinical study to test the safety, tolerability and feasibility of Deep Brain Stimulation (DBS) of the limbic pallidum in patients with severe Alcohol Use Disorder (AUD). Participants with severe AUD will undergo baseline medical and psychiatric assessments, cognitive and behavioral testing, and positron emission tomography (PET) imaging. One to two weeks later, participants will undergo neurosurgical implantation of DBS electrodes in the limbic pallidum and a neurostimulator. Four weeks after DBS system implantation, the DBS system will be turned ON and the stimulation parameters optimized. Participants will be followed biweekly then monthly, and will then undergo repeat comprehensive assessment after 6 and 12 months of DBS stimulation.
Study Population:	3 participants of all genders, 21-75 years old, with severe AUD and advanced liver disease (stage 3 liver fibrosis, or compensated cirrhosis), living in Western Pennsylvania.
Planned Sample Size:	*3*
Participating Institutions (if a multi-center clinical trial)	This study will be conducted at the University of Pittsburgh Medical Center in Pittsburgh, PA.

1.1 Study Schema



2 Background and Rationale

Study goal: We propose to test a novel treatment approach for severe AUD: neuromodulation of the reward circuit with Deep Brain Stimulation (DBS) of the limbic pallidum.

2.1 Background

The limbic pallidum (LP) is an output nucleus of the basal ganglia with dense connections within the reward circuitry, receiving inputs from the ventral striatum and projecting to multiple limbic areas, including the limbic thalamus, limbic hypothalamus, and ventral tegmental area[1-5]. The LP encodes the hedonic value and valence, positive and negative, of environmental stimuli. It integrates the various cues and contingencies to result in adaptive behaviors that seek rewards and avoid aversive outcomes [4, 6-13]. Reward-associated cues are assigned incentive value in the pallidum, such that LP neuronal firing both predicts, and is necessary for, behavioral reward seeking in response to these cues[9, 10]. Importantly, value signals encoded by the LP both precede and are more robust than those in the ventral striatum, the site more traditionally associated with this integrative role[6, 9, 14]. The LP plays a similarly vital role in the learning of avoidance behaviors in response to aversive stimuli, such that non-selective pharmacologic or optogenetic LP activation results in impaired learning of appropriate avoidance behaviors[11-13, 15-17]. Previous studies using single-unit recordings identify two populations of neurons that preferentially respond to these two types of stimuli, with GABAergic neurons primarily firing in response to appetitive stimuli and encoding reward and motivation, and glutamatergic and parvalbumin neurons primarily responding to aversive stimuli and encoding aversion[11, 13, 18-22].

Adaptive responses to stimuli are disrupted in substance use disorders (SUD), and this is reflected in changes to the LP. Pre-clinical studies demonstrate several substance-induced neuroadaptations in the LP that likely underlie such processing dysfunctions, such as alcohol-induced biased LP neuronal firing towards reward, or cocaine-induced alterations of baseline glutamate and GABA concentrations and neuronal firing in the LP[4, 23-27]. Importantly, neuromodulation of the LP using opto- or chemo-genetics inhibits relapse to drug seeking, including alcohol, in animal models of drug addiction, *without* affecting the physiology or behavior of non-drug treated animals[19, 25, 28-31]. These studies demonstrate the LP is necessary and sufficient for relapse to drug seeking. The LP is also implicated in the manifestation of anhedonia and apathy, such that increased firing of LP parvalbumin neurons is casually related to social withdrawal and behavioral despair in mouse models of depression[21]. This parallel role of the LP is highly relevant for *alcohol use disorder* (AUD), given that it is so often comorbid with depression and anxiety[8].

Preclinical findings are further bolstered by human case studies highlighting the role of the LP in impulsivity, motivation, and relapse to drug seeking: bilateral lesions of the LP result in immediate and sustained abstinence and loss of craving in subjects with severe alcohol and opioid use disorders[32, 33]. Grossly, the pallidums of binge-drinkers are noticeably smaller, and individuals with a history of cocaine addiction demonstrate molecular changes post-mortem, compared to controls[34, 35].

DBS involves implanting electrodes into the brain to allow circuit-based neuromodulation, which normalizes function through functional lesioning. DBS is currently standard of care for treating Parkinson's disease, essential tremor, and dystonia, and is approved by FDA Humanitarian Device Exemption for further indications[36-40]. It has unique advantages in its ability to (1) selectively target the circuit of interest, while minimizing off-target effects and (2) enact clinical improvement independent of disease etiology[41-47]. Due to its efficacy and favorable safety profile, DBS has been used in pilot trials for the treatment of SUDs like alcohol and opioids[48-56]. In animal models of AUD, ventral striatal DBS inhibits

relapse to alcohol seeking and other drugs. A case report and a pilot study of five patients implanted with ventral striatum DBS in patients with AUD have been reported[57-59]. Though the sample size was small, data suggested a significant and long-lasting efficacy in reducing relapse to alcohol. Pilot DBS trials for SUDs have exclusively targeted the ventral striatum; no SUD DBS trials have targeted the LP, despite the overwhelming pre-clinical and clinical literature regarding the role of the LP in reward and motivation processing and relapse to drug seeking.

Further DBS studies demonstrate the benefit of LP modulation in non-SUD disorders of impulsivity [60-64]; LP DBS in medically refractory patients with Tourette's syndrome and Lesch-Nyhan syndrome effectively decreased compulsive behaviors[39, 65-68]. Similarly, GPi DBS with closer volume of tissue activation to the LP was more effective in decreasing impulsivity measures in PD patients[69]. In the context of SUD treatment, modulating impulsivity is vital, as impulse control problems are central to addiction behaviors, especially relapse[70-72]. Given the observed therapeutic potential of DBS in AUD patients, the clinical evidence supporting the efficacy of LP-targeted neuromodulation in impulsivity disorders, and the pre-clinical evidence supporting role of neuromodulation in inhibiting relapse to drugs, including alcohol, the present study intends to investigate the safety and feasibility of LP DBS in patients with AUD, with the ultimate goal of conducting efficacy studies in the future.

Advantages of LP DBS over ventral striatum DBS: 1) Clinical cases show that bilateral lesions of the LP in patients with AUD result in sustained and complete remission of AUD [33, 73]. No such evidence is available for other brain regions, including the VS; 2) the LP plays a unique and critical role in integrating environmental stimuli to optimize adaptive behaviors (approach of rewarding outcomes and avoidance of aversive outcomes)[18, 74], a process that is impaired in substance use disorders; 3) encoding of rewards and reward prediction errors in the LP is more robust, necessary, and antecedent to encoding in the VS[6, 7, 9, 14]; 4) LP DBS has been shown to be efficacious in treating disorders with impulse control and compulsive behaviors (e.g., Tourette's, Lesch-Nyhan syndrome) [39, 60-68]; 5) LP DBS has been shown to be safe[39].

2.2 Rationale

Alcohol use disorder (AUD) remains a major cause of mortality, morbidity, and economic burden in the US, accounting for nearly 95,000 annual alcohol-related deaths (5% of US deaths) and estimated costs of $250 billion/year[75, 76]. Deaths result from liver disease, cardiovascular disease, cancers, and accidents[75, 77-80]. Severe AUD, meeting 6 or more AUD criteria in the DSM-V, makes up about 14% of all AUD patients and accounts for most of the healthcare and economic burden of AUD[81-83]. In this population, chronic excessive alcohol consumption (over 40g/day) invariably leads to alcoholic fatty liver disease. This can progress to liver fibrosis and eventually liver cirrhosis. While mild fibrosis (stages 0-2) is not associated with increased mortality, advanced fibrosis (stages 3-4) is associated with a 10-year mortality rate of 45% and 93% in compensated (asymptomatic) and decompensated (symptomatic) alcoholic liver disease (ALD) patients, respectively. Crucially, nearly 15% of patients with AUD will develop stage 4 liver fibrosis (cirrhosis), which itself carries a 5-year mortality rate of 45%, and accounts for about 23,000 deaths each year, and one-third of total liver transplants in the US[84-86].

Abstinence from alcohol is highly effective in improving outcomes of patients with ALD, raising the 5-year survival rate from 45% to 87%[84, 85, 87, 88]. Across all clinical stages of ALD, abstinence reverses histological features and improves clinical outcome. However, current pharmacologic and behavioral treatments of AUD have limited efficacy in achieving sustained abstinence[83]. Despite increased

knowledge of the neurobiology and circuitry of AUD, the relapse rate to alcohol use has not improved over the past 50 years and the 1-year relapse rate remains at nearly 55% in primary AUD and 90% in AUD among polysubstance use[89]. Thus, identifying novel and more efficacious treatments to maintain abstinence and prevent relapse to alcohol is an urgent public health priority. We propose to test a novel treatment approach for refractory AUD: neuromodulation of the reward circuit with DBS of the limbic pallidum.

As referenced above (section 2.1), the limbic pallidum commands a central role in reward circuitry, both in assigning positive or negative value to stimuli, and in integrating these cues to enhance adaptive behaviors to encountered stimuli. These adaptive behaviors are dysfunctional in SUD, where individuals will compulsively seek drugs despite major adverse outcomes, which is reflected in maladaptive changes to reward circuitry, including the LP. Previous studies, in both animal models and patients (discussed above), demonstrate the efficacy of LP neuromodulation in breaking the circuit of maladaptive processing and arresting drug seeking and relapse to drugs, including alcohol. In addition, LP DBS used for the treatment of disorders of impulsivity (non-SUD) demonstrate its ability to reduce compulsive and impulsive behaviors, which are a hallmark of drug addiction. With the intention of addressing a major cause of mortality and public health and economic burden, the overall objective of this proposal is to conduct an open label pilot study to demonstrate the safety and feasibility of LP DBS in patients with severe AUD and advanced ALD.

3 Hypotheses, Objectives and Endpoints

3.1 Hypotheses

3.1.1 Primary Hypothesis**: *DBS of the LP in subjects with severe AUD and advanced ALD is safe, tolerable, and feasible.***

3.1.2 Secondary Hypothesis**: *DBS of the LP in subjects with severe AUD and advanced ALD reduces alcohol use and improves overall functioning.***

3.2 Objectives

3.2.1 Primary Objective: **To demonstrate the safety, tolerability, and feasibility of LP DBS for the treatment of severe AUD.**

3.2.2 Secondary Objective: **To demonstrate preliminary efficacy of LP DBS to treat severe AUD.**

3.2.3 Exploratory Objectives: **To assess the effects of LP DBS on cue reactivity, reward processing, and impulsivity.**

3.3 Endpoints

Primary endpoints: safety, tolerability, and feasibility

Safety and *tolerability* will be evaluated based on adverse events associated with DBS implantation and stimulation (e.g., infection, bleeding, cognitive or behavioral side effects). We will screen for adverse events using 4 approaches: **1)** patient self-report, **2)** clinical evaluations (medical, neurologic, and psychiatric), **3)** questionnaires to screen for depression, anxiety, apathy, and mania, and **4)** neuropsychological evaluation to screen for any LP DBS effects on the various cognitive domains. These will be compared to DBS side effects observed in FDA approved indications like PD.

Feasibility will be evaluated based on **1)** our ability to recruit all 3 patients within the indicated timeframes, **2)** our ability to conduct the necessary evaluations in baseline and follow-up assessments (e.g., alcohol use, PET imaging, cognitive and behavioral tasks) and **3)** patients' adherence to the study protocol and participation in follow-up visits and assessments.
These outcomes will be monitored throughout the entirety of the study (including recruitment, screening procedure, clinical evaluations, DBS implantation, DBS titration, and all other study-related procedures).

Secondary endpoints: alcohol use, overall functioning, and target engagement
Alcohol use: this will be measured by calculating percent days abstinent (PDA), drinks per drinking day (DDD), blood phosphatidylethanol (PEth) and blood gamma-glutamyl transferase (GGT); PDA and DDD are obtained from TimeLine Followback (TLFB) assessment of alcohol use over the past 180 days for baseline evaluation, and over the past 30 days for follow-up evaluations after DBS implantation. PEth and GGT are blood tests obtained at baseline and every month during follow up visits.
Overall functioning and disability: this will be measured using World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) at baseline and during monthly evaluations after DBS implantation.

Target engagement: this will be measured through changes in brain metabolism with [^{18}F] fluorodeoxyglucose-PET (FDG-PET). Compared to healthy controls, AUD patients show lower cerebral glucose metabolism (CGM, a surrogate of neuronal activity) in multiple brain regions, as measured with FDG-PET, a finding that has been replicated by several groups [90-96]. Lower prefrontal cortex (PFC) CGM in AUD correlates with neuropsychological deficits (e.g., increased impulsivity) and relapse to alcohol[94-96]. Even after prolonged abstinence from alcohol, low CGM persists in several brain areas including the basal ganglia, orbitofrontal and cingulate cortices[96, 97]. Similar findings were reported in other SUDs and metabolic deficits have been associated with increased craving and compulsivity, and reduced self-control and response inhibition, which are all characteristic of SUDs [98, 99]. Successful therapeutic interventions (e.g., mindfulness training, neurofeedback) were shown to normalize the hypoactivity in affected brain circuits and restore inhibitory control across different misused substances[99, 100]. Ventral striatum DBS was recently shown to increase CGM in the PFC in a subject with severe SUD [101].

FDG PET scans will be obtained at baseline, 1 month after DBS surgery while the DBS is still OFF, then at 6 months after the DBS is turned ON.

Other pre-specified: cue reactivity, impulsivity, reward processing
These are all abnormal in AUD and are associated with vulnerability to relapse in AUD patients.

- Cue reactivity (CR) is the sensitized neurobiological and behavioral assessment of conditioned responses to drug-associated cues [102]. This can manifest as activation of reward circuits and drug craving upon drug-cue presentation[103-106]. CR correlates with AUD severity and predicts relapse risk [107-110]. We will measure CR with the Alcohol Cue Reactivity Task pre- and post-DBS using pictorial cues [111]. Pictorial alcohol cues are sensitive to neuroassessments and evoke strong self-report CR[112], particularly when personalized [113], while avoiding the inherent risks of exposing recently abstinent AUD patients to in-vivo alcohol beverages. CR will be measured with the Cue Reactivity Task; outcome measures: craving, positive affect, negative affect, calm, and excitement scores.
- *Impulsivity*: All types of impulsivity are implicated in AUD[70, 72, 114-120].

- Decisional impulsivity*:* **will be measured with the delay discounting task which** correlates with AUD severity and predicts risk of relapse [120, 121]***; o***utcome measure: discounting rate.
- ***Motor impulsivity****:* will be measured with Stop Signal Reaction Time task (SSRT) ***[122, 123]***. Motor impulsivity and loss of inhibitory control ***(measured with SSRT)*** are hallmarks of AUD [71, 124-126]; outcome measure: SSRT.

- *Reward processing:* will be measured with the Card Guessing Task (CGT); Reward processing is impaired in AUD[127-130]. This dysfunction is associated with abnormal neural activity recorded on EEG; the AUD-associated neurophysiological abnormalities include increased baseline spectral power (in the ß- and γ-bands) and reduced event-related spectral power[131-135]. CGT has shown that reward-processing correlates with an increase in event-related spectral power in the ß- and γ-bands, measured with EEG over the left ventrolateral PFC (vlPFC) [136]. To study the effects of LP DBS on the neural activity underlying reward processing in AUD, we will record brain activity with EEG while participants complete the CGT pre- and post-DBS[136, 137]; outcome measure: baseline and event-related spectral perturbations in the ß- (15-30 Hz) and g-bands (40-80 Hz) over the vlPFC (at electrode F7).
- *Risk taking:* will be measured with the Balloon Analog Risk Task (BART). BART measures risk taking which is predictive of alcohol-related behaviors in AUD patients [138-140]. Outcome measure: number of "adjusted pumps", defined as the average number of pumps on balloons, excluding those that burst [140].

4 Research Design

This will be an open-label trial to demonstrate the safety, tolerability and feasibility of LP DBS for treatment of severe AUD. The intervention is bilateral implantation of deep brain stimulation electrodes in the limbic pallidum in a single cohort of three patients. This study will be conducted at a single site (UPMC Presbyterian hospital, University of Pittsburgh). The study intervention will last from DBS implantation to the patients' 12-month follow-up evaluations (see details in section 6). Bias in research design is not a concern due to the open-label safety and feasibility nature of the study.

Since the primary outcomes of this study are safety, tolerability, and feasibility, adverse effects will be assessed on each participant at regular intervals throughout participation.

5 Human Subjects

5.1 Subject Population

The goal is to implant DBS in 3 participants (male and female), 21-75 years old, with severe AUD and advanced liver disease (stage 3 liver fibrosis, or compensated cirrhosis/stage 4 fibrosis), living in Western Pennsylvania. Due to potential screen fails, 3-10 subjects will be enrolled (consented) and screened. We will stop enrolling subjects when 3 participants are implanted with DBS. This study will not include vulnerable populations; only adults (>21) with the capacity and competence to fulfill informed consent will be allowed to participate.

All Participants will be referred to an outpatient addiction clinic to receive standard of care AUD treatment. We will keep track of the treatments received by every participant throughout the study duration.

Inclusion/exclusion criteria were chosen to maximize both patient safety and the benefit-to-risk ratio, given the invasive nature of this study.

5.2 Inclusion Criteria

1. Adults (all genders) 21 to 75 years old.
2. Severe primary Alcohol Use Disorder (AUD) (≥ 6 DSM-5 AUD criteria) with or without other substance use disorders.
3. Participants are seeking treatment for their AUD (participants receiving medications or other therapy for AUD are eligible).
4. Participants have insight into their alcohol use disorder (score >26 on the recognition subscale of the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES V.8)).
5. Participant has advanced compensated alcohol-associated liver disease (ALD). Compensated is defined as asymptomatic per clinical evaluation (by hepatologist or internist). Advanced is defined as fibrosis stage ≥ 3.
6. AUD is treatment refractory: unable to achieve sustained remission (>12 months) over the past 5 years, despite treatment attempts, with at least one treatment attempt involving completed residential or outpatient treatment program with pharmacotherapy, behavioral therapy, or both.
7. Stated willingness to comply with all study procedures and availability for the duration of the study.
8. Social support system and stable living arrangement to provide assurances that the subject will adhere to study requirements: family or friends who live with or near the subject, and can provide collateral information, monitor the subject's behavior, support, and encourage the subject to participate in follow-up visits and evaluations. This is evaluated by a neuropsychologist.
9. For females of reproductive potential: use of highly effective contraception for at least 4 weeks prior to DBS surgery and agreement to use such a method during study participation, and after study completion if they elect to keep the DBS system implanted and ON.

5.3 Exclusion Criteria

1. Pregnancy or lactation.
2. Non-English speaking.
3. AUD treatment with another investigational drug or other intervention within 3 months.
4. History of primary psychosis or Bipolar I disorder per the psychiatric evaluation or SCID-5 measure.
5. History of severe personality disorder that could interfere with study participation (e.g., antisocial personality disorder) per the psychiatric evaluation, neuropsychological evaluation, or SCID-5 measure.
6. IQ<75 as measured by WASI (Wechesler Abbreviated Scale of Intelligence) (evaluated by a neuropsychologist).
7. History of suicidal attempts in the past 5 years or current suicidal thoughts per psychiatric evaluation and Columbia-Suicide Severity Rating Scale (C-SSRS).
8. Decompensated ALD: clinically obvious ascites, hepatic encephalopathy, jaundice episodes, large esophageal varices with or without variceal bleeding, hepatorenal syndrome, per the clinical evaluation (by hepatologist or internist).
9. Coagulopathy: INR > 1.4, aPTT > 40 s, platelets < 100,000, abnormal platelet or fibrinogen function tests.

10. Current clinically significant medical or neurologic disease that affects brain function (e.g., recent stroke, myocardial infarction, seizures not due to alcohol withdrawal).
11. Clinically significant abnormality on structural brain MRI scan.
12. Life expectancy less than 18 months per the clinical judgement during medical evaluation (e.g., no terminal cancers).
13. Any labeled DBS contraindication or inability to have brain MRI: certain pacemakers, metal in body, inability to undergo awake operation, significant cardiac or other medical risk factors for surgery, infection, and coagulopathy.
14. History of liver transplant.

5.4 Recruitment Methods

We will recruit patients who have severe primary AUD and advanced compensated (asymptomatic) alcohol-associated liver disease (ALD). Severe AUD is defined as meeting 6 or more of the DSM-5 criteria [141]. Advanced ALD refers to fibrosis stage 3 or 4 diagnosed by liver US or liver fibrosis blood test. .

Recruitment will mainly be from inpatient services, outpatient clinics, Electronic Health Record (EHR), and research registries throughout the UPMC network. We will also use IRB-approved flyers for recruitment. Recruitment will be limited to facilities within 1-hour driving distance from UPMC Presbyterian Hospital, where all study evaluations and interventions will be performed, in order to limit the travel burden on participants for frequent assessment visits that are required for study enrollment. In order to alleviate financial burden, participants will be compensated for travel, parking, and food.

Inpatient recruitment will be led by Dr. Sharvari Shivanekar (Psychiatry Consult Liaison, Department of Psychiatry) and Dr. Payel Roy (Addiction Medicine Consult Service, Department of Medicine), who are primarily in charge of evaluating and treating all SUD patients, including AUD, throughout the UPMC system. The psychiatry Consult Liaison service sees around 1100 admitted patients per year, ~20% of whom are primary AUD patients (~220 AUD patients per year). The Addiction Medicine Consult Service sees about 1200 admitted patients per year, a third of whom are primary AUD patients (~400 AUD patients per year). They, or their team members, as well as the study coordinator will identify and prescreen potential participants from the above inpatient services and clinics listed below. If potential participants are identified, the study coordinator will reach out to the treating physician who is asked to discuss the study with the potential subject and to request the subject's permission to be contacted by the study team. Outpatient recruitment will include subjects from multiple clinics within the UPMC network, including the UPMC Alcohol-Related Liver Disease Clinic (Department of Medicine), Center for Psychiatric and Chemical Dependency Program Services (Department of Psychiatry) where Dr. Shivanekar and her team members see patients, Ambulatory Detoxification Clinics, and other clinics involved with AUD patients like the Alcohol Highway Safety Program (Department of Psychiatry). Identified patients will be provided the contact information for the study or will be approached by the study coordinator or a study investigator. Recruitment from the EHR will be enacted via Research Recruitment Alerts (RRAs) within the EpicCare interface. These alerts are triggered during clinical encounters in which the patient meets certain inclusion criteria for the study. Physicians may then assess the patient's interest in study participation and respond in the EHR accordingly. Study coordinators will be automatically notified of potential interested participants and may reach out by phone or email. The study team may prescreen the EMR prior to calling potential interested participants. The study will also leverage the Pitt+Me Research Participant Registry at UPitt to recruit participants to the study. Pitt+Me Registry is a recruitment tool run by the Clinical and Translational Science Institute (CTSI) at UPitt (see CTSI letter of support), which currently enrolls subjects who self-

report an interest in participating in research studies at UPitt and agree to be contacted regarding studies for which they could be eligible. Pitt+Me uses a proprietary algorithm that generates study matches based on self-reported interests and ICD-19/10 diagnoses from the UPMC electronic medical records (>6 million patients). Pitt+Me also uses social media to further engage the community. Currently, Pitt+Me enrolls more than 260,000 self-identified potential research participants. Of these, more than 164,000 are within the study's age range (21 - 75 years), 1,832 of whom have an alcohol-related disorder diagnosis in their electronic medical records, and 224 of whom also have alcohol-induced liver, pancreatic, or gastric disease (42 of these participants are Black). We will post our study descriptions and contact info to the Pitt+Me website. Interested subjects can pre-screen and potentially eligible participants will be referred to our study through the Pitt+Me Study Portal Dashboard.

If recruitment numbers are lacking with the above strategies, we will rely on CTSI recruitment facilitators who can help identify recruitment tools and resources in the local community, and assist with using social media to promote our research study. We will also rely on flier advertisements (e.g., on buses, AA meeting sites, hospitals lobbies), and digital advertisements using social media (e.g., Twitter, Facebook, podcasts).

Participants will be compensated for each visit; parking and food expenses during each visit will be covered, and they will additionally receive compensation for time spent on study activities. They 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 implantation or explantation surgery). They will also receive up to $70 for cognitive tasks (CGT and BART), $20/day for parking and $30/day for food. Participants will also receive a sum of $750 bonus upon completion of the study.

5.5 Screen Failures

Patients who have signed consent, but do not meet participation criteria will not be allowed to continue in the study; signed consents will be stored under double lock. During the in-person screening visit, patients' mental status will be evaluated by a psychiatrist, and then patients will undergo detailed neuropsychological evaluation to determine their competency and whether their informed consent is valid. If they are determined to not be competent, then their signed consent will be considered voided, and they will likewise not be allowed to continue in the study. If a patient later has indications that they now meet inclusion criteria (e.g., if platelets were 90,000 due to acute alcohol effects and then increased to 110,000), then they may be considered for re-screening and re-consent, before progressing to study participation.

6 Study Device

6.1 Device Selection

The hardware for DBS therapy will include the Percept PC Neurostimulator and the SenSight DBS Directional Leads, both from Medtronic (device brochures are provided in Appendix B). The SenSight electrodes will be surgically implanted bilaterally in the limbic pallidum in the brain, and the Percept stimulator will be implanted into the chest wall. The Percept stimulator will deliver electrical stimulation into the limbic pallidum via the SenSight electrodes. Both devices are FDA approved for Parkinson's disease, essential tremor, and epilepsy. They are also approved via Humanitarian Device Exemption in refractory obsessive compulsive disorder, dystonia.

Percept neurostimulator is the only stimulator that allows recording local field potentials from the area of stimulation. SenSight directional leads were specifically chosen because they allow directional stimulation, minimizing off-target stimulation and associated side-effects.

We have obtained a Right of Reference letter from Medtronic and we will obtain an Investigational Device Exemption from the FDA for the present study.

The intervention will last the entirety of the study, from the time of implantation and throughout the follow-up evaluations. Patients will be evaluated at the end of the study to determine whether intervention will continue after the study. Intervention may be cut short in cases of premature explantation (e.g., adverse events or elective study withdrawal – discussed below).

Implantation will be performed in two stages. First, the DBS directional leads will be neurosurgically implanted that is the same as standard of care DBS implantations for Parkinson's disease (except that the target here is the LP), with an inpatient stay of two to three days. To best guide the electrode placement to our area of interest, we will use each patient's structural MRI and white matter tractography in conjunction with volumetric computed tomography (CT) scan. Second, the neurostimulator will be implanted in an outpatient surgical procedure, 7-10 days after lead implantation; patients will be discharged the same day.

DBS optimization: Three weeks after the neurostimulator is implanted, we will optimize the DBS settings. DBS titration will be based on stimulation parameters used in previous OCD and SUD studies [101, 144-146]. We will start by screening each contact for clinical effect guided by craving scores and side effects such as photopsia (optic tract), tetanic contraction (posterior limb of internal capsule), or behavioral change (anterior limb of internal capsule). While it is unclear if LP DBS results in acute effects on alcohol craving, we will attempt to optimize DBS settings while measuring craving using the ACQ-SF-R questionnaire and Cue Reactivity task (we will monitor for acute changes in craving scores on the ACQ-SF-R and CR scales with the different DBS settings). If no clear clinical effect is observed, we will identify the optimal electrode contact and stimulation parameters using Lead-DBS software [147, 148]: we will 1) reconstruct and localize the electrodes and 2) simulate the VTiA at different contacts as described in our previous study [69]. DBS will be turned ON in a standard monopolar mode at 135 Hz at the primary and other DBS contacts while monitoring for side effects. We will use pulse width 90-150 μs and intensity 2-6 V, which proved to be the most effective in OCD and SUD DBS studies [101, 144, 145]. We will use symmetric biphasic pulses, shown to be more efficacious in ameliorating PD and tremor symptoms than other configurations [37, 149-151]. Stimulation intensity will be increased in small increments until we observe side effects or a voltage limit of 10V, whichever is lower, which will be considered the ceiling of stimulation. We will then reduce stimulation intensity to 70% of ceiling voltage.

DBS titration will occur over the course of 2 days. After optimization, DBS will be turned ON continuously at the optimized settings. We will continue to titrate the DBS settings during follow-up visits if participants experience delayed AE or continue to crave and relapse.

At the end of the study, if a participant experienced a significant clinical benefit (improvement of their AUD defined as significant reduction in alcohol use), and since it is not clear whether turning the DBS system OFF (or explanting it) will result in relapse, the participant will have the option to 1) keep the DBS system implanted and ON, 2) keep the DBS system implanted but OFF, or 3) have the DBS electrodes and neurostimulator explanted. All patients will have 3 follow-up visits (monthly) after the study completion. For options 1 and 2, we will continue to follow up the participants yearly (or more frequently if needed) for 5 years, and possibly for a longer duration. These follow-ups will involve standard of care clinical evaluations in the Neurology and Psychiatry clinics of the study investigators (K.M for Neurology and S.S. for psychiatry). During these visits, we will continue to screen for potential adverse effects, conduct neurological and psychiatric evaluations, including assessing their alcohol use. If the DBS did not improve a participant's AUD, we would explant the DBS electrodes and neurostimulator. For explantation, participants will be admitted to the hospital and the DBS system will be explanted. Participants will be monitored overnight in the hospital, and will receive a post-operative CT scan to ensure there are no complications from the surgery. These participants will be referred to the outpatient psychiatry clinic for standard of care follow ups.

6.2 Study Device Dispensing

The DBS system will be acquired from Medtronic Inc. (as above). The DBS leads will be surgically implanted by the neurosurgical team. The neurostimulator will be implanted in an outpatient surgical procedure, 7-10 days after lead implantation. We will follow the same standard of care procedures followed for implantation of DBS for Parkinson's disease (e.g., device identification number will be verified and recorded in the study records).

6.3 Intervention Delays and Modifications

If a participant experiences adverse effects related to stimulation, we will modify the stimulation parameters until the adverse effects have resolved.
If the adverse effects are refractory to DBS optimization, this will call for early explantation of the DBS system. There will not be modifications to the study device itself (both electrodes and stimulator are implanted).

6.4 Study Device Compliance

Participants can turn off the DBS system (Percept stimulator). This ability is given to them in case they experience delayed severe adverse effects while away from the clinical setting. The study team can monitor the device logs to know exactly when and for how long the device was turned off. DBS therapy is supposed to be continuous. If the device logs show that participants are turning off the device independent of adverse effects > 50% of the time, we will discuss with the participants the importance of keeping the DBS on all the time, and if this issue persists, we will withdraw the subject from the study and explant their DBS system.

6.5 Study Device Storage and Accountability

Between receipt of the DBS system and surgical implantation, the DBS system will be stored in the office of the principal investigator or the neurosurgeon MPI, which is separate from where the clinical supply is stored. Upon completion of the study, if the system is explanted, it will be disposed of.

6.6 Prohibited Medications

Patients receiving treatment with another investigational drug or intervention within three months will be excluded from participation. Patients with implanted devices/hardware (e.g., pacemakers, metal) which interfere with the ability to perform brain MRI will also be excluded (outlined in exclusion criteria).

List of prohibited medications:

- Anticoagulants (heparin, warfarin, or other oral anticoagulants like apixaban, rivaroxaban, dabigatran).
- Chemotherapy medications.
- Investigational medications for AUD that were started within the last 3 months before the trial.

6.7 List of allowable medications

Any medications not included in the prohibited medication list in section 6.6.

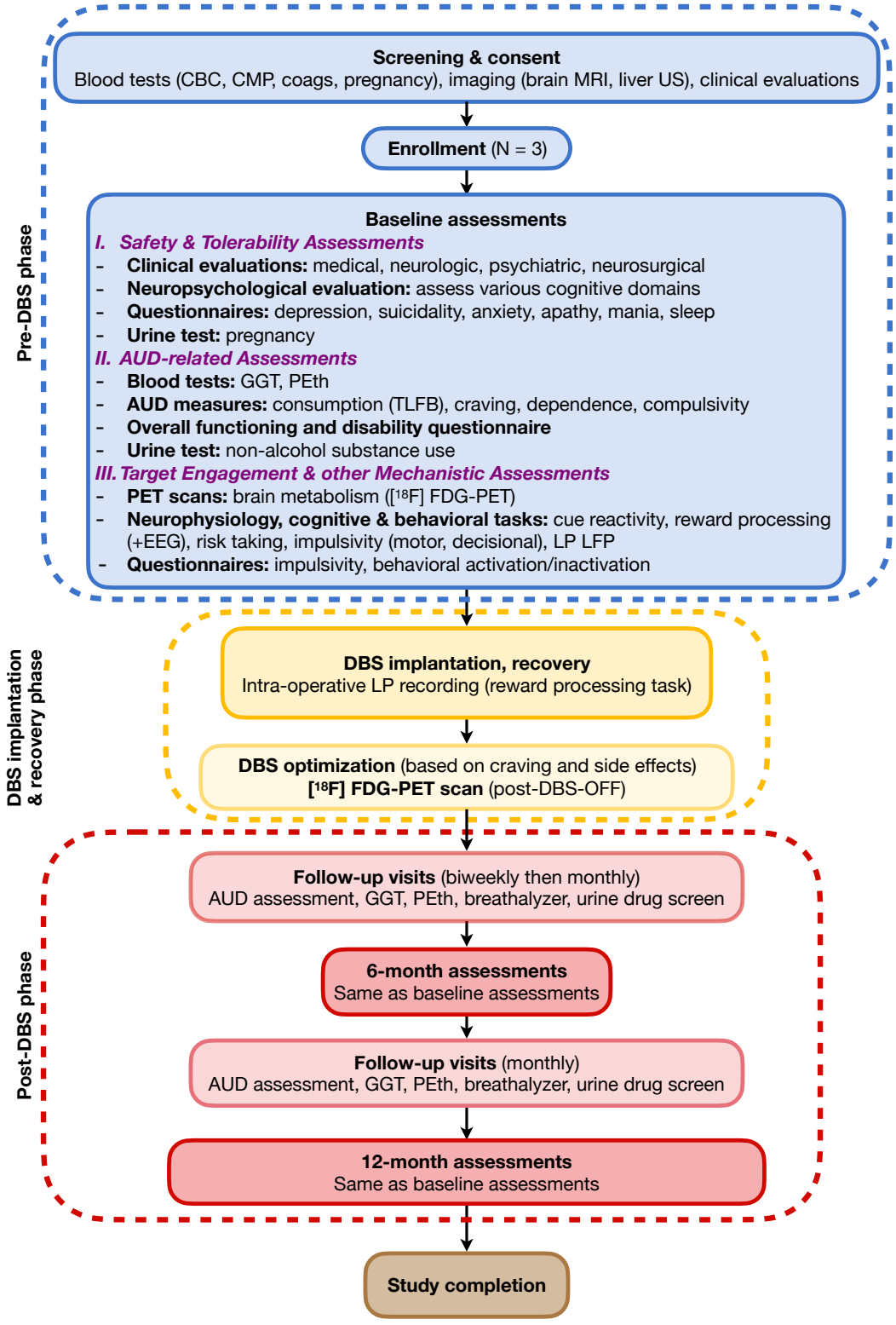
6.8 Breaking the Blind

Not applicable – study is not blinded.

7 Research Activities

Schedule of research activities is provided in Appendix A.

Overview of study design:



7.1 Screening Procedures

Pre-screening: Potential participants will undergo initial IRB-compliant pre-screening. For patients approached by a study investigator in an inpatient or outpatient clinic setting, pre-screening will occur in person at the time of recruitment. For patients who established contact over phone or email, pre-screening will be performed over the phone. Pre-screening will collect contact information, age, severe AUD diagnosis by DSM-V criteria, self-attestation of any medical, neurologic, of psychiatric diagnoses that might disqualify the potential participant from the study. We will also administer the Insight (SOCRATES) questionnaire and ask about prior AUD treatments. After initial pre-screening, potential participants will be scheduled for in-person consent and eligibility-screening.

The screening and baseline visits will occur over approximately a 4-20 day period. Depending on the resources and personnel availability, some procedures or assessment may occur on a different day than described. Refer to the Schedule of Activities in Appendix 1 for a comprehensive listing of all study procedures and assessments.

Consent and Eligibility Screening: The study coordinator will begin by reviewing the consent form with the potential participant. A physician investigator will answer any questions and ensure the participant understands the study rationale, procedures, and potential risks and benefits (outlined in the IRB-approved consent form), before the consent is signed. After each participant signs the consent form, the physician will sign the Investigator's Certification statement on the consent form. Signed consents will be stored under two sets of locks, and a copy will be provided to the participant. Participants will then undergo a diagnostic and eligibility evaluation that includes:

1. Blood tests – complete blood count (CBC: red blood cell count, white blood cell count, platelet count), complete metabolic panel (CMP: Glucose, Calcium, Sodium, Potassium, Bicarbonate, Chloride, Blood urea nitrogen, Creatinine, Albumin, Total protein, Alkaline phosphatase, Alanine aminotransferase, Aspartate aminotransferase, Bilirubin), coagulation tests (INR, PT, PTT, platelet function test, fibrinogen activity, fibrinogen antigen, thrombin time, reptilase time, thromboelastography), pregnancy test, and makers of chronic alcohol use (blood phosphatidylethanol (PEth) and blood gamma-glutamyl transferase (GGT)). We may also check liver fibrosis blood test panel to diagnose liver fibrosis in some cases (e.g., body habitus does not allow accurate liver elastography or if there is difficulty scheduling liver elastography). Some of the blood tests may occur during the baseline evaluation days. We will repeat the following blood tests on the morning of the surgery (INR, PTT, CBC, thromboelastography).
2. Imaging – structural brain MRI (3-Tesla, with contrast) and liver ultrasound; the MRI may be deferred if already available in the EHR from the last 2 years. The liver US may be deferred if subject is already diagnosed with liver fibrosis stage 3 or 4 or if liver fibrosis blood panel is used instead. Subjects to receive a liver ultrasound in the morning are asked to omit all food and fluids (except water and medications) from midnight the night before the liver ultrasound. Subjects scanned later in the day are asked to omit food and fluids (except water and medications) for at least 4 hours prior to the liver ultrasound.
3. Clinical evaluation – medical (including EKG), neurologic, and psychiatric (including a Structured Clinical Interview for DSM-5).

If all inclusion and exclusion criteria are met after evaluation, participants will be enrolled in the study and will be scheduled for pre-DBS baseline assessment. Participants will be asked to detox and abstain from alcohol use for at least 7 days prior to the DBS surgery.

In addition, during the screening, eligibility assessments, and pre-DBS evaluations, participants will be screened to ensure they are not intoxicated, and they will undergo formal mental status examination (part of psychiatric evaluation) and a detailed neuropsychological evaluation by a trained clinical neuropsychologist to ensure they have the necessary mental capacity and are competent to sign the informed consent. If the mental status or the neuropsychological evaluations show that the participant in question is not competent, they will not be allowed to continue in the study.

7.2 Randomization/Study Entry Procedures

Randomization will not be necessary as there is only one study arm.

7.3 Study Device Intervention

Refer to section 6 of the protocol for information on use of the study device. Also refer to section 6.3 for instruction on intervention delay and modification.

7.4 Safety and Efficacy Assessments/Procedures During Intervention

- **Clinical evaluations:** medical, neurologic, psychiatric, and neurosurgical evaluations will be obtained by Board-Certified clinicians in their respective specialties. The initial psychiatric evaluation includes a SCID-5 (Structured Clinical Interview for the DSM-V for research) and questions about what alcoholic beverages the subjects usually consume, which will be performed by the study psychiatrist or trained study staff. Follow-up psychiatric evaluations include CIWA scale and mental status examination. These evaluations are important to ensure participants meet eligibility criteria and to screen for any DBS adverse effects after the DBS is turned on.
- **Electrocardiogram:** this is standard-of-care clinical ECG; we will obtain it as part of the medical evaluation to ensure participants are fit for surgery.
- **Blood tests:** a qualified and well-trained nursing or other CTRC staff will obtain standard-of-care peripheral blood samples to test for liver function, blood coagulation, kidney function, pregnancy**,** and for markers for chronic alcohol use. Some of these tests are necessary for the safety of participants (e.g., liver function tests will help ensure participants are not in full liver failure, complete blood count to ensure platelets are not deficient, etc). Other tests are necessary to measure the outcomes of the study (e.g., blood markers of chronic alcohol use).
- **Urine tests:** urine drug screens and urine pregnancy tests will be obtained to screen for non-alcohol substance use and for pregnancy, respectively.
- **Breathalyzer tests:** obtained to estimate alcohol blood levels during evaluations, to ensure participants are not intoxicated.
- **Brain MRI:** tractography MRIs will enable surgical planning to target the DBS electrode to the desired brain region. Structural MRI after DBS implantation will allow accurate localization of DBS electrodes if this could not be clearly estimated from the post-op CT scan due to excessive artifact.
- **Head CT scans:** will be obtained to help with target planning (CT will be fused to the MRI image), and to ensure lack of bleeding and correct placement of the DBS electrode after surgery. 3 CT scans will be obtained (pre-op, post-op, and at the end of study – after DBS electrodes are

explanted). Low dose CT scans will also be obtained during PET imaging for attenuation correction.

- **PET scans** (Positron emission tomography): [^{18}F] fluorodeoxyglucose- (FDG) PET scans will be obtained pre- and post-DBS to assess target engagement and DBS-induced functional changes in brain circuits associated with AUD. Subjects to receive a PET FDG scan in the morning are asked to omit all food and fluids (except water, medications) from midnight the night before the FDG scan. Subjects scanned later in the day are asked to omit food and fluids (except water, medications) for at least 4 hours prior to FDG injection. Upon arrival to the imaging center, compliance to the dietary requirements will be confirmed and blood glucose level should be checked. Blood glucose level should be < 175 mg/dL (7.8 mmol/L). If blood glucose level >175 mg/dL, rescheduling the subject will be considered. If this is not an option, the scan will continue and a note will be made on the PET assessment form in the appropriate comment line following the blood glucose record.
- **Contraception:** Female participants with reproductive potential will be asked to use an effective method of contraception (birth control) from at least 4 weeks prior to DBS surgery until the end of the study in order to avoid exposing fetuses to radiation (see below), surgery and anesthesia, and unknown effects of DBS on fetuses. Choice of contraception will be decided by the participant in consultation with her PCP or OB/Gyn doctor.
- **QUESTIONNAIRES:** a variety of questionnaires are administered for various purposes as described below:
  - **AUD assessment:** this will be based on 4 questionnaires
    1) **Alcohol Timeline Followback** (TLFB): uses a calendar with some memory aids (e.g., drinking diary) to obtain estimates of daily drinking prior to interview date. We will use it to assess drinking over 180 days (for baseline pre-DBS assessment) or 30 days from the interview date (for follow-up visits, 6-, and 12-months post-DBS assessments). All study personnel administering TLFB will have proper training. If subjects have difficulty remembering their alcohol comnsumption over a 30-day period at a time, we will assess drinking on a weekly basis during the weekly phone call for MADRS (see below).
    2) **Alcohol Craving Questionnaire-Short Form** (ACQ-SF-R): 12-item questionnaire that measures 4 dimensions of alcohol urges and craving (Emotionality, Purposefulness, Compulsivity, and Expectancy); usually completed within 5 min.
    3) **Alcohol dependence scale** (ADS-25): 25-item questionnaire that assesses the severity of alcohol dependence based on questions that cover withdrawal symptoms, impaired control, insight into compulsive drinking, tolerance, and drinking related behaviors; usually completed within 5-10 min.
    4) **Obsessive Compulsive Drinking Scale** (OCDS): 14-item questionnaire that is sensitive and specific for the obsessive and compulsive aspects of drinking (thoughts, urges, ability to resist the urges); usually completed within 5-10 min.
  - **Overall functioning and disability.** For this assessment, we will use the **World Health Organization Disability Assessment Schedule 2.0** (WHODAS 2.0) questionnaire. This is a 36-question self-administered questionnaire recommended by the DSM-5 to evaluate overall functioning and disability given its high reliability [141]. The questions survey 6 domains related to the participant's wellbeing including cognition, mobility, self-care, getting along, life activities, and participation in society [152].
  - **Mood and anxiety assessments:** these questionnaires aim to screen for any adverse effects of DBS on mood and anxiety.

1) Montgomery Asberg Depression Rating Scale (MADRS): this is a 10-item scale widely used in clinical trials to screen for and assess depression severity. This will be administered weekly over the phone, and monthly during in-person follow up visits. If the phone screening shows a score that is 6 points higher than the previous screening or if it shows severe depression (>35), a study physician will evaluate the participant over the phone and decide if the participant needs to come in for an in-person urgent assessment for further evaluation and risk stratification.

2) Mood and Anxiety Symptom Questionnaire (Mini-MASQ): This is a 26-item scale (~15 min) that assesses 5 subscales of depression and anxiety including anhedonia.

3) Hamilton Anxiety Rating Scale (HARS): this widely used 14-item scale screens for general anxiety.

4) Apathy Evaluation Scale (AES): this is an 18-item scale administered over 10-20 min to screen for apathy by evaluating motivated goal-directed behaviors.

5) Young Mania Rating Scale (YMRS): this is an 11-item scale to screen for manic or hypomanic symptoms. This is usually completed within 5 min.

- **Suicidality:** the Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to assess suicidality to improve safety monitoring.
- **Pittsburgh Sleep Quality Index** (PSQI): This 10-questions self-rated questionnaire assesses overall sleep quality over the month prior to its administration. This is usually completed within 5 min.
- **Impulsivity and reward sensitivity questionnaires:**

  1) Urgency, Premeditation, Perseverance, Sensation seeking, Positive urgency, Impulsive behavior Scale (UPPS-P): this is a 59-item questionnaire that evaluates the different dimensions of impulsivity including the tendency to act under extreme negative or positive emotions, tendency to act without thinking, inability to focus on one task, and tendency to seek novel experiences. This will be used to evaluate DBS effects on impulsivity.

  2) Behavioral Inhibition System/Behavioral Activation System Scale (BIS/BAS): this scale is a 24-item self-report questionnaire that evaluates both the motivation to approach rewarding stimuli and the motivation to avoid aversive outcomes. This will be used to evaluate DBS effects on behavioral activation and inhibition.
- **Insight:** this will screen for participants' insight into their drinking problem.
  - Recognition subscale of the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES V.8)[153] (<5 min).

- **Electroencephalogram** (EEG): will be recorded during one of the behavioral tasks (Card Guessing Task, see below) (6 - 66 scalp sites, one below the right eye, and one at the nose tip). The EEG is needed as a physiological readout of the behavioral task.
- **Neuropsychological evaluation:** this is a standard neuropsychological evaluation done to ensure the participants have the cognitive capacity to understand the consent process, and to screen for any effects of LP DBS on the various cognitive domains (language, executive, visuospatial, learning and memory). This evaluation is administered as a combination of pencil and paper tasks and questions/answers format. This evaluation includes the following assessments:
  1) Orientation (~2 min): this provides a measure of the participant's mental state and attention.
  2) Wechsler Test of Adult Reading (WTAR) (~5 min): provides a measure of intelligence.
  3) Trail Making Test parts A and B (~3-8 min): tests processing speed.

4) Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) which includes list learning, story learning, copying a complex figure, line orientation task, picture naming task, coding task, digit span forward task, delayed recall of the learned list, delayed recall of the learned story, and delayed recall of the copied figure (~30 min): this assessment provides a measure of language and visuospatial functions.

5) Controlled Oral Word Association Test (~5 min): this provides a measure of verbal fluency. The timed task requires the participant to name as many words as possible that begin with a specified letter.

6) Digit Span from the Wechsler Adult Intelligence Scale- 4th Ed (backward and sequencing) (~5 min): this test provides a measure of working memory.

7) Vocabulary, Similarities, and Matrix Reasoning of the Wechsler Abbreviated Scale of Intelligence (~20-40 min): this provides a measure of language and executive functions.

- **Cognitive and behavioral tasks:** these tasks are used to measure cognitive and behavioral processes strongly associated with vulnerability to relapse to alcohol like cue reactivity, reward processing, and various aspects of impulsivity. These tasks are administered via a computer screen and the participants are required to press a button or keyboard stroke, or fill a paper questionnaire after presentation of cues on the screen. These tasks are described in detail in the Research Strategy Section and include:

  1) <u>Alcohol Cue Reactivity task</u> (CR). This task measures reactivity and craving in response to alcohol cues. Participants will be seated in front of a computer screen and will complete a 12-trial computer-automated CR procedure. Each trial consists of a relaxation prompt, a picture cue presentation (alcohol vs. neutral; the alcohol cues are informed by subjects' drinking preferences collected during the psychiatric evaluation), and a final prompt to fill out post-trial self-report ratings of craving, mood, and arousal based on how he/she felt while focusing on that picture. The CR task lasts approximately 15 minutes.

  As exposure to alcohol cues could cause craving, anxiety, and discomfort. Experienced Psychiatry Department study staff will be present at all times during cue exposure and will provide support and conduct relaxation techniques until craving returns to pre-exposure levels.

  2) <u>Card Guessing Task</u> (CGT). This task measures reward processing. The CGT consists of up to 240 trials (3-trial types; ~23 min) coded in Neurobehavioral Systems Presentation. Trials occur in the setting of alcohol vs. neutral cues. Subjects are asked to press one of two buttons indicating whether a card will show a low (1-4) or high (6-9) number. EEG will be recorded during the CGT.

  3) <u>Balloon Analog Risk Task</u> (BART). This task measures propensity for risk taking. A total of up to 350 trials will be performed. Trials will occur in the setting of either an alcohol-related or a neutral cue, followed by an image of a deflated red balloon. The participant will then press a button to increase the size of the balloon. With each pump after the first, the probability of balloon pop increases.

  4) <u>Delay Discounting</u> (DD). The DD task measures decisional impulsivity. This task consists of <u>two 15-minute runs</u>, each of which comprises up to 150 trials. In each trial, a picture cue (either alcohol-related or neutral) is then shown. Each trial presents the participant with a choice between an immediate small reward or delayed larger reward.

5) <u>Stop Signal Reaction Time Task</u> (SSRT). The SSRT task consists of 3 x 10-minute blocks, each with up to 128 trials (~30 min for the 3 blocks). Participants must respond when shown a black square (Go Signal) but then must withhold their response if the color of the square changes to red. This task measures motor impulsivity and behavioral control.

7.5 Safety and Efficacy Assessments/Procedures During Follow-up

The intervention (DBS) in this study is applied for the whole study duration. As such, the safety and efficacy assessments during follow-up visits are the same as what is listed in section 7.4. Participants will be evaluated biweekly then monthly for the duration of the study (12 months), and then monthly for 3 months after study completion (to evaluate for sustained and clinically meaningful effect) (see Schedule of Research Activities in **Appendix A**).

7.6 End of Study Safety and Efficacy Assessments/Procedures

If explanted, the patient will be monitored during the 24-hours post-surgery and will be assessed by post-op CT scan. A follow-up visit with the neurology/neurosurgery team will be scheduled 2 weeks later to ensure safety. They will then be referred to outpatient psychiatry clinic for standard of care follow-ups. Should the study team and the patient agree to leave the DBS system implanted, then the patient will be followed yearly for the next 5 years, possibly longer. These follow ups will involve standard of care clinical evaluations in the Neurology and Psychiatry clinics of the study investigators (K.M for Neurology and S.S. for psychiatry). During these visits, we will continue to screen for potential adverse effects, conduct neurological and psychiatric evaluations, including assessing their alcohol use.

7.7 Early Discontinuation Safety Assessments

Similarly to end-of-study, participants who are withdrawn from the study early will undergo explantation surgery of the DBS system. Again, these patients will be monitored overnight after surgery, and will receive a post-operative CT scan to ensure there are no complications. A follow-up visit with the neurology/neurosurgery team will be scheduled 2 weeks later to ensure safety. They will have 3 monthly follow-up visits after DBS explantation. They will then be referred to outpatient psychiatry clinic for standard of care follow-ups.

8 Potential Risks and Benefits

8.1 Reasonably Foreseeable Risks Related to Study Device

More than 208,000 DBS systems have been implanted thus far, the majority for fully FDA-approved indications, including PD, epilepsy, and essential tremor, or for Humanitarian Device Exemption indications, including obsessive compulsive disorder (OCD) and dystonia. The safety profile of DBS continues to improve, however there remains a certain level of risk to patients. In a systematic review of 52 DBS studies, including 2249 patients total, between 2008 and 2020, the overall complication rate was 16.7% (375/2249). These complications spanned different categories and a range of severities: systemic (0.9%), intracranial (2.7%), neurologic (4.6%), hardware (2.2%), and incisional (3.4%)[154]. A similar study included 96 DBS studies, including 8983 patients, investigated hardware-related complications. These included infections (5.1%), lead migration (1.6%), lead fracture (1.5%), lead failure (0.7%), neurostimulator malfunction (1.1%), and skin erosions (0.5%) [155]. No deaths were reported in either

systematic review. The risk of intracranial hemorrhage is likely higher in patients with alcohol use disorder and alcoholic liver disease due to the effects of liver disease and alcohol on platelets and other bleeding factors. Severe intracranial hemorrhage can be fatal in this patient population.

From the device brochure, Medtronic DBS therapy has a risk of adverse events related to the therapy, device, or procedure. These include: “intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications (including pain, infection, dehiscence, erosion, seroma, and hematoma), meningitis, encephalitis, brain abscess, cerebral edema, aseptic cyst formation, device complications (including lead fracture and device migration) 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.”

DBS Explantation risks: these include hemorrhage and infection but these risks are much lower than during implantation surgery (the risk of infection is low without implanted hardware and the hemorrhage risk is associated with lead insertion, not removal). There is also the possibility of emotional letdown feeling by participants whose DBS was not effective and will be explanted.

Risks associated with DBS titration/optimization include delirium, nausea, memory problems, seizures, mood disorder, mania, hallucinations, suicidal ideation, muscle weakness, shocking sensation, numbness, paresthesias, facial flushing, motor contraction, dizziness, headaches, pain, changes in vital signs, hyperactivity, euphoria, dry mouth, itching, insomnia, fatigue, restlessness, weight gain or loss, speech difficulties, blurred or double vision, unusual smell and taste sensations, and behavioral changes. In addition, it is possible that alcohol use will worsen with DBS stimulation. Specific risks associated with anteromedial GPi DBS targeting include tetanic contraction (posterior limb of internal capsule), photopsia (optic tract), behavioral changes (anterior limb of internal capsule), and behavioral and cognitive changes (substantia innominata).

A review of LP DBS in Tourette’s patients [39] reported 7 cases of stimulation-induced side effects that included lethargy, nausea, and paresthesias. However, all these symptoms are reversible with adjustment of stimulation parameters [39].

The device brochure also includes additional warnings about device interactions and precautions (see appendix B).

8.2 Reasonably Foreseeable Risks Related to Research Interventions

- **Loss of confidentiality:** This is associated with any of the study encounters
- **Electrocardiogram**: The participant may experience some skin irritation from the location of ECG leads.
- **Blood tests***:* The participant may experience some discomfort at the site of needle entry, and there is a risk of a "black-and-blue" mark. There is a remote risk of fainting or local infection. Blood tests may reveal incidental findings.
- **Liver ultrasound**: The participant may experience some discomfort from the pressure of the ultrasound probe on his/her abdomen.

- **Detox:** While undergoing detox the participant can experience alcohol withdrawal and may experience restlessness, sweating, loss of appetite, nausea, vomiting, agitation, irritability, anxiety, fast heart rate, tremor, disorientation, headache, insomnia, and seizures.
- **MRI scans with contrast:** (The below risks will be lessened by exclusion of participants with predetermined MRI contraindications - see exclusion criteria)
    - The MR-magnet may cause injury in subjects who have pacemakers or other implanted electrical devices, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware.
    - Gadolinium contrast used with MRI scans is associated with very low risk of rare vision problem in fetuses.
    - People with fear of confined spaces (claustrophobia) may become anxious during an MR-imaging.
    - People with back problems may have back pain or discomfort from lying in the scanner.
    - The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss.
    - The risks of an IV catheter (for contrast injection) include bleeding, infection, or inflammation of the skin and veins with pain and swelling. 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. People with kidney disease are at risk for a serious reaction to gadolinium contrast called “nephrogenic systemic fibrosis” which has resulted in a very small number of deaths.
    - MRI scans may reveal incidental findings.
- **PET scans** (FDG) & **CT head scans**:
    - Radiation: This proposal involves exposure to radiation from [^{18}F]FDG-PET scans, and CT scans. If subjects need to be screened for metal prior to MRI, they will receive an x-ray which could also be an additional source of radiation exposure. Participants will receive 3 radioactive injections ([^{18}F]FDG) over a period of 8 months, 3 low dose head CT scans for attenuation correction, and 3 regular head CT scans (over 13 months) for surgical planning and surgical care. The 12-month level of radiation exposure is therefore lower than the radiation dose exposure limit for RDRC studies. The maximum injected dose for each [^{18}F]FDG scan will not exceed 5 mCi. An individual subject who participates in the study will receive no more than 15 mCi of [^{18}F]FDG (5 mCi/scan) in a 12-month period. This will amount to a total radiation exposure equivalent to a uniform whole-body dose of 1.056 rem (0.352 rem*[^{18}F]FDG scan x 3 time points). The total radiation dose exposure from 3 low dose CT scans will be 0.048 (0.016/scan). The radiation dose from 2 regular head CT scans (only 2 regular CT scans in 12 months) will be 0.32 rem (0.16 rem/scan). Thus, the cumulative exposure from PET and CT scans is 1.424 rem. This is ~ 28% of the annual whole-body radiation exposure (5 rem) permitted to radiation workers by federal guidelines.

      The organ that will receive the largest absorbed radiation dose based on human dosimetry studies is the urinary bladder wall (7.2 rem for 15 mCi) for [^{18}F]FDG. As the dose-limiting critical organ for the protocol is the urinary bladder wall, the maximum

exposure to this organ will need to be limited to 15 rem/study. AUD subjects who complete all 3 PET scans will receive a total radiation dose-exposure-equivalent to the urinary bladder of 7.2 rem in a 12-month period. The proposed dose exposures are less than the single study annual limit for both whole-body (5 rem) and dose-limiting critical organ (15 rem) under proposed guidelines for RDRC studies.
This radiation dose is not expected to produce any harmful effects, although there is assumed to be no minimum level of radiation exposure for non-radiation workers considered to be totally free of the risk of causing genetic defects or cancer. The risk associated with the amount of radiation exposure participants receive in this study is considered relatively low and acceptable.
Radiation from CT and PET scans can be harmful to a developing fetus. No PET studies will be performed on pregnant or potentially pregnant women, as confirmed by urine pregnancy testing prior to FDG/PET scan. [18F]FDG is FDA approved for human use in PET imaging for assessment of abnormal glucose metabolism for numerous clinical indications. Its use in this protocol is off-label but considered to be generally safe and effective as approved by the University of Pittsburgh's Radioactive Drug Research Committee and IRB. [F-18] labeled PET radiotracer has a half-life of 110 minutes and is not considered to be a biohazard.
For reference, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil.

  - Pharmacology: The mass dose for [^{18}F]FDG used in these studies is negligible and is not associated with any pharmacological effects. However, as with any drug, the possibility of idiosyncratic reaction exists and will be mentioned in the consent forms. A physician is present at the PET facility. If adverse effects occur that require medical intervention, UPMC will administer it.
- **Fasting before PET scans or liver US:** This may cause feelings of hunger and in some subjects hypoglycemia.
- **Female contraception:** Side effects depend on the participant and the type of contraception method used. Symptoms span a wide variety, including nausea, headache, spotting between periods, breast tenderness, and mood changes.
- **Questionnaires:** The risks of AUD, mood and anxiety, sleep, and impulsivity assessments include 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 put the participant at greater risk.
- **Neuropsychological evaluation:** The risks of this assessment include discomfort from the nature of the questions or discomfort from the length of time required to complete the assessment.
- **Cognitive and behavioral tasks:** The risks of these tasks include discomfort from the nature of the tasks or discomfort from the length of time required to complete the tasks. Exposure to alcohol cues could cause craving, anxiety and discomfort. **Electroencephalogram:** The participant may experience some discomfort and some scalp/skin irritation from the location of EEG leads.
- **Financial risks during study**: All the costs of the study procedures and interventions will be covered by the study funding agency. However, participating in the study could incur financial burden on the participants in terms of lost productivity during study visit evaluations and interventions, travel and parking costs, and food costs.

- **Financial risks after study completion**: If DBS was not efficacious, it will be explanted and there will be no financial risks after study completion. However, if DBS was efficacious and the participant chooses to keep the DBS system implanted beyond the study period, there will be financial risks due to:
    1) The need for yearly follow-ups for up to 5 years and possibly longer in 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.
    2) The need to replace the battery of the neurostimulator when depleted (after several years). This cost will not be covered by the study.
    3) If a participant initially chooses to keep the DBS system implanted but decides to have it electively explanted later, after the study has ended. This cost will not be covered by the study.

8.3 Potential Benefits

According to previous studies into the role of LP in reward processing and substance use disorders, and based on the impact of LP DBS in modulating compulsive behaviors, targeting of the LP with DBS is expected to provide benefit in preventing relapse to alcohol, reduce the risk of ALD-related mortality, and improve quality of life. Reductions in alcohol consumption are associated with reduced prevalence of psychiatric comorbidities (e.g., anxiety, depression), lower psychosocial stress levels, and improved social functioning and self-confidence [156]. Overall, patients are expected to benefit from lower mortality risk and better overall functioning, independence, and quality of life.

9 Protection Against Risks

9.1 Management of device related adverse effects

Steps to prevent and manage risks related to DBS surgery, stimulation, and optimization:

DBS surgery: All participants will be required to sign a durable power of attorney because of the possibility that they may become unable to make decisions about their care and research participation during the course of participation. The surgery protocol, operation room, and DBS hardware are consistent with standards of clinical care. Post-op head CT will be obtained immediately after the surgery and prior to moving the participant to the recovery room. In the recovery room, blood pressure and mental status will be monitored by nursing every 30 min and a neurologist will perform serial mental status and neurological exams until the participant leaves the recovery room. Participants will be followed closely by the study team after the surgery through in-person post-op visits and regular phone calls and emails to monitor their recovery and screen for potential complications. If a non-emergent complication were to arise, the participants would be seen by the study physicians. If the complication were an emergency, they would be instructed to call 911 and report to the closest emergency department. In addition, and tominimize risk of bleeding related to the device surgery, we will check blood tests (platelet count, function, PT, aPTT, thrombin time, reptilase time, fibrinogen activity/antigen, thromboelastogram) that evaluate bleeding risk prior and then on surgery day.

DBS titration/optimization/stimulation: After DBS optimization and turning the DBS system ON, we will check in with all patients by phone 3-7 times per week to screen for adverse effects until their first follow-up visit 2 weeks later. Each participant will receive a copy of the Medtronic Patient Therapy Guide prior to DBS surgery and individual teaching regarding the contents of the Guide. Participants will also receive a smaller pocket-size Quick Guide reference and a patient controller for safety, which allows them to turn DBS system off in case of severe side effects from stimulation. In case of moderate side effects due to the stimulation, participants will be evaluated and the DBS re-programmed; stimulation-related side effects are usually reversible by adjusting the stimulation parameters and re-programming the DBS system. The system can be turned off if symptoms are more severe or unattenuated by re-programming.

Similarly, if participants experience **increased alcohol use** compared to baseline as indicated in their monthly AUD assessment, we will 1) adjust DBS stimulation settings, and 2) the participant will be evaluated by the study psychiatrist to identify the clinical risk from increased drinking and potential clinical interventions to mitigate this risk. If alcohol use continues to be elevated compared to baseline during two following evaluations, we will turn the DBS off and consult with the DSMB.

Risks of electromagnetic interference: The Percept neurostimulator is designed to protect against most electromagnetic interference. However, strong electromagnetic fields can still interfere with the system, even when the DBS system is turned off (interference can affect the DBS leads). In such cases, participants will be instructed on the potential risks and possible sources of electromagnetic interference, and what to do when interference is suspected: 1) move away from the source of the interference, 2) turn off the suspected source of interference, 3) use the control magnet to turn their DBS unit off, and 4) call the study team.

DBS explantation: similar to DBS implantation.

DBS risk after study completion: if participants with beneficial DBS choose to keep DBS implanted, they will be followed up in the Neurology and Psychiatry clinics of study investigators in standard of care visits. These evaluations will screen for delayed adverse effects caused by DBS.

9.2 Management of research related risks

- **Protecting confidentiality:** Confidentiality of patient information will always be maintained. All members of the study team will have the required human subjects and confidentiality training, which includes information about 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. Case report forms are coded by study identification numbers rather than any personal identifying information to avoid revealing the identity of subjects. Data analyses will be performed using the research codes as identifiers. 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. The key linking names and study identification numbers will be kept at the study site but separately from the data sets with limited access by study personnel. Only study personnel will have access to the data sets on protected servers.

- **Incidental findings:** In the case of incidental findings (e.g., blood tests, imaging), these will be discussed with the participant by a study physician who will refer them to their PCP or to a specialist for follow up, depending on the nature of the incidental finding.
- **Electrocardiogram:** This will be done by experienced staff to minimize skin irritation.
- **Blood tests:** These will be done by experienced nursing staff to minimize complications.
- **Liver ultrasound:** This will be done by experienced staff to minimize discomfort.
- **Brain MRI with contrast:** Subjects will be asked to complete an MR-screening form for each MR-scan. Participants will be screened for the presence of any contraindications to MRI before having any scan, and if they have any, they will be excluded from the study (see exclusion criteria) and will not receive an MR-scan. If subjects have a question about any metal objects being present in their body, they will inform the staff and an x-ray image will be obtained to rule out metal objects. In addition, all magnetic objects (watches, coins, jewelry, credit cards, etc.) must be removed before entering the MRI-scan room. All women of childbearing potential will have a pregnancy test performed no more than 24 hours before the MRI scan. The scan will not be done if the pregnancy test is positive. Participants will be fitted with hearing protection and subjects will notify staff of any hearing or ear problems. If a participant is claustrophobic, we will attempt to do the MRI scan in an open scanner or give them 1 mg oral lorazepam to help with the anxiety. If that remains an issue, the participant will be excluded from the study. We will test liver and kidney functions within 1 week of the MRI scan. Subjects will not receive gadolinium contrast if their kidney function is not normal.
  For the post-implantation MRI, we will follow the FDA-approved MRI recommendations detailed in Medtronic's labeling, found in the document titled "MRI guidelines for the Medtronic DBS systems" for model B35200.

- **Radiation exposure:** (PET scans, Head CT scans): The maximum whole body cumulative exposure from PET and CT scans is 1.056 rem in a 12-month period. The maximum total radiation dose-exposure-equivalent to the urinary bladder is 7.2 rem in a 12-month period. These are less than the single study annual limit for both whole-body (5 rem) and dose-limiting critical organ (15 rem) under proposed guidelines for RDRC studies. Please see section above regarding radiation exposure during this study.
  Female participants of childbearing age must use an effective method of contraception (birth control) from the time of enrollment until the end of the study in order to avoid exposure of fetuses to the radiation required by procedures this study. A pregnancy test will be obtained within 24 hours of every PET/CT scan.
- **Fasting before PET scans or liver US:** Subjects are allowed to drink water and take their meds. If they report symptoms of hypoglycemia like lightheadedness, we will check their blood glucose (part of the PET protocol) and if hypoglycemic, they may break their fasting. Subjects will be allowed to eat and drink after the PET scan or liver US are done.
- **Contraception:** If a participant experiences significant side effects from the contraception method she chose, we will recommend she consults with her PCP or OB/Gyn doctor to switch her contraception method.
- **Questionnaires:** If any of the questions trigger significant emotions that put the participant at risk, the participant will be evaluated and treated according to clinical care guidelines by the study team, including psycho-emotional support, medications, or admission, as deemed necessary by the treating study psychiatrist.
- **Neuropsychological evaluation:** Participants will be given breaks as needed during the evaluation.

- Alcohol withdrawal: participants will be educated about the risks of alcohol withdrawal and if they experience any withdrawal symptoms, they will be advised to come in for evaluation by study physicians or referred to a detox center.
- Cognitive and behavioral tasks: Experienced Psychiatry Department study staff will be present at all times during cue exposure and will provide support and conduct relaxation techniques until craving returns to pre-exposure levels. **Electroencephalogram**: This will be done by experienced staff to minimize discomfort.
- **Financial risks during study**: all the costs of the study procedures and interventions will be covered by the study funding agency. To minimize the financial burden related to lost productivity, travel, parking, and food costs, participants will be reimbursed for their time, parking and food costs for every study visit. They will receive $200 for every full day evaluation visit, $100 for every follow-up visit, and $200/day for every admission day to the hospital (during implantation or explantation surgery). They will also receive up to $70 for cognitive tasks (CGT and BART), $20/day for parking and $30/day for food. To reduce travel burden, we will also offer enrolled participants access to a ride service (e.g., Uber, Access). Participants will receive $750 bonus upon completion of the study.
- **Financial risks after study completion:** to minimize the financial risks after study completion, subjects that did not benefit clinically from the DBS will have the DBS system explanted. Subjects who benefited significantly from DBS will be given the option to have the DBS explanted (no financial risk beyond study duration). If they choose to keep the DBS implanted, we will work with their 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 they experienced from DBS. The clinical benefit translates into reduced mortality, reduced disability, improved overall functioning, and improved quality of life. We will also explain to the participants that even if they were to pay for the follow-up visits and battery replacement themselves, in a cost-benefit analysis, the financial risk from the incurred costs is minimal compared to the tremendous benefit these subjects receive from the treatment of their severe AUD with DBS (a priori, the DBS has to be efficacious in subjects who keep it implanted). We will also work with the participant's insurance company or CMS if after opting to keep the DBS system in, they decide to have it explanted after the study has ended, especially if it was deemed to be no longer necessary and the participant has achieved sustained remission.

10 Adverse Device Effects

The proposed clinical trial will use the following definitions:

Adverse effect. Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

Associated with the investigational device or, if applicable, other study treatment or diagnostic product(s). There is a reasonable possibility that the adverse effect may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse effect. Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Serious adverse effect. Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Unexpected adverse effect. Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s).

Unanticipated adverse device effect. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse effects will be assessed on each participant at regular intervals throughout participation. When an adverse effect is discovered, the event will be assessed for severity, relatedness and expectedness. All adverse events will be documented in the research records and followed until resolved or back to baseline state.

10.1 Assessment of Severity

The study team will promptly review documented adverse effects and abnormal test findings. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect, and 2) an assessment of the casual relationship between the adverse effect and any of the study interventions or procedures.

Adverse effects or abnormal test findings felt to be associated with the study interventions or procedures will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the study team.

Abnormal test findings: An abnormal test finding will be classified as an adverse effect if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention,
- The test finding leads to a change in study dosing or exposure or discontinuation of subject participation in the clinical study.
- The test finding is considered an adverse effect by the investigator-sponsor.

10.2 Relatedness

The proposed clinical trial will use the following definitions:

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The adverse effect, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.

- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The adverse effect, including an abnormal laboratory test result, occurs within a reasonable time after the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals.

- Possibly Related – There is some evidence to suggest a causal relationship. However, other factors may have contributed to the adverse effect. Although an adverse effect may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- Unlikely to be related – An adverse effect, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable and in which other drugs or chemicals or underlying disease provides plausible explanations.

- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the adverse effect is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

If the study team's final determination of causality is "unknown and of questionable relationship to the study interventions", the adverse effect will be classified as associated with the use of the study interventions for reporting purposes. If the study team's final determination of causality is "unknown but not related to study interventions", this determination and the rationale for the determination will be documented in the respective subject's case history.

10.3 Expectedness

The Multiple Principal Investigators will be responsible for determining whether an adverse event is expected or unexpected based on the known risks of DBS and similar interventions. An adverse event

will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described.

10.4 Adverse events reporting

A summary of the unanticipated adverse device effects that occurred during the previous year will be included in the FDA annual progress report as well as in the annual IRB continuing review and to the DSMB.

10.4.1 **FDA Reporting**

The investigator-sponsor will submit a completed FDA Form 3500A to the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the investigator-sponsor first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the investigator-sponsor will submit a completed FDA Form 3500Aas soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the sponsor-investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the investigator-sponsor will submit additional information concerning the reported adverse effect as requested by the FDA.

10.4.2 **IRB Reporting**

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the investigator-sponsor will report, to the IRB, any observed or volunteered adverse effect that is determined to meet all of the following criteria: 1) associated with any of the study interventions; 2) a serious adverse effect; and 3) an unexpected adverse effect. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator-sponsor's receipt of the respective information. Adverse effects which are 1) associated with any of the study interventions; 2) fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the investigator-sponsor's receipt of the respective information.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available. If the results of the sponsor-investigator's follow-up investigation show that an adverse effect that was initially determined to not require reporting to the IRB does, in fact, meet the

requirements for reporting; the investigator-sponsor will report the adverse effect to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made. Any major disputes between the study investigators and a participant, or between research investigators, will be promptly reported to the IRB.

11 Withdrawal of Subjects and Stopping Rules

11.1 Adverse Events Requiring Discontinuation

Safety Monitoring Boundaries: Every adverse effect (AE) will be evaluated for severity, expectedness and relatedness and reported to the DSMB. The study will be discontinued (pending DSMB review) if any of the following occurs:

- A higher rate or severity of AE that are definitely, probably, or possibly related to LP DBS compared to standard of care DBS, as assessed by the DSMB.
- Any death, suicide attempt, disability, or other serious AE that is definitely, probably, or possibly related to LP DBS.
- Increased alcohol use in one participant compared to baseline (>2x baseline DDD or <2x PDA) that did not improve with adjusting DBS settings, as identified by AUD assessments in 3 consecutive follow-up visits.

If the study team proposes a well-justified and implementable plan on mitigation of such events, then the study could resume if the DSMB, IRB, and FDA agree.

All other serious adverse events and unexpected events will be reported to and discussed with the DSMB prior to continuing protocol enrollment. The occurrence of a serious adverse event will be grounds for unblinding the data for that participant.

11.2 Other Criteria Requiring Discontinuation

If participants turn their DBS system off more than 50% of the time, which is unprompted by adverse effects, and if they continue to turn it off after discussion with the team, they will be withdrawn from the study and their DBS explanted.

Beginning chemotherapy or other investigational medications after enrollment will result in the subject's discontinuation from the study.

Beginning anticoagulation after enrollment and before DBS implantation will result in the subject's discontinuation from the study.

If a patient no longer wishes to continue their participation in the study, they may elect to withdrawal from the study. Normal recruitment procedures will resume to replace any participant withdrawals (see recruitment description in section 5.4).

11.3 Clinical Trial Stopping Rules

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (see ***section 11.1: Safety Monitoring Boundaries***). Written notification, documenting the reason for study suspension or termination, will be provided by the study team to study participants, DSMB, IRB, NIAAA, and FDA. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants:
  - A higher rate or severity of AE that are definitely, probably, or possibly related to LP DBS compared to standard of care DBS, as assessed by the DSMB.
  - Any death, suicide attempt, disability, or other serious AE that is definitely, probably, or possibly related to LP DBS.
  - Increased alcohol use in one participant compared to baseline (>2x baseline DDD or <2x PDA) that did not improve with adjusting DBS settings, as identified by AUD assessments in 3 consecutive follow-up visits.
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the DSMB, IRB and/or FDA.

12 Statistical Analysis

12.1 General Approach

The general analysis plan begins with data description, including basic summary statistics such as means, standard deviations, correlations, cross-tabulations, and checking for outliers and missingness patterns. Data will be evaluated for normality through goodness-of-fit tests and q-q plots. If systematic deviations from normality are detected, the corresponding variables will be appropriately transformed using logarithm or other Box-Cox transformations.

We will examine spaghetti plots for visualization of the individual trajectories over time for the longitudinal hypothesis. The analyses for the longitudinal data will consist of computation of summaries across time and at each time point. For any fitted models, we will evaluate uncertainty in the model parameter estimates and assess goodness of fit for each model using standard techniques such as residual analysis and regression diagnostics.

For testing hypotheses we will use standard methods such as the t-test; we will use the Wilcoxon and chi-square tests when appropriate. With small sample size, we will use exact methods to compute the significance level. For testing proportions, we will use the standard arcsin transformation of proportions to stabilize variance and improve the normal approximation.

For each analysis discussed, we will also consider models that control for socio-demographic descriptors for the individuals in the study when available.

Missing data:

We will enroll a replacement participant if withdrawal occurs. To account for missing data, we will use inverse weighted probability analyses and imputation-based methods, and conduct sensitivity analysis to assess the stability of conclusions across analyses.

12.2 Sample Size Determination

Since this study is primarily designed for the assessment of safety and feasibility, a cohort of 3 patients was decided upon per clinical judgement and experience.

12.3 Analysis of Primary Endpoints

The primary outcomes are:

1) *Safety and tolerability* measured as incidence of any serious adverse effect (AE), and incidence rate and severity of AEs that are definitely, probably, or possibly related to LP DBS throughout the study duration.
2) *Feasibility* measured as recruitment rate and completion rates of follow-up visits and assessments throughout the study duration.

The primary outcomes will be assessed continuously throughout the study.

H1. LP DBS for severe AUD will be deemed safe and well-tolerated by DSMB.

H1.a. LP DBS for severe AUD will not result in any serious adverse effects.

H1.b. The incidence rate of AE will be similar to standard of care DBS per the DSMB judgement.

H2. LP DBS for severe AUD will be deemed feasible.

H2.a. We will successfully recruit 3 participants for the study.

H2.b. Participants will complete >80% of all study follow-up visits and assessments.

Safety, tolerability, and feasibility will be assessed continuously throughout the study. We will screen for AEs using 4 approaches: 1) patient self-report, 2) clinical evaluations (medical, neurologic, and psychiatric), 3) questionnaires (e.g., screening for depression, suicidality, anxiety, apathy, mania) and 4) neuropsychological evaluation to screen for any LP DBS effects on various cognitive domains. Every AE will be evaluated for severity, expectedness and relatedness, and reported to the DSMB.

Safety and tolerability: The study will be deemed safe and tolerable if no serious *AE* that are definitely, probably, or possibly related to LP DBS occur during the study and if the AE severity and rate are not higher than standard of care DBS per DSMB's assessment.

Feasibility: the study will be deemed feasible if we successfully recruit the proposed number of participants and if participants complete >80% of all study follow-up visits and assessments.

12.4 Analysis of Secondary Endpoints

The secondary outcomes are:

1) *Alcohol use* measured as PDA, DDD, PEth, GGT at baseline and monthly after DBS implantation.
2) *Overall functioning* and disability measured with the WHODAS 2.0 scale at baseline and monthly after DBS implantation.
3) *Target engagement* measured with FDG-PET scans at 3 time points: pre-DBS baseline, post-DBS-OFF, and post-DBS-ON at 6 months.

The secondary outcome *PDA* as a measure of *alcohol use* is a proportion, collected at baseline and during follow-up and assessment visits (1 baseline and 12 monthly post-DBS measurements).

The other measures of alcohol use (*DDD, PEth, GGT*) and the overall functioning score *WHODAS 2.0* are continuous variables collected at baseline and during follow-up and assessment visits (1 baseline and 12 monthly post-DBS measurements).

Alcohol use and overall functioning

H3: LP DBS reduces alcohol use and improves overall functioning in subjects with severe AUD compared to baseline. Specifically, LP DBS increases PDA, and decreases DDD, PEth, GGT and WHODAS 2.0 score compared to baseline.

Primary analysis of H3: We will compare the baseline and 6-month time point using a paired t-test for each of the measures (PDA, DDD, PEth, GGT and WHODAS 2.0).

For PDA, the unit of analysis is the proportion of days X_{ij} in a month that participant i is abstinent during month j. To do the paired t-test, we use the two paired proportions X_{i0} (0 refers to the baseline measure) and X_{i6} (6 refers to the 6-month measure). We can use a t-test on the difference $D_i = (X_{i6} - X_{i0})$. This should be a reasonable approximation because the averages X over roughly n = 30

days should be approximately Gaussian. The Gaussian approximation can be improved by using the variance stabilizing transformation

$$Y_{ij} = 2arcsin\sqrt{X_{ij}}$$

Thus, we will do a t-test using the differences $2[arcsin\sqrt{X_{i6}} - arcsin\sqrt{X_{i0}}]$. With n = 3 participants, we have little power unless the effect is large (e.g., if PDA moves from 0.05 to 0.50).

Secondary analysis of H3: To assess the course of PDA, DDD, PhEt, GGT, and WHODAS 2.0 over the duration of the study while taking into account the repeated measures (13 measures for each participant – one at baseline and 12 post-DBS), we will use a **mixed-effects model**:

$$Z_{ij} = \mu + \alpha_i + \tau_j + \epsilon_{ij}$$

with random effect α_i for subject, a fixed time effect τ_j, and the error term (unexplained variation) ϵ_{ij}. We will have 39 measures (3 subjects times 13 measures per subject at months 0 to 12). For PDA, we will use the arcsin-transformed proportions described above to improve Gaussian approximation by stabilizing the variance.

Target engagement

H4: LP DBS will result in circuit specific target engagement measured with FDG-PET.

H4a. CGM (cerebral glucose metabolism) as measured with [^{18}F]FDG-PET in pre-defined cortico-limbic ROIs will be increased in post-DBS-ON compared to pre-DBS and to post-DBS-OFF conditions.

H4b. DBS-induced increases in CGM (%) at the 6-month time point will be associated with decreased alcohol use (PDA, DDD).

Analysis of H4(a): For each ROI in each of the scan types we will run a one-way Repeated Measures (RM) ANOVA comparing CGM between the 3 time points (baseline pre-DBS, DBS-OFF, and DBS-ON at 6 months), with post-hoc comparisons of DBS-ON vs. post-DBS-OFF, and DBS-ON vs. baseline.

Analysis of H4(b): We will use Pearson's correlation to assess the relationship between changes in CGM between post-DBS-OFF and 6 months and corresponding changes in measures of alcohol (PDA, DDD).

12.5 Planned Interim Analysis

Not applicable.

12.6 Exploratory Analysis

Cognitive and behavioral tasks

The outcomes of the cognitive and behavioral tasks (Cue Reactivity (CR), Card Guessing Task (CGT), Delay Discounting task (DD), Balloon Analog Risk Task (BART), and Stop Signal Reaction Time task (SSRT)) are collected at baseline and at the 6-, and 12-month time points. These outcome measures include:

- craving, positive affect, negative affect, calm, and excitement scores for CR
- β- and γ-spectral power for CGT
- discounting rate (k) for DD
- adjusted pumps for BART
- SSRT

H5: LP DBS will normalize reward processing (reduce baseline and increase event-related spectral power in the β- and γ-range) and reduce alcohol CR, temporal discounting, risk taking, and motor impulsivity post-DBS compared to baseline.

Analysis of H5: The outcome measures will be analyzed like the PET measure of target engagement measures, using one-way RM ANOVA between baseline values, DBS-ON at 6 months, and DBS-ON at 12 months, with post-hoc comparisons to the baseline.

Intra-operative neurophysiology

H6. Different neuronal populations in the LP encode rewarding vs. aversive stimuli and these neurons respond differently for alcohol vs. neutral cues.

H6.1: a population of LP neurons will show significant increase in neuronal firing during reward expectation.

H6.2: a different population of LP neurons will show significant increase in responding during loss expectation.

Analysis of H6.1 and H6.2: A 2-way repeated-measure ANOVA will be used to compare the firing frequency of the different epochs (first epoch represents baseline firing) in different trial types (win vs. neutral vs. loss) (dependent variable = firing rate, factor 1 = epoch, factor 2 = trial type), with post-hoc comparisons. In task responsive neurons, we expect to see significant epoch X trial type interaction, as well as significant effect of epochs and trial types.

13 Data and Safety Monitoring

13.1 Data Safety Monitoring Plan

Monitoring of subject safety and data quality will be the responsibility of all study personnel on the project, with primary responsibility and supervision by the principal investigators.

There will be an evaluation of the progress of the research study, including assessments of data quality, timelines, participant recruitment, accrual, and retention. The Investigator will also review the outcome and adverse effect data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed or should it be re-evaluated and changed. A summary report of data and safety monitoring meetings will be provided to the IRB at the time of the continuing review.

To protect confidentiality of patient information we will use established procedures such as storing data in locked cabinets within locked offices or locked data rooms. Report forms are de-identified to avoid revealing the identity of participants. Data analyses will be performed using the research codes as identifiers. 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. The key linking names and study identification numbers will be kept at the study site but separately from the data sets with limited access by study personnel. Only study personnel will have access to the data sets on protected servers.

Primary data management will be performed by MPIs and study staff. The Department of Psychiatry's Office of Academic Computing (OAC) will assist in data management for this proposal. The OAC comprises staff (system administrator, computer operators and programmers) and services (printer, file and database servers). The OAC provides a client/server environment for data entry and management, data processing, statistical and graphical analysis, electronic mail, and word processing. Demographic, psychiatric, biological, behavioral, and psychosocial assessment data can be entered via automated forms processed on a PC and stored in a SQL Server relational database management system on a database server computer (e.g., web-based questionnaires (WebDataXpress). Facilities include LINUX systems for time series, genetic and brain imaging data processing, management, and analysis, Microsoft SQL Server databases, servers and workstations dedicated to data collection.

File servers and workstations are behind a firewall, restricting access initiated from the outside. The Intranet server can be accessed from outside the firewall only by using Transport Layer Security and full UPMC account authentication and authorization. The database server and file servers are NOT accessible from outside of the firewall. Using the proxy server greatly reduces the possibility that an intruder can gain direct access to the web server. The only traffic permitted to the server will be via the 128-bit encryption SSL (Secure Socket Layer) protocol.

No local accounts are used and all access to files and databases is restricted. Login procedures for data entry and access are restricted to designated users through database software protection. The authorized service accounts have "insert-only" permissions to the database. Only select members of the study team have access to the specific folders that contain de-identified data.

All data will be kept for a minimum of 7 years after completion of the project.

13.2 Parameters to be Monitored

The following progress will be monitored throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of their data.

- An evaluation of the progress of the research study, including subject recruitment and retention, and an assessment of the timeliness and quality of the data.

- A review of collected data (including adverse effects, unanticipated problems requiring reporting and those captured on the non-compliance log, and subject withdrawals) to determine whether there is a change to the anticipated benefit-to-risk assessment of study participation and whether the study should continue as originally designed, should be changed, or should be terminated.

- An assessment of external factors or relevant information (e.g. pertinent scientific literature reports or therapeutic development, results of related studies) that may have an impact on the safety and study participants or the ethics of the research study.

- A review of study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data.

13.3 Frequency of Monitoring

The study team will review subject safety data as it is reported and documented. The study team will meet on a monthly basis to review subject recruitment, data, source documentation and identification of adverse events, complaints and confidentiality of subjects.

13.4 Clinical Monitoring

In accordance with 21 CFR 312.50 clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and that the conduct of the trial follows currently approved protocol.

Post-operative clinical site monitoring: after DBS implantation, participants will receive a post-operative CT scan to assess DBS electrodes placement and to screen for the presence of intracranial hemorrhage. Participants will also be clinically monitored overnight in the neurocritical care unit. While in the intensive care unit, participants will have routine assessments by clinical staff to screen for any signs or symptoms of 1) focal neurologic deficits (e.g., weakness, sensory loss, vision problems), 2) mental status changes, 3) increased intracranial pressure (e.g., headaches, somnolence), and 4) infection of the wound, brain, or meninges.

Clinical monitoring during follow-up visits: Participants are clinically assessed during follow-up visits to determine whether DBS surgery or stimulation, or any other study intervention (PET scan, etc…) has resulted in any adverse effects (medical, neurologic, neurosurgical, psychiatric, or other). In addition, to evaluate whether DBS manipulations adversely affect cognitive functions, neuropsychological testing is performed at baseline and after 6 months of DBS stimulation, and then at 12 months. If DBS-related side

effects related to stimulation parameters are observed, the DBS parameters will be changed. During the blinded portions of the study, adverse effects assessments will be made based on the assumption that the stimulation is ON.

If an adverse effect is deemed serious and potentially linked to the study, the blind may be broken, the device can be turned off, or the parameters can be changed.

All adverse effects will be followed by the study team until resolved or back to baseline state.

Adverse effects that are not responsive to changes in stimulation parameters will be brought to the attention of the DSMB to determine if the device should be removed and if the participant should be withdrawn from the study.

The participants will be asked to identify a family member or a friend who can contact the study team on their behalf if needed for safety concerns.

Finally, a nurse with physician back-up will be available 24 hours per day to answer their questions and address potential concerns.

13.5 Data and Safety Monitoring Board

Since the protocol used in this proposal is classified as “Greater than minimal risk”, an independent Data and Safety Monitoring Board (DSMB) will be created to review and oversee this study. The first meeting of the DSMB will take place before initiation of the study to discuss the protocol, approve the study commencement, and establish guidelines to monitor the study. Follow-up meeting frequency will be determined during the first meeting, and an emergency meeting will be called at any time by the Chairperson, should questions of patient safety arise. After initial approval and at periodic intervals (to be determined by the DSMB committee) during the study, the DSMB responsibilities are to:

1. Review the research protocol, informed consent documents, and plans for data and safety monitoring
2. Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, adverse events, patient withdrawals, unanticipated problems, performance of the trial site, and other factors that can affect the study outcome
3. Review safety data after the 3 participants have completed 6-months post-DBS assessments, and determine if the study met safety milestones (if the adverse events are not of a higher grade or incidence than expected)
4. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study
5. Review clinical center performance, make recommendations and assist in the resolution of problems reported by the study team
6. Protect the safety of the study participants
7. Report on the safety and progress of the study
8. Make recommendations to the study team, and if required, to the NIH/NIAAA concerning continuation, termination or other modifications of the study based on the observed beneficial or adverse effects of the study intervention
9. Monitor the confidentiality of the study data and the results of monitoring

10. Assist the study team by commenting on any problems with study conduct, enrollment, sample size and/or data collection
11. Each serious adverse effect will prompt a review by the DSMB, and the study will be suspended until it is determined whether the SAE is study-related or unrelated

The DSMB will include individuals with expertise in *Neurology, Psychiatry, Neurosurgery, Alcohol Use Disorder, DBS, Bioethics and Clinical Trials/Biostatistics*. Members will consist of persons independent of the investigators who have no financial, scientific, or other conflict of interest with the study. Written documentation attesting to absence of conflict of interest will be required.

The University of Pittsburgh Office of Clinical Research, Health Sciences / CTSI will provide the logistical management and support of the DSMB. A safety officer (chairperson) will be identified at the first meeting. This person will be the contact person for serious AE reporting. Procedures for this will be discussed at the first meeting.

14 Regulatory, Ethical, and Study Oversight

14.1 IRB Approval

The Investigator will obtain, from the University of Pittsburgh IRB, prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Investigator will promptly notify the University of Pittsburgh IRB of the deviation. The Investigator should also notify the sponsor of this event.

The IRB will review and approve the Informed Consent Document for the study and provide institutional oversight of data and safety issues. The study protocol will be approved prior to recruiting or obtaining consent from any participants. Moreover, the study will be reviewed at a minimum of annual basis (or more frequently as deemed necessary) by the IRB committee. Each participant will sign the approved Informed Consent Form prior to participating in the study.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable ICH Guidelines on GCP.

14.2 Informed Consent Procedures

Consent will be obtained prior to screening. The study coordinator will review the written informed consent form with the potential participant. A physician investigator will answer any questions and ensure the participant understands the study rationale, procedures, and the potential risks and benefits, all of which are included in the IRB-approved consent form, and the potential participant will decide whether to then sign the consent form. If the participant requires more time to decide about their participation in the study, then signing of the consent can be postponed to a later date, and the participant can review a copy of the consent in the meantime. Once signed, the original consent form will be stored under double lock and a copy will be given to the participant.

Participants must be able to consent for themselves in order to participate. Cognitive capacity and competency will be evaluated during the initial neuropsychological evaluation, and participants who are determined to lack full capacity to consent will be excluded.

Participants will be informed after the conclusion of all study procedures.

14.3 Protocol Deviations

Protocol deviations will not be permitted during the study. The occurrence of deviations will be monitored in conjunction with data and safety monitoring overseen by the DSMB. Deviations will be assessed for each participant at regular intervals throughout the study. Should a protocol deviation be identified at

any time, this will be reported to the IRB as soon as possible, and no later than 10 days following the investigator's receipt of the information.

- Events deemed to involve risk to the participant will be reported as "Unanticipated Problems Involving Risk to Human Subjects or Others".
- Incidents of non-compliance that adversely affect the rights and welfare of the participant or significantly compromise the quality of the research data will be reported as "Non-Compliance"
- Incidents of non-compliance that do not meet the above definition will not be reported to the IRB; however, these incidents will be recorded in the log.

A log will be maintained for the study and managed as part of the Data and Safety Monitoring Plan, in accordance with the requirements for research studies that are greater than minimal risk and meet the federal definition of a "clinical trial". This documentation will be available upon request. Further details on safety and clinical monitoring, as well as IRB and FDA reporting is discussed in section 13.

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Appendix A – Schedule of Research Activities

		I-Pre-DBS phase					II-DBS implantation & recovery phase				III-Open label, DBS-ON phase									Study completion			
		Screening		Baseline pre-DBS assessment			Surgery		follow-up	DBS optimization	Follow-up	6-months post-DBS assessment			Follow-up	12-months post-DBS assessment				Follow-up	Option 1	Option 2	Option 3
		phone , in person	outpatient visit 1 Day1	outpatient visit 2 Day 7 +/- 7	outpatient visit 3 Day 8 +/- 5	outpatient visit 4 Day 9 +/- 5	Admission 1 Days 20-21 +/- 14	outpatient visit 5 Day 27 +/-5	outpatient visit 6 Day 34 +/-7	outpatient visits 7-8 Days 50-51 +/-10	outpatient visits 9 to 14 Days 65, 80, 110, 140, 170, & 200 +/-7	outpatient visit 15 Day 230 +/- 7	outpatient visit 16 Day 231 +/- 5	outpatient visit 17 Day 232 +/- 5	outpatient visits 18 to 22 Days 262, 292, 322, 352 & 382 +/-7	outpatient visit 23 Day 412 +/- 7	outpatient visit 24 Day 413 +/- 5	outpatient visit 25 Day 414 +/- 5		outpatient visits 26-28 Days 444, 474 & 504 +/-14	DBS-ON yearly follow-up	DBS-OFF yearly follow-up	DBS explantation Admission 2, Days 415-416 +/-15
Initial sccreening	Phone, in person screening	X																					
	Chart review	X----------																	X				
Consent	Informed consent for study		X																				
	Informed consent for neurosurgergical procedures			X[b]			X[b]																
Neurosurgical evaluation	Neurosurgical evaluation			X			X	X	X														X
Medical evaluation	Past medical history Physical examination			X								X				X							
	EKG/telemetry			X								X				X							
Neurologic evaluation	Past neurological history Neurological exam			X								X				X							
Psychiatric evaluation	Past psychiatric history Mental status examination			X						X	X	X			X	X			X				
	SCID (Structured Clinical Interview for the DSM-V)			X																			
	SUD assessment			X						X	X	X			X	X			X				
Blood tests	CBC, INR, PT, PTT		X				X											X[e]					X
	CMP		X																				
	Thmboelastography					X	X											X[e]					X
	Platelet function, Fibrinogen activity/antigen, TT, reptilase time					X												X[e]					
	GGT				X					X	X	X			X	X							
	Phosphatidylethanol				X					X	X	X			X	X							
	Glucose					X				X			X										
	Liver fibrosis panel			X[c]																			
	Pregnancy test		X																				
Urine tests	Drug screen			X						X	X	X			X	X							
	Pregnancy test				X					X		X	X			X							
Breath tests	Breathalyzer									X											X		
Imaging	Liver US			X[c]																			
	Structural brain MRI			X						X[d]													
	Tractography brain MRI (DTI) (surgical planning)			X																			
	FDG-PET				X					X			X										
	Pre-, post-operative CT scan						X[a]																X
Neuropsychological evaluation	Orientation					X								X				X					
	Wechsler Test of Adult Reading					X								X				X					
	Trail Making Test parts A and B					X								X				X					
	RBAN					X								X				X					
	Controlled Oral Word Association					X								X				X					
	Digit span from Wechsler Adult intelligence scale					X								X				X					
	Vocabulary and Similarities of the Wechsler Abbreviated Scale of Intelligence					X								X				X					
	Matrix Reasoning					X																	
AUD assessment	Alcohol Timeline Followback			X						X	X	X			X	X			X				
	Alcohol Craving Questionnaire-Short Form			X						X	X	X			X	X			X				
	Alcohol Dependence Scale			X						X	X	X			X	X			X				
	Obsessive Compulsive Drinking Scale			X						X	X	X			X	X			X				
Cognitive & behavioral tasks	Alcohol Cue Reactivity				X					X	X^		X		X		X						
	Reward expectancy (card guessing task + EEG)				X		X						X				X						
	Risk taking (BART)				X								X				X						
	Decision impulsivity (Delay Discounting)				X								X				X						
	Motor impulsivity (SSRT)				X								X				X						
Questionnaires	Insight (SOCRATES)	X																					
	Overall functioning and disabilty (WHODAS 2.0)			X							X	X			X	X			X				
	Suicidality (C-SSRS)			X							X	X			X	X							
	Depression (MADRS)			X						X*	X*	X*			X*	X*							
	Anhedonia (MASQ)				X								X				X						
	Anxiety (HARS)				X								X				X						
	Apathy (AES)				X								X				X						
	Mania (YMRS)				X								X				X						
	Behavioral activation & inhibition (BIS/BAS)				X								X				X						
	Overall impulsivity (UPPS-P)				X								X				X						
	Sleep (PSQI)				X								X				X						
DBS implantation/ explantation	Implantation of Sensight Directional Leads — Medtronics (admission)						X																
	Implantation of Percept Neurostimulator — Medtronics (outpatient)							X															
	DBS explantation (admission)																						X
Limbic pallidum physiology	Intra-op physiology (Card Guessing Task+EEG)						X																
DBS titration	DBS titration (based on craving, side effects)									X	X^				X^								
Contraception	Females only			X----------															X		X		
Adverse events review							X----------												X	X			X
Medication review				X----------															X	X			X

End of Study (visit 25 day 414, or admission 2)

^ as needed if side effets or intense cravings

* MADRAS will be administered weekly over the phone in between monthly in-person visits

[a] Pre- and post-op CT scans will take place during admission 1

[b] surgical consent can occur during initial neurosurgical evaluation or during admission

[c] to determine fibrosis stage: either liver US test or fibrosis blood test

[d] MRI will be performed if electrodes not well visulaized with post-op CT

[e] if the DBS system is to be explanted

Appendix B – Device related information from manufacturer (Medtronic Inc.).

Percept brochure

SenSight brochure

Percept manual

SenSight manual

Medtronic DBS stimulators

Medtronic DBS MRI compatibility