Feasibility of Deep Brain Stimulation as a Novel Treatment for Refractory Opioid Use Disorder

Protocol No: DBS OUD 01

IDE Number: G190011

Approval:

Protocol Version 10.0 25 Jan 2023
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GLOSSARY

AIOP	Adult Intensive Outpatient Program
ASPD	Anti Social Personality Disorder
COAT	Comprehensive Opioid Addiction Treatment
CRC	Chestnut Ridge Center
CSSRS	Columbia Suicide Severity Rating Scale
DA	Dopamine Levels
DBS	Deep Brian Stimulation
DDU	Dual Diagnosis Unit
DSMB	Data Safety and Monitoring Board
EEG	Electroencephalogram
FDG	Fluoro-Deoxy-Glucose
fMRI	Functional Magnetic Resonance Imaging
GSR	Galvanic Skin Response
HDE	Humanitarian Device Exemption
HPLC	High pressure liquid chromatography
IDE	Investigational Device Exemption
IPG	Implanted Pulse Generator
IRB	Institutional Review Board
LFP	Local Field Potential
MAT	Medication Assisted Treatment
MRI	Magnet Resonance Imaging
NAc	Nucleus Accumbens
NIH	National Institutes of Health
NIDA	National Institute on Drug Abuse
OUD	Opioid Use Disorder
OCD	Obsessive Compulsive Disorder
PET	Positron Emission Tomography
PHI	Personal Health Information
RMH	Ruby Memorial Hospital
SUD	Substance Use Disorder
TENS	Transcutaneous Electrical Nerve Stimulation
TBI	Traumatic Brain Injury
THC	Tetrahydrocannabinol
US	United States
VC	Ventral Capsule
VS	Ventral Striatum
WV	West Virginia
WVU	West Virginia University

SCHEMA

PURPOSE	The purpose of this clinical study is to investigate the safety, tolerability, and feasibility of DBS of the NAc/VC for participants with treatment refractory opioid use disorder (OUD) who have cognitive, behavioral, and functional disability. This study is part of a NIDA U01 cooperative agreement award with WVU that will provide critical information for planning subsequent clinical trials.
DESIGN	This is an open-label, safety study for participants who have severe, treatment refractory OUD that are eligible to have DBS targeting the ventral internal capsule (VC) and nucleus accumbens (NAc).
DURATION	Participants will be followed in an inpatient service for approximately 2 weeks to gather screening and baseline data followed by DBS placement and up to 6 weeks inpatient for clinical stabilization and DBS titration. All participants will then be followed 2x week for 12 weeks in the outpatient setting and then 1x week through 52 weeks post titration. At the end of the study, participants may enter a long-term safety follow up for up to five years.
SAMPLE SIZE	Four participants will be enrolled in this study
POPULATION	Persons ages 21- 50 years who meet eligibility criteria.
OBJECTIVE	The overall objective of this study is to assess the safety and feasibility of using DBS to treat opioid use disorder.

PRIMARY ENDPOINTS

- Safety and tolerability, as measured by all adverse events related to DBS will be measured for a minimum of 24 weeks.
- Opioid use as measured by quantitative urine toxicology via high pressure liquid chromatography (HPLC)

SECONDARY ENDPOINTS

- Cognitive Function evaluation at 12 and 24 weeks following titration

- Drug overdoses defined according to the National Library of Medicine (www.nlm.nih.gov)
- Incidence of serious infectious disease complications (e.g., endocarditis, osteomyelitis, septic arthritis, etc.)
- Retention in traditional medication assisted treatment (MAT)
- Patient survival
- Safety and adverse events monitoring for 52 weeks post DBS titration
- Mood, craving and executive function at 12 and 24 weeks
- Other substance use as measured by quantitative urine toxicology via high pressure liquid chromatography (HPLC)
- Qualitative urine toxicology for opioids and other substance through 12 and 24 weeks
- Self-reported opioid and other substance use through 12 and 24 weeks
- Fluoro-Deoxy-Glucose (FDG) PET/CT (to examine for increased frontal metabolism following DBS of the NAc/VC) measured at pre-titration and Week 12 and 52 week follow up.
- If performed, ^{11}C Raclopride PET/CT (to examine for changes in dopamine following DBS of the NAc/VC) measured at pre-titration and Week 12 and 52 week follow up.
- Local field potentials (to examine for changes in the neural response in the NAc following DBS of the NAc/VC) measured pre-titration and Week 12 follow up.

1.0 STUDY OBJECTIVE

The overall objective of this study is to assess the initial safety, tolerability, and feasibility of using DBS to treatment refractory opioid use disorder (OUD). This overall objective will be attained through completion of the following specific aims:

- Evaluate initial safety and tolerability of DBS study in four participants with treatment refractory OUD.
- Demonstrate the physiological changes associated with NAc/VC DBS through PET imaging.

2.0 INTRODUCTION

2.1 Background

Opioid use disorder (OUD) is a troublesome pattern of opioid use that causes significant impairment or distress. It is estimated that almost 16 million worldwide have a current or past opioid-use disorder (Soyka, 2015). As per 2016 estimate, in the Unites State of America itself there were 11.8 million people who misused opioids (Substance Abuse and Mental Health Services Administration) The global burden of disease from opioid-related conditions approaches 11 million life-years lost from health problems, disabilities, and early death (Degenhardt, Whiteford, & Hall, 2014). Given the prevalence of opioid medical and nonmedical uses, it is considered to be one of the new epidemics and is the leading cause of the non-accidental death (Benumof, 2016). As per CDC (Centers for Disease Control and Prevention, Understanding the Epidemic) from 1999 to 2016, more than 630,000 people have died from a drug overdose, which is 5 times higher than in 1999 and opioid overdose itself was involved in around 66% of these deaths. As per the latest estimate by the CDC, about 115 Americans die every day from an opioid overdose (National Center for Health Statistics 2017, Wide-ranging online data for epidemiologic research (WONDER). OUD not only results in non-accidental deaths but also has a huge social and economic implications. The total economic burden was estimated to be $78.5 billion for opioid overuse and dependence, of which $28.9 billion was only related to increased health care cost (Florence, Zhou, Luo, & Xu, 2016). The OUD is specifically concerning for the West Virginia (WV), as the recent data show that West Virginia (WV) continues to have the highest drug overdose mortality in the nation with 52 deaths per 100,000 population (Hedegaard, Warner, & Miniño, 2017) well ahead of all other states.

Current treatment of OUD is far from ideal. State-of-the-art treatment, which includes medically assisted treatment (MAT) combined with psychosocial interventions result in a 50% response rate, at best. Individuals failing standard OUD treatment have a substantial risk of death. Given the enormously increasing socio-economical burden and the death risk with the OUD, newer and innovative treatment modalities are urgently needed. In addition to the need for newer and innovative treatments as individuals with addiction are literally dying in the streets, we also need to better understand the mechanisms of action for addiction for a specifically focused treatment in future.

Deep Brain Stimulation (DBS), where a tiny electrode is precisely placed deep inside the brain at a specific target with a computer assisted stereotactic technique and connected to a subcutaneous implanted pulse generator (IPG) giving an electrical stimulation to the area targeted/implanted, has demonstrated safety and efficacy in treatment refractory movement disorders and obsessive-compulsive disorder and is being investigated in a number of other neurobehavioral conditions, including but not limited to, obsessive compulsive disorders (OCD), depression, tourette's disease, eating disorders, traumatic brain injury, Alzheimer's disease and addiction (Alonso et al., 2015; de Haan, Rietveld, Stokhof, & Denys, 2015; Denys et al., 2010; Dougherty et al., 2015; Greenberg et al., 2010; Greenberg et al., 2006; Grover et al., 2009; Hamani et al., 2009; Houeto et al., 2005; Kalivas & Volkow, 2005; Laxton et al., 2010; Lipsman et al., 2017; Lipsman et al., 2013; Lozano et al., 2016; Mayberg et al., 2005; Muller et al., 2009; Rezai et al., 2018; Rezai et al., 2016; Smit et al., 2016; Whiting et al., 2013) With recent developments in the understanding of the neural basis of addiction (Kalivas & Volkow, 2005; Koob & Volkow, 2010, 2016) the Nucleus Accumbens (NAc) emerged as the key area of the nodal neural network with robust neural connections through the ventral internal capsule (VC). We hypothesize that in treatment refractory OUD, DBS of the (NAc/VC) will modulate the brain reward circuitry by increasing dopamine (DA) levels and thus increasing frontal lobe activity. This will thereby reduce opioid cravings and opioid use and additionally improve inhibition and decision making and thus improve outcomes (e.g. decreased drug overdoses).

The overarching goal of this study is to evaluate the safety, tolerability, feasibility of NAc/VC DBS for treatment refractory OUD. There is a high rate of morbidity and death, in addition to a huge health care burden associated with OUD (Benumof, 2016; Centers for Disease Control and Prevention, Understanding the Epidemic; Degenhardt et al., 2014; Florence et al., 2016; National Center for Health Statistics 2017, Wide-ranging online data for epidemiologic research (WONDER); National Institute on Drug Abuse. Overdose Death Rates, 2017; West Virginia Department of Health and Human Resources Bureau for Public Health West Virginia Drug Overdose Deaths Historical Overview 2001, 2015, 2017). In treatment refractory OUD, given the life threatening nature, innovative approaches and more invasive interventions including DBS warrant investigation.

The research team led by Dr. Ali Rezai at West Virginia University (WVU) is highly experienced in all the elements necessary to conduct this trial: state-of-the-art treatment of OUD, NAc/VC DBS surgery, titration and programming, neuroimaging, executive function assessment, and clinical trial management.

2.2 Preliminary Data

Current OUD Treatment Outcomes at WVU

The Comprehensive Opioid Addiction Treatment (COAT) program was developed at West Virginia University (WVU) in 2004 in response to the emerging opioid epidemic (Zheng et al., 2017). The COAT program uses a structured group-based multidisciplinary and multimodal approach including: 1) behavioral intervention (both group and individual therapy), 2) required participation in community peer recovery support groups, and 3) MAT with buprenorphine/naloxone. A key element of the COAT program includes continued maintenance on buprenorphine/naloxone rather than mandatory tapering. Clinic visits consists of a shared group-based 30-minute medical appointment with the prescribing physician followed by a 90-minute group psychotherapy session with a skilled therapist and case manager. In this model of care, participants advance through 4 stages of treatment, based on their sustained abstinence and program adherence: Stage 1- treatment initiation with weekly sessions, Stage 2 – those successfully sustaining abstinence for 90 days progress to attending clinic bi-weekly, Stage 3 – after one year of abstinence, monthly clinic sessions with group therapy, and Stage 4 – after two years of abstinence, monthly clinic sessions without group therapy.

The Intensive COAT program, where we will recruit participants for our proposed study, is for those patients who are unable to sustain abstinence in the standard COAT program. These patients are prone to relapse and fail to sustain recovery in the weekly group and are thus seen thrice weekly. While the WVU COAT program has successfully treated thousands of OUD patients, the treatment failure rate remains high, with only half of the patients continuing to be engaged in COAT at three months. According to a multisite, randomized trial, the rate of unsuccessful outcomes following the discontinuation of 12-weeks of medication assisted treatment (MAT) using buprenorphine-naloxone exceeded 90%. Moreover, even those who were stabilized on MAT, the rate of successful outcomes was less than 50 percent (Weiss et al., 2011), consistent with our own experience.

DBS of NAc/VC Investigations

In the past twenty years, the use of brain pacemakers or deep brain stimulation (DBS), has emerged as a promising new therapeutic approach for neuro/psychiatric disorders with over 170,000 DBS implants worldwide. DBS has the advantage of being adjustable and reversible since it can be turned off if unwanted effects are reported.

DBS is an FDA approved and Medicare reimbursed therapy for patients with Parkinson's disease, essential tremor, dystonia and OCD (under a Humanitarian Device Exemption [HDE]), and most recently, treatment refractory epilepsy. Patients with OCD undergoing DBS have obtained significant improvements in overall functioning, independence, quality of life enhancement, return to work or school and resumption of daily activities (Greenberg et al., 2010; Greenberg et al., 2006) and the same is true for the other medical conditions mentioned above, although they will not be reviewed in detail here (Malone et al., 2009; Rezai et al., 2018; Rezai et al., 2016). Several clinical investigations have explored the utility of DBS to treat a range of neurobehavioral disorders including OCD, depression, Tourette's disease, eating disorders, , traumatic brain injury, Alzheimer's, and addiction (Alonso et al., 2015; de Haan et al., 2015; Denys et al., 2010; Dougherty et al., 2015; Greenberg et al., 2010; Greenberg et al., 2006; Grover et al., 2009; Hamani et al., 2009; Houeto et al., 2005; Kalivas & Volkow, 2005; Laxton et al., 2010; Lipsman et al., 2017; Lipsman et al., 2013; Lozano et al., 2016; Mayberg et al., 2005; Muller et al., 2009; Rezai et al., 2018; Rezai et al., 2016; Smit et al., 2016; Whiting et al., 2013)

Although the exact mechanism of action of DBS is still unknown, it is clear that the effects of DBS are not achieved by a highly localized effect on neurons adjacent to the electrode but by modulating effects on neural networks associated with the target region (Benazzouz & Hallett, 2000; Chiken & Nambu, 2016; McIntyre, Savasta, Kerkerian-Le Goff, & Vitek, 2004; Montgomery & Gale, 2008; Udupa & Chen, 2015). A distributed mechanism of action is supported by the findings of a recent study using DBS of NAc to treat OCD (Figee et al., 2013). Using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), the authors showed that NAc-frontal network modulation of DBS was able to restore normal NAc function and cortico-striatal circuitry connectivity. Dysfunction in cortico-striatal circuitry is postulated to be a core feature of OUD, and therefore these findings provide a rationale for the use of DBS in the treatment of OUD.

The PI has extensive experience with DBS surgery in various brain targets with more than 2000 patients from 1997-2018 with a surgical complication rate of 1% hemorrhage (symptomatic 0.1%), 2% infection, and 2% device related complications (personal communication-AR), consistent with standards in the field. Dr. Rezai has further participated as a key investigator or PI in several NAc/VC DBS clinical trials for neurobehavioral disorders. These studies demonstrated: 1) safety and efficacy for intractable OCD (Greenberg et al., 2010; Greenberg et al., 2006), 2) safety but not efficacy in a randomized controlled trial for major depression (Dougherty et al., 2015), 3) safety and improved functional outcomes in pilot trials in Alzheimer's disease (Scharre et al., 2018) and traumatic brain injury (Rezai et al., 2016), and 4) lack of feasibility in a pilot trial of morbid obesity (Rezai et al., 2018). Furthermore, Dr. Rezai has experience in neuroimaging with DBS, demonstrating impact on brain circuitry (Rauch et al., 2006; Rezai et al., 2016; Scharre et al., 2018). Specifically, FDG PET studies of NAc/VC DBS in patients with OCD, and Alzheimer's disease have shown moderation of pathological brain glucose metabolism in the frontal cortex (Rauch et al., 2006; Scharre et al., 2018).

Research Studies in Support of the NAc as a DBS Target for Treatment of OUD

Animal Studies. DBS to the shell of the NAc in drug-seeking rats selectively blocked reinstatement of cocaine seeking induced by a priming dose of psychomotor stimulants (Vassoler et al., 2008) and conditioned place preference for morphine in rats is attenuated by DBS (Liu et al., 2008). Rats trained to self-administer cocaine in the presence of light showed decreased cue-induced reinstatement of cocaine when they were pretreated with deep brain stimulation of the NAc (Guercio, Schmidt, & Pierce, 2015).

Lesioning the NAc decreased food hoarding and gave rise to sustained weight reduction in obese mice (Halpern et al., 2011; Kelley & Stinus, 1985). Similarly, DBS stimulation of the NAc decreased caloric intake and also resulted in a sustained weight loss in obese mice (Halpern et al., 2013; Ho et al., 2015). Following high frequency DBS of the NAc in animals, there is a decrease in the firing rate of the orbitofrontal cortex pyramidal cells and enhanced synchronicity of the thalamo-cortical circuit (McCracken & Grace, 2007, 2009)

Human Studies. Review of the DBS literature reveals that stimulation of the NAc and VC has been performed since 1998 in patients with various neurobehavioral disorders including depression, OCD, other anxiety disorders, addiction, TBI, Alzheimer's disease and eating disorders. DBS of the the NAc/VC has been proven safe and beneficial for the treatment of OCD, leading to the FDA HDE approval in 2009 (Greenberg et al., 2010; Greenberg et al., 2006; B. Nuttin, Cosyns, Demeulemeester, Gybels, & Meyerson, 1999) A double-blind study involving stimulation of the NAc/VC showed a significant reduction of OCD symptoms (B. J. Nuttin et al., 2003). In addition, DBS has been shown to be safe and effective in open-label pilot study for major depression (Malone et al., 2009). In a recent double blind, phase III sham-controlled trial for depression, stimulation of the NAc/VC was found safe, but failed to show a significant difference in outcome between sham and real stimulation (Dougherty et al., 2015). Case reports also show that stimulation of the NAc/VC can contribute to smoking cessation (Mantione, van de Brink, Schuurman, & Denys, 2010) and to a reduction in heroin seeking behaviors (Zhou, Xu, & Jiang, 2011)

Recently, Figee et al., examined network changes induced by NAc/VC DBS with fMRI and EEG in fully implanted patients with OCD (Figee et al., 2013). Their findings suggest that modulation of NAc/VC activity changes frontostriatal connectivity. These changes correlated with symptoms improvement. Moreover, such a study highlights the fact that DBS effects may not just be confined locally, to the relatively small target area, but may be due to a broader modulation of several neural circuits and networks. Figee et al. also measured dopamine D2/3 receptor availability in the straitum with iodobenzamide single photon emission computed tomography in OCD patients. Following NAc/VC DBS there was a decrease in the binding potential in the NAc suggesting that DBS induced striatal dopamine release (Figee et al., 2014). In one of the recent study of NAc/VC DBS for heroin addiction done outside USA was very encouraging and 5 out of the 8 patients achieved abstinence from heroin for more than 3 years (Chen et al., 2018).

In summary, the reasons to consider DBS of the NAc/VC as an intervention for patients with treatment refractory OUD are threefold: 1) The NAc is heavily implicated in both normal and drug-induced reward processes and plays a key role in cue-induced craving. Moreover, the NAc acts as a ‘motivation gateway’ between the limbic system involved in emotion and systems involved in motor control, and is uniquely located to modulate activity in other regions of the brain. 2) OUD, characterized by dysfunction in several integrated neural pathways, creates the need for a treatment that directly targets and normalizes the affected brain circuits. 3) Preclinical studies and human case studies report encouraging results for DBS as a treatment for OUD and have shown that NAc/VC appears to be a promising and safe target.

3.0 STUDY DESIGN

This is an open-label, safety, tolerability, and feasibility study for participants who have treatment refractory OUD that are eligible to have deep brain stimulation (DBS) targeting the NAc/VC. The major objective of this study is to test safety, tolerability, and feasibility of DBS in this population.

4.0 STUDY POPULATION

4.1 Inclusion Criteria

A candidate will be eligible if he/she meets all the following criteria:

- Age 21-50 years at time of enrollment.
- Fulfills current DSM-5 (American Psychiatric Association Diagnostic and statistical

manual of mental disorders, 5th ed, 2013) diagnostic criteria for OUD (severe) and at least a 5-year history.

- Participants may have comorbid Substance Use Disorder diagnoses at mild, moderate or severe levels, however OUD must be the primary disorder the individual is seeking treatment and the other use disorders must occur in the context of relapse.
- Failed at least two levels of treatment (outpatient/COAT, intensive outpatient/intensive COAT, residential, inpatient, AIOP, DDU), which included buprenorphine/naloxone. Treatment failure is defined as the initiation and discontinuation/completion of treatment with subsequent substance relapse.
- At least one lifetime overdose survival. Drug overdose criteria and symptoms defined according to the National Library of Medicine.
-
- Demonstrated greater than 5 years of refractory symptoms of OUD.
- Family/Social Support/Involvement (as assessed via the Multidimensional Scale of Perceived Social Support)
- Is able to comprehend the consent form and provide informed consent.
- Women of reproductive potential must have negative pregnancy test and agree to use acceptable forms of contraception.

4.2 Exclusion Criteria

A candidate will be excluded if he/she meets any of the following criteria:

- Medical problems requiring intensive medical or diagnostic management.
- Diagnosis of acute myocardial infarction or cardiac arrest within the previous 6 months.
- History of a neurosurgical ablation procedure.
- Any medical contraindications to undergoing DBS surgery.
- History of hemorrhagic stroke.
- Life expectancy of < 3 years
- Past or present diagnosis of schizophrenia, psychotic disorder, bipolar disorder, or untreated depression other than one determined to be substance induced (assessed via SCID-5). Any treated depression considered to be non-substance induced has to have been in remission for one year.
- Baseline assessment on the Hamilton Depression Rating Scale (HAM-D) > 17
- Increased risk of suicide based upon any positive response regarding passive or active suicidal ideation with or without intent over the past 3 months or history of active suicidal ideation with intent within the past 3 years on the Columbia Suicide Severity Rating Scale (CSSRS).
- Meet the criteria for Cluster A or B Personality Disorders (assessed via SCID-5-PD).

- Diagnosis of dementia or any other disorder which has led to a clinically significant cognitive impairment (assessed via DRS-2).
- Personal history of any clinically defined neurological disorder, including organic brain disease, epilepsy, stroke, brain lesions, or multiple sclerosis.
- Personal history of previous neurosurgery (brain) or head trauma that resulted in loss of consciousness
- History of suicide attempt within the past 3 years .
- Parental history of completed suicide.
- Abnormal coagulation lab studies, defined as INR >1.4, abnormal PT/PTT.
- Platelet count < 75×109/L
- Uncontrolled hypertension (systolic > 185 mmHg and/or diastolic > 110 mmHg), demonstrated on each of three repeated measurements taken within one hour regardless of whether or not the patient is taking antihypertensive medications.
- Implanted neurostimulators (e.g., vagus nerve stimulator, spinal cord stimulator, DBS)
- Any current CNS infection or infection with the Human Immunodeficiency Virus (HIV) (due to potential for confounding the analysis of study outcomes).
- Unable to undergo MR-imaging because of implanted pacemakers, medication pumps, aneurysm clips, metallic prostheses (including metal pins and rods, heart valves or cochlear implants), shrapnel fragments, permanent eye liner or small metal fragments in the eye that welders and other metal workers may have, or if candidates are uncomfortable in small closed spaces (have claustrophobia) or cannot lie comfortably on their back for up to one hour.
- Documentation of MRI abnormality indicative of a neurological condition that may jeopardize the participant's safety, study conduct, or confound the participant's diagnostic assessments.
- Substance abuse treatment mandated by court of law.
- Known destruction and/or damage to the NAc, ventral striatum, or ventral capsule region as determined by MRI.
- Pregnant or planning to become pregnant.
- History of seizure disorder and/or epilepsy. Participants with documented febrile seizures will not be excluded. Seizures which are secondary to substance use and/or withdrawal will not be exclusionary as long as they occurred more than one year ago.
- Conditions requiring repeated MRI scans.
- Conditions requiring diathermy
- Uncorrectable coagulopathy and patients on anticoagulant/antiplatelet medications who cannot be off anticoagulants/antiplatelet medications during the standard perioperative care period..
- Primary language other than English.

- Any evidence of cutaneous bacterial infection (e.g., impetigo, cellulitis, etc.)
- Any evidence of systemic infection, including fever, malaise, or leukocytosis.

In the event that there is a discrepancy between medical records and other sources of information, specifically related to psychiatric diagnoses (e.g. suicidal ideation and/or attempts), members of the clinical study team will conduct a thorough investigation to reconcile these differences. Other sources of information include self-reported information provided by the subject, collateral information provided by others (e.g. members of the subject's support system), and clinical impressions of the treatment team. Similar reconciliation will be performed if conflicting documentation related to psychiatric history is present within medical records (e.g. inconsistent historical information documented in separate notes). Findings from this reconciliation will be presented to the study team and will be reviewed by collaborators at NIDA (study sponsor), designated project consultants, the DSMB (which includes external, non-WVU faculty), and the designated external independent eligibility reviewer. Eligibility will be determined after review of their recommendations.

4.3 Recruitment Process

Participants will be recruited from the WVU COAT program, a comprehensive treatment program that combines medication assisted treatment with psychosocial treatment for OUD. The program has been recognized by Substance Abuse and Mental Health Services Administration (SAMHSA) as "The West Virginia Model". There are currently multiple training sites throughout the state and practitioners across the nation come to learn about program to implement this treatment in their own region. COAT utilizes a multidisciplinary and multimodal approach including medication assisted treatment (buprenorphine/naloxone), behavioral intervention (both group and individual therapy) and case management services. There is ongoing enrollment in the COAT program with up to 700 active participants at any given time. As 50% of participants admitted into the COAT program are retained, there is a sufficient recruitment pool and experience suggests that study recruitment will not be a barrier to the conduct of this clinical trial.

For this protocol, we will recruit participants from the Intensive COAT program for those treatment refractory participants who are unable to sustain abstinence with standard COAT treatment and repeatedly relapsed and have thus been referred to intensive COAT. The standard treatment protocol for Intensive COAT includes thrice-weekly behavioral intervention and buprenorphine/naloxone maintenance. If a participant is deemed eligible and is enrolled, continued active participation and engagement in the Intensive COAT or standard COAT program, as clinically indicated, will be required throughout the duration of the proposed study.

4.4 Informed Consent

Informed consent will be obtained by the PI or their designee with documented specific knowledge of the study. The informed consent form will be reviewed with the participant and all questions will be addressed before the participant signs the consent form. Participants will be given an explanation of the study, including the screening process and required testing; educated on the possible risks and benefits to participating Participants will have the option to consent to videotaping throughout the study. The videotapes will be used for educational purposes. It will be explained that the results of the screen will determine if they will be invited to participate in the next phases of the study. It will also be explained that even after passing the initial screen and entering the study phase, subsequent assessments may determine that he/she is not a suitable candidate and be discontinued from the study. The specific procedures will be outlined and the risks and benefits clearly described. The participant will be given a copy of the signed consent, and a copy of the consent will be placed in the patient's medical record as well as the research file.

The screening process will consist of routine physical, neurological, and psychiatric examinations, laboratory tests, cognitive examinations and neuroimaging.

4.5 Concomitant Therapy

For this study, a prescription medication is defined as one that can be prescribed only by a properly authorized/licensed clinician. All supportive care is allowed, there are no restrictions on the medications allowed concomitantly during participation on the trial. Medications to be reported in the Case Report Form for the duration of the study, from the time of informed consent to the end of follow-up, are concomitant prescription medications related to buprenorphine/naloxone maintenance. All other concomitant medication may be abstracted from medical records as needed during data analysis or adverse event reporting. All supportive care is allowed, there are no restrictions on the medications allowed concomitantly during participation on the trial. Likewise, medications may be added, tapered, or withdrawn as determined by the clinical treatment team and/or study investigators.

During the conduct of the trial, shortwave/ultrasound/microwave therapy and implantation of metallic items (eg. prostheses) or other neurostimulators are not allowed as concomitant therapy, however there are no other restrictions on procedures during participation on the trial. Procedures to be reported in the Case Report Form for the duration of the study, from the time of informed consent to the end of follow-up, include all medical and surgical procedures including elective ones.

5.0 STUDY PROCEDURES

The study design will consist of the following five study phases with the corresponding schedule of events related to testing and procedures:

Table 1. Table of Events

Method	Phase I	Phase II	Phase III	Phase IV	Phase V	Phase V	Phase V
	(Upto 5 weeks)		(Up to 3 weeks)	(Up to 3 Weeks)	(12 week timepoint)	(24 week timepoint)	(52 week timepoint)
	Screening	Baseline	DBS Surgery	DBS Titration and Stimulation	Follow Up	Follow Up	Follow Up
Structural /Functional MRI[1]	✓		✓		✓		✓
X-Ray, chest[2]	✓						
Electrocardiogram (ECG)	✓						
History and Physical Examination	✓						
Vital signs[3]	✓	✓	✓	✓	✓	✓	✓
Blood and urinalysis test[4]	✓				✓		
MRSA screening nasal swab	✓						
Urine toxicology[5]	✓	✓	✓	✓	✓	✓	✓
Pregnancy test[6]	✓	✓	✓	✓	✓	✓	✓
Neurological Examination	✓						
NIH Stroke Scale[7]	✓	✓	✓	✓	✓	✓	✓
Psychiatric Examination	✓			✓			
Cognitive and Behavioral Testing[8]	✓	✓	✓	✓	✓	✓	✓
Affective/Emotional Assessments[8]	✓	✓	✓	✓	✓	✓	✓
Opioid and other substance use assessments[8]	✓	✓	✓	✓	✓	✓	✓
Executive Function Measures[8]	✓	✓	✓	✓	✓	✓	✓
Physiological Monitoring[8]	✓	✓	✓	✓	✓	✓	✓
Adverse Effects	✓	✓	✓	✓	✓	✓	✓

C11-Raclopride PET/CT[9]				✓	✓		✓
FDG PET/CT Scan				✓	✓		✓
Local Field Potentials[10]				✓	✓	✓	✓
EEG[11]	✓	✓	✓	✓	✓	✓	✓

[1] Structural MRI scan to be obtained approximately one week prior to surgery (but no more than 2 weeks prior to the surgery date) and may be completed at the end of the three-week surgical recovery period prior to the DBS titration and programming, and at the 12 and 52 week follow-up visits. Structural MRI may also be performed at PI's discretion if clinically indicated prior to or after DBS surgery. Functional MRI (resting state and task-based using a cue reactivity paradigm) may be performed prior to DBS surgery, at the end of the three-week surgical recovery period, and at the 12 and 52 week follow-up visits. and in conjunction with LFP acquisition/cue reactivity at long term follow up visits.

[2] Chest x-ray obtained during screening/baseline evaluation.

[3] Vital signs will be measured daily throughout the inpatient stay, twice weekly during follow up through week 12, and then once weekly through the week 52 follow up visit.

[4] Labs tests at screening include pregnancy test, CBC with Diff, BMP (Na, K, Cl, HCO3, BUN, Creat, Glucose), PT/INR, PTT, Type and Screen, HIV1/HIV2, Hepatitis C, Urinalysis, liver function panel. Labs at 12 week follow up visit include CBC with Diff, BMP (Na, K, Cl, CO_2, BUN, Creatinine, Glucose), and liver function panel.

[5] Qualitative urine toxicology will be obtained twice weekly through the 12 week follow up, and then once weekly through post-titration Week 52. Quantitative urine toxicology (HPLC) for Cocaine, Amphetamine, Delta-9-tetrahydrocannabinol, benzodiazepines, morphine, heroin, Suboxone, fentanyl, and opioids/opioid analogs will be performed at screening and at 4, 8, and 12 weeks following discharge.

[6] Pregnancy testing: Serum hCG will be performed on all women of childbearing potential at screening and at the 12 week and 24 week follow up visits. Urine pregnancy will be performed twice weekly through the 12 week follow up, and then once weekly through post-titration Week 52. When being performed prior to MRI, pregnancy test must be within 24 hours of the MR imaging.

[7] NIHSS will be performed at screening/baseline, then immediately post-operatively, after each titration/stimulation adjustment, and then monthly through post-titration Week 52.

[8] Refer to Appendix A

[9] PET scans with and without Methylphenidate, may be performed

[10] Local Field Potentials (LFPs) to be measured during specific tasks and as clinically indicated

[11] EEG may be measured during screening/baseline and post-surgical phases while the subject is at rest and/or during specific tasks (e.g. delayed discounting)

[12] Up to 3 weeks outpatient and approximately 2 weeks inpatient

Phase I and II: Screening and Baseline

Screening of participants from the COAT clinic to determine if they meet the inclusion/exclusion criteria. Critical to assuring recruitment of appropriate patients meeting the eligibility criteria, Dr. Daryl Shorter, a board-certified addiction psychiatrist, but not a member of the study team, will review each candidate's de-identified records prior to enrollment and may unilaterally veto enrollment of any patient he deems inappropriate for this protocol. This independent evaluation is to reduce bias from the investigators enrolling their own patients.

Study participants will complete an inpatient stay for approximately 2 weeks at Chestnut Ridge Center (CRC; the inpatient psychiatric hospital of WVU) on the addiction service where they will undergo screening (Phase I) and then baseline assessment (Phase II) prior to DBS placement. After providing informed consent, screening assessments may be initiated prior to their admission to the CRC as inpatients. If performed prior to inpatient admission, screening assessments will be conducted within 3 weeks of the admission date.

After completion of the screening period, if the participant is assessed as being appropriate for the surgery, the participant will undergo the baseline assessment and then will undergo the DBS placement (Phase III) at Ruby Memorial Hospital (RMH), which includes a total time of up to a 3-week recovery period at RMH and CRC. Following the surgical recovery period, the participants will undergo titration sessions (Phase IV) for up to 3 weeks at CRC. Once titration is complete the participants will be discharged from inpatient care to continue outpatient monitoring 2 times a week for 12 weeks while continuing with the COAT program. This may be at the intensive COAT program or the standard COAT program based on the clinical stability of the participant. After the primary outcome assessments 24 weeks after titration, they will be followed for up to 52 weeks following DBS titration (Phase V) or until study participation ends.

Participant Replacement Guidelines

Participants who have signed the informed consent document and have been enrolled in the trial may withdraw that consent at any time during the trial. Data collected up to the time of consent withdrawal will remain in the database as part of the study. Participants withdrawing consent before deep brain stimulator (DBS) implantation will not have any collected data relevant to the safety or tolerability of the device or other study endpoints. For that reason, one additional participant may be recruited to the study for each participant withdrawing consent prior to DBS placement, thereby assuring the required number of participants from whom study endpoints are collected. Participants withdrawing consent after DBS placement will not trigger additional participant recruitment.

Screening/Baseline assessments will include:

- Blood and urine will be collected for the following lab tests:
  - CBC with Differential
  - BMP (Na, K, Cl, CO_2, BUN, Creatinine, Glucose)
  - PT/INR
  - PTT
  - Type and Screen
  - HIV1/HIV2
  - Hepatitis C
  - Liver function panel
  - Pregnancy test as applicable
  - Urinalysis
  - Qualitative urine toxicology
  - Quantitative Urine Toxicology (HPLC)
    - Cocaine
    - Amphetamine

  - Delta-9 tetrahydrocannabinol
  - Benzodiazepines
  - Morphine
  - Heroin
  - Suboxone
  - Fentanyl
  - Opioids and any detectable opioid analogs
- MRSA screening by nasal swab
- History and physical examination, neurological examination, psychiatric examination
- ECG
- Imaging tests (MRI/Chest x-ray)
- Vital signs

Demographic and Drug and Alcohol Use Inventory: Demographic information including age, sex, education, ethnicity and characterizes years, recent (days in the past 30) (Mahoney, Kalechstein, Newton, & De La Garza, 2017), and daily drug use for opioids and other illicit substances. (Paper- or computer-based assessment will be completed at Screening)

Behavioral Assessments *(Approximate time to administer-2 hours*)

The study will utilize various established neuroimaging tests as well as neuropsychological, behavioral, mood, cognitive, and addiction measures to evaluate the status of the participant. These measures are employed to support the primary and secondary objectives of the study.

Structured Clinical Interview for DSM-5 Axis I Disorders (SCID-5) (First et al., 2016a): The SCID-5 is a semi-structured interview guide for making DSM-5 diagnoses. It is administered by a clinician or trained mental health professional that is familiar with the DSM-5 classification and diagnostic criteria. Guide covers the DSM-5 diagnoses most commonly seen in clinical settings including depressive and bipolar disorders, schizophrenia spectrum and other psychotic disorders, substance use disorders, anxiety disorders, obsessive-compulsive disorder, posttraumatic stress disorder, attention-deficit/hyperactivity disorder, and adjustment disorder. This paper-based measure uses an algorithmic approach to scoring, assessing, and diagnosing DSM-5 disorders and takes approximately 45 minutes to administer. (Paper-based assessment will be completed at screening.)

Structured Clinical Interview for DSM-5 Axis II Personality Disorders (SCID-5-PD) (First et al., 2016b): SCID-5-PD is a semi-structured interview guide for making DSM-5 diagnoses. The SCID-5-PD is the updated version of the former Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) to assess the 10 DSM-5 Personality Disorders across Clusters A, B, and C as well as Other Specified Personality Disorder. This measure is designed to build rapport, the SCID-5-PD can be used to make personality disorder diagnoses, either categorically (present or absent) or dimensionally. Assessment will be completed at screening.)

Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet, Dahlem, Zimet, & Farley, 1988): Brief research tool designed to measure perceptions of support from 3 sources: Family, Friends, and a significant Other. The scale is comprised of a total of 12 items, with 4 items for each subscale. (Assessment will be completed at screening).

Brief Psychiatric Rating Scale (BPRS) (Overall, Gorham, 1988) is a clinician administered instrument which assesses the level of 18 symptom constructs such as hostility, suspiciousness, hallucination, and grandiosity. The rater enters a number for each symptom construct that ranges from 1 (not present) to 7 (extremely severe). (Assessment will be completed at baseline, pre/post DBS surgery, and post each titration session at Investigator discretion)

Depression and suicidal ideation assessment and monitoring
(To be administered at screening, three times weekly during the inpatient period, post each titration session, twice weekly during the outpatient period through the 12 week follow up, and then once weekly through Week 52 post-titration. To be administered in the long-term follow up period quarterly (approximately every three months) or more frequently at investigators discretion based on clinical assessment (e.g. subjective changes in craving, mood, etc.) and after any stimulation adjustments. During the inpatient titration phase, these required post-titration assessments will count toward the three-time weekly inpatient assessment requirement as long as they remain within normal limits following the titration session. If a titration session is performed during the outpatient phase or long-term follow up period, these required post-titration assessments will count towards the outpatient assessment requirement as long as they remain within normal limits following the titration session.

Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) is an multiple item questionnaire used to assess depression and has been clinically validated. Depression is rated based on the responses and takes about 10 minutes to complete.

Columbia–Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011) is a suicidal ideation and behavior rating scale and has been clinically validated. It is assessed through a series of questions for suicidal risk and takes about 5-10 minutes to complete.

Cognitive Assessments (Clinical Neuropsychological Measures)

(These standard clinical measures of cognitive/neuropsychological function will be administered at screening/baseline, and 12, 24 and 52 weeks following titration with approximate time to administer-2 hours)

Dementia Rating Scale – 2nd Edition (DRS-2) (Jurica, 2001): Measures cognitive function at lower ability levels where some other evaluation instruments are limited by floor effects. The DRS-2 also can be used to track changes in cognitive status over time. By design, the DRS-2 measures deficits in a large range of higher cortical functions and differentiates deficits of varying severity levels. Utilizes frequently as a screener for DBS eligibility. Estimated administration time is 30 minutes.

Wide Range Achievement Test-Fourth Edition, Reading Subtest (Wilkinson, 2006): The WRAT-4 is an individually administered test of word reading. The participants read the words and the examiner determines whether the word is pronounced correctly. The participants are not corrected if they do not say the word correctly. The total number of correctly pronounced words is transformed into a Standard Score with a mean of 100 +/- 15. Age norms are used. The test is used to roughly approximate the participant's general ability (IQ). It takes about 5 minutes to administer. Estimated administration time is 5 minutes.

Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II) (Wechsler, 2011) Provides an index of estimated intellectual functioning via the Vocabulary, Similarities, Block Design, and Matrix Reasoning subtests. Estimated administration time is 30 minutes.

Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) – Digit Span Subtest (Wechsler, 2008): The Digit Span subtest will assess focused auditory attention and concentration. Estimated administration time is 5 minutes.

California Verbal Learning Test-Second Edition, Short Form (CVLT-II-Short) (Delis D.C., 2000): The CVLT-II-Short measures verbal learning and memory. It includes 9 words across a series of 4 trials, free recall following a short delay, free and cued recall following a delay, recognition, and forced choice. This test will provide information on the effects of DBS on verbal learning and memory. Estimated administration time is 15 minutes.

Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996): Assess visual learning and memory (outcome variables: the number of figure details recalled across the three learning trials, number recalled following a 25 minute delay, and number correct when presented in recognition format). Estimated administration time is 10 minutes.

Trails Making Test Parts A and B (TMT-A, TMT-B) (Reitan, 1958)): The TMT provides a measure of visual scanning and mental flexibility. It involves drawing lines between letters and numbers, in sequential order. Estimated administration time is 10 minutes.

Controlled Oral Word Association Test (COWAT) and Animal Fluency (Lezak, 1995): The COWAT provides a measure of verbal fluency. The timed task measures include phonemic fluency, which requires the participant to name as many words as possible that begin with a specified letter in one minute. Also includes semantic fluency which requires the participant to name as many animals as the can in one minute. Estimated administration time is 5 minutes.

Stroop Color-Word Interference Task (SCWT) (Stroop, 1935): Assess information processing and inhibition (outcome variables: total number of words read and colors named in 45 seconds). Estimated administration time is 5 minutes.

Wisconsin Card Sorting Test (WCST) (Berg, 1948): Assess the ability to display flexibility in the face of changing schedules of reinforcement. A number of stimulus cards are presented to the participant. The participant is told to match the cards, but not how to match; however, he or she is told whether a particular match is right or wrong. Estimated administration time is 10 minutes.

Embedded Performance Validity Tests – Obtained via the WAIS-IV Digit Span subtest (Wechsler, 2008) and CVLT-II-SF Forced Choice Recognition (Delis D.C., 2000). Assesses the participant's engagement during testing.

<u>Affective/Emotional Measures</u> <u>*(Approximate time to administer is 30 minutes)*</u>

Comprehensive Psychopathological Rating Scale (CPRS) (Asberg, Montgomery, Perris, Schalling, & Sedvall, 1978): The CPRS rates anxiety and depression and is completed by the participants using paper and pen. This paper- or computer-based measure takes less than 5 minutes to complete. (To be administered at screening/baseline, three times weekly during the inpatient period, twice weekly during the outpatient period through the 12 week follow up, and then once monthly through Week 52 post-titration.)

Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978): The YMRS scale consists of 11 items to monitor the development of hypomanic/manic symptoms during the study. Items 5, 6, 8, and 9 are rated on a scale from 0 (symptom not present) to 8 (symptom extremely severe). The remaining items are rated on a scale from 0 (symptom not present) to 4 (symptom extremely severe). Items 5, 6, 8, and 9 (irritability, speech, content and disruptive-aggressive behavior) are given twice the weight of the remaining 7 in order to compensate for the poor condition of severely ill participants. The YMRS total score ranges from 0 to 60.This paper- or computer-based scale is done with a clinician or other trained rater with expertise with manic participants and takes 5-10 minutes to complete. (To be administered at screening/baseline, three times weekly during the inpatient period, post each titration session, twice weekly during the outpatient period through the 12 week follow up, and then once monthly through Week 52 post-titration. During the inpatient titration phase, this required post-titration assessment will count toward the three-time weekly inpatient assessment requirement as long as it remains within normal limits following the titration session. If a titration session is performed during the outpatient phase, this required post-titration assessment will count towards the once or twice weekly outpatient assessment requirement as long as it remain within normal limits following the titration session). YMRS will also be performed after any titration in the long-term follow up period.

Profile of Mood States-Short Form (POMS-SF) (Curran, Andrykowski, & Studts, 1995): The POMS-SF is a commonly used measure of psychological distress. It provides a rapid, accurate assessment of fluctuating mood states. The POMS will provide another assessment of the potential changes in mood following DBS. This paper- or computer-based assessment takes 3-5 minutes to complete. (To be administered at screening/baseline, three times weekly during the inpatient period, twice weekly during the outpatient period through the 12 week follow up, and once monthly through Week 52 post-titration.)

Positive Affect Negative Affect Schedule-Short Form (PANAS-SF) (Watson, Clark, & Tellegen, 1988) as measure of negative and positive affect. The PANAS consists of 10 items: five positive items and five negative items. Participants will indicated whether they agree with a statement (e.g. I feel upset right now) on a 5-point scale (1 = not at all to 5 = extremely). This paper- or computer-based assessment takes approximately 3 minutes to complete. (To be administered at screening/baseline, three times weekly during the inpatient period, twice weekly during the outpatient period through the 12 week follow up, and once monthly through Week 52 post-titration.)

Barratt Impulsiveness Scale (BIS) (Patton, Stanford, & Barratt, 1995): 30-item self-report questionnaire assessing impulsive personality traits. Each item is rated on a 4-point scale ranging from 1 (never) to 4 (always) with a range from 30–120. This paper- or computer-based assessment takes 5 minutes to complete. (To be administered at screening/baseline, three times weekly during the inpatient period, twice weekly during the outpatient period through the 12 week follow up, and once monthly through Week 52 post-titration.)

Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995): The SHAPS is a brief (14-item) self-report instrument that measures anhedonia. It has been validated in both healthy volunteers and psychiatric participants including those with depressive, psychotic spectrum and substance use disorders. This paper- or computer-based measure takes 2-5 minutes to complete. (To be administered at screening/baseline, three times weekly during the inpatient period, twice weekly during the outpatient period through the 12 week follow up, and once monthly through Week 52 post-titration.)

Opioid and Other Substance Consumption and Craving Measures *(Approximate time to administer these paper- or computer-based assessments is 30 minutes).*

Brief Substance Craving Scale (BSCS) (Dyrenforth, Goldsmith, Mezinskis, Cohen, 1995) The BSCS is a 16 item, self-report instrument which assesses craving for substances of abuse over a 24 hour period. Intensity and frequency of craving are recorded on a five-point Likert scale. (To be assessed up to twice daily, based on subject's availability, from screening through Week 52 post-titration.)

Timeline Follow-back (TLFB): The TLFB is an assessment method that obtains estimates of daily opioid and other substance use. Using a calendar, the participants provide a retrospective estimate of daily substance use since their previous self-report. This paper-and-pencil or smartphone/tablet measure takes 5 minutes to complete. (To be administered at screening/baseline, three times weekly during the inpatient period, twice weekly during the outpatient period through Week 52 post-titration.)

Sensitivity to Reinforcement of Addictive and other Primary Rewards (STRAP-R) (Goldstein et al., 2010). This 3-item test assesses participant's response to substances and natural reward. This smartphone/tablet measure takes 5 minutes to complete. (To be administered at screening/baseline, three times weekly during the inpatient period, twice weekly during the outpatient period through the 12 week follow up, and then once monthly through Week 52 post-titration.)

Cue Presentation and Craving Measurements: A set of 20 images of opioid and other substance related pictures from our laboratory library will be presented. Prior to and immediately after viewing the cues, participants will complete paper- or computer-based assessment visual analog scale (VAS) designed to assess craving and mood. This assessment takes 5 minutes to complete. (Craving VAS (without cues) will be administered on a smartphone/tablet up to twice daily, based on subject's availability, from screening through Week 52 post-titration. Cue presentation/Cue Induced Craving VAS Measurements will be performed up to three times weekly from screening throughout the inpatient period, once weekly through Week 24 post-titration, and once monthly through Week 52 post-titration. Cue presentation/Cue Induced Craving VAS Measurements may be conducted more frequently at the investigator's discretion. In the long-term follow up period, cue reactivity will be performed quarterly (approximately every 3 months) or more frequently at investigators discretion based on clinical assessment (e.g. subjective changes in craving, mood, etc.) and may be performed in conjunction with data collection from the Percept device.

Experimental Measures of Executive Function

The proposed study will employ a series of experimental cognitive tests focused on elements of executive function that supplement the clinical neuropsychological measures. The following tasks will be administered to participants via a smartphone/tablet to capture day-to-day variability in measures of response inhibition, working memory, cognitive flexibility, and attention. In addition to the analysis of performance scores that data will be integral for the development of a machine learning model to predict recovery and relapse. The battery of tests will take approximately 15 minutes.

The Eriksen Flanker Task (Eriksen, 1974) is a response inhibition test to assess the participant's ability to suppress a response that is inappropriate based on the task rules. Participants are to respond, left or right, to the direction of the middle arrow (target arrow) of five aligned items. The task consists of congruent stimulus (the direction of the target arrow and flanker arrows are the same), incongruent stimulus (the direction of the target arrow is opposite of the flanker arrows), and neutral stimulus (flanker items are different then the target arrow). The dependent variable is the measurement of reaction time to select the direction of the target arrow. The standard findings are that the incongruent stimulus has greater reaction times as compared to congruent and neutral stimulus. (To be assessed up to twice daily, based on participant's availability, from screening through Week 52 post-titration.)

N-Back Task (Kirchner, 1958) is a measure of working memory where participants monitor a series of stimuli and respond whenever a stimulus is presented that is the same as the one presented in a predefined previous trial. Test are defined as items that are 1, 2, or 3 items back from the current stimulus whereas 1-back is less difficult then then 3-back since less information is needed in working memory to correctly respond. The dependent variable is the percentage of correctly identified items. (To be assessed up to twice daily, based on subject's availability, from screening through Week 52 post-titration.)

The Psychomotor Vigilance Task (PVT; Dinges, Powell, & Computers, 1985) is a reaction time test that measures a person's sustained attention to a cue presented on a screen at random inter-stimulus intervals. In addition to the measures of reaction time to correct responses the errors of commission (responding when there is not response cue) and omission (failing to respond to a response cue). A variation of the PVT will also be utilized to examine cognitive flexibility. A rule set, which changes between trials, will be given to the participant where they will have to respond to specific colors and withhold respond from others (i.e. respond to red dots and not green). (To be assessed up to twice daily, based on subject's availability, from screening through Week 52 post-titration.)

Balloon Analogue Risk Task (BART) (Lejuez, Read, Kahler, Richards, Ramsey, Stuart, Strong, Brown, 2002) The Balloon Analogue Risk Task is a computerized measure of risk taking behavior. The BART models real-world risk behavior through the conceptual frame of balancing the potential for reward versus loss. In the task, the participant is presented with a balloon and offered the chance to earn money by pumping the balloon up by clicking a button. Each click causes the balloon to incrementally inflate and money to be added to a counter up until some threshold, at which point the balloon is over inflated and explodes. Thus, each pump confers greater risk, but also greater potential reward. If the participant chooses to cash-out prior to the balloon exploding then they collect the money earned for that trail, but if balloon explodes earnings for that trial are lost. Participants are not informed about the balloons breakpoints; the absence of this information allows for testing both participants' initial responses to the task and changes in responding as they gain experience with the task contingencies. Risk taking is a related, but phenomenologically distinct process from impulsivity. (To be administered up to twice weekly, based on subject's availability, from screening through the inpatient period, and may be performed once weekly during outpatient phase through Week 24, and approximately once monthly through Week 52 post-titration). To be administered in the long-term follow up period quarterly (approximately every three months) or more frequently at investigators discretion based on clinical assessment (e.g. subjective changes in craving, mood, etc.)

Delayed Discounting Task (Richards, Zhang, Mitchell, de Wit, 1999) assesses cognitive functions which are often impaired in substance users including: decision-making, impulsivity, and inhibitory control. This task presents subjects with hypothetical choices between $10 available after a specified delay (i.e., 1, 2, 30, 180 or 365 days) and a smaller amount available immediately (e.g., "Would you rather have $10 in 30 days or $2 now?"; Richards et al., 1999). An adjusting amount procedure is used to derive indifference values (i.e., the primary outcome on this measure) between the delayed standard and immediate adjusting options for each of the five delays assessed. An indifference value reflects the smallest amount of money an individual chooses to receive immediately instead of the delayed standard amount ($10) at the specified delay. (To be administered (May be performed in combination with EEG; To be administered up to twice weekly, based on subject's availability, from screening through the inpatient period, and may be performed once weekly during outpatient phase through Week 24, and approximately once monthly through Week 52 post-titration). To be administered in the long-term follow up period quarterly (approximately every three months) or more frequently at investigators discretion based on clinical assessment (e.g. subjective changes in craving, mood, etc.).

Dot-Probe Task (Halkiopoulos, 1981) Assesses selective attention. Two stimuli, one of which is neutral and one of which is threatening, appear randomly on either side of the screen. The stimuli are presented for a predetermined length of time (most commonly 500ms), before a dot is presented in the location of one former stimulus. Participants are instructed to indicate the location of this dot as quickly as possible, either via keyboard or response box. (To be administered up to twice weekly, based on subject's availability, from screening through the inpatient period, and may be performed once weekly during outpatient phase through Week 24, and approximately once monthly through Week 52 post-titration)

Physiological Monitoring via wearable devices such as a wrist device and/or finger ring: The participant will wear a Garmin watch and/or Oura ring as much as possible for the duration of the study (inpatient and outpatient). Measures of continuous heart rate and activity are collected as well as spot measurements of heart rate variability, body temperature, and rate of respiration. Sleep durations (onset and offset) will also be measured from the two devices. Data from the Garmin watch and Oura ring will be uploaded automatically into the RNI cloud infrastructure (FusionSports's Smartabase). ECG (heart rate data) and GSR (Galvanic Skin Response) may be collected from Shimmer3 (https://imotions.com/shimmer3-gsr/) units. Eye tracking (measures of fixation, saccade, scan patterns, pupil dilation) may be collected from Tobii pro x3-120 (https://www.tobiipro.com/product-listing/tobii-pro-x3-120/) during cue presentation sessions.

Interoceptive processing (Park, 2016) will be used to assess how the nucleus accumbens processes and predicts interoceptive signals. Tactile and/or auditory stimuli will be presented at different intensities, and the participant will have to reply whether he/she perceived the stimulus or not. May be performed in combination with EEG. (To be administered up to two times during each inpatient study phase and up to once monthly during the outpatient follow-up phase).

NIH Stroke Scale (NIHSS): NIHSS will be performed at screening/baseline, then post-operatively, after each titration/stimulation adjustment, and then monthly through Week 52 post-titration. In the long-term follow up period, the NIHSS will be performed after any stimulation adjustments.

The National Institutes of Health Stroke Scale (NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. A trained observer rates the patient's ability to answer questions and perform activities. Ratings for each item are scored with 3 to 5 grades with 0 as normal, and there is an allowance for untestable items. The paper- or computer-based assessment requires less than 10 minutes to complete.

PET/CT Scans

The study will utilize PET imaging to demonstrate the physiological changes associated with NAc/VC DBS. FDG PET/CT will be used to assess changes in prefrontal brain metabolism with DBS. FDG PET/CT will be collected at WVU. ^{11}C Raclopride PET/CT may be conducted to measure changes in dopamine brain metabolism, through the measurement of dopamine binding, associated with NAc/VC DBS. If conducted, this will be in collaboration with the National Institute of Drug Abuse (NIDA), who have developed expertise in PET dopamine imaging, ^{11}C Raclopride PET/CT will be conducted at NIH Clinical Center in Bethesda, Maryland, and images will be analyzed by investigators at WVU and NIDA. Participants, accompanied by an RN experienced in behavioral health and addiction, will be transported by medical transport to and from the NIH Clinical Center for PET/CT scans. Before travelling to NIH the PI or delegated physician will determine if they continue to have decision making capacity. This will involve an overnight stay the evening before the PET/CT scans at the Clinical Center under the care/supervision of Dr. David "Ted" George of NIH.

If conducted, there will be a total of nine PET/CT scans performed for each participant during this study 1) Session one with three scans at the end of the three week surgical recovery period and prior to the DBS titration and programming 2) Session two with three scans at 12 weeks after completion of the titration period. 3) Session three with three scans at 52 weeks after completion of the 52-week enrollment. Each session will consist of three PET scans: 1) FDG PET/CT to assess prefrontal brain glucose metabolism, 2) ^{11}C -Raclopride PET/CT placebo (no methylphenidate) and 3) ^{11}C-Raclopride PET/CT (with methylphenidate) challenge to determine binding potential of dopaminergic D2/D3 receptors and dopamine release. Methylphenidate will be administered orally at a dose of 60 mg prior to the scan per the standard protocol developed at NIDA.

CT Scans

Two high resolution CTs of the head will be obtained, one prior to surgery and one post-operatively to verify placement of electrodes. The patient will require a CT scan of the head after application of the Leksell stereotactic frame on the morning of surgery, co-registered to pre-operative MRI scans, for intra-operative anatomic localization per standard care. The patient will also require a CT scan, co-registered to pre-operative images, immediately after implantation of intracranial leads to confirm placement of the electrodes and to evaluate for intracranial hemorrhage and air. The participant may require an additional CT scan post-operatively for clinical reasons, for example to identify intracranial bleeding.

MRI Scans

High resolution MRI of the brain will be obtained approximately one week prior to surgery (but no more than 2 weeks prior to the surgery date) and may be completed at the end of the three week surgical recovery period prior to the DBS titration and programming, and at the 12 and 52 weeks follow-up visits. Additional Structural MRI may be completed at investigator's discretion, if clinically indicated, prior to or after DBS surgery. Functional MRI (resting state and task-based using a cue reactivity paradigm) may be performed prior to DBS surgery, at the end of the three week surgical recovery period, at the 12 and 52 weeks follow-up visits and in conjunction with LFP acquisition/cue reactivity at long term follow up visits.

MR-imaging uses a strong magnetic field and radio waves to take pictures of the brain. The MR-scanner is a metal cylinder surrounded by a strong magnetic field. During the MR-imaging, the patient will lie on a table that can slide in and out of the cylinder. The patient will be in the scanner about 40 minutes. The patient may be asked to lie still for up to 15 minutes at a time. During the task-based fMRI, opioid and other substance related pictures may be presented for approximately 10 minutes while the subject is in the MRI. Prior to and immediately after viewing the cues, participants will rate their craving levels. While in the scanner the patient will hear loud knocking noises and will be fitted with earplugs or earmuffs to muffle the sound. The patient will be able to communicate with the MR-staff at all times during the scan and may ask to be moved out of the machine at any time.

During part of the MR-imaging a contrast agent (Gadolinium) will be given through an IV catheter. A needle will be used to guide the catheter into an arm vein. The needle will be removed, leaving only the catheter in the vein. The catheter will be taped to the skin to hold it in place.

Electroencephalogram

Electroencephalogram (EEG) will be used to evaluate the electrical activity in the brain during pre- and post-surgical phases of the study. EEG may be performed while the subject is at rest or while completing specific tasks (e.g. delayed discounting, interoceptive processing).

Phase III: DBS Surgery

DBS surgery will be performed using standard stereotactic implantation of FDA approved leads (Medtronic Neurological) bilaterally in the NAc/VC in each participant using standard stereotactic techniques used for this DBS target since 1999. The specific target can be directly visualized on axial, coronal, and sagittal T1, T2, and inversion-recovery MRI scans that are obtained approximately one week prior to the surgery (but no more than 2 weeks prior to the surgery date).

On the day of surgery, standard clinical care requires a head CT with the stereotactic head frame and merging of the CT and MRI images for targeting the NAc/VC. The DBS electrodes implanted into the NAc/VC will be connected to pulse generators (Medtronic Percept PC, Activa RC or PC systems, as considered appropriate clinically) in the chest wall in the usual standard fashion as for all DBS procedures. After DBS placement, patients will undergo a post-operative CT scan on the same day as surgery to rule out hemorrhage. After DBS surgery, the participants will be followed on the neurosurgical step-down unit and patient ward until deemed clinically stable, at which point they will be transferred to our inpatient addiction psychiatry service for a up to a total time of 3 weeks post DBS surgery. DBS surgery involves FDA approved standard stereotactic implantation of DBS electrodes (Medtronic Neurological Model 3387S) bilaterally in the NAc/VC in each participant using anatomical and physiological guidance and single cell microelectrode recording. The specific target can be directly visualized on axial, coronal, and sagittal T1, T2, and inversion-recovery MRI scans, similar to what has been described previously for this target in the literature. The trajectory planning will be based on avoidance of vasculature while maximizing the approach through the internal capsule to the ventral striatum and the NAc. The anatomical target will correspond to the stereotactic targets coordinates of approximately 5 to 10mm lateral to the midline, 1 to 5 mm anterior to the anterior commissure, and 2 to 5mm ventral to the anterior commissure. Single-cell micro-electrode recording will be performed to verify the anatomical target traversing the internal capsule white matter with white matter recordings and cells in the NAc. The DBS electrodes implanted to the target will be connected to pulse generators (Medtronic Percept PC, Activa RC or Activa PC in the chest wall in the usual fashion as for all DBS procedures.)

To investigate the role of the NAc/VC in addictive behaviors we will assess the extent to which its local field potentials and single unit activity track the computation of value for choices that relate to addiction (i.e., items representing drugs) vs. control items (e.g., food items). In an intraoperative experiment, we will collect trial-by-trial estimates of decision confidence while patients chose between pairs of items. We expect neural activity in the NAc/VC to differ between addiction-related vs. control items. Together with computational models of decision making, these data will help determine optimal lead placement and refine future therapies for addiction.

Phase IV: DBS Titration and Stimulation

Up to a three-week time period will be allocated for initial programming, titration, and safety check/follow-up, while inpatient for safety. Titration will be based on stimulation parameters used in previous studies examining the role of DBS of the NAc in the treatment of OCD and depression, Since it is difficult to titrate stimulation parameters for efficacy in OUD while in a sheltered hospital setting, the titration stimulation will be based, first, on the absence of adverse effects, and, second, on whether the stimulation parameters help to maximize performance on a range of cognitive tasks selected to index decision making and cognitive control (e.g. Flanker, N-Back, and Psychomotor Vigilance tasks) and the discretion of the research team with regards to behavioral addiction features. The optimum setting and as well the effect of DBS will be determined based upon reported craving, mood, and/or physiological response.

The DBS system is turned on with a standard monopolar or bipolar setting, as deemed necessary per the medical team, after reviewing each contact setting while the participants are being monitored for adverse effects. Stimulation will be delivered initially at 90-185 Hz, in pulse widths ranging from 90 - 210 μsec. The polarity, frequency, pulse width and intensity will be adjusted using the standard range used for OCD and depression based on previous experience with NAc/VC DBS. Stimulation will be used on the electrode contact mapped to the stereotactic target used during surgery, unless side effects at that contact preclude any stimulation. During this phase, the Percept PC neurostimulator may be accessed to obtain local field potentials recorded from the patient's brain during initial adjustments and programming.

Amplitude of stimulation will be increased in small increments, slowly, while the patient is monitored for immediate side effects. Immediate side effects can include sensory changes, motor symptoms, immediate mood changes, non-specific drowsiness, discomfort, or eye deviation. The stimulation will not exceed the 30 μcoulomb/cm^2

charge density safety limit. After the programming session and safety follow-up of up to three weeks, participants will be discharged to home and monitored via standard visits with the COAT program as per the protocol.

During the DBS Titration and Stimulation Phase, in the event that no adjustments are needed, there may be sessions conducted similar to a typical titration session with the exception that no changes will actually be made to the stimulation parameters. This will be performed in an attempt to decrease any anticipatory bias on behalf of the subject (e.g. knowing that an adjustment will be made and subsequently anticipating that there will be an effect). After completion of the titration and stimulation phases, participants may have their stimulation parameters adjusted to maintain or improve efficacy at the discretion of the treatment team during the follow up phase of the study. There may also be sessions conducted where no changes are made to the parameters to decrease the potential of anticipatory bias as mentioned above.

Each participant will be given a copy of the Medtronic Patient Therapy Guide, which describes the DBS unit and its care, before the DBS unit is implanted, as well as individual teaching regarding the contents of the Guide from the study team. Participants will also receive a smaller pocket-size Quick Guide reference. At discharge, the participants will be given the Medtronic patient controller for safety. The access will be set to "limited: view battery status only". In this setting, the participants can confirm that the stimulator is on and working correctly, but they cannot see the voltage at which they are programmed. If severe side effects are experienced and the stimulator needs to be turned off, they will be able to do so with their patient controller.

Participants and their caregivers will be instructed on care of the DBS, including avoiding magnetic fields They will be instructed to carry their DBS controller with them when attending medical appointments and emergency visits (for the rare event that the DBS unit must be turned off). Participants will be given a wallet ID card describing the DBS unit.

Phase V: Follow-up and Monitoring

After discharge from the hospital they will return to the clinic twice weekly for 12 weeks and then once weekly for the remainder of the study. See Table 1 and Appendix A for detailed lab testing to be performed at Week 12 follow up.

After discharge from the hospital, any further requirements for inpatient treatment related to OUD will follow the COAT program standard of care.

The impedance of each DBS electrode will be assessed at each outpatient visit to ensure the device is properly functioning and connected. DBS settings will be maintained at previously-set levels unless adverse effects are noted, in which case the settings will be adjusted back to the previous level at which the participant had no adverse effect. After completion of the titration and stimulation phases, participants may have their stimulation parameters adjusted to maintain or improve efficacy at the discretion of the treatment team during the follow up phase of the study. There may also be sessions conducted where no changes are made to the parameters to decrease the potential of anticipatory bias as mentioned previously. The Percept PC device allows recording of local field potentials non-invasively from the implanted DBS system. Patients with an implanted Percept PC will be able to have events marked either in clinic or in the community (by themselves or the care/investigative team). These events could include increased cravings or feelings of wellness for example. The Percept PC device will also record averaged local field potentials continuously against time and these will be obtained from the Percept PC device at programming sessions to be evaluated later. The Percept can also record and stream local field potential data in realtime. This feature may be used during the planned behavioral (e.g. cue induced craving) and cognitive (e.g. delayed discounting, balloon analog risk task) assessments.

The primary outcome of safety will be formally assessed at 24 weeks post titration phase as an outpatient.

Final safety assessment will occur at 52 weeks post DBS titration. We will monitor depression and suicidality for the duration of the 52 weeks post titration follow-up, at minimum, on a weekly basis using the HAM-D and C-SSRS.

Participants are followed for 52 weeks and we will post the results on ClinicalTrials.Gov no later than 24 weeks after the last participant has completed follow up or hastened to within 12 weeks if at any point the trial is stopped for safety by WVU IRB or the FDA.

The results of this study will be specifically generalizable to those individuals with OUD who are disabled from their life threatening condition and/or are Medicare beneficiaries.

Long-Term Follow up Period

Participants who consent to the long-term follow up will have assessments quarterly (approximately every 3 months), or more frequently at investigators discretion based on clinical assessment (e.g. subjective changes in craving, mood, etc.), for up to 5 years including LFP recordings, cue reactivity (with/without fMRI), HAM-D, CSSRS, BART and Delayed Discounting

5.1 Duration

It is anticipated that the study will take approximately 52 weeks to complete following completion of inpatient DBS titration. After the completion of the 52 week protocol, patients who remain in treatment with the COAT program (or comparable WVU Behavioral Medicine program) and consent to the long-term follow up will be followed approximately every 3 months, or more frequently at investigators discretion based on clinical assessment (e.g. subjective changes in craving, mood, etc.), for a period of up to 5 years. If the patient is no longer in a WVU Behavioral Medicine program, we will attempt to contact them via available methods (e.g. phone, email) and they may still participate in the long-term follow up.

When evaluated during these long-term follow-up visits, DBS impedances will be checked similar to as described above during the Phase V: Follow-Up and Monitoring Phase to ensure that the device is working properly. Changes in LFPs may be measured in association with cue-induced craving (cue reactivity) and experimental measures of executive function (BART, Delayed Discounting), safety measures (HAM-D, CSSRS), and other assessments (e.g. interoceptive processing) if the Percept PC device is used. When LFPs are obtained in conjunction with behavioral/executive tasks, it is necessary to produce an identifiable signal that can be aligned to both the events in the behavioral task and the LFP signal to ensure that the responses and signal are synchronized. This will be achieved via a commercially available transcutaneous electrical nerve stimulation (TENS) device which can produce artifacts within the LFP recordings and serve this synchronizing function without undesirable side effects (Thenaisie et al. 2021). An adhesive electrode pad connected to the TENS unit will be placed on the patient's upper body in proximity to the DBS device. TENS stimulation will consist of one or more short (< 1 second) pulses of no greater than 5 mA, 80-100 Hz, charge-balanced current. A current of 5 mA is below the reported thresholds for a patient to detect (Dailey et al. 2013) and have no known risks.

a) Battery Replacement – Participants may receive either the Activa or Percept PC neurostimulator at the discretion of the Principal Investigator as described in section 5.3 and 7.0. Replacement with the Percept PC neurostimulator will be possible for those participants who received the Activa neurostimulator during initial placement. Given that this will provide us with the ability to measure LFPs in participants who did not previously have the Percept device, data may be collected in similar fashion as described above and in Table 1 and Appendix A which includes LFP acquisition as clinically indicated, at rest, and during specific tasks such as cue reactivity with/without fMRI). Also, given that the Percept device passively collects LFP data, when checking the impedances of the device during follow-up visits to ensure proper functionality, this LFP data will be automatically downloaded for all patients who receive this device. Participants who initially received the Activa device and already had a replacement with the Percept device will have the DBS stimulator turned off for up to 3 days in an inpatient setting for a washout period to record LFPs in a DBS off-state (non-stimulation).

b) DBS Stimulation Adjustments – Over time, the participant may develop tolerance to the stimulation and/or the final DBS settings established in the trial may no longer be optimal (e.g. evidenced by the participant's increased cravings, reductions in mood, etc.). In these cases, an adjustment of DBS parameters may be warranted at the discretion of the study investigators. If changes are made to the settings, pre-/post-stimulation behavioral changes will be measured and safety profile assessments will be performed (e.g. HAM-D, YMRS. CSSRS, NIHSS, BPRS (if necessary)). Any side effects will be assessed in similar fashion as when these adjustments were made during the 52 week protocol enrollment period.

c) Participants who do not consent to be in the long-term follow up phase will have the device explanted as there is no mechanism to ensure the safety of these participants when not under regular observation.

UADEs and SAEs that are attributable to the device and/or stimulation will be reported according to FDA and IRB reporting criteria

5.2 Potential Benefits

Patients may not receive any health benefit from participating in this study. NAc/VC DBS may suggest a novel therapeutic approach for individuals with treatment refractory OUD and to learn about the effects of DBS in the modulation of brain networks in patients with OUD. This knowledge may lead to new clinical insights that will improve treatment for OUD.

5.3 Potential Risks

General Risks Associated with DBS

The general risks associated with DBS for OUD are similar as with DBS applications involving Parkinson's disease, dystonia, essential tremor, chronic pain, Tourette's, epilepsy, OCD, major depression, and TBI. The potential risks for any DBS procedure are divided into three categories. These include risks associated with the actual surgical implantation of the DBS lead and pulse generator, risks associated with the implantable device, and risks associated with the programming of the device.

The surgical risks for DBS implantation are the same as for any intracranial stereotactic procedure. This includes hemorrhages (intraparenchymal, subdural or epidural hematoma), paralysis, coma and/ or death, stroke, leaking of cerebrospinal fluid, seizures, infection, allergic reaction, temporary or permanent neurological complications, confusion or attention problems, pain at the surgery sites and headaches.

The risk of a seizure due to deep brain stimulation (DBS) is less than 1%. The risk of a seizure associated with DBS in this study may be no different than when DBS is used for other medical conditions.
If a seizure occurs while participant is an inpatient at WVU, immediate actions will be taken by qualified medical personnel to reduce the risk of injury and prolonged seizure activity. These actions will be in accordance with WVU Medicine approved patient care protocols and latest American Epilepsy Society guidelines for treatment of seizures that occurs in a hospital or inpatient setting. All outpatient medical emergencies including seizures will follow standard 911 protocol. The risks associated with the devices include mechanical, electrical, software, and others device related system failures. Additional risks include battery failure, electric shock and reactions to the components of the device. The lead or lead extension connector may move, which would require surgical intervention to readjust.

Stimulation related side effects are most commonly reversible by adjusting the stimulation parameters and re-programming. In addition to re-programming, the system can be turned OFF and the intensity placed at 0 V. A recent summary of the risks profile for DBS in movement disorders is reviewed in Rezai et al. (Rezai et al., 2008**).** These include suicidal ideation, depression, gastrointestinal disturbances, nausea, muscle weakness or partial paralysis, jolting or shocking sensation, numbness, paresthesias, facial flushing and motor contraction, dizziness, headaches pain, changes in vital signs, hyperactivity or euphoria, pain or discomfort, dry mouth, itching at the surgical site, insomnia, increased fatigue, cognitive disturbance, restlessness, weight gain or loss, speech and visual difficulties, blurred or double vision, unusual smell and taste sensations, cognitive and/or behavioral changes, mood changes, and energy level changes.

A list of potential titration and programming related side effects include:

- Depression (feeling sad, down, or blue, and/or a loss of interest in things usually enjoyed)
- Changes in mood (positive and negative)
- Anger, aggression

- Gastrointestinal disturbances (changes in digestion) or nausea
- Tingling sensation (paresthesia)
- Dizziness or lightheadedness (disequilibrium)
- Facial and limb muscle weakness or partial paralysis (inability to move arms or legs) (paresis)
- Facial flushing (red or rosy facial color) or facial muscle contractions
- Jolting or shocking sensation (sudden movements)
- Hypomania
- Numbness (hypoesthesia)
- Increased heart rate
- Increased respiratory rate
- Increased blood pressure
- Hyperactivity or euphoria (hypomania)
- Pain or discomfort
- Headaches
- Dry mouth
- Itching at the surgical site(s)
- Irritability
- Insomnia
- Increased fatigue (feeling exhausted or moving slower than usual)
- Cognitive disturbance ("cloudy" thinking)
- Restlessness
- Weight gain or weight loss
- Sleep disturbance
- Speech and visual difficulties
- Blurred vision
- Double vision
- Unusual smell and taste sensations
- Changes in mood, memory, thinking and energy level

There are potential adverse events that could be related to the non-surgical procedures.

Risks associated with the implantable DBS device. The risks associated with the device include mechanical, electrical, software, and others device related system failures. Additional risks include battery failure, electric shock and reactions to the components of the device. The lead or lead extension connector may move, which would require surgical intervention to readjust.

The brain stimulation system may affect the operation of other surgically placed devices, such as cardiac pacemakers, and implantable defibrillators, which may interfere with the device function. Electrocautery, external defibrillators, radiation therapy, ultrasonic devices may interfere with the function of the neurostimulator and may even cause some damage to it. In addition, the electrical signal from the neurostimulator may interfere with the function of an external defibrillator. The safety of external defibrillators on patients with this surgically placed system has not been established.

Electromagnetic interference (EMI) is a field of energy (electrical, magnetic or a combination of both) that is generated by various equipment found in medical, work, and home environments.

This equipment can create enough interference to do the following:

- Turn the neurostimulator off or on
- Cause stimulation that can result in an uncomfortable sensation
- Reset the neurostimulator to factory settings, which will require reprogramming

The neurostimulator is designed to protect against most EMI. However, strong electromagnetic fields and permanent magnets can interfere with the system. Even when the DBS is turned off, interference can affect the lead(s). Subjects will be instructed on the risks and potential sources of EMI, and what to do if EMI is suspected.

They will be instructed to move away from the source of the EMI or if possible, turn off the suspected source of EMI. They will be instructed to use the control magnet to turn the DBS unit on or off.

Additional Concerns. There may be pain, lack of healing, or infection where the brain stimulation system parts are surgically placed.

- The brain's stimulation system parts may wear through the participant's skin, which can cause an infection or scarring.
- The lead or lead/extension connector may move. Participants may need surgery to re-adjust the location.
- Components or parts of the brain stimulation system may break or fail to work properly. Participants may need surgery to replace the system parts.
- The brain stimulation system could stop because of mechanical or electrical problems. Either of these would require surgery. DBS service life depends on individual use.
- The participant's body may have an allergic reaction to the brain stimulation system. The system materials coming in contact with tissue include titanium, polyurethane, silicone, and nylon. The body could also reject the system (as a foreign body).
- There is the possibility of tissue damage resulting from the programming

parameters or a malfunction of one of the parts of the brain stimulation system.

DBS systems have a battery life of approximately 2-9 years, depending upon the uses and the model; WVU Medicine will provide follow up care (at no cost to the participant) related to battery replacement, as well as any other related follow-up DBS care.

Using the different configurations of the Percept PC device may lower battery life. The minimum expected battery life, even with maximal use, is well within the 2-9 years of current DBS systems and use of the Percept PC device is, on average, not expected to significantly alter battery life of the system. We estimate an average time of live streaming LFP data to be 180 hours or on average 3 hours per week (as clinically indicated). This use will result in an estimated average loss of battery life of less than six months (1 hour of live streaming = loss of 20 hours of battery life). We estimate the typical battery life lost from live streaming to be approximately 165 days over the course of a 52 week follow up (which equates to a 5-6% loss of the 2-9 year battery life). As an example, we will obtain live streaming LFP during tasks involving experimental measures of executive function (e.g., BART and Delayed Discounting) and cue reactivity (assesses cue induced craving). The extent of live streaming will be variable, subject dependent and may be far less than estimated.

Risks of DBS System Revision. There is a possibility that the DBS system may need to be revised (removed, replaced, or repositioned) before the end of the research study. Possible reasons for revision might be infection, malfunction, or other reasons. If revision is necessary, the participant will need to have surgery similar to when the system was put in. There might be a "buildup" of scar tissue (related to the original surgery) that may make replacement of the leads unsafe. In some cases, it may not be possible to remove the leads. If the electrodes or stimulator need to be removed, then the operation to remove them may be associated with additional risks of bleeding, infection, pain, and surgical or anesthesia complications. Replacement with the Percept PC neurostimulator will be possible for those participants who received the Activa neurostimulator during initial placement.

5.4 Other Risks

Blood Sample Risks. The risks of drawing blood include temporary pain from the needle stick, bruising, bleeding, and rarely, infection.

X-ray Risks. X-ray technology uses radiation. The average amount of radiation that the average person would receive from the x-rays for the research study is less than that received from natural sources of radiation in a year. At this level, no harmful effects of radiation have been demonstrated and the risk, if any, is minimal.

Medication-Related Risks. During the study, participants will be asked to continue the same medications they were taking before the surgery. As a result, they may experience the side effects associated with these medications. Some neurologic medications cause withdrawal reactions if they are stopped suddenly. Withdrawal reactions can include anxiety, feeling dizzy, headaches, and possibly seizures. For this reason participants should not stop taking any medications suddenly without specifically discussing it with the study doctors.

Risks of MRI. People are at risk for injury from the MRI magnet if they 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. Participants will be screened for these conditions before having any scan, and if they have any, they will not receive an MRI scan. If participants have a question about any metal objects being present in their body, they should inform the staff. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

It is not known if MR-imaging is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan. The scan will not be done if the pregnancy test is positive. People with fear of confined spaces may become anxious during an MR-imaging. Those 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. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, the participants will let MR-imaging staff know right away. Participants will notify staff of any hearing or ear problems. Participants will be asked to complete an MR-screening form for each MRI scan. There are no known long-term risks of MRI scans.

The risks of an IV catheter 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. If participants have diabetes, kidney disease or liver disease, a blood test of kidney function will be done within 4 weeks before any MR-scan with gadolinium contrast. Participants will not receive gadolinium for a research MR-scan if their kidney function is not normal.

Medtronic DBS systems are MRI Conditional and safe in the MRI environment as long as certain conditions are met. If the conditions are not met, a significant risk is tissue lesions from component heating, especially at the lead electrodes, resulting in serious and permanent injury including coma, paralysis, or death. DBS of the Nucleus accumbens is off label and therefore there are unknown risks in general.

Risks of Radiation Exposure from Positron Emission Tomography (PET), Computer-assisted Tomography (CT), chest radiograph, and intra-operative fluoroscopy.

This research study involves exposure to radiation from six C^{11} Raclopride PET/CT scans (if conducted), three FDG PET/CT scans, two CT scans, one chest x-ray, and intra-operative fluoroscopy. The participant may require another CT to evaluate for the development of a blood clot while the electrodes are in place (for clinical care reasons). The amount of radiation participants will receive in this study is estimated at 4.2 rem, which is below the guideline of 5 rem per year allowed for research participants by the NIH Radiation Safety Committee. 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.

The MRI, CT, PET, fluoroscopy, and chest radiograph used in this study can be harmful to a developing fetus. Therefore, sexually active women who are able to get pregnant must use effective methods of contraception (birth control) from the time of screening until the end of the study in order to avoid exposure to the radiation required in by procedures this study. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally occurring radioactive forms of water and minerals. This research gives the participant’s body the equivalent of about 11.8 extra years' worth of this natural radiation.

A possible health problem seen with radiation exposure is the development of a second cancer later in life. This extra cancer risk is higher at younger ages and for girls and women. The extra lifetime risk of dying of a fatal cancer due to the radiation exposure from this research may range from about one in 2,000 to about one in 700. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all.

6.0 SAFETY ENDPOINTS

The study safety endpoints will include a characterization of all adverse events (AE) for all participants, including those related to the implant surgical procedure, the implantable device, and stimulation of the NAc/VC in patients with OUD. In addition, these safety profile elements will be compared across the various phases of the study. Patients with clinically significant complications related to surgery (hemorrhage, stroke, infection) will not undergo DBS implantation or further participation in the study.

7.0 PLAN FOR REPORTING ANTICIPATED AND UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

All serious unanticipated problems, major protocol deviations, serious adverse events (SAEs) and unanticipated device effects will be reported to the IRB as soon as possible, but not more than 5 days after the PI first learns of the event. As is required for device research, the PI will report to the IRB any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency as soon as possible, but no later than 5 working days after the emergency occurred.

All SAEs will be reported to NIDA within 72 hours of the PI being aware of the event.

At the time of continuing review, the PI will provide the WVU IRB with an aggregated summary of all unanticipated problems and all protocol deviations. The PI is responsible for detecting, documenting, and reporting unanticipated problems, adverse events (AEs), including serious adverse events (SAEs), and deviations in accordance with IRB requirements, and federal regulations. Relatedness to the research of all adverse events will be determined by the PI or designated co-investigator.

Serious Adverse Events

An adverse event or suspected adverse reaction is considered serious if, in the view of the investigator or the sponsor, it results in any of the following:

- Death
- A life-threatening adverse experience
- Prolongation of existing hospitalization or new hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) is any serious adverse effect on the health and/or safety or any life threatening problem or death caused by or associated with the device and/or stimulation if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participant.

Unanticipated adverse device effects will be categorized as they related to:

- The implanted components (lead, extension, neurostimulator)
- The lead/extension tract or neurostimulator pocket
- The burr hole site.

An event will not be considered related to the device when it is the result of:

- A preexisting medical condition
- A medication.

Device Malfunction

A device malfunction is the failure of a device to meet its performance specifications or other performance as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed (21 CFR 803.3).

The PI will report UADEs as soon as possible, but no more than 10 working days after the PI first learns of the event. For IDE research, the PI will report deviations from the investigational plan that were intended to protect life or physical well-being of a subject in an emergency to the IRB within 5 days. Unanticipated adverse device effects will be reported to the IRB and not more than 5 days after the PI first learns of the event.

Documentation of Adverse Events

The study PI and co-investigators will be responsible for the evaluation, monitoring, and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this clinical investigation. The study participants will be evaluated for any possible AEs from the time written study informed consent is obtained until study closure or the subject exits the study. Please note that the following will not be considered an AE:

- Reprogramming of the DBS system due to lack of efficacy.
- Transient undesirable stimulation-produced effects that occur during programming sessions that resolve with or without programming changes prior to the subject leaving a study follow-up visit and do not require follow-up medical care.
- Any normal expected postoperative complaints or symptoms, unless the event involves a clinically significant change in a patient's severity or duration of symptoms, or that requires clinical intervention other than the ordinary postoperative care. The following are some expected postoperative outcomes that ***may*** occur: headache, incision pain, nausea, vomiting, low grade fever, dizziness, sleepiness, nervousness, insomnia, constipation, urinary retention, confusion, etc.
- Any pre-existing condition, unless a worsening of that condition in terms of nature, severity, or frequency develops.
- Medical or surgical procedure unrelated to the clinical protocol (i.e., dental or elective cosmetic procedure)
- Routine neurostimulator replacement for battery depletion (will be documented as a system modification) Replacement with the Percept PC neurostimulator will be possible for those participants who received the Activa neurostimulator during initial placement.
- Technical observation or a device event that does not result in a medically undesirable situation for the participant.

All AEs from the time the study informed consent is signed through the final study visit will be recorded as AEs on the study event log, each event being documented separately. All AEs and SAEs will be followed until:

- AE is resolved, has returned to normal/baseline, or has stabilized.
- Participant has withdrawn from the study.
- AE is judged by the investigator to be no longer clinically significant
- Study closure.

In the long-term follow up period, only UADEs and SAEs that are attributable to the device and/or stimulation will be reported according to FDA and IRB reporting criteria.

All non-serious adverse events will be reported to the FDA and IRB during the continuing review. All adverse events, which include serious adverse events, will be categorized unrelated, unlikely, possibly, probably, or definitely related as follows:

Not related: Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.

Unlikely related: Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause, which can by itself explain the occurrence of the event.

Possibly related: Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.

Probably related: Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and the event is more likely explained by the product than any other cause.

Definitely related: Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and there is no other cause to explain the event.

As applicable, relationship may also be categorized as related to:

- Surgical/Procedure-Related: associated with surgical implantation of the DBS system;
- Device-Related*: caused by the implanted system;
- Stimulation-Related*: caused by the electrical stimulation of the nervous system while treating the participant's symptoms;
- Disorder-Related: an event that might reasonably be attributed to the patients underlying disease state.
- NA = Not related.

If considered at least possibly related, multiple relationship(s) could also be associated with each adverse event.

*For those events that are determined to be at least possibly related to stimulation or the DBS device, the sponsor/investigator will report the strength of the relatedness using the following definitions:

Definite: The event is resolved with reprogramming of the stimulation parameters and is confirmed by the reappearance of the event when the device settings are returned to the settings programmed at the time the event was observed;

Probable: The event resolves upon reprogramming of the stimulation parameters and cannot be reasonably explained by the participant's current clinical state;

Possible: The event may have been produced by the study participant's clinical state; however, the effect of stimulation cannot be ruled out.

In addition, the relationship between the device/procedure and the occurrence of each adverse event may be assessed and categorized using the criteria above in addition to clinical judgement. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, and other risk factors may also be considered.

Reporting of Serious Adverse Events

Adverse events (AE) will be monitored by direct questioning and examination at each study visit and by patient self-report. NCI Common Toxicity Criteria (NCI-CTCAE v.5.0) grade 3 or higher in the neurology domain will be considered as severe AE prompting evaluation of the cause. Any grade 4 or higher in any other NCI-CTCAE domain will also be considered a severe AE, prompting evaluation of cause. Any subject withdrawal due to a severe or serious AE will be submitted orally immediately and in writing within 15 working days to the Data and Safety Monitoring Board (DSMB) and the IRB for evaluation, and an assessment of the safety of continuing the entire study protocol will be made. Care will be provided to attempt stabilization of the patient's condition and an investigation will be initiated for possible concurrent conditions causing the deterioration, including imaging, urine and blood tests. The DBS leads and unit can be removed at the patient's request, or with the patient's consent if judged necessary by the investigators. Similarly, new persistent neurologic deficit(s) or worsening of previous deficit(s) causing intolerable patient distress will prompt changing the DBS paradigm and if needed termination of DBS and subject withdrawal. The same measures described above will be employed.

The PI will make a preliminary determination of whether the SAE is related to the DBS system or therapy. The DSMB will make the final determination of relatedness.

The sponsor /investigator will report the available information on all SAEs to the FDA within 10 working days of learning of the event. Any SAE which occurs during the study, whether related to the DBS-system or not, will be reported to the DSMB. Any SAE related to the DBS system will be reported to the device manufacturer.

The inpatient screening/baseline, DBS surgery, and DBS titration phases, and hospitalization for DBS battery replacement and period of DBS-off state for washout to collect LFPs, will not be considered an SAE. Likewise, if the participant is admitted to the hospital during follow up Phase 4 or 5 through the COAT clinic standard of care, the hospitalization will not be considered an SAE if it was related to pre-existing conditions (e.g. inpatient hospitalization for substance use treatment and/or deemed not related to the study intervention by the PI, co-investigators and/or study team (consultation will be made with consultants, DSMB, and NIDA as appropriate in making this determination.

8.0 DATA SAFETY AND MONITORING

This study will be monitored by an independent DSMB. The DSMB will be composed of 5 individuals, 2 with collective expertise in addiction and behavioral medicine, 1 with neurosurgical expertise, 1 with expertise of neurologic critical care, and 1 with statistical expertise.

Prior to the review of the protocol, each member of the DSMB discloses in writing to the sponsor any potential conflicts of interest, actual or implied by appearance. Should an unanticipated situation arise that the Board member feels represents a conflict of interest, the Board member should recuse themselves.

Ongoing Study Meetings: During study conduct the DSMB will meet prior to the start of enrollment and every six months or more frequently as needed (details regarding meeting time frames following key events can be found below). The DSMB may meet in person or via teleconference. During these meetings the DSMB will be assigned to review study data, including all adverse events, patient withdrawals, and baseline and any re-evaluation data.

- Interim data review: The DSMB will review interim data to detect evidence of or trending of adverse effects and determines if the trial should continue as originally designed, or whether it should be changed or stopped.
- Progress evaluation: The DSMB may also evaluate the progress of the trial, including assessments of data quality/completeness, achievement of recruitment goals, protocol adherence, accrual and retention of participants, and other factors that may affect the study outcome.
- Protection of confidentiality: Study participant confidentiality will be maintained by providing only de identified data to the DSMB. All source data will be stripped of identifiers and given a study assigned number before providing to the board. The DSMB will protect the confidentiality of study participants, trial data and the results of the monitoring.
- For each participant, the DSMB will meet within 2 weeks following the completion of the titration phrase, review AEs, and provide a go/no-go vote before enrolling the next participant.
- DSMB will meet within 2 weeks of every SAE.
- DSMB will meet biannually after all 4 patients titrated.

The DSMB will evaluate the safety of the subjects as pre-specified in the protocol, and the DSMB will make recommendations to researchers to continue, to amend, or to terminate a clinical trial. The DSMB will be assigned to review study data, including all adverse events, patient withdrawals, and baseline and any re-evaluation data. Each SAE and significant medical event 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. DSMB analysis of safety data will be performed after the first participant has completed 12 weeks of ON stimulation.

During the long-term follow-up, the DSMB will review any UADEs and SAEs that are attributable to the device and/or stimulation within 2 weeks.

TRIAL STOPPING RULES

If repeated (more than 2) SAE or 2 patients develop SAE that are probably or definitely related to the DBS implantation or stimulation, this will trigger a review by the DSMB and the FDA. DSMB will meet within two weeks of every SAE. At the time of the review by the DSMB and the FDA, enrollment, and/or treatment if indicted, will be paused until a determination is made. The DSMB and the FDA will recommend to the PI to resume or stop the protocol. The following specific conditions will result in a pause and review by the DSMB and the FDA for final determination of stopping the study:

- Any participant with a symptomatic intraparenchymal hemorrhage or acute subdural hematoma. (The expected incidence of symptomatic intracranial hemorrhage with DBS surgery is 1-3%).
- Confusion lasting more than 2 weeks after surgery in 2 patients.
- Postoperative edema or symptoms that do not resolve with a month of onset in 2 patients.
- Infection requiring hospitalization or extend the post-operative period for more than a week in 2 patients.
- 2 patients that develop post-operative seizures without a preoperative diagnosis of seizure disorder.
- Worsening neurological status due to study related procedures according to a change on the NIH Stroke Scale of a least 5 for greater than one week in 2 patients.
- A single death.

Additional Stopping Criteria

The assessments described below will be administered to establish baseline measurements of psychosis, mania, depression, and/or suicidality prior to DBS surgery and following DBS surgery before the first titration session. The symptoms noted above may emerge following surgery and/or titration. If the clinician or study staff observe any of these symptoms clinically/behaviorally, these assessments will be re-administered. In addition, following the titration sessions, these measures will be administered and compared to the baseline assessments to monitor changes.

While the primary objective of the titration sessions is to determine the optimal DBS settings in achieving the desired outcome (e.g. reduced craving), these potential side effects will be monitored during the process of optimizing the DBS settings. Assessing the resolution of these potential side effects, if present and necessary, will be performed as described below. If any of these symptoms arise and do not remediate, this will trigger DSMB consultation.

- Symptom: Psychosis
- Assessment: Brief Psychiatric Rating Scale (BPRS)
- Stopping Criteria: If patient endorses moderate scores or higher (raw score ≥4) on items related to psychosis post-surgery or post-titration sessions for >24 hours and if symptoms do not resolve with further titration.

- Symptom: Mania
- Assessment: Young Mania Rating Scale (YMRS)
- Stopping Criteria: If patient endorses moderate scores or higher (raw score of >25) persistently for one week post-surgery or during titration and if symptoms do not resolve with further titration.

- Symptom: Depression
- Assessment: Hamilton Rating Scale for Depression (HAM-D)
- Stopping Criteria: If patient endorses severe scores or higher (raw score of >17) persistently for one-week post-surgery or during titration and if symptoms do not resolve with further titration.

- Symptom: Suicidality
- Assessment: Columbia Suicide Severity Rating Scale (C-SSRS)
- Stopping Criteria: If patient endorses active thoughts of self-harm post-surgery or post-titration sessions for >24 hours and if symptoms do not resolve with further titration.

In addition, if an annual review indicates that the study is not likely to be completed within a reasonable timeframe the protocol will be stopped. Finally, other SAE and unanticipated problems will be reported to and discussed with the DSMB prior to continuing protocol enrollment.

If the adverse events are not of a higher incidence than expected, enrollment may continue. If adverse events are of a higher incidence than expected, then additional analysis of causal effects will be performed. All DSMB reports will be sent to the PI who will forward copies to the IRB and FDA and may request discussion with the IRB and FDA regarding the need for an amendment.

9.0 MONITORING PLAN

The data management for this study will maintain a level of data integrity and confidentiality that will provide optimum adherence to all 21 CFR regulations, while providing a standardized method of data collection and recording to enable the investigators, sponsors and regulatory agencies to accurately reconstruct the events of a study, confirm protocol compliance, and produce data that is accurate and appropriate in demonstrating study results.

- Study coordinators at the RNI will perform primary data collection based on source documents following good documentation practices (GDP) at all times. Source data for the study may be paper based surveys and questionnaires, EMR or a copy of the CRF labeled clearly as SOURCE may also be used as source to collect data not captured in the EMR.
- Paper or electronic case report forms (CRFs) that have been validated by a Quality control check will be used to collect study data.
- Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal quality control and quality assurance process.
- Internal Quality Control: All data collected (CRF Pages) will be 100% source verified on an ongoing basis (as data becomes available) by a qualified clinical research team member.
- Review of the regulatory documents will be performed by a qualified clinical research team member prior to study initiation and prior to each participant enrollment.
- QA review will be performed periodically during each subjects study participation and at least once every quarter. This will include verification of data completeness and accuracy for records that reflect safety and study endpoints, protocol adherence and regulatory documents. Written reports will be provided to the PI that will include scope of the review and observations.
- All electronic records and computer systems used for recording, transmitting or storing data will be 21 CFR 11 compliant.
- All evaluation forms, assessment results, and other records that leave the site will be identified by coded number only to maintain participants' confidentiality. All study records will be kept locked at the RNI or CRC. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participants, except as necessary for monitoring or auditing purposes.

10.0 PROCEDURES FOR MINIMIZING RISKS

Participants, after screening for eligibility, will be recruited for participation in the study. Consent will be conducted by members of the study team, and all risks and benefits will be described to the participants in written and oral presentation. Participants will be made to understand that their participation is voluntary, and that they will be provided with any new information that develops during the study that might affect their decision to continue with the study. A sixth-grade reading level will be considered when developing the consent materials, and the informed consent will be on file with the WVU IRB.

Participants will be pre-screened for decision-making capacity prior to the consenting process. A clinical determination will be made at the time of the consent by a WVU Medicine Behavioral Medicine Clinician to determine if participants are competent for consenting.

All evaluation forms, assessment results, and other records that leave the site will be identified by coded number only to maintain participants' confidentiality. All study records will be kept locked at the WVU Rockefeller Neuroscience Institute. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participants, except as necessary for monitoring by the IRB.

If serious adverse events become evident, the study will be terminated after review and recommendation by the DSMB. All participants previously enrolled will be immediately contacted regarding findings.

Vulnerable subjects: We consider participants in this study to be vulnerable due to the presence of OUD and the resultant stigma engendered by this diagnosis. Special protections for participants include a full-time patient navigator on call to address emergent issues as well as a Certificate of Confidentiality that is extended to participants in all NIH-supported trials.

Women of reproductive potential must use acceptable forms of contraception from the time of enrollment through the completion of study participation.
Acceptable effective methods of contraception for this study include:

- Hormonal contraception (birth control pills, injected hormones, hormonal implants, or vaginal ring).
- Intrauterine device.
- Barrier methods (condom or diaphragm) combined with spermicide.
- Surgical sterilization (hysterectomy, tubal ligation, or vasectomy)

It is important for the participant to know that no method of birth control is totally effective in preventing pregnancy except for surgical sterilization (hysterectomy or tubal ligation) and total abstinence from sexual relations.

The long-term effects of DBS on pregnancy and a fetus are not known. The MR-imaging, CT scans, PET scans, and surgery used in this study can be harmful to a developing fetus. At a minimum, pregnancy testing will be performed on all women of childbearing potential at screening, monthly, and before MR-imaging, CT scan, PET scans, and surgery. Presence of confirmed pregnancy will result in study discontinuation if DBS surgery has not yet been done. If pregnancy occurs after DBS placement, imaging studies will not be performed, however, the participant will be followed through the duration of the study, and pregnancy outcome will be assessed.

The investigators involved with this study have a great deal of expertise with the conduction of DBS surgeries. The surgical team has over 20 years of experience with DBS with over 2000 DBS implants for various indications. The study inclusion/exclusion criteria have been developed to select those who would most likely benefit from this study as well as excluding those with higher risks. Study participants will be monitored after DBS implantation in neurosurgical and physiological monitoring units with personnel experienced in the care of complex neurosurgical participants and monitoring neurological status. After surgical stabilization, participants will be monitored on an inpatient addiction service, which is staffed by personnel experienced in monitoring psychiatric and addiction care.

We plan a number of measures to mitigate occurrence of adverse events. Patients will be carefully examined for presence of infection prior to DBS placement. Specifically, patients with any evidence of cutaneous bacterial infection (e.g., impetigo, cellulitis, etc.) will be excluded as will patients with any evidence of systemic infection, including fever, malaise, or leukocytosis. As surgical -site infections occur with increased frequency among nasal carriers of Staphylococcus aureus, we screen all potential DBS candidates for staph nasal carriage and, if present, treat with mupirocin to eliminate the carrier state prior to DBS implantation. We also instruct all patients to use chlorhexidine wash prior to the surgery.

Our standard of care for all DBS surgeries includes 24 hours of peri-operative prophylactic IV antibiotics after implantation of the DBS lead 5-7 days of prophylactic oral antibiotics after the pacemaker battery implantation.

Patients will additionally be carefully followed for evidence of implant/hardware infection, not only in the post-operative period but throughout the subsequent year. Any evidence of possible hardware infection will be pursued for definitive diagnosis and treatment for which infectious diseases consultation will be sought.

The risk of infection will be further mitigated chiefly by careful and meticulous surgical technique. Should the patient present with signs or symptoms consistent with wound breakdown or infection, contrast enhanced imaging will be obtained to ensure there is no intracranial involvement. The most conservative reports give a risk of infection around 1/20 over the lifetime of the device, with about 1/40 requiring lead explantation over the life of the device. Treatment will then consist of a combination of antibiotics, wound cultures, surgical exploration and wound revision, and if the implanted system is deemed to be unsalvageable, explantation. Multiple reports have shown that up to 50% of infections/wound breakdowns associated with deep brain stimulation can be successfully treated without lead explantation. Should explantation become necessary after an infection, it will almost always lead to a rapid resolution of both wound healing and infection issues. The risk of explantation will be mitigated by using meticulous surgical technique and a very experienced implanting surgeon. Also, the risk will be mitigated by utilizing conservative strategies if appropriate to avoid DBS explantation.

The risk of intracranial hemorrhage will be mitigated by meticulous surgical planning and stereotactic techniques. Hemorrhage will also be evaluated with post-operative CT scans obtained on every patient to ensure that if a hemorrhage occurs, it is diagnosed early and treated early as well. Prevention of hardware damage is chiefly done with good surgical technique in applying strain relief loops of the wire at the cranial and pectoral sites of the implant as well as keeping wires away from pressure points, where skin wearing can cause breakdown. Other risks associated with the surgery are much rarer than hemorrhage, infection/wound breakdown, and hardware damage. These will be managed according to the best evidence and experience of the implanting surgeon.

The risk of explantation after a DBS surgery is about 1 in 40 over the lifetime of the device when implanted for movement disorders. Reasons for explantation are usually wound breakdown/infection or damage to cranial DBS lead wire or other portion of the system. This risk can be minimized by using meticulous surgical technique and ensuring adequate healthy scalp/skin coverage over the implanted device. Should explantation become necessary, it carries a similar risk profile to the implantation surgery, although these risks, especially brain hemorrhage, are less likely to occur.

Risks are minimized in all of the non-surgical procedures including phlebotomy as well as the neuroimaging procedures by having trained and highly experienced personnel performing all those tasks/procedures.

After the surgery, the DBS system will be interrogated and monitored by individuals who have expertise in programming of neurostimulators. In the event that after titration is complete, symptoms develop that affect the safety or quality of life of the patient, stimulation parameters first will be adjusted. If these symptoms persist, stimulation will be discontinued. Symptoms that would necessitate divergence from the protocol would include any condition or occurrence that would be deemed serious and significantly divergent from typical clinical symptoms seen with OUD patients. Examples might include any unexplained sudden or severe cognitive and functional loss or severe behavioral disturbances out of the ordinary for this population that is profoundly affecting quality of life of the participants.

Participants may also terminate from the study if they wish at any time. Study participants may also wish to discontinue stimulation for any reason. DBS systems will also be removed if the participant/representative asks for removal. Subjects who prematurely withdraw from the study due to an adverse event will be followed (e.g. telephone contact, and/or follow-up visits, etc.) until resolution of the event. In addition, a designated investigator/programmer will have access to treatment status at all times and provide that information to appropriate medical personnel in the event of medical emergencies. The DBS device may be explanted for participants who are discontinued from the study for any reason.

Risks to confidentiality are negligible in this protocol, since participants will not be identified by name, or by any personal data, in any summary reports or publications. Case Report Forms (CRFs) will be maintained in locked files and password-protected databases. Subject identification codes will be used in place of names, with the key linking data to names kept separate from the data. Data and safety monitoring activities for this study will continue until all subjects have completed their participation in the study.

11.0 DATA AND STATISTICAL CONSIDERATIONS

The study seeks to assess the safety and feasibility of enrolling 4 participants with treatment refractory opioid use disorder. The primary endpoint is safety, which will be assessed through meticulous collection and grading of all adverse events as well as attribution as to whether or not the adverse events are related to study procedures or to DBS (See safety plan for details). Descriptive statistics will be used given the small sample size (n=4).

Secondary endpoints include the following and will be assessed using descriptive statistics:

Opioid and other substance exposure as determined by quantitative urine toxicology via high pressure liquid chromatography (HPLC) will be measured at screening/baseline and 4, 8, and 12 weeks of outpatient follow-up. Comparisons will be made between baseline (pre- DBS implantation) and post-surgery follow-up, measured at 4, 8, and 12 weeks following discharge. Qualitative urine toxicology obtained twice weekly through 12 weeks and once weekly from weeks 13-52; in conjunction with self-reported substance use throughout the study. Comparisons will be made between baseline (pre- DBS implantation) and post-surgery follow-up, measured at 12 weeks and 24 weeks following discharge. Exploratory analyses will include the data collected through the 52-week study completion.

Mood (depression and anxiety), via the Comprehensive Psychopathological Rating Scale (CPRS), will be assessed three times weekly during the inpatient phases, two times weekly through Week 12 follow up, then once monthly through Week 52. Comparisons will be made between baseline (pre-DBS implantation), measured at 12 weeks and 24 weeks after titration. Exploratory analyses will include the data collected through the 52-week study completion.

Craving will be assessed up to twice-daily using a 100mm Visual Analog Scale (where 0 = no craving, and 100 = maximum craving) which will ask “How much do you crave opioids right now?” Daily ratings will be averaged for one week prior and one week after selected time points (baseline (pre-DBS implantation), measured at 12 weeks and 24 weeks after titration). Cue-induced craving will be assessed up to three times weekly during screening/baseline, DBS surgery and titration periods; up to once weekly through Week 24, then once a month through Week 52. Daily ratings will be averaged for one week prior and one week after selected time points (baseline (pre-DBS implantation) and compared to week 12 and week 24 after titration. Executive function will be assessed per Appendix A and analyzed using descriptive statistics. Measures will be averaged for one week prior and one week after selected time points (baseline (pre-DBS), 12 and 24 weeks after titration. Exploratory analyses will include the data collected through the 52-week study completion as well as data collected during the long-term follow-up.

Change in FDG PET/CT from baseline (defined as pre-titration/programming) compared with 12 and 52 weeks post-titration.

The metabolic images (normalized to whole-brain metabolism) will be analyzed using the Statistical Parametric Mapping (SPM) (Friston et al., 1995) package SPM12 (Wellcome Trust Centre for Neuroimaging) or other appropriate image processing tool as appropriate. Specifically, the PET images will be spatially normalized to the stereotactic space of the MNI using a 12-parameter affine transformation. The SPM2 FDG template (PET.mnc) was used to normalize the metabolic images, which were then normalized to their mean signal intensity. These normalized and transformed images will be used for comparisons between baseline (pre-titration) and 12 weeks following titration to examine increases in the prefrontal cortex metabolism.

In addition, if performed, the following will be used:

- Change in ^{11}C Raclopride PET/CT from baseline (defined as pre-titration/programming) compared with 12 and 52 weeks post-titration.
- Change in ^{11}C Raclopride PET/CT using methylphenidate challenge to determine binding potential of dopaminergic D2/D3 receptors from baseline (defined as pre-titration/programming) compared with 12 and 52 weeks post-titration.
- If collected, the ^{11}C Raclopride images will be analyzed according to procedures described by Volkow et al.(Volkow et al., 2013). We will estimate the distribution volume (DV) for each voxel, and a custom MNI template, which was previously developed using DVimages from 34 healthy subjects that were acquired with ^{11}C Raclopride and the same PET scanning sequence (Wang et al., 2012), will be used for the spatial normalization of the DV images. Data will be analyzed via SPM 12, confined to ROIs in the basal ganglia and NAc, to evaluate changes at baseline (pre-titration) and 12 and 52 weeks following titration.

In addition, if performed, comparisons in resting state and task based functional connectivity (assessed via fMRI) from baseline (defined as pre-titration/programming) compared with 12 and 52 weeks post-titration.

Evaluations of neuropsychological functioning will be assessed using descriptive statistics between baseline (pre-DBS), 12 and 24 weeks following titration for the neuropsychological battery which includes, but is not limited to: 1) Wide Range Achievement Test-Fourth Edition, Reading Subtest, 2) Wechsler Abbreviated Scale of Intelligence, 3) Wechsler Adult Intelligence Scale-Fourth Edition – Digit Span Subtest, 4) Trail Making Test, 5) Stroop Color Word Test, 6) Controlled Oral Word Association Test and Animal Naming Test, 7) California Verbal Learning Test 8) Brief Visuospatial Memory Test-Revised, 9) Dementia Rating Scale – 2nd Edition, and the Wisconsin Card Sorting Test (WCST). Similar analyses will be conducted for the experimental measures of executive functioning comparing baseline, 12 and 24 weeks following titration. Exploratory analyses will include the data collected during the final assessment at the 52-week study completion as well as the experimental measures of executive functioning data collected during the long-term follow-up.

12.0 REGULATIONS AND ETHICAL CONDUCT OF THE STUDY

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR 21 CFR Part 812)

This protocol will be reviewed and approved by the WVU IRB responsible for oversight of the study.

13.0 DEVICE DESCRIPTION

The devices to be used in this study are the standard Medtronic devices which are FDA approved for movement disorders such as Parkinson's' disease, essential tremor, dystonia, OCD and recently epilepsy.

The device consists of a lead, a neurostimulator, and an extension that connects the lead to the neurostimulator. Medtronic Model 3387S, DBS leads will be used for this study, besides the DBS implanted pulse generator (IPG) or battery Activa RC neuostimulator 37612 or Activa PC Neurostimulator 37601, and Model 37086 Extension, and related DBS therapy accessories.

Model 3387S, DBS Lead. The DBS lead consists of a polyurethane protective sheath with four platinum/iridium electrodes near the tip of each lead that deliver stimulation to the target site. The leads are stereotactically introduced into the target and fixed at the skull with a burr hole cap and ring.

Model 37612 Activa RC or 37601 Activa PC or Model B35200 Percept PC Neurostimulators. The neurostimulator is implanted subcutaneously in the subclavicular or upper abdominal region. It is comprised of a battery and integrated circuits that are hermetically sealed within an oval-shaped titanium enclosure. The neurostimulator delivers electrical stimulation pulses with a variety of parameters, modes, and polarities. The electrical pulses are carried from the neurostimulator to an implanted deep brain stimulation lead by means of a lead extension. The Percept PC Neurostimulator also has the ability to record and export local field potentials from the implanted brain electrodes.

Model 37086 Extension. The extension is a set of wires within silicone tubing that connects the lead to the neurostimulator, providing an electrical path that allows stimulation to be delivered to the target site. The extension is subcutaneously passed from the scalp area, where it connects to the lead, through to the subclavicular area or upper abdominal region, where it connects to the neurostimulator.

Recharger Model 37651. The Activa RC is a rechargeable neurostimulator and is charged externally for the internally implanted IPG in subclavicular or upper abdominal region with the Medtronic charger for Activa DBS Therapy - Medtronic, Inc. Model 37651. It has 3 components; the AC power supply and its cord, the charger and an antenna. The antenna establishes communication with the subcutaneously implanted Activa RC IPG, which can be used over a belt or the strap. The Therapy screen of the patient therapy controller (Model 37642 RC therapy controller), supplied with the patient or caregiver, shows the neurostimulator battery status and charging requirements can be tailored for the individual patients. While charging, the charging status is displayed on the neurostimulator charging screen and when the neurostimulator battery is fully charged, the Neurostimulator Charge Complete screen appears and the charger stops.

Model CT900A. The clinical programmer Model No CT900A is an FDA approved device, which is a tablet based programming device and works wirelessly. It has an encrypted Bluetooth connection from the programmer to the communicator and has a proprietary, proximal telemetry from the communicator to the implanted device. The Medtronic Clinical Programmer Model CT900A contains the necessary software and options to program neurostimulator.

Model 8880T2. The Model 8880T2 communicator is a telemetry head and connects wirelessly through an encrypted Bluetooth connection to the clinician programmer model no. CT900A. The device is kept close to the IPG and once establishes the connection with the clinical programmer, DBS setting is programmed as per the requirement.

Model 37642 RC Therapy Controller or Model A620 Percept PC patient programmer. The therapy controller is designed for use by a patient or caregiver. Using the therapy controller, the patient or caregiver can turn therapy on or off, check whether the therapy is on or off, and check the condition of the neurostimulators battery. The Percept PC patient programmer also has the ability to mark events based on patient perceptions.

The Medtronic Deep Brain Stimulation components have been commercially approved as components of the Medtronic Activa Tremor Control System (PMA P960009, and all associated amendments) Medtronic Activa Parkinson's Control Therapy (P960009) and Medtronic HDE H050003 (S001)

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1 Appendix A

			Phase	Phase I	Phase II	Phase III	Phase IV	Phase V					
			Procedure	Screening	Baseline	DBS Surgery	DBS Titration	Follow-Up	**12 Week Follow-up Visit 1**	Follow-Up	**24 Week Follow-up Visit 2**	Follow-Up	**52 Week Follow-up Visit 3**
			Inpatient / Outpatient	Inpatient				Outpatient					
			Duration	Up to 5 weeks[1]		Up to 3 weeks	Up to 3 weeks	52 weeks					
			Time Point (Week)	-7 and -6		-5 – -3	-2 – 0	1 – 11	12	13 – 23	24	25 – 51	52
	Inclusion Requirement		**Procedure / Assessment**										
Medical History and Medical Assessments	Yes	1	Medical History / Physical Examination	x									
	Yes	2	Neurological Examination	x									
	Yes	3	Psychiatric Examination	x			x						
	Yes	4	NIH Stroke Scale	x		x (post-operatively)	x (post-each titration)	x (1x monthly)					
	Yes	5	Lab Tests	x					x				
	Yes	6	X-Ray	x									
	Yes	7	MRSA Nasal Swab	x									
	Yes	8	Urine Toxicology (Qualitative)	x (2x weekly)				x (2x weekly)		x (1x weekly)			
	No	8.1	Urine Toxicology (Quantitative)	x				X (Weeks 4 and 8)	x				
	Yes	9	Pregnancy (Qualitative)	x (2x weekly)				x (2x weekly)		x (1x weekly)			
Medical History and	Yes	9.1	Pregnancy (Serum)	x					x		x		

			Phase	**Phase I**	**Phase II**	**Phase III**	**Phase IV**	**Phase V**					
			Procedure	Screening	Baseline	DBS Surgery	DBS Titration	Follow-Up	**12 Week Follow-up Visit 1**	Follow-Up	**24 Week Follow-up Visit 2**	Follow-Up	**52 Week Follow-up Visit 3**
			Inpatient / Outpatient	Inpatient				Outpatient					
			Duration	Up to 5 weeks[1]		Up to 3 weeks	Up to 3 weeks	52 weeks					
			Time Point (Week)	-7 and -6		-5 – -3	-2 – 0	1 – 11	12	13 – 23	24	25 – 51	52
Medical Assessments	Yes	10	Vital Signs	x (1x daily)				x (2x weekly)		x (1x weekly)			
	Yes	11	ECG	x									
	Yes	12	Demographic & Drug / Alcohol Use Inventory	x									
	Yes	13	Adverse Events	x	x	x	x	x	x	x	x	x	x
	Yes	14	Concomitant Medications	x	x	x	x	x	x	x	x	x	x
	Yes	15	MR Checklist	x									
Behavioral Assessments	Yes	16	SCID-5	x									
	Yes	17	SCID-5-PD	x									
	Yes	18	MSPSS	x									
	No	19	BPRS		x	x (pre / post-surgery)	x (post-titration prn)						
	Yes	20	HAM-D[6]	x	x (3x weekly)			x (2x weekly)		x (1x weekly)			
	Yes	21	C-SSRS[6]	x	x (3x weekly)			x (2x weekly)		x (1x weekly)			
Cognitive Assessments	Yes	22	DRS-2	x					x		x		x
	No	23	WRAT-IV		x				x		x		x
	No	24	WASI-II		x				x		x		x

			Phase	Phase I	Phase II	Phase III	Phase IV	Phase V					
			Procedure	Screening	Baseline	DBS Surgery	DBS Titration	Follow-Up	**12 Week Follow-up Visit 1**	Follow-Up	**24 Week Follow-up Visit 2**	Follow-Up	**52 Week Follow-up Visit 3**
			Inpatient / Outpatient	Inpatient				Outpatient					
			Duration	Up to 5 weeks[1]		Up to 3 weeks	Up to 3 weeks	52 weeks					
			Time Point (Week)	-7 and -6		-5 – -3	-2 – 0	1 – 11	12	13 – 23	24	25 – 51	52
	No	25	WAIS-IV (DS)		x				x		x		x
	No	26	CVLT-II (Short)		x				x		x		x
	No	27	BVMT-R		x				x		x		x
	No	28	TMT A&B		x				x		x		x
	No	29	COWAT		x				x		x		x
	No	30	SCWT		x				x		x		x
	No	31	WCST		x				x		x		x
	No	32	Performance Validity Tests		x				x		x		x
Affective / Emotional Assessments	No	33	CPRS	x		x (3x weekly)		x (2x weekly)		x (1x monthly)			
	No	34	YMRS[6]	x		x (3x weekly)		x (2x weekly)		x (1x monthly)			
	No	35	POMS-SF	x		x (3x weekly)		x (2x weekly)		x (1x monthly)			
	No	36	PANAS-SF	x		x (3x weekly)		x (2x weekly)		x (1x monthly)			
	No	37	BIS	x		x (3x weekly)		x (2x weekly)		x (1x monthly)			
	No	38	SHAPS	x		x (3x weekly)		x (2x weekly)		x (1x monthly)			
Opioid and Other Substance Use	No	39	BSCS[2]	x (Up to 2x daily)									
	No	40	Craving VAS[2]	x (Up to 2x daily)									

			Phase	Phase I	Phase II	Phase III	Phase IV	Phase V					
			Procedure	Screening	Baseline	DBS Surgery	DBS Titration	Follow-Up	**12 Week Follow-up Visit 1**	Follow-Up	**24 Week Follow-up Visit 2**	Follow-Up	**52 Week Follow-up Visit 3**
			Inpatient / Outpatient	Inpatient				Outpatient					
			Duration	Up to 5 weeks[1]		Up to 3 weeks	Up to 3 weeks	52 weeks					
			Time Point (Week)	-7 and -6		-5 – -3	-2 – 0	1 – 11	12	13 – 23	24	25 – 51	52
(Craving and Use)	No	41	Cue Presentation / VAS[2]	x (Up to 3x weekly)				x (1x weekly)				x (1x monthly)	
	No	42	TLFB	x		x (3x weekly)		x (2x weekly)					
	No	43	STRAP-R[2]	x		x (3x weekly)		x (2x weekly)		x (1x monthly)			
Experimental Measures of Executive Function	No	45	Eriksen Flanker[2]	x (Up to 2x daily)									
	No	46	N-Back[2]	x (Up to 2x daily)									
	No	47	Psychomotor Vigilance[2]	x (Up to 2x daily)									
	No	48	Balloon Analogue Risk Task[2]	x (Up to 2x weekly)				x (1x weekly)				x (1x monthly)	
	No	49	Delay Discounting[2]	x (Up to 2x weekly)				x (1x weekly)				x (1x monthly)	
	No	50	Dot-probe Task[2]	x (Up to 2x weekly)				x (1x weekly)				x (1x monthly)	
	No	50.1	Interoceptive processing	x (Up to 2x during each inpatient study phase)				Up to once monthly					
Continuous Physiological Monitoring	No	51	Heart Rate[3]	x (continuously)									
	No	52	Heart Rate Variability[3]	x (continuously)									
	No	53	Sleep Duration[3]	x (1x daily)									

			Phase	**Phase I**	**Phase II**	**Phase III**	**Phase IV**	**Phase V**					
			Procedure	Screening	Baseline	DBS Surgery	DBS Titration	Follow-Up	**12 Week Follow-up Visit 1**	Follow-Up	**24 Week Follow-up Visit 2**	Follow-Up	**52 Week Follow-up Visit 3**
			Inpatient / Outpatient	Inpatient				Outpatient					
			Duration	Up to 5 weeks[1]		Up to 3 weeks	Up to 3 weeks	52 weeks					
			Time Point (Week)	-7 and -6		-5 – -3	-2 – 0	1 – 11	12	13 – 23	24	25 – 51	52
	No	54	Sleep onset/offset[3]	x (1x daily)									
	No	55	Body Temperature[3]	x (continuously)									
	No	56	ECG[3,4,5]	x (Up to 2x weekly)									
	No	57	Eye Tracking[3,4,5]	x (Up to 3x weekly)				x (Approximately 1x weekly)				x (Approximately 1x monthly)	
	No	58	GSR[3,4,5]	x (continuously)									
	No	58.1	Respiration[3] Rate	x (continuously)									
	No	59	Structural and Functional MRI[7]	x		x			x				x
	No	60	CT Scan			x (pre/post DBS surgery							
Neuroimaging	No	61	FDG PET/CT			x (pre-titration)			x				x
	No	62	C^{11}-Raclopride PET/CT (Placebo)			x (pre-titration)			x				x
	No	63	C^{11}-Raclopride PET/CT (Methylphenidate)			x (pre-titration)			x				x

			Phase	Phase I	Phase II	Phase III	Phase IV	Phase V					
			Procedure	Screening	Baseline	DBS Surgery	DBS Titration	Follow-Up	**12 Week Follow-up Visit 1**	Follow-Up	**24 Week Follow-up Visit 2**	Follow-Up	**52 Week Follow-up Visit 3**
			Inpatient / Outpatient	Inpatient				Outpatient					
			Duration	Up to 5 weeks[1]		Up to 3 weeks	Up to 3 weeks	52 weeks					
			Time Point (Week)	-7 and -6		-5 – -3	-2 – 0	1 – 11	12	13 – 23	24	25 – 51	52
	No	64	Local field potentials[8]				x	x	x	x	x	x	x
	No	65	EEG[9]	x	x	x	x	x	x	x	x	x	x

[1] Baseline and Screening procedures will occur over a two week inpatient phase. Screening assessments may be initiated prior to their admission to the CRC as inpatients. If performed prior to inpatient admission, screening assessments will be conducted within 3 weeks of the admission date.

[2] Administered on Electronic Device (Smartphone/Tablet/Computer)

[3] Assessed via Wearable Technology

[4] Assessed during Cue Presentation

[5] These are exploratory endpoints and may be collected as specified in the text.

[6] Assessments are also completed post each titration

[7] Structural MRI scan to be obtained may be completed at the end of the three-week surgical recovery period prior to the DBS titration and programming and a the 12 and 52-week follow up visits. Structural MRI may also be performed at PI's discretion if clinically indicated prior to or after DBS surgery. Functional MRI (resting state and task-based using a cue reactivity paradigm) may be performed prior to DBS surgery, at the end of the three-week surgical recovery period, and at the 12 and 52 week follow-up visits and in conjunction with LFP acquisition/cue reactivity at long term follow up visits.

[8]Local field potentials (LFPs) to be measured during specific tasks and as clinically indicated

[9]EEG may be measured during screening/baseline and post-surgical phases while the subject is at rest and/or during specific tasks (e.g. delayed discounting)