# A Randomized, Sham-Controlled Trial Investigating Deep Brain Stimulation as a Novel Treatment for Refractory Opioid Use Disorder

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Ali Rezai, MD
Principal Investigator

**CONTENTS** **PAGE**

PROTOCOL TEAM

**Principal Investigator:**

Ali Rezai, MD

**Co-Investigators:**

Sally Hodder, MD
James J. Mahoney, III, PhD
Daisy Thompson-Lake, PhD
James Berry, DO
Wanhong Zheng, MD
Manish Ranjan, MD
Daniel Farmer, DO

**GLOSSARY**

| | |
|---|---|
| ASPD | Antisocial 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 |
| 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 |
| TBI | Traumatic Brain Injury |
| VC | Ventral Capsule |
| VS | Ventral Striatum |
| WVU | West Virginia University |

**SCHEMA**

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| PURPOSE | The overall objective of this study is to assess the safety, tolerability, and feasibility of using deep brain stimulation (DBS) to treat opioid use disorder (OUD) as well as investigate the potential impact on substance use and risk factors associated with drug use recurrence. 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 a randomized, sham-controlled, partial crossover study investigating DBS, targeting the nucleus accumbens (NAc) and ventral internal capsule (VC), for participants with severe, treatment refractory OUD. |
| DURATION | Participants are monitored in an inpatient service for approximately 1-2 weeks to gather screening and baseline data (Phase I) prior to DBS placement. Post-implantation they remain for up to 2-3 weeks as inpatients for clinical stabilization (Phase II) and DBS titration (Phase III). Half of the participants are randomized to receive Active DBS (DBS-ON) and half are randomized to receive Sham DBS (DBS-OFF). All participants are followed twice a week for 12 weeks in the outpatient setting (Phase IV). At 12 weeks, participants randomized to DBS-OFF are crossed over to active stimulation and re-admitted to the inpatient service for 1-2 weeks to complete active titration (weeks 13-14). After titration, these participants are discharged to outpatient and followed twice a week for 12 weeks in the outpatient setting (Phase V). All participants remain with the DBS active for one-year post-stimulation (Phase VI), and are monitored weekly for safety. At the end of the study, participants may enter a separate long-term safety follow-up for up to five years. |
| SAMPLE SIZE | Twenty participants will be enrolled in this study to achieve a final sample size of 16 participants who will complete the primary outpatient endpoint (Week 12). |
| POPULATION | Persons aged 22- 50 years who meet eligibility criteria. |
| OBJECTIVE | The overall objective of this study is to conduct a prospective, randomized, sham-controlled trial of DBS in participants with treatment refractory OUD. Objectives also include an evaluation of the safety and tolerability of NAc/VC DBS and the effect of NAc/VC DBS on opioid use, the brain reward circuitry through evaluation of dopamine in the basal ganglia and NAc (18F-fallypride PET), and the effect on prefrontal cortex function through the measurement of executive function. |

PRIMARY/SECONDARY OUTCOME ENDPOINT

- *Between-Subject Comparisons* – Participants receiving 12 weeks of Active DBS stimulation will be compared to participants receiving 12 weeks of Sham DBS stimulation.

PRIMARY OUTCOMES

1) Safety and tolerability, as measured by all adverse events related to DBS.
2) Opioid use as measured by quantitative urine toxicology via gas chromatography/ mass spectrometry (GC/MS).

SECONDARY OUTCOMES

Impact of Active (DBS-ON) versus Sham (DBS-OFF) NAc/VC DBS on:

1) Brain reward circuitry through evaluation of dopamine in the basal ganglia and NAc (18F-fallypride PET) and prefrontal cortex glucose metabolism (FDG PET).
2) Cognitive functioning, assessed with behavioral scores and/or MRI data.
3) Quantitative urine toxicology for non-opioid substances (e.g. cannabis, cocaine, amphetamine, benzodiazepines) as measured via GC/MS.
4) Qualitative urine toxicology for opioids and other substances. Salivary toxicology may be conducted as an alternative if the participant is unable to physically present to clinic.
5) Substance craving, assessed with behavioral scores and/or MRI data.
6) Emotional functioning (depression and anxiety).
7) Drug overdoses defined according to the National Library of Medicine (www.nlm.nih.gov).
8) Incidence of serious infectious disease complications (e.g., endocarditis, osteomyelitis, septic arthritis, etc.).
9) Retention in comprehensive behavioral treatment.
10) Patient survival.

ADDITIONAL OUTCOME ENDPOINTS

- *Within-Subject Comparisons (Phase V Endpoint)* – For those initially randomized to Sham DBS condition (DBS-OFF), following crossover to active stimulation, comparisons of the initial 12 weeks of stimulation "OFF" will be made to the 12 weeks of stimulation "ON" for the primary and secondary outcomes listed above.
- *Within-Subject Comparisons (Study Completion)* – For all participants, comparisons following 52 weeks of active stimulation will be made to pre-surgical baseline for the primary and secondary outcomes listed above.

EXPLORATORY OUTCOMES

- Local field potentials (to examine for changes in the neural response in the NAc following DBS of the NAc/VC)
- Functional connectivity via resting state and task-based fMRI (to examine for changes in the reward circuitry and associated regions following DBS of the NAc/VC)
- Structural brain changes pre- and post-treatment. (e.g., cortical morphometry, subcortical volume and white matter integrity)

- Exploratory voltammetry analysis recording neural responses to cues from the nucleus accumbens

## 1.0 STUDY OBJECTIVE

The overall objective of this study is to assess the safety, tolerability, and feasibility of using deep brain stimulation (DBS) to treat opioid use disorder (OUD) as well as investigate the potential impact on substance use and risk factors associated with drug use recurrence. This overall objective will be attained through completion of the following co-primary specific aims:

- Evaluate safety and tolerability of DBS in 20 participants with treatment refractory OUD.
- Demonstrate the impact of Active DBS versus Sham DBS on opioid use as measured by quantitative urine toxicology via gas chromatography/ mass spectrometry (GC/MS)

## 2.0 INTRODUCTION

### 2.1 Background

Novel treatments for OUD are desperately needed. In 2020, there was an estimated 9.5 million people who misused opioids (Center for Behavioral Health Statistics and Quality, 2021). Drug overdose deaths from suicide and unintentional overdose have increased dramatically since 2017 (Bohnert and Ilgen 2019). In 2021, the documented number of drug overdoses was the highest in recorded history; there were >107,000 overdose deaths and >75% of these overdose deaths involved opioids many of which were synthetic opioids such as fentanyl (Ahmad et al., 2022). The toll of this opioid epidemic goes well beyond overdose survivals and deaths. Rates of Hepatitis C (HCV) have steadily increased over the past decade and once again future generations may be affected as the number of pregnant women with HCV has doubled in recent years and this virus may be transmitted by a pregnant woman to her infant (CDC, 2017). The morbidity and mortality secondary to the opioid epidemic is clearly one of the greatest public health problems that the U.S. currently faces. In addition to the detrimental impact on health, there are significant financial consequences, specifically, the total economic burden is 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 et al., 2016).

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% success rate, at best. For example, in a multisite, randomized trial, the rate of unsuccessful outcomes following stabilization on MAT over 12 weeks was less than 50% (Weiss, Potter et al. 2011). A recent review of extended release injectable naltrexone revealed that many patients never even start the treatment because of withdrawal symptoms and those who start often discontinue (Jarvis, Holtyn et al. 2018). In addition, extended release Naltrexone and buprenorphine have unacceptably high relapse rates, with 24-week relapse rates (65% vs. 57%, respectively) (Lee, Nunes et al. 2018). Individuals failing standard OUD treatment have a substantial risk of death.

Given the enormously increasing socio-economic burden and death risk with OUD, newer and innovative treatment modalities are urgently needed. In addition, we need to better understand the mechanisms of action for addiction to develop specialized, focused treatments in future.

In DBS a tiny electrode is placed deep inside the brain at a specific target using a computer assisted stereotactic technique. This electrode is connected to a subcutaneous implanted pulse generator (IPG) which gives electrical stimulation to the area targeted/implanted. DBS has demonstrated safety and efficacy in treatment refractory movement disorders and obsessive-compulsive disorder (OCD) and is being investigated in a number of other neurobehavioral conditions, including but not limited to depression, Tourette's syndrome, 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., 2016, 2018; 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 use and additionally improve inhibition and decision making; thus, improving outcomes (e.g., decreased drug overdoses).

The overarching goal of this study is to further assess the safety, tolerability, and feasibility of using DBS to treat OUD as well as investigate the potential impact on substance use and risk factors associated with drug use recurrence. 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, 2017; Degenhardt et al., 2014; Florence et al., 2016; Haddy et al., 2017; National Center for Health Statistics, 2017; West Virginia Department of Health and Human Resources Bureau for Public Health, 2017). Given the life-threatening nature of treatment refractory OUD, 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

### 2.2.1 Current OUD Treatment Outcomes at WVU

The Comprehensive Opioid Addiction Treatment (COAT) program was developed at 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) medically assisted treatment with buprenorphine/naloxone. A key element of the COAT program includes continued maintenance on buprenorphine/naloxone rather than mandatory tapering. Clinic visits consist 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, 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. WVU also has a 30 bed 28-day residential SUD treatment program which also includes an additional 12 beds for detoxification services and managements. For the current study, participants will be recruited from these locations.

### 2.2.2 Prior DBS of NAc/VC Investigations

In the past twenty years, the use of brain pacemakers or 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 treatment refractory epilepsy. 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). For example, 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).

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) lack of feasibility in a pilot trial of morbid obesity (Rezai et al., 2018) and 4) safety and improved functional outcomes in pilot trials in Alzheimer's disease (Scharre et al., 2018) and traumatic brain injury (Rezai et al., 2016). 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).

### 2.2.3 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 et al., 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, anxiety disorders, addiction, TBI, Alzheimer's disease and eating disorders. DBS of the NAc/VC is proven safe and beneficial for the treatment of OCD, approved by the FDA HDE 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 was 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 symptom 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 striatum 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). One recent study of NAc/VC DBS for heroin addiction, done outside USA, was very encouraging with 5 of 8 patients achieving 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.

### 2.2.4 WVU/RNI Study Investigating the Safety and Feasibility of NAc DBS for Refractory OUD

In 2019, we initiated a National Institute on Drug Abuse (NIDA) sponsored single-arm clinical trial (ClinicalTrials.gov Identifier; NCT03950492) to evaluate safety and feasibility of a neuromodulation approach using DBS of the NAc for treatment-refractory OUD. Four participants (all males, ages 20-46) with longstanding history of severe, treatment-refractory OUD and multiple overdoses underwent bilateral image-guided stereotactic NAc and internal capsule DBS implantation. The study protocol involved the following phases: screening, baseline, DBS implantation and titration (all conducted inpatient), and the outpatient follow-up phases. Following the baseline phase, bilateral quadripolar DBS electrodes (lead 3387, Medtronic) were implanted stereotactically in the NAc and the ventral internal capsule (VC) and connected to the neurostimulator in the chest. The DBS parameters of polarity, pulse width, frequency, and intensity were optimized during the inpatient titration phase and guided by the participants' reported

anxiety, mood, and substance cravings. Subsequently, participants were discharged to outpatient follow-up with the primary outcome endpoint being Outpatient Week 12 as well as a long-term follow-up (Outpatient Week 52, primary study completion). Outcomes included safety, substance use, cue-induced craving (visual analog scale (VAS); 0 = no craving, 100 = maximum craving), anxiety (Brief Scale for Anxiety; BSA), and depression (Montgomery Asberg Depression Rating Scale; MADRS).

DBS surgery was safe in all participants with no complications. To date, participants #1 and #3 (both of whom have completed the primary 52-week protocol) have sustained abstinence from all substances per urine toxicology (>29 and >12 months respectively). Both evidenced significant reductions ($p<0.001$) in cravings for multiple substances, and reductions in depression and anxiety. These two participants remain actively engaged in their treatments showing improved functional outcomes including social functioning (e.g. re-establishing relationships with family) and employment. Participant #4 (who has also completed the primary 52-week protocol) had episodes of substance relapse post-DBS, however importantly, substance use frequency/severity are improved relative to pre-surgical baseline and he remains engaged in treatment. Significant post-surgical changes in craving were not evident in this participant, but significant post-surgical reductions ($p<0.001$) in anxiety and depression were noted. Participant #2 had DBS explanted during Outpatient Week 11 due to persistent non-compliance with the research protocol and treatment. There were no safety concerns for Participant #2 through the time of DBS explantation. In conclusion, DBS of the NAc is safe and feasible with a potential for reducing substance use, craving and relapse among persons with previously treatment-refractory OUD.

## 3.0 STUDY DESIGN

This is a randomized, sham-controlled, partial crossover study investigating DBS targeting the NAc and VC for participants with severe, treatment refractory OUD. The major objective of this study is to further test safety, tolerability, and feasibility of DBS in this population as well as investigate the impact of DBS on opioid use.

### 3.1 Randomization and Blinding Procedures

Randomization will occur after all inclusion criteria have been met and following the completion of DBS implantation. Participants will be randomized 1:1 to either the Active (DBS-ON) or the Sham (DBS-OFF) arm. Details of the procedure will be provided in a randomization-specification document. The date/time of the randomization will be collected in the electronic Case Report Form (eCRF) maintained by a designated team member who is not directly involved in study conduct. This study will be performed in a double-blinded manner, with Investigators, study staff, and participants unaware of treatment assignment. During the titration phase, there will be specified staff performing the active/sham titrations who will be aware of randomization status; however, they will play no role in the evaluation of study participants.

### 3.2 Breaking the Blind

After a participant completes the Outpatient Week 12 visit, that participant's treatment assignment is unblinded. Participants randomized to the "DBS-OFF" arm will be re-admitted to the inpatient service for active titration and discharged once active DBS setting are deemed optimal by the investigator and study team. Participants initially randomized to the "DBS-ON" arm will continue to receive active stimulation and be followed in the outpatient setting.

*Emergency unblinding procedure:* Code-breaking and unblinding in the event of medical emergencies can be done by the Investigator via the designated team member maintaining the randomization eCRF and who is not directly involved in study conduct. Unblinding by the Investigator should occur only in the event of an AE/SAE for which it is necessary to know the treatment assignment to determine an appropriate course of therapy for the participant. The Investigator should first discuss options with the Sponsor and DSMB, if possible; with due consideration of the safety of the participant. Participants for whom the code has been broken by the Investigator will be encouraged to attend all post-treatment visits as indicated in the Schedule of Activities. Code breaking will be documented in the eCRF.

# 4.0 STUDY POPULATION

## 4.1 Inclusion Criteria

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

- Age 22-50 years at time of enrollment.
- Fulfills current DSM-5 (American Psychiatric Association diagnostic and statistical manual of mental disorders, 5$^{th}$ ed, 2013) diagnostic criteria for severe OUD with at least a 5-year history.
- Participants may have comorbid SUD diagnoses at a mild, moderate or severe level, however, OUD must be the primary disorder for which the individual is seeking treatment and the other use disorders must occur in the context of relapse.
- Unsuccessful outcomes (initiated and discontinued/completed treatment with subsequent drug recurrence) following at least two levels of treatment (e.g., outpatient Comprehensive Opioid Addiction Treatment (COAT), intensive outpatient/intensive COAT, residential, inpatient) at least one of which included buprenorphine/naloxone.
- At least one lifetime overdose survival. Drug overdose criteria and symptoms defined according to the National Library of Medicine (www.nlm.nih.gov).
- 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.
- No evidence of systemic infection at time of surgery. The participant will not necessarily be excluded if this criteria is met; however, neurosurgical standard of care will be followed accordingly (e.g., postponement of surgery until participant is appropriately treated).

## 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 must have been in remission for one year.
- Baseline assessment on the Hamilton Depression Rating Scale (HAMD) of > 17.
- Increased risk of suicide based upon any positive response regarding passive or active suicidal ideation with or without intent over the past three months or history of active suicidal ideation with intent within the past three years on the Columbia Suicide Severity Rating Scale (CSSRS).
- History of medically verified suicide attempt within the past three years
- Parental history of completed suicide.
- 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 clinically significant cognitive impairment.
- Personal history of any clinically defined neurological disorder, including organic brain disease, medically uncontrolled epilepsy, stroke, brain lesions, or multiple sclerosis.
- Personal history of previous neurosurgery (brain), severe TBI, or head trauma that resulted in loss of consciousness (>24 hours) which was not medically/substance induced.
- Abnormal coagulation lab studies, defined as INR >1.4, abnormal PT/PTT deemed clinically significant (repeat labs for confirmation at discretion of investigator)
- Platelet count < 75×109/L (repeat labs for confirmation at discretion of investigator).
- Medically uncontrolled hypertension (systolic > 185 mmHg and/or diastolic > 110 mmHg), demonstrated on each of three repeated measurements taken within one hour regardless of whether the patient is taking antihypertensive medications.
- Implanted neurostimulators (e.g., vagus nerve stimulator, spinal cord stimulator, DBS)
- Any current Central Nervous System infection or infection with the Human Immunodeficiency Virus.
- 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 make-up or small metal fragments in the eye that welders and other metal workers may have, or if candidates are uncomfortable in small 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 use treatment mandated by court of law.
- Known destruction and/or damage to the NAc, ventral striatum, or VC region as determined by MRI.
- Pregnant or planning to become pregnant.
- History of medically uncontrolled epilepsy. Participants with documented febrile seizures will not be excluded. Seizures which are secondary to substance use and/or withdrawal and/or provoked seizures will not be exclusionary if they occurred more than one year ago.
- Conditions requiring repeated MRI scans.
- Conditions requiring diathermy.
- Uncorrectable coagulopathy; patients on anticoagulant/antiplatelet medications who cannot be off these medications during the standard perioperative care period
- Unable to speak, read and understand English fluently.
- Any evidence of cutaneous bacterial infection (e.g., impetigo, cellulitis, etc.). The participant will not necessarily be excluded if this criteria is met; however, neurosurgical standard of care will be followed accordingly (e.g., postponement of surgery until participant is appropriately treated).

In the event that there is a discrepancy between medical records and other sources of information, 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 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 the DSMB (if consensus across the study team cannot be reached), and the designated external independent eligibility reviewer. Eligibility will be determined after review of their recommendations.

### 4.3 Recruitment Process

Participants will be recruited internally from WVU Behavioral Medicine and Psychiatry (BMED) programs which includes outpatient (COAT, Intense Outpatient Program (IOP)), residential (CHH), and acute inpatient (Dual Diagnosis Unit) programs. The primary recruitment program will be COAT, 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. If a participant is deemed eligible and is enrolled, continued active participation and engagement in the WVU BMED treatment program, as clinically indicated, will be required throughout the duration of the proposed study. Participants will also be recruited externally from non-WVU sites after thorough consultation with the external treatment providers. These participants will have the same requirements regarding continued treatment during enrollment, either via transferring care to WVU or collaboration and consultation with their external treatment providers.

### 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 explained the study, including the screening process and required testing; and educated on the possible risks and benefits to participating. 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 they are 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. Participants will have the option to consent to videotaping throughout the study. The videotapes will be used for educational purposes.

### 4.5 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 DBS implantation will not have any collected data relevant to the safety or tolerability of the device or other study endpoints. Additional participants may be recruited to the study for each participant withdrawing consent prior to DBS placement or failing to reach the primary 12-week endpoint, thereby assuring the required number of participants from whom study endpoints are collected. The DBS device may be explanted for participants who are discontinued from the study for any reason. If a participant withdraws consent before the 12-week outpatient endpoint, the designated team member maintaining the randomization eCRF and who is not directly involved in study conduct will ensure that the randomization schema is adjusted to ensure that there are an equitable number of participants enrolled in each Sham and Active arm.

### 4.6 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. Likewise, medications may be added, tapered, or withdrawn as determined by the clinical treatment team and/or study investigators. Medications to be reported in the eCRF 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. During the conduct of the trial, shortwave/ultrasound/microwave therapy and implantation of metallic items 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 eCRF 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 six study phases with the corresponding schedule of events related to testing and procedures:

| ***Phase*** | I[1] | II | III[2] | IV | V[3] | VI |
|---|---|---|---|---|---|---|
| | Screening/ Baseline | Surgery/ Recovery | Titration | Outpatient Follow-Up | | |
| ***Inpatient/ Outpatient*** | Inpatient | | | Outpatient | | |
| ***Duration*** | 2 weeks | 1 week | Up to 2 weeks | 12 weeks | 12 weeks | 40 weeks |

| **Assessment** | | | | | | |
|---|---|---|---|---|---|---|
| Medical History/Physical Examination | x | | | | | |
| Neurological Examination | x | | | | | |
| Psychiatric Examination | x | | | | | |
| ECG | x | | | | | |
| Demographic & Drug/Alcohol Use Inventory | x | | | | | |
| MR Checklist | x | | | | | |
| X-Ray | x | | | | | |
| MRSA Nasal Swab | x | | | | | |
| Lab Tests (blood work) | x | | | x | x | |
| NIH Stroke Scale | x | x | x | x | x | x |
| Urine/Salivary Toxicology (Qualitative) | x | x | x | x | x | x |
| Urine Toxicology (Quantitative - HPLC) | x | | | x | x | x |
| Pregnancy (Qualitative) | x | x | x | x | x | x |
| Pregnancy (Serum) | x | x | x | x | x | x |
| Vital Signs | x | x | x | x | x | x |
| Adverse Events/Adverse Device Events | x | x | x | x | x | x |
| Con Meds | x | x | x | x | x | x |
| SCID-5 | x | | | | | |
| SCID-5-PD | x | | | | | |
| MSPSS | x | | | | | |
| BPRS | x | x | x | x | x | x |
| HAM-D | x | x | x | x | x | x |
| CSSRS | x | x | x | x | x | x |
| YMRS | x | x | x | x | x | x |
| CPRS | x | x | x | x | x | x |
| BIS | x | x | x | x | x | x |
| DVPRS | x | x | x | x | x | x |
| SURE | x | x | x | x | x | x |
| NIH Quality of Life Measures | x | x | x | x | x | x |
| TLFB | x | x | x | x | x | x |
| Cue Presentation/Cue Induced Craving VAS | x | x | x | x | x | x |
| WRAT-IV | x | | | | | |
| WASI-2 | x | | | x | x | x |
| Standard Cognitive Battery[4] | x | | | x | x | x |
| NIH Cognition Toolbox | x | | | x | x | x |

| ***Phase*** | I[1] | II | III[2] | IV | V[3] | VI |
|---|---|---|---|---|---|---|
| | Screening/ Baseline | Surgery/ Recovery | Titration | Outpatient Follow-Up | | |
| ***Inpatient/ Outpatient*** | Inpatient | | | Outpatient | | |
| ***Duration*** | 2 weeks | 1 week | Up to 2 weeks | 12 weeks | 12 weeks | 40 weeks |

| | | | | | | |
|---|---|---|---|---|---|---|
| Eriksen Flanker | x | x | x | x | x | x |
| N-Back | x | x | x | x | x | x |
| Balloon Analogue Risk Task | x | x | x | x | x | x |
| Delay Discounting | x | x | x | x | x | x |
| Structural MRI | x | x | | x | x | x |
| Functional MRI | x | x | | x | x | x |
| CT Scan | | x | | | | |
| FDG PET/CT | x | x | | x | x[6] | x[6] |
| 18F-fallypride PET/CT (Placebo) | | x | | x | | |
| 18F-fallypride PET/CT (Methylphenidate) | | x | | x | | |
| LFP Capturing | | x | x | x | x | x |
| EEG[5] | x | x | x | x | x | x |

[1] Screening and Baseline procedures will occur over a two-week inpatient phase and/or while the subject is outpatient (within 3 weeks of inpatient admission).

[2] Those randomized to Sham will complete an Active Titration session (Phase IIIb) following Phase IV after cross over from Sham to Active stimulation conditions

[3] Phase V will only apply to those participants randomized to Sham initially. Procedures will be identical to Phase IV so that within-subject comparisons (12 weeks "DBS-OFF" versus 12 weeks "DBS-ON") can be made.

[4] The standard neuropsychological battery includes the following: California Verbal Learning Test-Second Edition, Short Form (CVLT-II-Short), Brief Visuospatial Memory Test-Revised (BVMT-R), Trails Making Test Parts A and B (TMT-A, TMT-B), Controlled Oral Word Association Test (COWAT) and Animal Fluency, Stroop Color-Word Interference Task (SCWT).

[5] EEG may be measured during screening/baseline and post-surgical phases while the subject is at rest and/or during specific tasks

[6] Optional

## 5.1 Phase I: Screening and Baseline Phase

After providing informed consent, study participants will complete an inpatient stay at a WVU facility (e.g., Chestnut Ridge Center (CRC); the inpatient psychiatric hospital of WVU or the Center for Hope and Healing (CHH) a residential treatment program at WVU) for approximately 1-2 weeks where they will undergo screening and baseline assessments to determine study eligibility prior to DBS placement. Alternatively, screening assessments may be initiated prior to their inpatient admission to the CRC. If performed prior to inpatient admission, screening assessments will be conducted within 3 weeks of the admission date.

## 5.2 Phase II: DBS Surgery

After completion of the screening period, if the participant is assessed as being appropriate for the surgery, the participant will then undergo the DBS placement (Phase II) at Ruby Memorial Hospital (RMH), which includes approximately 1-2 weeks recovery period at RMH and CRC/CHH. 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. 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, obtained approximately one week prior to the surgery (but no more than 2 weeks prior to the surgery date). 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. After DBS placement, patients will undergo a post-operative CT scan on the same day as surgery to rule out hemorrhage. 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 two weeks post DBS surgery.

## 5.3 Phase III: DBS Titration and Stimulation

Up to a two-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 as well as the parameters utilized in the initial pilot study conducted by the team. Since it is difficult to titrate stimulation parameters for efficacy in OUD the optimum stimulation will be based first on the absence of adverse effects and second, on whether the stimulation parameters help to improve craving, mood, and/or physiological responses; or at the discretion of the research team with regards to behavioral addiction features.

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, 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 slowly in small increments while the patient is monitored for immediate side effects. These can include sensory changes, motor symptoms, immediate mood changes, non-specific drowsiness, discomfort, or eye deviation. The stimulation will not exceed the 30 μcoulomb/cm² charge density safety limit. After the programming session and safety follow-up (up to two weeks) participants will be discharged from inpatient/residential setting and monitored via outpatient visits and with the behavioral medicine program as per the protocol.

For participants randomized to the "DBS-ON" arm, 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 are made to the stimulation parameters. These sessions are performed in an attempt to decrease any anticipatory bias on behalf of the subject (e.g., knowing an adjustment is being made and subsequently anticipating 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.

For participants randomized to the "DBS-OFF" condition, titration sessions will be conducted identically to the "DBS-ON" arm, the only difference is that no stimulation is delivered and therefore, no actual adjustments made. Following outpatient Week 12, the participants randomized to the "DBS-OFF" condition will be re-admitted to the hospital for 1-2 weeks to receive the active titration and stimulation sessions as described above.

Before the DBS unit is implanted, participants will be given a copy of the Medtronic Patient Therapy Guide, which describes the DBS unit and its care (e.g., avoiding magnetic fields) and receive individual teaching regarding the contents of the Guide. Participants will also receive a smaller pocket-size Quick Guide reference. At discharge, the participants may 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 programmed voltage. They will also be able to mark events (e.g. increased craving) with the device (see section 5.4 for further details). 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; however, it will be recommended that the participant contact the study team first before doing so. Participants 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.

### 5.4 Phase IV: Primary Endpoint – Follow-up and Monitoring (12 Week Outpatient Phase)

The primary study endpoint is 12 weeks post-discharge to the outpatient phase. All participants (regardless of randomization condition) will return to the clinic twice weekly during the first 12 weeks, any further requirements for inpatient treatment related to OUD will follow the

WVU BMED program standard of care. See Table 1 for detailed assessments to be performed at Week 12.

The impedance of each DBS electrode will be assessed at every outpatient visit to ensure the device is functioning properly 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 or a different setting at the discretion of the investigative team. Participants may have their stimulation parameters adjusted at the discretion of the treatment team to maintain or improve efficacy 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.

The Percept PC device allows recording of local field potentials non-invasively from the implanted DBS system. The Percept PC can also record and stream local field potential data in real time. This feature may be used during the planned behavioral (e.g., cue-induced craving) and cognitive assessments (e.g., delay discounting, balloon analog risk task). The Percept PC device will also record averaged local field potentials continuously and these will be obtained from the Percept PC device at programming sessions to be evaluated later. Patients with an implanted Percept PC will be able to have events marked either in clinic or in the community (by themselves using the patient controller or the care/investigative team in the clinic). For example, these events could include increased cravings or feelings of wellness.

### 5.5 Phase V: Secondary Endpoint – Exploratory Follow-up and Monitoring (Sham Arm – 12 weeks DBS-OFF vs 12 weeks DBS-ON)

At 12 weeks, participants randomized to DBS-ON already have active stimulation which will continue; therefore, Phase V applies to *only those participants initially randomized to the sham arm* (i.e., DBS-OFF). Following completion of Phase IV (the 12-week outpatient primary endpoint), participants randomized to DBS-OFF are crossed over to active stimulation and re-admitted to the inpatient service for up to two weeks to complete active titration (Phase IIIb). They are then discharged as outpatients where they will, again, be followed twice weekly for 12 weeks in the outpatient setting. The secondary analysis is a within-subject analyses of 12 weeks DBS-OFF vs 12 weeks DBS-ON within these participants.

### 5.6 Phase VI: Tertiary Endpoint – Exploratory Follow-up and Monitoring (52 weeks post-active stimulation)

Once DBS is activated and titrated, all participants are followed weekly up until 52 weeks post-activation. For the Active arm this will be study weeks 13-52, for the Sham arm this will be weeks 26-66, (the shift in weeks accounts for 12 weeks of DBS-OFF stimulation and the two-week readmission for active titration). Final safety assessment and analyses will occur at 52 weeks post-active DBS titration.

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.

## 5.7 Long-Term Follow up (> 52 weeks post-active stimulation)

After the completion of 52-weeks with active DBS stimulation, patients may be eligible to participate in a separate long-term follow-up study. During these long-term follow-up visits, battery replacement, stimulation adjustments and DBS impedances will be checks to ensure that the device is working properly. Participants who do not consent to be in the long-term follow up study 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

## 5.8 Study Measures and Assessments

The study will utilize various medical procedures/assessments along with established behavioral, neuropsychological, cognitive, neurological, and neuroimaging assessments/measures/tasks to evaluate the status of the participant. These measures are employed to determine eligibility and/or support the primary and secondary objectives of the study.

### 5.8.1 Medical Procedures/Assessments

| | **Participants** | **Phase Endpoint** | **DBS status** |
|---|---|---|---|
| Phase I | All | Screening/Baseline | All: Pre-implantation |
| Phase II | All | Recovery after surgery | All: Implanted at surgery |
| Phase IIIa | Active only | Successful titration<br>(~1-2 weeks post-surgery) | Active arm: Titrated to active stimulation<br>Sham arm: Sham titrations (inactive stim) |
| Phase IV | All | Outpatient Week 12 | Active arm: DBS On<br>Sham arm: DBS Off |
| Phase IIIb | Sham only | Successful titration<br>(~1-2 weeks) | All: Active Stimulation |
| Phase V | Sham only | 12 weeks post-activation | Sham: Active, post-unblinding and titration |
| Phase VI | All | 52 weeks post-activation | All: Active Stimulation |

Blood collection to be performed for the following analyses at Phase I, endpoint of Phase IV/V.

- CBC with Differential
- BMP (Na, K, Cl, $CO_2$, BUN, Creatinine, Glucose)
- PT/INR
- PTT
- Type and Screen (Only collecting during Phase I)
- HIV1/HIV2
- Hepatitis C
- Liver function panel
- Serum pregnancy test (if applicable)

Urine collection will be performed for the following analyses:

- Urinalysis – *Completed during Phase I and at the completion of Phase IV and V).*
- Qualitative Urine Toxicology – *Completed at least once during outpatient screening (if applicable), twice weekly during inpatient phases (Phases I-III), twice weekly during Phase IV and V, and once weekly throughout Phase VI. Salivary toxicology may be completed if participant is unable to physically present to clinic.*

- Quantitative Urine Toxicology (GC/MS) – *Completed during Phase I, every four weeks of Phase IV and V, and once at the completion of Phase VI.*
    - Analyses on the following substances and substance metabolites will be performed: Cocaine, Amphetamine, Delta-9 tetrahydrocannabinol, Benzodiazepines, Morphine, Heroin, Buprenorphine, Fentanyl, Opioids/opioid analogs
- Urine pregnancy test (if applicable) – *Completed twice weekly during inpatient phases (Phases I-III), twice weekly during Phase IV and V, and once weekly during Phase VI.*

The following medical procedures will also be performed during screening/baseline (Phase I):

- MRSA screening by nasal swab
- History and physical examination, neurological examination, psychiatric examination
- Electrocardiogram
- Chest x-ray
- Vital signs (also monitored daily during inpatient phases and weekly during the outpatient phases)

5.8.2 Behavioral Assessments

Demographic and Drug and Alcohol Use Inventory: Demographic information including age, sex, education, ethnicity and characterizes years, recent (days in the past 30) (Mahoney, 2017), and daily drug use for opioids and other illicit substances. *Completed at Screening/Baseline (Phase I) and takes approximately 20 minutes to administer.*

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 and uses an algorithmic approach to scoring, assessing, and diagnosing DSM-5 disorders. 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/bipolar disorders, schizophrenia spectrum and other psychotic disorders, substance use disorders, anxiety disorders, obsessive-compulsive disorder, posttraumatic stress disorder, attention-deficit/hyperactivity disorder. *Completed at Screening/Baseline (Phase I) and takes approximately 45 minutes to administer.*

Structured Clinical Interview for DSM-5 Axis II Personality Disorders (SCID-5-PD) (First et al., 2016b): The SCID-5-PD is a semi-structured interview guide for making DSM-5 diagnoses 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 or dimensionally. *Completed at Screening/Baseline (Phase I) and takes approximately 45 minutes to administer.*

Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet, Dahlem, Zimet, & Farley, 1988): The MSPSS is a 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. *Completed at Screening/Baseline (Phase I) and takes approximately 5 minutes to administer.*

Depression and Suicidal Ideation Assessment and Monitoring

*(Completed at least once during outpatient screening, three times weekly during the inpatient phases (Phase I-III), post each titration session, up to twice weekly during Phase IV and V,*

*and once monthly during Phase VI. 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, 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): The HAM-D is a 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): The C-SSRS 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.

Brief Psychiatric Rating Scale (BPRS) (Overall, Gorham, 1988): The BPRS 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). *Completed at Screening/Baseline (Phase I), pre/post DBS surgery, and post each titration session at Investigator discretion and takes approximately 10 minutes to administer.*

Comprehensive Psychopathological Rating Scale (CPRS) (Asberg, Montgomery, Perris, Schalling, & Sedvall, 1978): The CPRS assesses symptoms of anxiety and depression via participant's self-reported responses. *Completed up to three times weekly during the inpatient phases (Phase I-III), up to twice weekly during Phase IV and V, and once monthly during Phase VI. This assessment takes approximately 5 minutes to complete.*

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. The YMRS total score ranges from 0 to 60. *Completed up to three times weekly during the inpatient phases (Phase I-III), up to twice weekly during Phase IV and V, and once monthly during Phase VI. 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. This assessment takes approximately 5 minutes to complete.*

Barratt Impulsiveness Scale (BIS) (Patton, 1995): The BIS is a 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. *Completed up to three times weekly during the inpatient phases (Phase I-III), up to twice weekly during Phase IV and V, and once monthly during Phase VI. This assessment takes approximately 5 minutes to complete.*

Defense & Veterans Pain Rating Scale (DVPRS) (Polomano, 2016): The DVPRS 2.0 is a pain assessment tool that utilizes a numerical rating scale enhanced by functional word descriptors, color coding, and pictorial facial expressions matched to pain levels. Four supplemental questions measure how much pain interferes with usual activity and sleep, and affects mood and contributes to stress. *Completed up to three times weekly during the inpatient phases (Phase I-III), up to once weekly during Phase IV and V, and once monthly during Phase VI.*

*This assessment takes approximately 5 minutes to complete.*

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. *Completed up to three times weekly during the inpatient phases (Phase I-III), up to twice weekly during Phase IV and V, and once weekly during Phase VI. This assessment takes approximately 5 minutes to complete.*

Cue Reactivity and Craving Visual Analog Scale (VAS): A set of substance-related stimuli (e.g., photos, computer images) will be presented to the participant. Prior to and immediately after viewing the cues, participants will complete paper- or computer-based assessment VAS designed to assess craving and mood. Cue presentation and VAS Measurements may be conducted more frequently at the investigator's discretion. *Completed up to three times weekly during the inpatient phases (Phase I-III), every four weeks during Phase IV, V and VI.*

Substance Use Recovery Evaluation (Neale, 2016): The SURE is a 21-item (five factors) psychometrically valid, self-report measure which assesses recovery from drug and alcohol dependence. *Completed up to once weekly during the inpatient phases (Phase I-III), once weekly during Phase IV and V, and once monthly during Phase VI. This assessment takes approximately 5 minutes to complete.*

Quality of Life in Neurological Disorders Measures (Neuro-QoL) (Cella, 2012): The Neuro-QoL is self-administered by the participant on an iPad, available through the NIH Toolbox app with trained staff providing guidance and scoring. The Neuro-QOL includes validated measures that evaluate and monitors physical, mental, and social functioning. Domains assessed include anxiety, depression, emotional/behavioral dyscontrol, stigma, and sleep disturbance. The primary QoL outcome measure will be composite score for each domain. *Completed up to once weekly during the inpatient phases (Phase I-III), once weekly during Phase IV and V, and once monthly during Phase VI. This assessment takes approximately 5 minutes to complete.*

### 5.8.3 Cognitive Assessments

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 total number of correctly pronounced words is transformed into a Standard Score with age-corrective normative data. The test is used to roughly approximate the participant's general ability (IQ). *Completed during screening/baseline (Phase I). This assessment takes approximately 10 minutes to complete.*

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. *Completed during Phase I and at Phase IV-VI endpoints. This assessment takes approximately 45 minutes to complete.*

NIH Toolbox Cognition Battery (NIHTB-CB) (Gershon et al., 2013): The NIHTB-CB consists of assessments designed to yield different measures of cognitive performance. The NIHTB-CB tasks include the following which generates a Fluid Cognition Composite Score: 1) Dimensional Change Card Sort Test; 2) Flanker Inhibitory Control and Attention Test; 3) Picture Sequence Memory Test; 4) List Sorting Working Memory Test; 5) Pattern Comparison

Processing Speed Test; and includes the following tests which generate a Crystalized Cognition Composite score: 6) Picture Vocabulary Test; 7) Oral Reading Recognition Test. Supplementary measures including the Auditory Verbal Learning Test and Oral Symbol Digit Test will also be administered. The NIHTB-CB automatically generates age-corrected and fully corrected t-scores, allowing for comparison to average scores from a nationally representative sample. *Completed during Phase I and at Phase IV-VI endpoints. This assessment takes approximately 45 minutes to complete.*

Standard Neuropsychological Battery: This includes validated neurocognitive measures which cover several domains to yield a comprehensive assessment of functioning. This battery includes the following measures described below. *Completed during Phase I and at Phase IV-VI endpoints. This assessment takes approximately 60 minutes to complete.*

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

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.

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).

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.

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.

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).

### 5.8.4 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.

Eriksen Flanker Task (Eriksen, 1974): The Flanker task is a response inhibition test to assess the participant's ability to suppress a response that is inappropriate based on the task rules.

Participants respond either left or right based on the direction of the middle arrow (target) of five aligned items. The task consists of congruent stimulus (the direction of the target and flanker arrows are the same), incongruent stimulus (the direction of the target is opposite of the flanker arrows), and neutral stimulus (flanker items are different shape e.g., a square than the target arrow). *Completed up to once weekly during the inpatient phases (Phase I-III), up to once weekly during Phase IV and V, and up to once monthly through Phase VI. This assessment takes approximately 5 minutes to complete.*

N-Back Task (Kirchner, 1958): The N-Back task is a working memory measure where participants monitor a series of stimuli and respond whenever a stimulus is presented that is the same as one presented in a predefined previous trial. For example, 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. *Completed up to once weekly during the inpatient phases (Phase I-III), up to once weekly during Phase IV and V, and up to once monthly through Phase VI. This assessment takes approximately 5 minutes to complete.*

Balloon Analogue Risk Task (BART) (Lejuez, Read, Kahler, Richards, Ramsey, Stuart, Strong, Brown, 2002): The BART is a computerized measure of risk-taking behavior which 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 trial, 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. *Completed up to once weekly during the inpatient phases (Phase I-III), up to once weekly during Phase IV and V, and up to once monthly through Phase VI. This assessment takes approximately 5 minutes to complete.*

Delayed Discounting Task (Richards, Zhang, Mitchell, de Wit, 1999): The Delayed Discounting Task assesses cognitive functions which are often impaired in substance users including: decision-making, impulsivity, and inhibitory control. This task presents subjects with hypothetical choice of a smaller immediate reward or a larger delayed reward, for example, "Would you rather have $2 now or $10 in 30 days?" The delay of the larger amount varies as a function of time e.g., a delay of 1, 2, 30, 180 or 365 days. The primary outcome measure is an indifference value calculated at each delay time point. This value reflects the smallest amount of immediate money (smaller sooner) an individual chooses over a delayed larger amount (larger later). *Completed up to once weekly during the inpatient phases (Phase I-III), up to once weekly during Phase IV and V, and up to once monthly during Phase VI. This assessment takes approximately 12 minutes to complete.*

### 5.8.5 Neurological Assessments

National Institutes of Health Stroke Scale (NIHSS): In the long-term follow up period, the NIHSS will be performed after any stimulation adjustments. The 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. *Completed during Phase I, once post-surgery, post each titration session, and then once monthly through endpoint of Phase VI. This assessment takes approximately 10 minutes to complete.*

## 5.9 Neuroimaging

### 5.9.1 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 brain metabolism with DBS. FDG PET/CT will be collected at WVU. 18F-fallypride PET/CT will be conducted to measure changes in dopamine brain metabolism, through the measurement of dopamine binding, associated with NAc/VC DBS.

There will be a total of 2 PET/CT sessions performed for each participant during this study: 1) Session one includes three scans at the end of the surgical recovery period and prior to the DBS titration and programming 2) Session two includes three scans at the 12-week outpatient primary endpoint (end of Phase IV).

Each of these sessions above will consist of three PET scans: 1) FDG PET/CT to assess brain glucose metabolism, 2) $^{18}$F-fallypride/CT placebo (no methylphenidate challenge) and 3) $^{18}$F-fallypride 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. FDG PET/CT may also be completed following 52 weeks of active stimulation as well as 12 weeks following active stimulation for the group initially randomized to receive sham DBS.

### 5.9.2 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.

### 5.9.3 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 surgical recovery period prior to the DBS titration and programming, at the endpoint of Phase IV, and V and endpoint of Phase VI. Additional structural MRI may be completed at investigator's discretion, if clinically indicated, prior to or after DBS surgery. Structural (e.g., T1-weighted, Diffusion weighted imaging) and functional MRI (resting state and task-based paradigms) may be performed

prior to DBS surgery, at the end of the surgical recovery period, at the endpoint of Phase IV, Phase V, and Phase VI. Scans may also be acquired in conjunction with LFP acquisition.

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 30-40 minutes. The patient may be asked to lie still for up to 15 minutes at a time. During the task-based fMRI, if time allows, neurocognitive or craving assessments similar to those described above may be presented to the participant via a computer monitor and the participant will be able to complete the task by responding using a response box. 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.

### 5.9.4 Micro-electrode Recording

The microelectrode recording (MER) is a standard process for DBS surgery. During DBS surgery a microelectrode is inserted into the brain to record and map the neural structure and to plan/modify the final DBS stimulating electrodes placement. In addition to standard MER recording, to record electrochemical measurements of neural activity, an electrochemical probe will be lowered into the cannula through the same track used for the microelectrode recording prior to inserting the DBS electrode. A behavioral task will be performed by the patient while electrochemical data is recorded. Our goal is to take the opportunity to record of electrochemical measurements of neural activity during behavioral tasks (described above) without significantly prolonging or compromising any aspect of the surgical procedure. The tasks take less than 15 minutes for each DBS placement to complete, thus adding no more than 30 minutes total to the procedure. The electrochemical probe will pass through the same tissues for the microelectrode recordings, and no other sites.

### 5.9.5 Local Field Potential Recording

To observe the functioning of the NAc in association with DBS therapy and symptom severity over time, local field potentials (LFP) will be measured using by recording functionality of the Medtronic Percept PC stimulator device. During recordings, patients will sit quietly in a chair with the data receiver positioned nearby, either at rest (to acquire a baseline or “resting state” measurement) or performing one the computer-based tasks listed above. An EEG cap or a transcutaneous electrical nerve stimulator (TENS) device will be used to synchronize the electrical artifacts produced by DBS pulses. This allows the LFP recordings from the Percept PC to be synchronized to the events produced from the task computer during data analysis.

Additionally, patients may be provided with a juice reward system. Juice rewards are an effective way of stimulating NAc activity and will facilitate the use of LFP data in understanding the effects of DBS on reward processing. Juice is given via a straw-like mouthpiece via food-safe tubing, gated by a computer-controlled solenoid valve. The task computer briefly opens the valve to give an immediate, pleasant outcome that drives NAc activity. When used, patients may be

provided with the option to select a juice flavor from among a few commercially available options. The entire juice reward system will be sanitized before and after each use, and a new unused mouthpiece will be provided for each session.

5.9.6 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).

## 5.10 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.

## 5.11 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 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 0V. 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, paresthesia, 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 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
- Increased fatigue (feeling exhausted or moving slower than usual)
- Cognitive disturbance (“cloudy” thinking)
- Restlessness
- Weight gain or weight loss
- Insomnia/Sleep disturbance
- Speech and visual difficulties

- Blurred/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 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 parts of the brain-stimulation system 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 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 listed above 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.

***Risks of Electrochemical Electrode.*** The risks from recording brain activity during research tasks are no greater than the risks associated with the DBS procedure, as placement of the electrodes is a standard component of the surgical procedure. The risks from using the chemical-sensing probe are believed to be of equal risk to placement of the standard DBS electrodes. Of concern in any surgery is the effect of additional surgical time on exposed tissues. Participation in this type of study in the past has not been found to increase the risk of complications or adverse events. The neurosurgeon will be considering the safety and well-being of the patient at all times and has the authority to stop the research procedures or not allow them to be performed. There is a possible increased chance of infection because of the research probe but, like the regular surgery electrodes, the probe will be sterilized and kept in sterile packaging.

## 5.12 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. 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 NAc is off label and therefore there are unknown risks in general.

Other mental implants e.g., 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.

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 if their kidney function is not normal.

***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 18F-Fallypride 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 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 700-2,000. 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.

## 5.13 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 need to be treated accordingly before surgery and neurosurgical standard of care processes will be followed. 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 meticulous surgical techniques, 24 hours of peri-operative prophylactic IV antibiotics after implantation of the DBS lead and 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.

Some individuals, such as those with a history of intravenous drug use (IVDU), may be at a higher risk of infection than others. All patients will be hospitalized as inpatients for at least one week prior to surgery and for approximately 2-4 weeks post-surgery during the recovery and stimulation/titration phases. As mentioned above, they will be regularly assessed for infection in the weeks surrounding implantation. Moreover, during their inpatient hospitalization, patients will reside in a locked unit and are monitored 24 hours per day/7 days per week, thus significantly reducing the possibility of acute infection secondary to IVDU during hospitalization. Once discharged to the outpatient phase, patients are monitored twice weekly for the first 12-26 weeks (depending on whether they were randomized to active/sham conditions) and then once weekly

throughout 52 weeks of active stimulation. Monitoring of infection will occur routinely during all follow-up visits and AE assessments. In addition, urine toxicology will be performed during this visit and there will be routine medical examinations to assess whether relapse has occurred. If the patient experiences a relapse, especially via the intravenous route, the investigator will determine whether antibiotics should be prescribed prophylactically. If there is any suggestion or proven infection at any point pre- or post-surgically, the patient will be treated aggressively per standard of care including appropriate antibiotics in consultation with team, including but not limited to neurosurgery and infectious disease, and the patient will be followed up with regularly until infection resolves.

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 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 terminate from the study or discontinue stimulation at any time and 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. 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.

## 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.

### 7.1 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.

## 7.2 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.

## 7.3 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 five days. Unanticipated adverse device effects will be reported to the IRB and not more than five days after the PI first learns of the event.

## 7.4 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.

### 7.5 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.

### 7.6 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 from surgery 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 deemed definitely related to study procedure.

### 7.7 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 observes 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.

## 8.0 DATA SAFETY AND MONITORING

To ensure ensures that the trial is conducted, recorded and reported in accordance with the protocol, SOPs, GCP and applicable regulatory and ethical requirements, this study will be monitored by an independent monitor and a DSMB.

The independent monitor will be selected qualified by training and experience to monitor the progress of the investigation. The monitoring plan will be tailored to minimize the risks identified based on considerations such as the objective, purpose, design including patient population and intervention, complexity, blinding, size and endpoints of the trial. Following are the key responsibilities of a monitor:

Verify that the investigator(s) have adequate qualification, expertise and the resources to carry out the trial. The monitor should also ensure that the investigator will be available for the proposed duration of the trial.

Ascertain that the required institutional facilities (laboratories, equipment, staff, space for storage, etc.) are available throughout the trial.

Verify or make provisions to ensure the following:

- Only eligible participants are enrolled in the trial.
- Sufficient amount of IP is available at the site, and is stored in appropriate conditions.
- IP is supplied to only to eligible participants at the specified dose(s) and time(s).
- The receipt, use, return and disposal of IP at the site is controlled and documented as prescribed.
- The protocol and all approved amendments (if any) are followed.
- The investigator(s) has received the current version of Investigators Brochure and the trial supplies, as required.
- All essential documents are maintained by the investigator at site.
- All parties involved in the trial are adequately informed of the trial and its various aspects, and follow the GCP guidelines and prescribed SOPs.

The monitor should ensure that the site staff have been adequately trained and comply with the protocol, SOPs, and other aspects of the trial.

The monitor should also assist with providing guidance on Case Record Form (CRF) completion.

The monitor must ensure that all CRFs are completed accurately in accordance with original observations (source data verification), entries are legible, complete and dated. The monitor should verify the following:

Critical data, required by the protocol is reported accurately on the CRFs and is consistent with the source documents.

Any modification(s) with the dose and/or therapy are documented for each trial participant.

Ensure that the investigational product is retrieved and disposed or returned to the sponsor, in accordance to the protocol.

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 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.

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 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 source verified on an ongoing basis (as data becomes available) by a qualified clinical research team member.

## 9.0 DATA AND STATISTICAL CONSIDERATIONS

### 9.1 Primary Outcomes/Endpoints

Co-primary outcomes for the proof-of-concept study include: 1) safety and tolerability and 2) impact on opioid use among participants. Participants receiving 12 weeks of Active DBS stimulation will be compared to participants receiving 12 weeks of Sham DBS stimulation.

1) The safety/tolerability primary endpoint will be assessed comparing Grade 3 and 4 adverse events between the Active (DBS-ON) and Sham (DBS-OFF) arms throughout Phase IV (Outpatient Week 12). We will provide a list of all adverse events and their grading. We will also categorize adverse events by organ system and assess relatedness to any aspect of this proof-of-concept study. Statistical tests will be performed at the request of the Data and Safety Monitoring Board (DSMB).
2) Opioid use will be evaluated through the use of quantitative urinary toxicology using gas chromatography/mass spectrometry. For each subject, quantitative urine toxicology will be collected at baseline (during screening) and during Outpatient Follow-Up Week 4, 8, and 12. We will evaluate the area under the curve (AUC) as the primary endpoint for each subject, using the functional data analysis method to fit a smoothing curve for each individual data over time. The AUC data can be standardized by the divided time interval as the mean urine drug concentration over the period. For the descriptive purpose, we will

plot those individual AUC curves with a mean-curve based on such functional data analysis for each treatment group. The statistical inference on the AUC data as a continuous variable is based on Wilcoxon's rank-sum test between the DBS-ON and DBS-OFF arms throughout Phase IV.

### 9.2 Secondary Outcomes/Endpoints

1) Brain reward circuitry through evaluation of prefrontal cortex glucose metabolism (FDG PET) and dopamine in the basal ganglia and NAc (18F-fallypride PET).

   - 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.
   - $^{18}$F-fallypride PET 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 DV images from 34 healthy subjects that were acquired with $^{11}$C Raclopride (similar to $^{18}$F-fallypride) 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 Outpatient Week 12 with and without methylphenidate to determine binding potential of dopaminergic D2/D3 receptors.

2) Performances on the NIH Toolbox Cognition Battery (NIHTB) and the standard neuropsychological battery will be assessed and analyzed using repeated measures ANOVA. In addition, experimental measures of executive function will be assessed and analyzed using repeated measures ANOVA. These measures include the following:

   - Eriksen Flanker Task (Eriksen, 1974): response inhibition.
   - N-Back task (Kirchner, 1958): working memory.
   - Balloon Analogue Risk Task (Lejuez, 2002): risk-taking behavior.
   - Delayed Discounting Task (Richards, 1999): decision-making, impulsivity, and inhibitory control.

3) Similar to Primary Outcome #2, gas chromatography/mass spectrometry will be utilized to assess exposure to non-opioid substance use (e.g., cannabis, cocaine, amphetamine, benzodiazepines) at baseline (during screening) and at 4, 8, and at 12 weeks of outpatient

follow-up. AUC Comparisons will be made between baseline (pre-DBS implantation) and post-surgery follow-up, measured at Outpatient Week 4, 8, and 12 weeks.

4) Qualitative urine toxicology will be obtained twice weekly Phase IV and until 24 weeks post-activation and once weekly until 52 weeks post-activation (salivary toxicology may be conducted as an alternative if the participant is unable to physically present to clinic). Chi-square analyses will be used to determine differences in total number of positive results between sham and active arms.

5) Substance craving will be assessed within two contexts: a) without substance related cues and b) with substance related cues during a cue reactivity paradigm.
   a) Substance craving without cues: Baseline craving ratings prior to initiating the cue reactivity task will be assessed and analyzed using repeated measures ANOVA.
   b) Substance craving with cues (via a cue reactivity task): Cue-induced craving ratings will be assessed and analyzed using repeated measures ANOVA.

6) Mood (depression and anxiety) assessed via the Comprehensive Psychopathological Rating Scale (CPRS) will be assessed and analyzed using repeated measures ANOVA.

7) Drug overdoses, serious infectious disease complications, retention in comprehension behavioral treatment, and patient survival will be assessed weekly throughout the Outpatient phase and chi-square analyses will be utilized to determine differences (Yes/No) between active and sham arms.

The outcomes listed above will be evaluated in the following contexts:

- *Between-Subject Comparisons (Primary Endpoint)* – Participants receiving 12 weeks of Active DBS stimulation will be compared to participants receiving 12 weeks of Sham DBS stimulation.
- *Within-Subject Comparisons (Secondary Endpoint)* – For those initially randomized to Sham DBS condition (DBS-OFF), following crossover to active stimulation, comparisons of the initial 12 weeks of stimulation "OFF" will be made to the 12 weeks of stimulation "ON" for the primary and secondary outcomes listed above.
- *Within-Subject Comparisons (Tertiary Endpoint)* – For all participants, comparisons at 52 weeks of active stimulation will be made to pre-surgical baselines in line with the primary and secondary outcomes listed above.

## 10.0 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/approved by the WVU IRB responsible for oversight of the study.

## 11.0 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. The Medtronic leads used in this study include the Model B33005(M) or Model B33015(M) (primary), the Medtronic DBS implanted pulse generator (IPG)/neurostimulator include the Model B35200 Percept PC (primary), Model 37612 Activa RC, or Model 37601Activa PC, and the Medtronic extensions include the Model B34000 (primary) or Model 37086. Specific details of the lead, neurostimulator, and extension, as well as other DBS accessories/components, are described below.

***Model B33005(M) or Model B33015(M) (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. The primary leads used in this study (Model B33005(M) or Model B33015(M)) use the Medtronic developed Sensight™ technologies which combines the benefits of directionality with the power of sensing LFPs from the implanted brain electrodes. The following SenSight™ components are also included: Lead Test Cable (Model B31040), Lead Cap Kit (Model B31020), Burr Hole Device (Model B31000), Burr Hole Device Kit (Model B32000), and Extension Tunneler Kit (Model B31030)

***Model B35200 Percept PC, Model 37612 Activa RC, or Model 37601 Activa 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 LFPs from the implanted brain electrodes.

***Model B34000 or 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. The primary extension used in this study (Model B34000) will be utilized in combination with the Sensight™ leads referenced above.

***Model 37651 (Recharger)***. 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 (Clinical Programmer).*** The clinical programmer 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 (Communicator).*** The 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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