Approved Protocol:
Effectiveness of Deep Brain Stimulation for Treating People with Treatment-Resistant Obsessive-Compulsive Disorder

Butler Hospital

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BUTLER HOSPITAL
INSTITUTIONAL REVIEW BOARD
PROTOCOL FOR RESEARCH INVOLVING HUMAN SUBJECTS

I. TITLE OF PROJECT: **DATE:** 07/27/16
Controlled Trial of Deep Brain Stimulation for OCD
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Funding (Source, P.I.): NIMH (Greenberg PI)

Check if applicable:
/_ / **Use of Radioisotopes**
/_ / **Investigational New Drug**
IND/IDE# Humanitarian Device Exemption (HDE) H050003
Investigational Device Exemption (IDE) G070235
/_ / **Student Research**
Student _____

Duration of Project: 5 years
Duration for Individual Subjects: 1 year
Specific Location(s) of Project: Butler Hospital

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APPROVED FOR SUBMISSION TO IRB:
_____
Signature of Primary Reviewer

Research Subjects (check if applicable):
/_ / **Minors**
/_ / **Fetuses**
/_ / **Mentally retarded or disabled**
/_ / **Abortuses**
/_ / **Pregnant Women**
/_ / **Prisoners**
/_ / **Special racial/ethnic group**
Specify _____

ATTENTION: Before completing this protocol, consult the **IRB Guidelines** (rev, 10/01).

For IRB Use Only

_____ _____
Date Approved **Institutional Review Board**

II. DESCRIPTION OF STUDY

A. Specific Aims

The overall goal of this proposal is to complete the first definitive controlled trial of a neurosurgical procedure for a severe psychiatric illness. Our preliminary data show promising therapeutic effects of deep brain stimulation (DBS) in treatment refractory obsessive-compulsive disorder (OCD). The target stimulation site, the ventral anterior limb of the internal capsule and adjacent ventral striatum (VC/VS), was based on ten years of our preliminary work in lesion and DBS procedures for OCD. In addition to our empirical data there is a well-defined theoretical rationale as the VC/VS contains neuronal connections consistently implicated in OCD. In contrast to lesions, DBS is reversible and adjustable and has been refined during approved use in over 35,000 patients worldwide for medically intractable Parkinson's disease, tremor, and dystonia. In seven years of preliminary work we have refined the surgical targeting, stimulation parameters, and patient selection, permitting the design of a definitive controlled trial, an essential next step in development and wider use of DBS for OCD, and for other neuropsychiatric disorders, including highly resistant depression.

Deep brain stimulation (DBS) will be used as a clinical treatment in intractable OCD either "on label" under the FDA Humanitarian Device Exemption (HDE) mechanism or as an investigational device under the FDA Investigational Device Exemption (IDE). We will use a parallel controlled design to compare effects of three months of double -masked sham versus active DBS on OCD severity. We propose a five-year study in order to gather crucial long-term effectiveness and tolerability data. A total of 6 patients will be enrolled at the Butler site, with 30 patients enrolled overall across the nine collaborating clinical sites (Butler Hospital, Cleveland Clinic, George Washington University, Kaiser Permanente (Northern California), Massachusetts General Hospital, Mount Sinai Medical School, University of Florida, Wake Forest University the Mayo Clinic and the University of Chicago). The University of Rochester is scientific study site. They will be involved in data analysis and other scientific aspects of the study, but no clinical work or patient contact will take place there. The primary efficacy measure will be the Yale Brown Obsessive Compulsive Scale (YBOCS). We will also assess effects on comorbid depression, functioning, and quality of life, as well as potential adverse effects in multiple domains. Patients will have the option to participate in companion PET studies at Massachusetts General Hospital. One study involves 3 FDG PET scans (at baseline, 3 months after optimization and 6 months after optimization). The other study involves one O15 PET scan done after implantation but before any chronic DBS. Patients may choose to participate in one, both or neither of these studies. In addition, patients may choose to participate in additional learning task studies.

B. Background

Deep brain stimulation involves bilateral stereotactic placement of stimulating "leads" into specific brain structures. DBS leads each have four independently programmable electrode contacts. Leads are attached to permanent subcutaneous wires and battery-powered implantable neurostimulators (INSs). Noninvasive INS programming can achieve a balance between maximal benefit (reduction in disabling OCD symptoms), while minimizing adverse effects (eg, sensorimotor effects such as dysarthria or paresthesias; as well as behavioral side effects, e.g., hypomania, insomnia, or increased anxiety).

DBS is FDA-approved for Parkinson's disease, severe tremor, or dystonia that is medically intractable. Over 35,000 patients worldwide have had DBS for movement disorders. The treatment has been called the greatest therapeutic advance for Parkinson's patients in decades. For severe primary dystonia FDA approved DBS under a Humanitarian Device Exemption (HDE) mechanism, allowing limited clinical use since April 2003. In the first step towards limited approval of DBS for a severe psychiatric disorder, DBS received an FDA Humanitarian Use Device (HUD) designation for intractable OCD (defined in Inclusion Criteria, below). REMOVE: HDE approval is expected two months from the date of this IRB protocol submission.

Clinical investigations indicate promise for DBS in OCD. About 100 patients have received DBS for OCD worldwide since the late 1990s. A consistent pattern of encouraging reports has emerged across centers (see e.g., (Greenberg 2002). The most effective target has been centered in the anterior limb of the capsule at the A-P level of the anterior commissure. In our own long-term series, a full clinical response (≥ 35% reduction in Yale-Brown Obsessive-Compulsive Scale (YBOCS) score) in 50%, and a partial response (25% YBOCS decrease) in an additional 25% of otherwise untreatable patients. These benefits, which persisted over three years, were accompanied by gains in real-world functioning (Greenberg et al 2006).

These and similar results indicating 50-65% marked improvement across pilot studies led to the application by Medtronic, Inc. (device manufacturer) for humanitarian approval for DBS for OCD. Under HDE approval, DBS becomes available on a limited basis as a clinical (i.e., reimbursable) treatment. But the FDA standards for HDE approval are probable benefit and an acceptable safety profile, not definitive efficacy data. Thus, this treatment will only be fully developed if the efficacy of DBS for OCD is firmly established, as has happened for intractable dystonia, where DBS is moving towards full FDA approval based on more recent controlled data. There have been no adequate controlled studies for DBS in OCD.

Our aims under this proposal are:

1) To determine the effects of three months of masked active vs. sham VC/VS stimulation on OCD symptoms, functioning, and quality of life in patients with highly resistant OCD, using a parallel group controlled design.
2) To obtain comprehensive data on adverse effects including changes in personality, neuropsychological function, psychiatric symptoms, and neurological status, and other potential adverse effects.

Group data will be analyzed in concert with collaborating investigators performing clinical work at collaborating clinical sites (Massachusetts General Hospital, Cleveland Clinic, University of Florida; total N=30). Patients will be invited to participate in collaborative neuroimaging work at MGH (via separate informed consent).

C. Experimental Method

1. Brief Description of Subjects (The criteria below match those specifying the qualifying patient population in the FDA-approved HUD for DBS for OCD.)

Patients will have severe DSM IV OCD and resulting major functional impairment. Adequate treatment attempts with all proven OCD therapies will have failed. They will be 18 to 75 years old, the minimum age chosen to avoid the theoretical risk of disruption of brain development during earlier ages when there is marked brain plasticity. As a practical matter, demonstration of chronicity (≥5 years) and inadequacy of the multiple treatment approaches required is unlikely in many patients younger than their 20s. To reduce risks of DBS-induced mania or hypomania, patients with a bipolar disorder history are excluded. Only subjects who are able to give fully informed voluntary written consent would be accepted. Patients who enter will be free to withdraw from the study at any time without affecting their access to other treatments at any of the above institutions.

Inclusion criteria

(a) OCD, diagnosed by Structured Clinical Interview for DSM-IV (SCID-IV), judged of disabling severity with a Yale-Brown Obsessive Compulsive Scale (YBOCS) score of at least 30. In addition, impaired functioning indicated by a Global Assessment of Functioning (GAF) score of 45 or less.

(b) Highly treatment-refractory illness is documented. That is, there must be demonstration of persistence of severe symptoms and impairment for five or more years despite at least three first-line and two second-line treatments, as follows: *i)* at least three adequate trails of, or documented intolerance to, different serotonin transporter inhibitors (fluoxetine, sertraline, fluvoxamine, paroxetine, citalopram, escitalopram, or clomipramine for ≥ three months at the maximum tolerated dose). These trials may include any of the agents above, but must include an adequate course of clomipramine, either alone or in combination with a more selective serotonin transporter inhibitor.
ii) Augmentation of one of the selective SRIs with a neuroleptic, and clonazepam (each for at least two weeks), and
iii) adequate behavior therapy (≥20 sessions of exposure and response prevention (ERP) by a therapist with substantial expertise in OCD treatment as determined by the investigators. In practice, several trials ERP have usually been attempted and proven ineffective or intolerable. One of these trials must have been tried in combination with medication therapy.
(c) Age between 18 and 75 years.
(d) Able to understand and comply with instructions.
(e) Able to give fully informed, written consent in the judgment of the site Consent Monitor.
(f) Either drug free or on a stable drug regimen for at least six weeks.
(g) Good general health.
(h) It is also very helpful, though not an absolute requirement, to have a family member or significant other person who sees the patient regularly and can communicate with the study team as needed, and if necessary to accompany the patient to study visits.
(i) The local referring psychiatrist is willing to provide ongoing care during and after the trial, working closely with the research team. The local psychiatrist must agree that the study psychiatrist will prescribe medications during the three-month masked phase.
(j) Has a platelet count greater than 125,000 per cubic millimeter and a PT and PTT within normal limits.

Exclusion criteria
(a) Current or past psychotic disorder.
(b) Full-scale IQ below 75 on the Wechsler Abbreviated Scale of Intelligence (WASI) or cognitive impairment that would affect a participant's ability to give informed consent or provide interview or self-report data reliably, as determined by the Consent Monitor and the site psychiatrist.
(c) A clinical history of bipolar mood disorder.
(d) Any current clinically significant neurological disorder or medical illness affecting brain function, other than a tic disorder.
(e) Any clinically significant abnormality on preoperative magnetic resonance imaging (MRI).
(f) Any labeled DBS contraindication, and/or inability to undergo presurgical MRI (cardiac pacemaker, pregnancy, metal in body, severe claustrophobia), infection, coagulopathy, inability to undergo an awake operation, significant cardiac or other medical risk factors for surgery.
(g) Current or unstably remitted substance abuse, dependence, or a positive urine toxicology screen.
(h) Pregnancy and women of childbearing age not using effective contraception.
(i) Unable to adhere to operational and administrative study requirements (in the investigators' judgment).
(j) Clinical history of severe personality disorder.
(k) An inability to control suicide attempts, immanent risk of suicide in the investigator's judgment, or a history of serious suicidal behavior. This is defined, using the Columbia-Suicide Severity Rating Scale (CSSRS),as: either i) one or more actual suicide attempts in the preceding 3 years the lethality of which is rated at 3 or higher or ii) one or more interrupted suicide attempts with a potential lethality judged to result in serious injury or death.

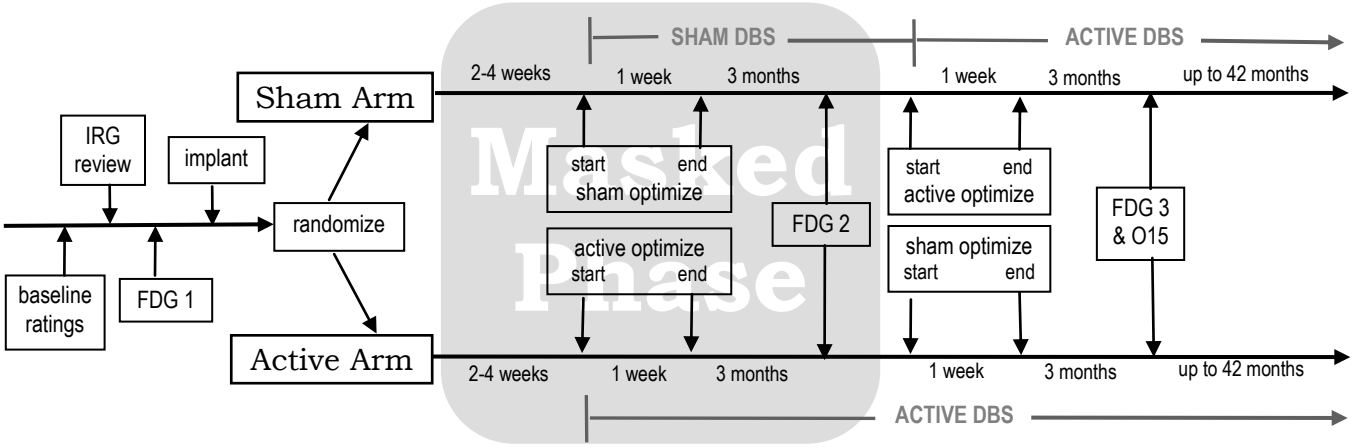
(l) Current diagnosis of body dysmorphic disorder.
(m) Evidence of dementia or other significant cognitive impairment on neuropsychological evaluation.

2. Study Design

(See Overview Figure, below). The study will use a parallel controlled design. Seven to eight patients will be implanted at Butler Hospital/Rhode Island Hospital (a total N of 30), then randomized to receive either 1) double-masked active DBS optimization followed by 3 months of masked active DBS or 2) double-masked sham optimization followed by 3 months of sham DBS. The groups will be matched for baseline YBOCS severity and gender using urn randomization. The primary outcome measure will be improvement in OCD symptoms using the YBOCS as a continuous endpoint. All patients in the sham arm will receive open DBS after three months. We will use secondary measures to determine how DBS affects symptoms which are commonly comorbid in this population (eg, depression or non-OCD anxiety), social and occupational/school functioning, and quality of life, to determine overall benefit at the three month end of masked DBS and after long-term open stimulation. Patients may choose to participate in the following additional studies: FDG PET scans, an O15 PET scan, and/or a study involving learning tasks. All of these studies are intended to illuminate the mechanisms of therapeutic effect of DBS.

To obtain an estimate of practice effects and test-retest reliability coefficients in this patient population for data analysis, we will use the same cognitive battery and testing schedule in a comparison group of OCD patients (N=24, recruited 8 per site,) who would otherwise be candidates for surgery (i.e., meet study entry criteria) but have declined this treatment option.

DBS safety will be assessed with: 1) Adverse effect questionnaires covering multiple domains, including those specific to DBS in this population as observed in our pilot work; 2) A comprehensive neuropsychological battery, including measures of personality features affected by frontobasal systems dysfunction, administered twice, at pre-surgical baseline and after 12 months of open continuation DBS; 3) Neurologic examinations at baseline and after 12 months of open DBS. The study will last for five years in order to obtain long-term effectiveness, safety and tolerability data.



Concurrent Therapies. Medication will be tapered to a minimum stable regimen by 6 weeks before implantation, in consultation with the most recent treating psychiatrist, as in our preliminary DBS OCD studies. The unmasked psychiatrist will prescribe during the blinded phase. Complete medication withdrawal is not required. Even if anti-OCD agents provide little benefit, withdrawal may expose severely ill individuals to an unacceptable risk of worsened OCD or comorbid depression and possibly of suicidality. Intermittent benzodiazepine treatment may be initiated during double masked DBS testing if needed for insomnia or extreme anxiety, but no other medication changes will be allowed. Patients may also continue

already established behavior therapy (of ≥4 months duration) during blinded study phases, but no new therapy may be started until masked testing is completed (3.5 months after implantation).

Measures

The instruments for Primary Efficacy Assessment are:

● Yale-Brown Obsessive-Compulsive Scale (YBOCS), a validated and reliable 40-item measure of the duration, severity, and functional impact of core OCD symptoms identified on an accompanying checklist (Goodman et al. 1989). Developed by investigators on this study, this is the most widely used measure of efficacy for OCD treatment studies.

● The clinician-rated Global Assessment of Functioning (GAF) (Hall 1995), and the Social and Occupational Function Assessment Scale (SOFAS), validated in psychiatric populations, will be used as global measures of psychiatric and functional status.

The instruments for Secondary Efficacy Assessment are:

● The Hamilton Depression Rating Scale (HDRS) will be administered at baseline and again at the 3 month time point. The Montgomery Asberg Depression Rating Scale (MADRAS) will be used to quantify the severity of depressive symptoms at preoperative baseline and will serve as the principal, validated, change measure throughout the study (Montgomery & Asberg 1979). In addition, the Behavioral Activation for Depression Scale (BADS) will assess any change in the extent to which the patient is engaging in life activities (Kanter et al. 2006) and the Cognitive-Behavioral Avoidance Scale (CBAS) will quantify changes in cognitive and behavioral avoidance typical of depression (Ottenbreit & Dobson 2004).

● The Hamilton Anxiety Rating Scale (HARS) will be used as a validated measure of anxiety at baseline and throughout the study. (Hamilton 1959)

● The clinician-rated Clinical Global Impression (CGI) Severity and Change scales (Hawley et al. 2002), and the patient-rated Patient Global Impression (PGI) scale will be used as validated global measures of illness severity and change.

● The two-item clinician-rated Clinical Global Impression – Exposure Therapy (GIT) will be used to assess a patient's ability to engage in behavioral/exposure therapy.

The quality of life measures are:

● The short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), a reliable and valid 16-item self-report of quality of life in 8 domains, widely used in treatment studies (Rapaport et al. 2005).

● The Range of Impaired Functioning Tool (LIFE-RIFT), a brief, validated, rater-administered scale measuring functioning in the home, work, school, interpersonal relationships, and recreation (Leon et al. 1999).

In the clinical interview the following safety measures will be administered:

● Adverse Events Questionnaire (AEQ) and accompanying Case Report Form (AEQ-CRF) will be used to assess potential major and minor adverse events in multiple domains, including psychiatric, neurological, and cognitive effects. The AEQ was based on one used in multiple DBS clinical trials, and includes cognitive and behavioral screening items used in the Cleveland Clinic DBS clinic for movement disorder patients. We have also added items for the adverse events observed in pilot DBS for OCD work across sites, plus further items covering other potential psychiatric and cognitive adverse events.

● A modified Young Mania Rating Scale (YMRS) (Young et al. 1978), this clinically validated scale will be used as a systematic screen for DBS-induced mania or hypomania. Although scores above 8 have been considered evidence of manic symptomatology in bipolar patients, the unmasked physician will use this scale and screening questions to assess whether *any* hypomanic symptoms require clinical intervention including DBS adjustment.

● The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to assess severity of and changes in suicidality. This scale provides a more specific classification system for the different levels of suicidality than any other measure (Posner 2007).
● Potential cognitive impairment will be assessed using the Mini-Mental State Examination (MMSE) (PAR 2007).

At the end of the formal consent session, the following measure will be administered by the Consent Monitor:
● A patient's understanding of the study protocol, risks and benefits will be assessed using the Dartmouth Informed Consent Evaluation Feedback Tool, revised to suit this study (ICEFT-R).

During the screening process, the following form may be used:
● The Cognitive-Behavioral Treatment History Form (CBTH) (Abramovitz, 2006) will be used during screening to help assess whether a patient has received and 'adequate trial' of CBT.

Neuropsychological Battery
The following neuropsychological measures will be administered during this investigation. It is important to note that although the measures have been placed under different headings reflecting various cognitive abilities, optimal performance on most measures is dependent on a variety of cognitive abilities and, similarly, most tests are not pure measures of one, single cognitive construct. Thus, the placement of the tests under different headings is somewhat arbitrary and others may disagree. This is particularly true for the Executive Cognitive measures. The measures were chosen to provide sufficient breadth with particular focus on cognitive abilities that are known to be impacted by OCD. In addition, a heavy emphasis was placed on measures of frontal function and memory given the known fiber pathways that course through the ventral capsule/ventral striatum

Tests in the neuropsychological battery assess the following functions:
● *Learning and Memory*: California Verbal Learning Test (CVLT-II), a test of verbal learning and memory (Delis et al 2000); Brief Visuospatial Memory Test (BVMT-R), similar to the CVLT procedurally, but using nonverbal/spatial stimuli (Benedict 1996); Wechsler Memory Scale - Third Edition (WMS-III), a widely used scale that assesses auditory, visual, and working memory (Wechsler 1997). The Digit Span (DSp) subtest from the Wechsler Memory Scale-III (WMS-III) (Wechsler 1997) taps basic auditory attention span (Digit Span forward) by having the patient repeat sequences of digits of increasing length forwards and backwards. The Digit Span backward component of the test also assesses working memory. The Visual Span (VSp) subtest of the WMS-III is a nonverbal analogue to the Digit Span subtest. The Letter Number Sequencing (LNS) subtest from the WMS-III is another auditory working memory measure that requires accurate recitation of a random list of digits and letters in correct numerical order following by alphabetical order Wechsler Abbreviated Scale of Intelligence (WASI) serves as a reliable and well validated brief measure of intellectual ability. It is comprised of four subtests measuring a variety of domains including visuomotor skills, nonverbal fluid abilities, vocabulary and fund of accrued knowledge. (Wechsler 1999)
● *Executive Function (planning and ability to change response sets)*: Delis-Kaplan Executive Functioning System (D-KEFS) includes the Trailmaking A & B tests which measure psychomotor speed, sequencing, and mental flexibility/set switching and **Delis-Kaplan Executive Function System (D-KEFS)** (Delis, Kaplan et al. 2001) **Color Word Interference Test** is based on the Stroop Test (Golden 1978), a test of the ability to inhibit conflicting responses (Delis et al 2001); The **D-KEFS Word Fluency Test** (Delis, Kaplan et al. 2001) is based on the Controlled Oral Word Association (COWA) (Benton, Hamsher et al. 1983) test. This measure is sensitive to dysfunction involving frontal cortical regions. Wisconsin Card Sorting Test (WCST), a widely used measure of executive functions, in which the correct response varies throughout the test, requiring the participant to abstract a solution and switch from one solution to another (flexibly computerized version PAR

2003). Please note that although the WCST lacks alternate forms to minimize practice effects, it was included as a paradigmatic test of frontal function; and the Iowa Gambling Test, which has been demonstrated to be sensitive to ventromedial frontal dysfunction (PAR 2007). Other measures that are sensitive to executive cognitive abilities or disruption to the frontal regions of the brain include the **Similarities** and **Matrix Reasoning** subtests of the WASI (described above). These measures assess conceptual reasoning skills

● *Psychomotor Function*: Grooved Pegboard Test (GPT) is widely used in the psychomotor domain (Mathews & Klove 1964).

● *Visuospatial Processing*: Judgment of Line Orientation Test (JOLO), assessing visuospatial functions associated with right posterior regions, independent of motor skills (Benton & Varney 1978). Rey Complex Figure Test (RCFT) is a widely used neuropsychological test for the evaluation of visuospatial constructional ability and visuospatial memory. Recently, the RCFT has been a useful tool for measuring executive function that is mediated by the prefrontal lobe. (Meyers & Meyers 1995)

● *Language*: Boston Naming Test (BNT-2), a 60-item test of confrontation naming. It was chosen because it is sensitive to functions subserved by left posterior brain regions, and places minimal executive demands on the participant (Kaplan & Goodglass 1983).

● *Frontal Lobe-Associated Behaviors*: Frontal Systems Behavior Scale (FrSBe). This validated 46-item test assesses disturbances associated with frontal dysfunction. An informant rates how often the patient exhibits each behavior at baseline and during DBS. The FrSBe measures frontal lobe-associated behaviors not captured by traditional cognitive tests. Three FrSBe subscales were demonstrated by factor analysis to reflect the 3 prefrontal systems; disinhibition (orbital circuit), executive (dorsolateral prefrontal cortex circuit), and apathy (medial circuit)(Grace & Malloy 2001). The FrSBe discriminates frontal from nonfrontal lesion effects, and correlates with decline in activities of daily living and with caregiver burden even after controlling for executive dysfunction.

● The Stop Signal Reaction Time Task (SSRT) is a visual choice reaction time task that requires participants to respond to a target stimulus on all trials, but to try to inhibit initiated responses on trials in which a tone follows the target. In every trial, participants will see either an 'X' or an 'O' displayed on the screen. They will be instructed to respond as quickly and accurately as possible by pressing the left arrow ('X') or right arrow ('O'). In 25% of the trials a stop signal (an auditory tone) will occur at a particular stop-signal delay (SSD) after the beginning of the stimulus presentation, signaling the participant to withhold his/her response on that trial. If the SSD is short, inhibition is relatively easy. If the SSD is long, the participant's motor response will be further into execution, leaving little time to inhibit its completion. Reaction time and accuracy will be measured.

● The Self Ordered Pointing Task (SOPT) consists of 4 sets of abstract images, with three trials in each set. This task has been shown to be sensitive to DLPFC functioning. The SOPT is designed to make increasing demands on working memory: the first set has six images, the second eight images, the third set has ten images, and the last set has twelve images. The number of correct responses, the order of responses, and the time to completion of each trial will be recorded. If the participant continues to touch the same location on the page, the examiner instructs the participant that they are unable to use that particular strategy but may respond in any other way that they wish. The ratio of number of correct responses by trial to possible correct responses will be used in statistical analyses.

● Wide Range Achievement Test - Fourth Edition (WRAT-IV) - Measures academic achievement in the areas of reading, spelling, and math computation. (Wilkinson & Robertson 2006)

● NEO Personality Inventory Revised (NEO PI-R) - The NEO PI-R is a widely used self-report measure of personality. The NEO PI-R measures five personality domains including neuroticism, extroversion, openness, agreeableness and conscientiousness (Costa & McCrae 1985).

● The Obsessive Compulsive Trait Core Dimensions Questionnaire is a measure of harm avoidance and incompleteness to be completed by the participant.

Visit and Assessment Overview *(Table, above)*. Diagnostic and Presurgical Evaluations are done in the screening phase, involving up to 2 visits. Two to four weeks after implantation, patients have Active or Sham Optimization outpatient visits. Visits will then be monthly (at a minimum) for three months to the end of masked testing. Visits during open continuation DBS occur at Months 6, 9, 12, 18 months and then every 6 months until the study ends. To reduce subject/family burden due to travel, ratings at 9, 18, and 24 months, and every 6 months thereafter, will be via telephone. Travel reimbursement will be equitable regardless of where patients live. A trained independent rater will give all efficacy measures during the masked phase. Clinicians familiar with adverse effects of DBS in OCD patients will administer the safety and tolerability measures.

Neuropsychological Testing will be obtained at presurgical baseline, and after 12 months of open continuation DBS. Tests will be administered by a highly experienced research neuropsychologist, Paul Malloy, PhD (Butler), who will assure that administration is standardized within study patients over time.

Comparison Neuropsychological Test Group. To obtain an estimate of practice effects and test-retest reliability coefficients in this patient population for data analysis (below), we will use the same cognitive battery and testing schedule in a comparison group of OCD patients (N=24, recruited 8 per site,) who would otherwise be candidates for surgery (i.e., meet study entry criteria) but have declined this treatment option. Given the likely effects of both OCD severity and comorbid depression on the cognitive assessments, these comparison patients will be group matched for baseline YBOCS and for depression severity on the MADRS. We chose these matching variables because we thought them the most important, and balancing groups on > 2 variables is problematic. Age corrections are incorporated into the normative data for the neuropsychological measures; thus matching for age is not critical for these neuropsychological measures. Potential group IQ differences are another concern. We do not expect these based on our pilot data, which found no significant differences across the three sites. If such differences emerge in this study, we would account for them in the analysis (discussion: Data Analysis, below).

Raters. Raters and patients will be masked to stimulation status in the controlled study phases and will continue ratings in the open study phases.

<u>Treatment Phase</u>

Device Implantation. Our stereotactic surgical procedure was developed starting in 1999 by the three sites in this application working closely with our Belgian collaborators (B. Nuttin et al.). We have refined the targeting empirically, based on stimulation effects, over the past 5 years (Preliminary Studies). Brain lead insertion is under local anesthesia. Neurostimulator (INS) and connecting wire implantation are under general anesthesia. Using coordinates individually determined by stereotactic imaging (MRI and CT), custom tetrapolar brain leads (Medtronic Model 3387 or 3387 IES) are inserted along the trajectory of the anterior limb of each internal capsule (see Nuttin et al., 1999), extending into ventral striatum. An extension wire from the scalp connects each lead to a subcutaneous INS in the chest. After implantation, the patient has an overnight inpatient stay to monitor for possible complications including hemorrhage or infection. The leads and neurostimulators will be implanted either on the same day or two different days as a staged procedure. If the procedure is staged, the first stage will be the implantation of the DBS leads. The second stage will be the connection of the leads to implantable neurostimulator (INS). With either the single or staged procedure, a connector is placed on the distal end of the DBS lead which is placed in a subgaleal pocket. If the surgery is a single stage, the INS will be implanted immediately and connected to the distal end of the lead. If the procedure is staged, then, during the battery placement, a small incision is made over the parietal area to get the distal ends, while leaving the primary incision closed. The extension is tunneled to the incision (e.g., infraclavicular) where the INS is implanted. After implantation of the leads and/or INS, the patient has an overnight inpatient stay to monitor for possible

complications including hemorrhage or infection. In the case of a staged procedure the patient may or may not be discharged between stages, depending on the length of time between the two stages. Postoperative evaluation includes physical and neurological examinations, CBC, electrolyte panel, plain x-rays of head, neck, and chest including a shunt series to ensure integrity of connections and to document hardware position. A head CT is obtained within 24 hrs to screen for intracranial hemorrhage. This CT is later coregistered to the preoperative MRI to document lead placement accuracy. Absent significant complications, the patient is discharged home the following day with DBS off to allow resolution of cellular reactions to insertion.

MER. During implantation, microelectrode recording may be performed. The patient may choose whether they participate in the MER portion of the surgery. The purpose of microelectrode recording (MER) in this study is to obtain research data on single neuron responses in ventral striatum to behaviorally relevant stimuli. Such data remain extremely rare, and might lead to new ways of designing stimulation protocols for OCD and related disorders (i.e., "responsive stimulation"). MER can also provide a limited direct clinical benefit - i.e., can verify if an implantation track includes cellular areas at the margins of the anterior limb of the internal capsule. It may also help verify the location of the border between the ventral capsule white matter and adjacent ventral striatum. MER is performed using standard approaches (Gross 2006) using FDA approved MER equipment. When the microelectrode has been advanced to the target nucleus, MER data are recorded while patients perform a simple behavioral task, lasting between 30 minutes to 1 hour. Patient view a series of images on a computer screen and press buttons or move a joystick in response to the stimuli. The response box (buttons and joystick) is rigidly mounted to the operating bed so that it is easier for the patient to make responses. Subjects may choose not to participate in this task at any time, even during the operation. Patients who choose not to participate will undergo the very same surgical procedures e.g., deep brain stimulation based upon stereotactic coordinates.

Two to four weeks after implantation the patient returns to begin double-masked outpatient sham or active DBS Optimization (below). A second CT scan will be performed approximately 3-4 weeks after implantation, if needed. This will be necessary in case the degree of pneumocephalus makes determining actual lead locations lead via fusion with preoperative MRI problematic. Stimulation parameters will not be changed for the purposes of this scan.

Assignment to Active or Sham Treatment Group. After implantation, patients will be assigned to receive double-masked active or sham DBS, 15 patients per group, for 3 months. We will use site and gender as the only variables for urn randomization (Stout et al 1994).

Active DBS Optimization.
The methods for optimizing/adjusting the DBS parameters of those in the active group are exactly as described for the sham group. It is equally as important that the mask be maintained in the active group as it is in the sham group.

Optimization will occur twice for each patient during this study. Patients in the Sham Group will receive Sham Optimization after implantation and active optimization after the Masked Phase. DBS will not be turned on during the Sham Group's sham optimization. Patients in the Active Group will receive active optimization after implantation and again after the Masked Phase. This will achieve the goal of equalizing visits between the active and sham groups.

For patients in the active group, DBS parameters will be optimized/adjusted based on acute effects on mood and anxiety, not on YBOCS scores. Patients will not be exposed to OCD-symptom eliciting material during optimization to assess their responses to DBS. Since patients will leave the testing room between DBS

adjustments, they may be exposed to naturalistic symptom triggers. Any responses to such triggers should be noted qualitatively. DBS amplitude will be set below the threshold for side effects as much as possible. Based on experience, we expect these to include paresthesias in the face or upper body, epigastric sensations, facial muscle tightness, dysarthria, or more rarely, olfactory/gustatory phenomena or memory flashbacks. All of these effects stopped within seconds when parameters were changed. Charge densities will never exceed the FDA limit of 30 μCoulomb/cm^2. Note that the charge calculations we use give CD values for the surface area of a single electrode, actual CD will depend on the total number of electrodes active at each polarity.

The following observed effects will be reported via the LOES scale: eye contact, facial expression, spontaneity, nervousness, positive mood and energy. Indicate whether the patient exhibits a unilateral smile. Have the patient report on changes in mood and side effects

Day 1: threshold mapping protocol

Step 1. Set frequency to 135 Hz.
Step 2. Test right side using the following steps:
a) Start with monopolar stimulation and case + at pulse width of 90 μSec. Now test each contact (0 -, 1 -, 2 -, 3 -) at 2V, at 4V, and at 6V only if no effect has been observed at 2V or 4V
b) Still with monopolar stimulation and case + at pulse width of 150 μSec. Now test each contact (0 -, 1 -, 2 -, 3 -) at 2V, at 4V, and at 6V only if no effect has been observed at 2V or 4V
c) Switch to bipolar stimulation with 3+, and use the results from steps 1 and 2 to determine best pulse width, if unsure use 120 μSec. Now test the following configurations each at 2V, at 4V, and at 6V only if no effect has been observed at 2V or 4V
0 -, 1 -
1 -, 2 -
Step 3. Turn off right side stimulation and test left side using steps a) through c)
Step 4. Set bilateral stimulation at the most promising (i.e., maximize benefit while minimizing side effects) setting observed during the threshold mapping. If no promising setting emerged, use the following bilateral settings:
contacts: 1 -, 2 -, c+
amplitude: 6 V
pulse width: 90 μSec
frequency: 135 Hz
Step 5. Wait 30 minutes. If no side effects have emerged, the patient may leave.
Step 6. The study nurse calls to check in on the patient that evening.

Minimum number of configurations tested on Day 1 = 40
Maximum number of configurations tested on Day 1 = 60

Days 2 through 5: effect optimization
In patients for whom the set of predetermined starting are ineffective, these days will be used to try to produce an effect an effect on spontaneity of social interaction (eye contact, initiation of speech), observed affect, subjective mood and nervousness, and observed motivation. Adjustments initially should focus more on increasing voltage *more than* altering pulse width or frequency settings.

Exactly how many days will be involved will remain flexible, but should generally hold to the 5-day schedule as much as possible to protect the blind.

For example, a patient could come in *2 or 3 days* over the course of 5, perhaps over other day. Attempts should be made to minimize the length of time patient patients who travel and require hotel rooms and need to stay for the initial optimization, ideally to one week and no more than two weeks, with visits kept roughly equivalent for active and sham patients.

Suggested configuration for the 387 lead included: 1-2- (monopolar or bipolar), 0-1-2- (monopolar or bipolar); 1-2-3- (monopolar or bipolar); 0-1-2-3- (monopolar) Frequency will be at least 135 Hz, PW at least 90 μSec.

Sham Optimization and Masking Procedure. Visits, ratings and other procedures will occur on the same schedule for the active and sham DBS groups from the start of Optimization until the 3-month masked DBS phase ends. The Masking Procedure described here will be identical for the active and sham patients. The only difference being that no actual parameter changes will be made for patients in the sham group as their DBS will be turned off.

During masked programming sessions the telemetry head of the DBS programming device is taped over the patient's chest. The unmasked programmer (usually the study physician) sits with the status of programming console out of the patient's view. A small cardboard shield will be affixed to the programming console to conceal whether it is turned on or off from the patient. The programmer records parameter changes (whether real or sham) and patient responses on the appropriate crf. This procedure is the same for all patients whether in the sham or the active group, with the exception of any actual programming changes for those in the sham group.

DBS Adjustment During the 3-Month Double-Masked Phase. After the optimization phase, adjustments for inadequate response (judged by the unmasked clinician) will involve adding an active cathode - either 0, 3, or potentially both, if both 1 and 2 are already active and negative. Intensity will be adjusted downwards as needed to observe the charge density limit based on measured impedance or to reduce intensity below any emergent side effects.

After the one week optimization phase, adjustments for treatment emergent adverse effects (determined by the unmasked clinician) will involve intensity reduction first, typically by 1-3V to below a detectability threshold, and, if this is insufficient, reducing the number of active cathodes by one, or changing to a different active cathode (from contact 0 to 1, e.g.) We will consider unilateral DBS, if necessary, to reduce adverse effects.

Open Continuation Phase. During open DBS, behavior therapy or medication changes will be allowed, and documented by the research team. During the open phase patients will be given a Medtronic Access Review device so that they can check stimulator battery status and DBS on or off, as an added safety measure. This device does not allow patients to change DBS amplitude, protecting against the risk of hypomania at higher currents.

Surgical Follow-up/INS Replacement. This will occur as needed, most often limited to INS replacement after battery depletion, which entails outpatient surgery under local anesthesia, expected every 10 - 24 months. All patients will be initially implanted with either the Activa PC or SC INSs. Replacement INSs may also be either Activa PCs or SCs. However, if the study psychiatrist feels they are good candidates, patients may choose to have their INSs replaced with Medtronic's Activa RC rechargeable battery and, in cases deemed appropriate by the surgeon, pocket adaptors. No Activa RC INSs will be used for initial implantation or, therefore, during the masked phase. This device requires the patient to regularly recharge the battery, thus the study psychiatrist will assess which patients will be best suited for this option. No INSs

will be replaced with Activa RCs during the blinded phase of the study.

The Activa RC offers the option of using constant current rather than constant voltage in programming. The constant current option may be used for patients receiving the Activa RC. There is the possibility that the constant current stimulus waveform might be more efficient in modulating neural activity in the circuits of interest, possibly leading to use of lower currents. If such a gain in efficiency were large enough, that in turn would lengthen recharge intervals, reducing patient burden (and conceivably extending the life of the device as well). There is also the hope that symptom relief might be better with an alternative DBS waveform using constant current stimulation. To implement this change, we would do a focused electrode survey (bilaterally). That is, contacts that were found to be active in improving symptoms will be tested in constant current mode, beginning at levels below those current levels calculated for constant voltage mode (based on measured impedance), as they are for unipolar and bipolar electrode surveys now in the protocol. We will continue to adhere to our observation routine for new parameters (observing patients after a new parameter setting) so that we can alter setting below thresholds for adverse effects (hypomania is the effect of greatest concern based on experience). As per our existing procedures, we will stay in close contact with study patients after setting changes and have them return for DBS adjustments, as we deem clinically needed. Whether long-term DBS uses constant voltage or constant current mode will be determined by clinical judgment as to which mode produces the best outcomes for a given patient. Such judgments will include YBOCS OCD severity, functional status, recharge interval, and adverse effect burden. As now, safety limits for charge density would be observed.

The Activa RC also provides additional programming options: interleaved programs and program groups. We have less specific plans for testing program groups or interleaved stimulation. If these permit stimulation regimes similar to those used before this option was available, we would like to explore these options. Again, we would use clinical endpoints to determine if these appeared beneficial in a given patient. However, it is difficult to be more specific at this stage, before we have any actual experience with the Activa RC device. It should be noted that there is the possibility that patients who have partial responses or essentially no responses might respond better to these new programming options. What we envision therefore would be a limited used of these new options during programming visits. We would consider using program sets or interleaved stimulation if an otherwise poorly- or non-responsive patient appeared to benefit.

Additional Optional Studies. Patients may choose to participate in the imaging studies performed at MGH. One study involves three FDG PET scans: at baseline, 3 months after optimization and 6 months after optimization. The other imaging study involves an O15 PET scan, which occurs after the 6-month timepoint. Both of these studies take place at MGH and are described in detail in separate consent forms approved at MGH. Patients may also choose to participate in learning task studies. One study is an Avoidance/Reward Competition task that will investigate the responses and response times during a task involving a choice to avoid or not avoid an aversive stimulus in order to receive a reward. This study will take place at MGH and is described in detail in a separate consent from approved at MGH. Participation in this task can be combined with the PET visits if the patient is participating in the imaging study, reducing the number of visits to MGH. The second learning task study is an Extinction Recall (ER) task. This task may take place at Butler Hospital particularly for Butler site patients or neuropsychological comparison group subjects who choose to participate in it. A separate Butler Hospital consent form will be used for participation in this study.

Extinction Recall Task. Using a procedure developed by our group, we will measure conditioning, extinction and extinction retention before and after three months of DBS. We hypothesize that DBS applied chronically to the VC/VS will enhance extinction recall.

We will obtain ER data on 14 patients per treatment group, for a total of 28 patients. All patients will undergo ER testing at time 0 (before surgery), and after 3 and 6 months of DBS. (Neuropsychological comparison group subject will undergo ER testing at baseline and the one-year follow-up.) The active group receives two ER tests during active DBS, after 3 months of (masked) stimulation and again at 6 months (after 6 months total of DBS). The sham group has ER testing at the same intervals: at 3 months of sham DBS, and again at 6 months (after 3 months of open-label DBS). Even though we have obtained preliminary test-retest data on healthy volunteers, which indicated the measures are stable on repeated testing, the 3-month ER test in the sham group is needed as an additional control for nonspecific effects after implantation and follow-up. The ER test after six months of continuous DBS (in the active group) will allow us to determine if the changes in fear conditioning, extinction learning, and extinction recall we hypothesize will occur during chronic DBS will be stable between 3 and 6 months. This is important to establish, since if DBS facilitates extinction, then stable changes in extinction measures should be associated with stable clinical improvement in OCD after DBS.

The protocol for fear conditioning is identical to that we developed and validated (Milad et al., 2007). Each ER test takes place on two consecutive days at 0, 3, and 6 months. The conditioned stimulus (CS+) is a visual cue, the unconditioned stimulus (UCS) is a mild shock to the fingers, and the measure of conditioned responses is the skin conductance response (SCR). The equipment consists of a "turnkey" differential aversive conditioning system (Coulbourne Instruments, Allentown, PA). In the Conditioning phase, a CS+ (e.g. blue light) is paired with the UCS and a second CS (e.g., red light) is presented during the Conditioning phase and is never paired with the UCS (CS-). The Conditioning phase will consist of a total of 5 CS+ and 5 CS- trials. The shock UCS is delivered immediately following CS+ offset with no delay between the CS+ offset and the UCS onset. After approximately 1 minute, the Extinction Learning phase will begin. During Extinction Learning, 10 CS+ and 10 CS- trials will be presented. On Day 2 (the test day), during the Recall phase, 10 CS+ and 10 CS- trials will be presented. No shocks are delivered during Recall. Contrasting CS+E vs. CS- during extinction recall allows us to assess SCR that are specific for extinction recall.

Subjects will receive $100 per day ($200 per two-day session) as compensation for participation. If the subjects withdraw from the study before finishing, they will receive $20/hr for each hour they participated.

4. Data Analysis

Overall Data Management. The PI and Project Director will be responsible for and supervise data management and data. Data will be stored at in password-protected SPSS version 10 files, on a secure research server with data backup preformed nightly. Hard copies of data capture forms will be kept in locked files to which only authorized study personnel will have access. Descriptive data will be provided for all subject groups (e.g. mean age, sex, education, diagnosis, etc.). Symptom rating scales will be scored as they are in clinical use. Data Analysis will be conducted using SPSS. Data will be analyzed through analysis of variance (ANOVA), followed by appropriate post-hoc analyses.

D. Material Inducements

Symptom ratings and neuropsychological assessments will be used as they are for approved uses of DBS in movement disorders, where they are part of clinical assessment. No compensation will be offered for the measures administered in this study, except for those in the Neuropsychological Comparison Group (patients who do not undergo surgery). They will receive $100 for the neuropsychological test sessions.

E. Training of Research Personnel

All research personnel will be trained to properly administer the study instruments by the PI and Co-PIs. All staff will receive training in responsible conduct of research based on the HHS Office of Research Integrity manual (Steneck 2004), to include data management and procedures for maintaining data confidentiality and patient safety.

III. HUMAN SUBJECTS

A. Subject Population

Participants will be patients with DSM-IV OCD of disabling severity, refractory to prolonged treatment trials with conventional medications, medication augmentation, and behavior therapy (exposure and response prevention). Inclusion and Exclusion criteria are listed above. Subjects will be patients of any race, ethnic group or gender who remain disabled with major OCD despite adequate trials of appropriate treatments. Participation or lack of it will not affect access to conventional treatments at Butler Hospital. Only subjects who are able to give fully informed voluntary written consent would be accepted. Patients who enter will be free to withdraw from the study at any time without affecting their access to other treatments at any of the above institutions. They will be at minimum 18 years old. In general, patients will continue their pre-surgical medication regimen, unless changes are viewed as medically necessary by the investigators and referring psychiatrist.

B. Recruitment and Consent Procedures

Recruitment will take place primarily via patient groups, including the Obsessive-Compulsive Foundation; and via contacts with professionals expert in OCD treatment, including presentations at national professional meetings. We will also develop a website with study information for potentially interested clinicians, patients, and families, and will list the study on ClinicalTrials.gov (now also required by many journals for publication of results). Any materials developed for the web, or other advertisements for patients, will be submitted to the IRB for approval prior to postings.

We will require that the cases of prospective patients will undergo a second process of review, by a group independent of the investigators, with expertise in OCD diagnosis and treatment and will include a patient advocacy representative. This Independent Review Group will assure that prospective patients meet the criteria above. The Group reviews written materials as to the diagnosis, severity, adequacy of previous treatment. Members of the Group will make written determinations about whether patients meet entry criteria and are able to give informed consent. If reports from all members are not received in a timely manner, the decision of the Group will be based on those reports received, provided there are at least three out of the five expected reports. The committee will review the decisions by a telephone conference, only as deemed necessary by the Group chairperson. The Group includes John Griest, MD, who has personally treated more than 1000 patients with OCD and who will strive to assure that prior treatment trials have been adequate and unsuccessful, and, as patient advocate, James McNulty, past president of the National Alliance for the Mentally Ill.

Consent for this study is a multistage process. Written informed consent for screening procedures is obtained on the first visit. Diagnostic and screening ratings are completed, followed by complete medical, neurological and neurosurgical evaluations. Case materials are presented to the Independent Review Group. If the Group agrees that study criteria are met and that the patient is appropriate for the study, consent for study treatment procedures will be obtained and the patient will enter the treatment protocol. The consent process may be videotaped with the Consent Monitor (Rev. D. Shire). The Consent Monitor may meet with the patient prior to the consent process and/or IRG approval to preliminarily assess their ability to provide fully informed consent. The Consent Monitor will assess whether that the patient understands the study procedures, and asks any questions they may have. The Monitor will, in addition to the study team, explain adverse effects to low literacy or non-native English speaking patients. The PET component will be discussed at the same session, with the Monitor present. It will be made clear that that PET study participation is not mandatory to receive DBS. Participants will be informed that they may discontinue their participation at anytime without penalty.

C. Potential Risks

While DBS has a generally favorable safety profile in its approved uses for movement disorders, its beneficial effects in those conditions entail potential risks. Likewise, the potential benefit of DBS for in intractable OCD would not be achieved without risk. The major risks are related to surgical implantation, failure of the device, and to the stimulation itself (Greenberg and Rezai 2003). The informed consent language specifies the most common potential adverse effects, the most serious potential adverse events, and includes the approximate proportion of the adverse events that were due to device implantation vs. active stimulation.

Implantation Risks. Although implantation is associated with pain or discomfort for several days afterwards, its major risks are seizure, hemorrhage, and infection. In trials of DBS for movement disorders, incidence of seizure was 1% per procedure, usually controlled with anticonvulsants. The risk of intracerebral hemorrhage in the same series was 6.3%, potentially leading to neuropsychological deficits, possible paralysis, aphasia, coma, or death. The incidence of serious hemiparalysis/hemiparesis due to hemorrhage was 3.8% in that cohort. There is a 4-9% chance of infection overall, primarily involving superficial sites. In that case the brain leads would be removed and the subject treated with intravenous antibiotics. Following treatment of the infection, the procedure could be repeated.

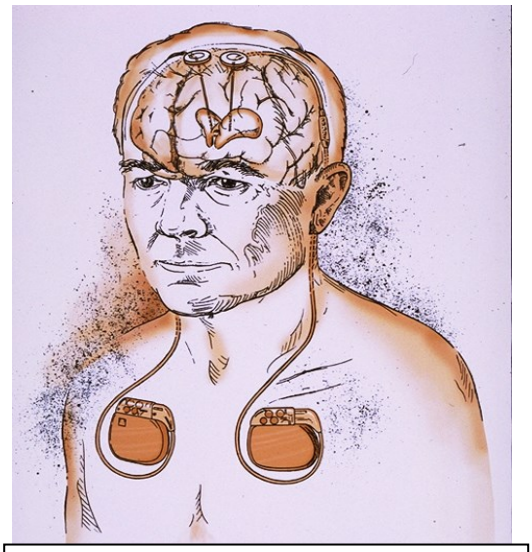


Figure 5. DBS devices implanted

The above adverse event rates were derived from safety data on bilateral implantation of DBS leads into the subthalamic nucleus or the globus pallidus interna for the treatment of Parkinson's's disease, previously submitted to the FDA as part of the approval process for DBS for movement disorders. Our own discussions with the FDA concluded that an estimate of the risks of lead implantation at the target used in this study, the VC/VS can be derived from the largest series of open thermocapsulotomy procedures available, at the Karolinska Institute in Sweden. Thermocapsulotomy uses a thermal probe slightly larger in diameter than the DBS leads (2 mm vs. 1.3 mm for the DBS lead), implanted into the anterior limb of the internal capsule following the same trajectory for DBS lead implantation in this study. Two of 50 patients had intracranial hemorrhages after thermocapsulotomy. One of these was small and asymptomatic, while the other was associated with the adverse effects of confusion, apathy, and short-term memory loss. In this patient, these adverse effects resolved over approximately three months (B. Meyerson MD, unpublished data). Our experience with internal capsule DBS implantation for OCD has been that 1 of 22 patients developed an asymptomatic hemorrhage after implantation (approximately 1 X 1.5 cm in size), which resolved rapidly on CT over the next week. This hemorrhage was thought to result from puncture of superficial bridging veins, with blood tracking down the implantation cannula into the brain parenchyma. We have changed the implantation procedure to include opening the dura to minimize hemorrhage of this type. In addition, 1 of 14 patients developed a seizure in the operating room minutes after device implantation. That patient was treated with phenytoin as a precaution for the subsequent month, which was then tapered without seizure recurrence over the next 9 months. High doses of antidepressants were felt to predispose this patient to an implantation-related seizure, and since then we have tapered high doses of medication known to reduce seizure thresholds before surgery, a procedure we would also follow in this proposed study, plus using an intraoperative phenytoin load to further reduce this risk.

There is additional surgical risk associated with the transition from regular Soletra or Kinetra INSs to the rechargeable Active RC INS. Since both leads are powered off of one Activa battery, replacement of the

extension wires is required to make the proper connection to the new battery system. The extension wires are attached to the intracranial electrodes within the scalp. The proximal connection of the old extension wires to the intracranial electrodes must be undone, and new extension wires need to be attached and tunneled down to the battery location. There is a small chance that this revision may result in damage to the intracranial electrodes, which would then require additional surgery to replace them. In the worst-case scenario, this would delay therapy and incur all the risk of intracranial electrode placement. Usually, what this extra step would mean is that there is an additional incision at the scalp in addition to the incision at the battery site, and there is a small risk that, relative to the usual replacement surgery, the scalp site would also be at risk for infection. Transitioning from the Activa PC or SC to the RC does not involved the risk described here as the connections on the PC and SC are the same as that on the RC.

Microelectrode Recording Risks. The main theoretical risk of MER is an increased risk of hemorrhage or infection (the latter due to prolongation of the procedure by about 30-60 minutes total, including the time needed to advance the microelectrode to the target). Risk of infection is no greater than that in routine clinical implantation of DBS for movement disorders where MER is commonly used. Our review of the literature finds that incremental risk of hemorrhage due to a single MER pass to the intended implantation target has not been clearly demonstrated. No additional burr hole in the skull is made, and the burr hole is covered during the recordings. We therefore judge the additional risk, if any, to be small. The additional risk therefore seems mainly to be due to the prolongation of patients' time in the OR and the increased discomfort that will entail.

Device-related complications include fracture of leads, disconnection, lead movement, and malfunction. There was approximately a 10% chance of equipment failure or lead wire breakage in initial movement disorder studies. In case of device failure, the procedure would be repeated to repair the equipment or the lead wire. There is also the possibility that following surgery the system can be negatively affected by electromagnetic interference, for example retail theft detection devices, airport scanning equipment or metal detectors, cardiac pacemakers or defibrillators, diathermy, ultrasonic equipment, radiation therapy, electrocautery, and MRI. The most serious of these potential interactions were 2 fatalities when patients with implanted DBS systems were exposed to therapeutic (as opposed to diagnostic) ultrasound or diathermy, which resulted in extreme heating of the electrode due to transfer of energy to the brain via the electrodes. Those events have resulted in additional warnings to patients receiving DBS for FDA-approved uses, including highlighting these risks in the consent form. A schematic DBS system is shown in Figure 5, which also appears in the informed consent. In general, patients are informed to discuss any device-based (MRI, ultrasound, etc.) diagnostic or therapeutic procedure they are considering with the study team.

Stimulation Risks. Sensorimotor adverse effects of effects DBS include paresthesias, muscle contraction, dysarthria, and diplopia. Notably, DBS has induced psychiatric symptoms in Parkinson's patients (Anderson and Mullins 2003). DBS of the globus pallidus interna caused stimulation-related bouts of mania and hypomania (Miyawaki et al 2000). DBS of the subthalamic nucleus (STN) or Fields of Forel/zona incerta in provoked marked affective change (Berney et al 2002; Pollak et al 2002), including hypomania (Kulisevsky et al 2002), mirthful laughter (Limousin et al 1998), marked depression (Bejjani and Damier 1999), and dysphoria, anhedonia, apathy, and blunted affect (Stefurak et al 2003). All these behavioral effects in movement disorders, proved fully reversible when stimulation was changed. Effects on mood, memory, cognition or behavior, including impulsivity and suicidal behavior have also been reported in patients with movement disorders (Funkiewiez et al 2004), emphasizing the need for close patient monitoring. Many stimulation-related effects are transient even without parameter changes.

In OCD and depression, we and collaborators have observed sensorimotor effects of DBS at the VC/VS target, including paresthesias, muscle tightness, and dysarthria. One patient with depression had two

unwitnessed syncopal episodes of unknown etiology during DBS. Since those episodes might have represented seizures induced by DBS and/or concomitant medications, those medications were stopped, and the patient was placed on anticonvulsant prophylaxis, without recurrence of syncope.

Untoward behavioral effects of DBS in OCD and depressed patients have included hypomania, anxiety, acutely worsened depression and other effects (e.g., insomnia, agitation). As expected, all were rapidly reversed when stimulation parameters were changed. Not surprisingly, when DBS is effective, battery depletion or stimulation interruption due to electromagnetic interference may result in rapid symptom re-emergence and even possibly a rebound increase in severity over baseline, again emphasizing the need for close monitoring.

Using the stimulation target and devices in this proposal, adverse psychiatric effects we have observed include transient hypomanic symptoms (4 of 14 patients – on one of the patients these symptoms lasted for close to the four day threshold for a DSM-IV hypomanic episode), transiently worsened OCD (3 of 14 patients), memory flashbacks (1 of 14 patients), and olfactory/gustatory hallucinations (1 of 17 patients). These effects either proved transient (lasting minutes) without changes in the DBS technique or were rapidly reversed (also within minutes) after the stimulation technique was changed.

We believe we can minimize some of these risk of stimulation itself by using lower initial stimulation amplitudes. In addition, as a precaution, patients will be given control magnets and instructed how to use them to stop any active stimulation that might be causing such adverse effects. This information will be reviewed at several points during the study, including the consent process, and in the review of the Patient Manual given to study patients. In addition, patients will be given a patient programming device (Access Review, Medtronic, Inc.) that will allow them to check on the status of the stimulation, and, on the advice of a study physician (typically the PI), modify or stop the stimulation if necessary.

Other risks are inherent in patients with severe and treatment-resistant OCD, a devastating condition. In our extensive clinical research experience, patients applying for experimental treatment of any type are severely symptomatic. All of these DBS patients were experiencing profound impairment in social or occupational functioning, in addition to severe subjective distress. They and their treating physicians felt that surgical intervention was the only available option, since they had failed multiple conventional treatments. Suicidal ideation in this group can result from either profound demoralization due to severe chronic OCD, comorbid depressive illness, or both. There have been suicide attempts and even several deaths by suicide in OCD patients who were on the waiting list for surgery both in the U.S. and in Belgium (B. Nuttin, personal communication, 8/03). One patient died by suicide during a trial of DBS for OCD at the University of Michigan. That study used a different DBS stimulating electrode and a more anterior surgical target. The stimulators were functioning normally at autopsy, so abrupt stimulation cessation did not account for that event. The patient had a history of suicidality predating enrollment, which the investigators believed most likely explained the suicide (Abelson et al 2005). We will attempt to minimize suicidal behavior and completed suicide by excluding those patients judged at immanent risk of suicide during screening & evaluation, and by close monitoring of participants in our study.

There are additional theoretical risks. These include the possibility of adverse interactions between stimulation and ongoing medication treatment, which may result, for example, in weight gain, sedation, or syncope (see above) beyond that produced by medication alone. This is described in the consent, together with the instruction to notify study investigators in the event of this or any other adverse effects at any time during the study.

Potential changes in cognitive functioning will be carefully assessed as described above. In theory, this risk might exist with prolonged use of the stimulator, especially if higher stimulation intensities are used. We will make every effort, including stimulation modification or, potentially, cessation, if clinically significant cognitive or other adverse effects appear. Overall, the neuropsychological data available to date indicate that DBS for OCD is a safe procedure from a neuropsychological perspective (Gabriels et al 2003). Furthermore, preliminary data suggest that many patients actually demonstrated significant improvements on memory tests beyond what would be expected with practice effects (Kubu et al., submitted). It is important to gather further data on cognitive effects of DBS in OCD.

There is a theoretical risk of histotoxicity due to chronic exposure of the target tissue to electrical current or to the device materials themselves. The DBS electrodes are made of a platinum-iridium combination. Histopathologic changes produced by reactions to implanted materials have been extensively studied in animal models. The platinum-iridium combination produced no apparent histological or blood-brain barrier damage when evaluated in the cat (Mortimer et al 1970). Risks associated with electrical stimulation of the nervous system have been characterized by Agnew, McCreery and Yuen (Agnew et al 1990), who established a safety threshold for charge density per phase and charge per phase of stimulating pulses. Charge densities of over 30 μC (micro Coulomb) per square centimeter per phase have been established as the charge density limit for the Kinetra Model INS that we will use in this study. The stimulator can produce charge densities in excess of this value, but not when used according to the procedures for calculating the charge density at particular use parameters described in the next section. In the one case of an OCD patient receiving VC/VS DBS who came to autopsy (she died due to a recurrence of breast cancer, unrelated to DBS), there was no evidence of tissue damage on microscopic examination, beyond the ~1.3mm diameter track of the lead itself (S.N. Haber, personal communication, 5/2003).

The DBS devices can be removed if it is judged to be in a participant's best interest by the investigators and/or the patient. Typically the stimulator is removed leaving the leads in place, to minimize the risk of hemorrhage if the brain leads are removed. In the past subjects that have had the leads left in place have not experienced adverse advents except for a restriction against future MRI scans. Currently, MRI scans after DBS brain leads are implanted are not recommended by the FDA, a restriction which could limit the availability of MRI as a diagnostic tool. Since the safety of MRI scans (using 1.5 Tesla MRI systems) with DBS leads in place has been demonstrated recently (Rezai et al 2002), this restriction is being re-evaluated by the FDA and we expect it to be removed in the very near future. However, the available safety data suggest that MRI can be performed safely with DBS leads in place only using specific scanner models and sequences, and use of only those techniques must be assured. Having DBS implants would not restrict the participant from future neurosurgical procedures. ECT treatment of a given patient might be contemplated at some point. Leaving the leads in place might make subsequent ECT treatments problematic due to the possibility of current shunting via the electrodes. However, ECT has reportedly been performed safely in one movement disorder patient with DBS devices implanted (Chou et al 2005). Treating and research physicians will review potential risks of ECT before deciding whether to proceed or, e.g., to consider brain lead removal. The risk of hemorrhage upon removal appears to be on the order of 1% (A. Rezai, MD, personal communication 12/03).

The risks of preoperative MRI (before the leads are implanted) and postoperative CT scans are relatively minor. MRI scanners produce loud that exposes individuals to a risk of hearing loss. Subjects will wear earplugs to reduce this risk. Patients also may experience discomfort when inside the confined bore of an MRI scanner.

Other risks are no different from those of conventional medication and psychotherapeutic treatment for OCD, or those of standard clinical laboratory evaluations and blood drawing.

Although individuals judged to be at immanent risk of suicide on evaluation will be excluded from this trial, participants who fail to respond to DBS may be at increased risk for continuing severe OCD, with an attendant risk of suicide.

Risks due to Assessment Administration. Answering the symptom rating questions may involve sensitive information that could cause discomfort. The study participant may decline to answer any question that causes discomfort. The neuropsychological tests may be tedious, and can be particularly difficult to complete for highly symptomatic OCD patients whose obsessive thoughts and compulsive rituals may interfere (variably) with test completion.

Risks due to Learning Tasks. The electric shocks that the patient will receive during the extinction recall task may be uncomfortable, but they should not be painful or dangerous. Subjects may also feel some discomfort from the Airstim device during the ARC task. The air pressure is uncomfortable, but not painful, and will never exceed the manufacturer's safety limits. Subjects are free to stop the experiment at any time, should any portion prove too uncomfortable.

Protection of the Subject (measures to minimize potential risks and to ensure confidentiality)
We have developed a series of procedures to maximize safety. We will carefully assess potential adverse effects in multiple domains throughout this study.

The PI will be responsible for minimizing the overall burden of risk to which the subjects are exposed, and will monitor the day-to-day safety of patients enrolled. The PI is responsible for assuring that this study adheres to the IRB- and FDA-approved protocols (the latter contained in either the FDA-approved HDE or the FDA-approved IDE) for this research. Note that if any precautions beyond those listed here are required by the FDA, this protocol will be amended to include them.

All patient-related anticipated protocol deviations will be reported to the IRB prior to their occurrence and will be subject to IRB approval or disapproval.

Screening and Evaluation. Done by or under the direct supervision of the PI, this will ensure that prospective patients meet diagnostic, severity, chronicity, and other inclusion and exclusion criteria. Particular attention will be paid to the adequacy of prior treatment trials so that patients who fail to satisfy the stringent operational definition of severe, treatment-resistant OCD are not enrolled and thereby exposed to the risks inherent in this study.

Consent Monitoring. Prospective patients, family members and significant others will have several opportunities to review the informed consent and ask questions, beginning after the initial screening. The consent process will be ongoing. When written informed consent is obtained, that process will be videotaped, and the videotapes will be available to the Independent Review Committee. A Consent Monitor at each site will personally meet with prospective patients, usually when consent is obtained, to explain study procedures and risks (most serious, most common, and least common) and to assure that they understand the investigational treatment proposed and its therapeutic limitations. The Monitor will similarly explain the study to low-literacy patients or non-English speakers, and assess their understanding. A qualified translator will be available as necessary to assist in both functions if there are language barriers. The Consent Monitor will report his assessment of the patient's consent to the Independent Review Committee/DSMB at the initial case review, and maintain contact with participants and families on a regular basis during the conduct of the study to provide ongoing assessment of the patient's understanding of and willingness to continue in the study.

Neurosurgical Risk Management. The main protection against risks of surgical implantation rests with the skill and experience of surgeons implanting the electrodes in the brain. The targeting is done on 2 different stereotactic software packages and cross-checked to maximize accuracy of lead placement and to reduce the chance of encountering structures (e.g., sulci) where implantation-induced hemorrhage is more likely. Postoperative CT scans will be obtained to verify accuracy of lead placement and assess for potential hemorrhage. The risk of seizure due to implantation will be minimized by preoperative tapering of high doses of medications known to reduce seizure thresholds, and preoperative phenytoin loading, as clinically appropriate. Participants will be monitored after implantation in post-anesthesia recovery rooms and, where appropriate, in intensive care units. Patients will be maintained on a neurosurgery/neurology unit for their overnight stay, where personnel are well aware of methodology for monitoring neurological status. The study neurosurgeon is highly experienced with stereotactic neurosurgery and with DBS implantation in particular. The neurosurgeon works in close collaboration with the interdisciplinary team. The PI will attend all implantation procedures and monitor psychiatric status of the patients. The study neurologist (Dr. S. Salloway) will monitor neurological status as needed. There is also the risk, primarily of discomfort and local scarring of the skin of the chest, from the need to replace the INSs during chronic therapy. Replacement is done as outpatient surgery, under local anesthesia. With the Kinetra devices we expect replacement to be necessary between 1 and 2 years on average based on our prior experience with DBS at this target. This will cut in half the frequency of stimulator replacement. Replacement has been well-tolerated from a surgical standpoint by patients in three pilot studies (as in clinical use). A rechargeable device is in development, projected to be available in several years, which should lengthen the replacement interval to up to 9 years.

We will make every effort to minimize the risks inherent in use of the rechargeable device. In cases deemed appropriate by the surgeon, pocket adaptors will be used. Though this will add to the amount of hardware in the IPG pocket, it will eliminate the need to retunnel the extension wires and thereby reduce the surgical risk. However, it may require that the patient have each of their original IPGs replaced with an Activa RC rather than running both leads off of one Activa RC. Reducing risk rests, in part, with the skill of the surgeon performing the device implantation, but also rests on the clinical team managing the ongoing assessment and stimulation management for patients enrolled. Those issues include selecting study patients who, in the Investigators' judgment, will be most likely to reliably recharge the device as often as necessary. We will work closely with the device manufacturer, Medtronic, Inc. to establish recharge intervals based on use parameters. We will also continue our practice of close follow-up both in person and by telephone so that we are in a position to recognize any adverse effects associated with the change to this device and may intervene in a timely manner as needed.

DBS Risk Management. Adverse effects due to active stimulation (detailed above) are the most common risks of this procedure. In general these have been transient (lasting minutes) without changes in the DBS technique or were rapidly reversed (also within minutes) after the stimulation technique was changed (see Preliminary Data). Patients will be given control magnets and instructed in how to use them to stop any active stimulation that might be causing adverse effects. This information will be reviewed at several points during the study, including the consent process, and in the review of the Patient Manual given to study patients. Patients will be closely monitored by the study nurse (RM) to allow for such adverse effects to be identified and for modification of DBS as needed. In addition, patients will be given a patient programming device that will allow them to check on the status of stimulation, and, on the advice of a study physician (typically the PI), stop the stimulation if it is producing untoward effects, including potential effects on affective state, behavior, cognition or sensorimotor function. As an added safety measure, any patients not living within a two hour drive of Providence must have a local referring psychiatrist who is willing to provide continuing care, including stimulation adjustment if necessary, for the duration of the study. A DBS programming physician (typically the PI) will train referring psychiatrists in DBS programming, using the

FDA-approved Physician Manuals, and communicate with local physicians as necessary about programming and other aspects of patients' care.

Histoxicity Risk Management. A review of the literature has established 30 μC (micro Coulomb) per square centimeter per phase as the charge density limit, above which tissue damage due to electric stimulation is possible. The Kinetra® stimulator we plan to use can produce charge densities in excess of this value at the active electrode contacts of either the Model 3387 or 3387 IES brain lead which we propose to implant in the study participants. To minimize this risk, use parameters will be set so that this limit is not exceeded. We will use the equation below, provided by the FDA, to select the appropriate boundary values for amplitude and pulse width for the Model 3391 lead:

Charge density (μC/cm2) = Voltage (volts) x Pulse Width (msec)
Lead Surface Area (cm2) x Impedance (ohms)

Electromagnetic Interference Risk Management. As noted above, certain devices may interfere with the operation of the DBS system (e.g., retail theft detection devices, airport scanning equipment, cardiac pacemakers, defibrillators or MRI). The most serious potential interaction has been with therapeutic (as opposed to diagnostic) ultrasound or diathermy, resulting in 2 fatalities. Those events have resulted in additional warnings to patients receiving DBS for FDA-approved uses in clinical practice. To minimize these risks, we have taken additional steps, beyond those mandated by the FDA, with this proposed study. First, the patients will receive both oral and written instruction on which environments and situations they may encounter in daily life may pose a risk of electromagnetic interference. This information will be reviewed with family and/or significant others during the consent process, and again before implantation and during the initial phase of active stimulation when we will review the Patient Manual we have developed for this study with patients and family/significant others. The Patient Manual includes a detailed description of these risks and how patients may avoid them. In addition, we have created a 1-page, user-friendly, summary of situations to avoid and those which should pose no problems ("Important Precautions with DBS"), plus a wallet-sized card emphasizing that patients must absolutely avoid therapeutic ultrasound and diathermy. Participants will receive another wallet card identifying them as having DBS devices implanted so that they can be hand-searched when necessary and so avoid theft or metal detectors. These materials are given to patients before surgical implantation and reviewed again postoperatively, at the start of outpatient DBS optimization and treatment. Patients, family/significant others are instructed to call, and to have other health care professionals call, the PI with any questions on this or other issues.

Management of Risk due to INS Battery Depletion. We will minimize the risk of interruption of DBS (due to battery depletion), and return of depressive symptoms or potential rebound worsening by calculating the expected battery life remaining in the INSs based on the stimulation parameters used (amplitude, pulse width, and frequency), and schedule the outpatient INS replacements in advance to minimize any potential interruption of treatment. Additionally, the inconvenience and cosmetic concerns of battery replacement, which we estimate will be necessary every 1 to 2 years using a new INS model (Kinetra®) with roughly twice the battery life of the current Soletra® model. Finally, patients and family/significant others will be instructed to contact the study nurse and the PI at any time, 24 hours a day, 7 days a week, in the event of any marked symptom worsening so that the potential causes of clinical deterioration can be determined and addressed.

Management of Psychiatric Risks, Including Potential Suicidality. Clinical deterioration, including possible increases in suicidality, may be due to fluctuations in severity of a comorbid depressive illness, intercurrent life stressors, inadvertent device shutoff, battery depletion or any other device malfunction, or

possibly due to the stimulation itself. Because hypomania is a risk of DBS treatment, albeit reversible in known cases to date, this trial will be limited to patients who have not had a manic episode in the preceding 3 years to reduce the risk of triggering a sustained manic episode in patients with bipolar illness. The main measure taken to reduce these risks will be maintaining close contact with patients and family/significant others. During the initial stimulator adjustments patients will be seen at least weekly and with additional telephone contact by the study nurse several times a week, allowing intervention in case of clinical deterioration. Patients, family and significant others will be told to notify the investigators immediately in the event of worsening of depressive symptoms, mood, anxiety, cognition, general level of functioning, or medical adverse events. The intervention may include DBS adjustment (by an unblended investigator, usually the PI), medication changes, or acute psychiatric hospitalization if clinically necessary. During the chronic open DBS phase, patients will be in telephone contact with the research team (study nurse) at least every 2 weeks, with monthly clinic visits. All of these contacts and clinic visits will, as much as possible, include family members or others in close touch with patients to maximize the monitoring information received. This will reduce the risk that a clinical deterioration would occur without intervention. In addition, the PI will be notified immediately if a patient obtains a score of 2 or more on the HDRS suicide item, or any increase in score on the YMRS, which could indicate hypomanic or manic symptoms.

"Escape Criteria": The most likely cause for dropouts will be clinical worsening in the sham condition. If a patient's symptoms worsen to the point that they become actively suicidal or requires psychiatric hospitalization because of this symptom worsening and a resulting deterioration in functional status, the patient would exit the blinded arm of the protocol and receive open stimulation. Active suicidality will be defined using the Columbia- Suicide Severity Rating Scale (C-SSRS) as an acutal attempt with a lethality rated as 3 or higher, or an interrupted attempt with potential lethality judged to result *in serious injury or death.* Other possibilities include protocol violations or inadvertent breaking of the blind. All potential dropouts will be reviewed by the DSMB for determining whether their data should be included in the analyses.

MRI Scan Risk Management. Here, the most serious risks are from MRI unrelated to the study. Although some MRI procedures can be performed safely in patients who have an implanted DBS system, MRI using a full body radio-frequency (RF) coil or a head transmit coil that extends over the chest area is contraindicated due to the possibility of lead heating and potentially serious brain tissue damage. MRI can also cause induced voltages in the stimulator and/or lead possibly causing uncomfortable, jolting, or shocking levels of stimulation. We inform patient verbally, in the informed consent, and in wallet cards not to have full body MRI, and beyond that ask them to have any physicians contemplating MRI contact us to ensure they do not undergo any contraindicated procedures, including MRI. Often CT scans can be used for diagnosis instead of a body MRI.

Preoperative MRI Risk Management: Participants will be screened using a detailed form to ensure there are no contraindications to undergoing MRI scans (eg, metallic foreign bodies in eyes or head, metal prostheses, severe claustrophobia, pregnancy – screened by a urine pregnancy test). They will be closely monitored to ensure they are as comfortable as possible, and scan time will be kept to the minimum necessary. Patients will be told to alert investigators via intercom if they are distressed so they can be made more comfortable or the scan can be discontinued. Subjects will wear earplugs to reduce the risk of hearing loss from exposure to loud noise during MRI scans.

CT Scan Risk Management. Participants will be screened to ensure there are no contraindications to undergoing the noncontrast CT scan used to verify brain lead placement (e.g., pregnancy – screened by a urine pregnancy test, severe claustrophobia). They will be closely monitored to ensure they are as

comfortable as possible, and scan time will be kept to the minimum necessary. Patients will be told to alert investigators via intercom if they are distressed so the scan can be discontinued.

Management of Learning Task Risks. The aversive stimuli, both air puffs presented to the eye and mild shock, are presented using standard laboratory equipment, which have been extensively used in human studies and have been well tolerated. As with all the experimental paradigms a patient might undergo in this study, we will closely monitor participants for untoward reactions or distress and modify or terminate the tasks as needed to minimize any distress they experience. Participants may choose to stop the task at any point.

PET Scan. The radiation exposure from the three PET scans, which span over 6 months, totals about 22.5% of the allowed annual exposure. Participants will be screened to determine if they have already had or anticipate significant radiation exposure during the year of the scan. The research PET scans will be cancelled to avoid excessive total radiation exposure. Woman of childbearing potential will have a urine pregnancy test before each PET study. Women found to be pregnant will not be scanned. Lying still in the scanner for an extended period of time (about 30 minutes) may cause temporary discomfort including claustrophobia. Investigators will make every effort to make patients as comfortable as possible (such as by placing a supportive cushion beneath their knees) during the PET scans. Patients may stop the scan at any time by asking to the investigators or study staff to do so. Patients may experience discomfort at the site of the intravenous line, needed for injection of the FDG tracer, and, in rare cases, infection. These adverse effects will be managed medically as needed. There is no known additional risk due to PET scanning in patients who have DBS systems implanted.

[O-15] PET imaging. The scan may be performed at any time after Month 6. However, it will likely occur during the same trip to MGH as the third FDG PET scan, approximately 6 months after initial optimization. If the patient's DBS is acutely on at that time, it will need to be turned off 2 hours prior to the scan. Patients who have had acute stimulation turned off 2 hours prior to the scan will be in close contact with MGH study staff to monitor and address any effects that arise. Subjects may ask to have a scan stopped and discontinue participation in the study at any time, for reasons of claustrophobia or discomfort arising during stimulation manipulations. As noted above, we have selected relatively low stimulation intensities, which should with the 3387 electrode result in charge densities of approximately 6 μC/cm2 assuming a single contact impedance of 1000 ohms. The risks of EEG in this setting are minimal, limited to the possibility of skin irritation due to electrode and electrolyte gel application to the scalp. We therefore expect very mild if any adverse effects due to stimulation itself. Subjects' emotional state will be closely monitored throughout the day of the PET scan by study staff at MGH.

Management of Risks to Confidentiality. Strict standards of confidentiality will be maintained. As noted above, all paper records, forms and data will be stored in secure files to which only members of the investigative team will have access. Computer records will be protected by standard measures that limit access of the data to trained research project personnel. Any information that might potentially allow an individual participant to be identified will not be allowed in any publications or reports sent to individuals outside the study, except, as noted above, as required by the FDA. Under the HDE monitoring program, this will include the FDA, the device manufacturer (Medtronic, Inc.), and other hospitals making DBS available for OCD under the HDE approval. Under the IDE monitoring program, this will include the FDA and the device manufacturer (Medtronic, Inc.).

Data and Safety Monitoring Plan. Data Safety Monitoring Board (DSMB). A group of experts in DBS and in OCD will act as a Data Safety Monitoring Board, with semi-annual teleconference meetings to monitor the study's progress and identify and protect against risks that may emerge during this research. The

board will be chaired by Christopher McDougle, MD, an internationally recognized expert in clinical trials of neuroleptic augmentation for treatment-resistant OCD, and Chair of the Department of Psychiatry at Indiana University. Biostatistics expertise will be provided by Lee Baer, Ph.D., in the Departments of Psychology and Biostatistics at Massachusetts General Hospital. Dr. Baer is also a leading expert in behavioral therapies for OCD, including severe cases. Dr. Erwin Montgomery, a neurologist at the University of Wisconsin, is internationally recognized as expert in the clinical uses and mechanisms of action of DBS for neurologic illness. An additional function of the DSMB will be to review all potential subject dropouts due to protocol violations to determine whether their data should be included in the analyses.

Information on Possible Risks Not Currently Identified. For a previous pilot study, the investigators have an approved Investigational Device Exemption (IDE) reviewing available safety data from Medtronic, Inc. We also monitor our own and collaborators' cumulative experience. Medtronic is also performing ongoing, FDA-mandated studies of the long-term safety and effectiveness the DBS devices in movement disorders. Information that might affect a potential participant's decision to undergo DBS implantation or which might affect a current participants decision to continue DBS may result.
If new significant risks are identified, participants will be informed immediately.

E. Potential Benefits

Although efficacy of DBS for otherwise intractable OCD has not been definitively established (and is not required for approval under the HDE mechanism), the available data indicate that a substantial proportion of patients (half or more) may experience durable clinical benefit from the procedure.

F. Risk-Benefit Ratio

As noted above, intractable OCD is a devastating condition. In our extensive experience over more than 10 years, patients applying for neurosurgical treatment are severely symptomatic. These patients were experiencing profound impairment in social or occupational functioning, in addition to severe subjective distress. They and their treating physicians felt that surgical intervention was the only available option, since they had failed multiple conventional treatments. Suicidal ideation, suicide attempts, and suicide have occurred in this group, including while patients were on waiting lists for surgery.

In summary, patients appropriate for this study are individuals who have been suffering from a prolonged illness that is characterized by immense subjective distress and severe functional impairment, one possible complication of which is death due to suicide (generally undertaken by the patient in an effort to obtain relief from the symptoms of the illness). In this context, the risks of electrode implantation and stimulation, a largely reversible procedure, are justified. The other risks encountered in this study are no different from those of conventional drug and psychotherapeutic treatments of OCD. The risks of a phase of sham stimulation, during which patients may continue to suffer with severe symptoms that have been unresponsive to conventional OCD treatments, will be managed by procedures outlined above, including escape criteria for early activation of the devices if there appears no reasonable clinical alternative. Risks of sham stimulation are inherent in the attempt to acquire controlled data on DBS efficacy in this population.

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V. CRITERIA FOR WAIVER OF AUTHORIZATION FOR USE OF PROTECTED HEALTH INFORMATION (PHI)

A. Does the requested use of PHI involve more than minimal risk to privacy?
☐**YES** ***[if " YES," project is not eligible for PHI Waiver]***
☒**NO** ***[if "NO," address 1-3 below]***

1. Plan to Protect Patient Identifiers from Improper Use and Disclosure

- **a.** Any on site electronic file containing PHI is password protected.
- **b.** All subjects will be assigned a number to which they are referred so that only their number is associated with their data file.
- **c.** All paper files containing subject responses are kept under lock and key.
- **d.** Patients will not be personally identified in any publications or reports of this research.
- **e.** Only trained research staff will have access to patient charts and data.
- **f.** Only information relevant to the protocol will be recorded.
- **g.** The master list and copy containing subject names and study numbers will be password-protected on computer equipment in a locked office.

2. **Plan to Destroy Identifiers or Justification for Retaining Identifiers**
   Identifiers will be retained so that they may be used for data analysis in this protocol and future investigations. As required by the FDA, medical records will be archived for 10 years upon completion of the study.

3. **Assurances that the PHI will not be Re-used or Disclosed**
   PHI collected as part of the study protocol is shared only with the collaborative site on the project and is shared in de-identified form only.

B. Could the research be practicably conducted without a waiver?
☐**YES** ☒**NO**

C. Could the research be practicably conducted without access to and use of the PHI?
☐**YES** ☒**NO**

VI. DESCRIPTION OF NEEDED PHI

Name, date of birth, gender, ethnicity, telephone numbers, address, email address, clinical diagnoses, treatment history, family history of OCD, clinical rating scores, neuropsychological test results.