Thalamic Deep Brain Stimulation for the Treatment of Refractory Tourette Syndrome

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Principal Investigator: Shannon Dean, MD, PhD_____
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1. Abstract

The purpose of this pilot study is to investigate the use of deep brain stimulation (DBS) of the medial thalamus in 10 subjects with treatment-resistant Tourette Syndrome (TS). Tourette Syndrome is a type of tic disorder with a prevalence of 1-10 per 1000, and in its milder forms can affect 0.6% of the population (1). Patients with Tourette Syndrome also suffer from other psychopathologies including obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), learning difficulties, and sleep abnormalities (1) Treatment for Tourette Syndrome includes nonpharmacologic interventions such as behavioral therapy, habit reversal technique, and comprehensive behavioral intervention (CBIT) for tics (1). First line medication therapy includes drugs such as clonidine, guanfacine, and topiramate, and failing these often atypical and typical neuroleptics are tried. For patients failing medical therapy, deep brain stimulation has been used at a few centers (2-4). DBS is in other early phase clinical trials in other psychiatric disorders such as treatment-resistant depression and early results are promising.

This pilot study will investigate the use of DBS in treatment-resistant Tourette Syndrome who have exhausted all other therapeutic alternatives but continue to have persistent disabling tics. Of note, DBS is not FDA approved for use in patients with Tourette Syndrome. The method will be similar to that used in thalamic deep brain stimulation in patients with Essential Tremor. However, the electrode will be placed in a different region of the thalamus, namely the region of the centromedian nucleus, substantia periventricularis, and the nucleus ventro-oralis interna (Ce-Spv-Voi, Hassler nomenclature) (5,6). The choice of this target was guided by results from early lesioning studies (7), and by the role of the ventral thalamic nuclei as elements with strong projections to prefrontal cortex and striatum which are regions known to be involved in the pathophysiology of the disease (8). Frequent monitoring and clinical assessment with psychiatric scales will be used to monitor the treatment response.

There is a subset of patients with TS who continue to have persistent tics despite multiple adequate medication trials with appropriate medical therapy. There are currently no available treatments for such patients who generally have poor function and are chronically disabled, unable to work, live independently or have meaningful social relationships. Neuroimaging studies in patients with TS have revealed information about pathological neural circuits that could be suitable targets using deep brain stimulation (9,10,11,12,13).

2. Objectives (include all primary and secondary objectives)

2.1. Primary Objectives

- To evaluate the efficacy of DBS of the thalamic Ce-Spv-Voi complex on tic frequency and severity in10 subjects with treatment-resistant Tourette Syndrome.
- To evaluate the safety of DBS of the thalamic Ce-Spv-Voi complex in 10 subjects with treatment-resistant Tourette Syndrome.

2.2. Secondary Objectives

- To evaluate the efficacy of DBS of the Ce-Spv-Voi complex on cognitive symptoms in 10 subjects with treatment-resistant Tourette Syndrome and any other concurrent psychopathologies including obsessive-compulsive disorder, and attention deficit hyperactivity disorder.

3. Background

DBS has been used successfully for the treatment of patients with treatment-resistant movement disorders such as Parkinson's Disease (PD) (14), tremor (15) and dystonia (16). Stimulation of electrodes implanted in deep brain structures modulates activity in brain circuits leading to symptom improvement. More recently, DBS has been proposed as a therapeutic alternative for patients with treatment-resistant depression after scientists observed that the subgenual cingulate region (Brodmann area 25) is overactive in patients with depression refractory to traditional treatments such as antidepressants and electroconvulsive therapy (17). DBS is unique among neurosurgical techniques in that it can easily be studied in a placebo-controlled study design; patients can serve as their own controls in crossover designs in which the stimulator is turned on or off in a blinded fashion. Controlled trials of DBS in depression are currently ongoing. Additional benefits of DBS include that unlike ablative surgery, DBS is reversible and produces little to no tissue damage (18). Because of these advantages, investigators at Johns Hopkins plan to develop a protocol for DBS to target tics in patients with treatment-resistant Tourette Syndrome (defined as patients with persistent tics that have not responded to front-line medical agents such as clonidine, guanfacine, or topiramate). In addition, the intended DBS target may also affect other concurrent psychopathologies such as ADHD or OCD (1).

3.1 Target Choices

Data from neuroimaging studies in patients with TS converge on the finding that TS could involve the dysfunction of cortico-striato-pallido-thalamo-cortical (CSPTC) neural circuits. Thus, modulation of circuit dysfunction with DBS has the potential to be an important treatment modality for patients with medically refractory TS. In a seminal paper summarizing a body of research on CSPTC neural circuits, Alexander, DeLong and Strick described parallel, segregated basal ganglia circuits that share common neuroanatomical characteristics: each involve excitatory glutamatergic projections of multiple areas of the cortex in a topographically organized fashion to part of the striatum, the major input area of the circuit (19). Similar to the development of deep brain stimulation for affective disorders and movement disorders, the targeting choices for the DBS treatment of TS include elements of the CNS linked in a widely connected system. Guided by the original lesioning studies of Hassler and Dieckmann (7), the Maastricht group has focused on stimulation of three separate thalamic regions, namely the centromedian nucleus (representing an intralaminar nucleus), the midline substantia periventricularis, and the nucleus ventro-oralis internus (Voi) (8). Possible mechanisms for efficacy of this stimulation target include the role of the ventral nuclei as elements in the CSTC loops as well as the projections from the midline and intralaminar nuclei to prefrontal cortex and the striatum all of which are thought to be involved in the pathophysiology of the disease (8). GPi has also been proposed as a treatment target as well since it acts as a modulatory element on this circuitry (8,20). And since TS is so often associated with OCD, anterior internal capsule is also being considered (4,20). Unfortunately, there are no animal models for TS, so electrophysiological characterization of the structures involved have been difficult and targeting guidance less well justified (4).

An excellent review of the history of lesioning procedures in TS has been provided by Temel and Visser-Vandewalle (8). Some of the more recent and commonly used targets have been the set of thalamic nuclei described by Hassler and Dieckmann in 1970 (7, 21, 22). This procedure included bilateral lesions in the centromedian nucleus, the substantia periventricularis (a midline thalamic nucleus), as well as the nucleus ventro-oralis internus (Voi). Substantial improvements in tic number and frequency occurred in the lesioned patients (7, 21, 22). In addition to the limbic leucotomy and anterior capsulotomy described above for the treatment of TS (23,24,25), other authors have attempted lesioning bilateral dentate nuclei (26),

performing a cingulotomy in the context of TS coupled with severe OCD (27), lesioning the infrathalamic region (28,29), and even combinations of thalamic and zona incerta lesioning(30). Many of the patients undergoing perithalamic lesioning outside of the set of nuclei described by Hassler and Dieckmann were reported to have decreases in TS symptoms but most had substantial side effects as well (8).

3.2 Initial Stimulation Data

Early clinical reports on the effectiveness of DBS for TS included those of the Dutch Flemish Tourette Surgery Study Group (2, 5) with bilateral thalamic stimulation, as well as a case of bilateral GPi stimulation for refractory TS by Diederich et al. (3). In these two reports, there were substantial reductions in the numbers and frequencies of tics and compulsive behavior (2, 3). Additionally, Flaherty et al. recently published a case of a patient with TS undergoing bilateral anterior internal capsule DBS placement (with the last electrode in the nucleus accumbens.) At 18 months of follow-up the patient demonstrated significant reductions in tic frequency and severity as well (4). A series of 5 patients with TS were examined in a double-blind fashion by Maciunas et al. after undergoing bilateral DBS placement at the Visser-Vandewalle target in the medial and ventral thalamus (31). Four stimulation states were examined in a blinded fashion, including either unilateral stimulation, both on, or no stimulation. The bilateral stimulation state showed statistical improvements in motor and vocal tic numbers and other TS symptom inventories, with 3/5 patients exhibiting marked improvement (31). Additionally, Servello et al. reported on 18 patients undergoing bilateral thalamic stimulation in the same target for refractory TS. These patients demonstrated significant improvements as well up to 18 months of follow-up (32). And more recent positive results were obtained by Ackermans et al. using the thalamic Ce-Spv-Voi complex target in a small double-blind trial involving six patients (6). This group demonstrated a 37% improvement in the Yale Global Tic Severity Scale between DBS on and off states.

4. Study Procedures/Overview of Study Design

4.1. Overview of Study Design

This study is an open-label pilot study to determine the feasibility of DBS of the thalamus (Ce-Spv-Voi complex) in 10 subjects with treatment-resistant Tourette Syndrome (TS). After subjects are determined to have decision-making capacity by an independent psychiatrist or neurologist who is not a member of the study team, they will come in for 3 consecutive baseline visits and will be evaluated by two different study physicians (psychiatrist and/or neurologist) to determine that he/she has a diagnosis of TS. TS symptom scales will be performed at each visit. Subjects who are eligible will undergo a pre-operative diagnostic MRI along with a planning stereotactic planning MRI, and will undergo neurosurgical implantation of the DBS device followed by implantation of a neurostimulator under the chest wall. Subjects will be monitored at Weeks 1, 2, 3, 4 and then at Months 3, 6, 9 and 12 after implantation of the neurostimulator. At each visit, subjects will be assessed for adverse events and will undergo routine procedures for monitoring patients who undergo DBS, including recording concomitant medications, optimization of stimulation parameters, TS symptom scale assessments to document changes in symptoms, and neuropsychological assessment to document any changes in cognition. No blinding will be performed. Subjects will continue their pre-surgical psychiatric medications and any changes in medications will be documented at each study visit.

The subjects will be followed for one year after implantation. We estimate three implantations per year will be performed, implying just over three years required to complete the implantations. We estimate the full

study duration to be 5-6 years to complete the initial 13 Visits for all of the subjects, prior to the long-term follow-up segment of the study which involves visits approximately semiannually for 2 years followed by annually for the duration of device implantation.

Because this study is being conducted on a vulnerable clinical population, an independent psychiatrist that is not a member of the investigational study team with experience in capacity assessments will assess the decision-making capacity of each potential subject prior to any study-related activities.

If the subject is found to have capacity to provide informed consent, prior to any study-related activities, the subject must provide written informed consent. The PI explains the study (characteristics of the DBS device and neurosurgical procedure for implantation, required procedures, potential hazards, and possible adverse reactions) to all prospective participants. The PI will maintain each subject's Informed Consent Form, signed and dated by the subject and the PI, in the subject's file.

Movement assessments will be videotaped during the clinical examinations. The videotapes will be utilized for clinical, research, and teaching purposes. Since the movements and expressions of the face are crucial to the characterization of the motions and emotions of the subject, the face and eyes of the subjects will be included in the videotapes. Videotapes may also be utilized for clinical, research, and teaching purposes. Portions of videotapes may be presented at professional conferences and published in hard copy and online journals. The names and all identifiers of the subjects will be deleted from all videotapes before presentation or publication.

4.2. **Assessment for Decision-Making Capacity**

The independent psychiatrist or neurologist will meet with the potential subject prior to any study-related activities and review elements of the study with the patient discussing the potential benefits and risks. The independent psychiatrist or neurologist will conduct a thorough assessment of the decision-making capacity of the subject to determine if the subject understands and are able to appropriately judge the potential risks of the study and is able to provide informed consent. The subject will be interviewed to determine if he/she understands the research project and procedures, appreciates the effects of research participation on his/her own situation, is able to reason about participation and is able to communicate a choice about participating in this study. If the potential subject shows mild deficits in any one of these areas (understanding, appreciation, reasoning and choice), the independent psychiatrist or neurologist may provide feedback with multiple learning trials, since previous studies have demonstrated that such interventions can improve subjects' decision-making (33).

4.3. **Visit 1 – Baseline Visit #1**

After the subject has been determined to have decision-making capacity to provide informed consent, the following assessments must be conducted at Visit 1:

- Written informed consent
- Review inclusion and exclusion criteria
- Detailed medical history including review of medical records, current medications and duration of prior TS medication trials
- DSM-IV SCID to determine subject has diagnosis of TS by one study psychiatrist or neurologist (first evaluator), for ages 15-17 this will be the K-SADS assessment.
- Complete physical examination including height, weight and vital signs

- EKG, blood samples (CBC, and complete metabolic panel) for clinical laboratory tests
- Urine sample for urine toxicology screen and urine pregnancy test (for females)
- TS symptom scales, including the Yale Global Tic Severity Scale (YGTSS), the Yale-Brown Obsessive Compulsive Scale (YBOCS) for OCD symptoms, and the WHO Adult ADHD Self-Report Scale (ASRS) for ADHD symptoms.
- Assessment of depression, anxiety, or symptoms of mania using the Hamilton Depression Rating Scale (Ham-D), the Beck self-reporting Anxiety Inventory (BAI), and the Young Mania Rating Scale (YMRS). For ages 15-17, the Ham-D and BAI scales will be replaced with the Beck Youth Inventory.
- Columbia Suicide Severity Scale (CSSS).
- Neurocognitive battery – consisting of the Grooved Pegboard test, the Judgment of Line Orientation, the Trailmaking Test (A&B), the Hopkins Verbal Learning Test, and the Verbal Fluency test (COWAT). And for this visit only, the Mini-Mental State Examination (MMSE), the Wechsler Abbreviated Scale of Intelligence (WASI), and the Brief Visuospatial Memory Test – Revised (BVMT-R). (20)
- Subject to be referred to his/her medical physician for a pre-operative evaluation to determine if safe to undergo surgery and anesthesia
- Global Assessment of Function (GAF, DSM-IV Axis V) of no more than 50 (to demonstrate that subject's condition is severe and disabling)
- At the conclusion of this visit, all subjects who meet all inclusion/exclusion criteria will be given an appointment card for the next study visit.

4.4. **Visit 2 – Baseline Visit #2**

Approximately 2 weeks after Visit #1.

At this visit, the following assessments will be performed:
- DSM-IV SCID to confirm subject has diagnosis of TS by **a different** study psychiatrist or neurologist (second evaluator), for ages 15-17 this will be the K-SADS assessment.
- Repeat TS / OCD / ADHD symptom scales: YGTSS, YBOCS, and the WHO ASRS.
- Repeat Ham-D, BAI, and YMRS for depression, anxiety, and/or mania symptoms. For ages 15-17, the Ham-D and BAI scales will be replaced with the Beck Youth Inventory.
- Urine sample for urine toxicology screen (must be negative for illicit substances for subject to continue in study)

At the conclusion of this visit, all subjects who continue to meet all inclusion/exclusion criteria will be given an appointment card for the next study visit.

4.5. **Visit 3 – Baseline Visit #3**

Approximately 2 weeks after Visit #2.

At this visit, the following assessments will be performed:
- Repeat TS / OCD / ADHD: YGTSS, YBOCS, and WHO ASRS.
- Repeat Ham-D, BAI, and YMRS for depression, anxiety, and /or mania symptoms. For ages 15-17, the Ham-D and BAI scales will be replaced with the Beck Youth Inventory.
- CSSS

- Urine sample for urine toxicology screen (must be negative for illicit substances for subject to continue in study) and urine pregnancy test (for females).
- Schedule pre-operative diagnostic MRI and frame-based MRI (to aid with stereotactic targeting of the electrode). Head CT examinations will be used if there are contraindications to MRI.

If all 3 baseline YGTSS tic subscale scores are not at least 35 the subject will be excluded from re-evaluation for entrance into the study for 6 months. All three urine samples must be negative for illicit substances.

At the conclusion of this visit, all subjects who continue to meet all inclusion/exclusion criteria will be given an appointment card for the next study visit. **The next study visit is the neurosurgical procedure for implantation of the DBS device. The pre-operative diagnostic MRI must be performed for the subject prior to the next visit.** The neurosurgical procedure should be planned for 2 – 3 weeks after Baseline Visit #3. This pre-operative MRI may also be used for coregistration with CT imaging obtained the morning of surgery for surgical planning of the lead placement, if the patient's symptoms preclude MRI imaging with the stereotactic frame the morning of surgery.

4.6. Visit 4 – Neurosurgical Procedure for Implantation of DBS System

Approximately 3 weeks after Visit #3.

At this visit, the device will be implanted by the neurosurgical study team according to standard operating procedure utilized for implantation of DBS in the subthalamic nucleus. This involves the use of a stereotactic frame, and MRI images obtained with the patient wearing the frame the morning of the surgery. If the patient's symptoms preclude MRI imaging while wearing the frame, CT imaging will be obtained instead, and these images will be coregistered with the previously acquired diagnostic MRI for target planning. The bilateral thalamic targets include the centromedian nucleus, the substantia periventricularis, and the nucleus ventro-oralis internus. The target is calculated relative to the AC-PC line using an atlas based approach. We will determine the location of the midpoint of the AC-PC and then target a point lateral by 5 mm, and posterior by 4 mm remaining in the same plane as the AC-PC line. This target was adapted from the previous study of Ackermans et al. (2). An additional aid in localization will be the use of microelectrode recordings during the case to identify thalamic bursting cells. This has been performed by our operative team in standard thalamic placement of DBS electrodes for the treatment of tremor (34).

The surgical procedure will performed under local and IV sedation. If the patient's symptoms preclude this, the procedure will be performed under general anesthesia (this would typically be in the context of large amplitude tics making long time positioning on the operative table unsafe). For subjects undergoing general anesthesia, the FDA approved Clearpoint DBS placement system (MR Interventions) will be used in one of the iMRIS operating room suites, or the Leksell frame in the non-MRI equipped operating rooms. Fluoroscopy will be used in the operating room to check for lead placement or lead migration during the placement procedure. The fluoroscopy unit is draped into the surgical field, and arranged for lateral views of the skull.

A head CT examination immediately after the lead placement procedure will be obtained while the patient is still wearing the stereotactic frame (this is our standard procedure for other movement disorder DBS cases). This will allow us to check for hemorrhage, the amount of pneumocephalus, and lead placement. The operating room will be reserved, and the operative field kept sterile should the need arise to revise the

lead positioning or evacuate a hemorrhage. The frame will be removed once the head CT examination is cleared by the operative surgeon.

A neurocritical care team will stabilize and monitor the patient in the postoperative period.

The required study documentation must be filled out by the neurosurgical team:
- Surgery Form
- Adverse events

After the subject is stable and discharged, the subject will be given an appointment card for the next study visit. **The neurostimulator will be implanted under the chest wall at the next visit.**

4.7. Visit 5 – Implantation of the Neurostimulator

Approximately 1 week after Visit #4.

Approximately one week after the subject is discharged from the hospital from the neurosurgical implantation, the subject will return for implantation of the neurostimulator under the chest wall. The intracranial electrode will be connected to the neurostimulator plus battery that powers the electrode.

The following assessments will be conducted:
- New/changed adverse events
- Record changes in concomitant medications
- TS and associated condition symptom scales (YGTSS, YBOCS, and the WHO ASRS). Repeat Ham-D, BAI, and YMRS for depression, anxiety, and /or mania symptoms. For ages 15-17, the Ham-D and BAI scales will be replaced with the Beck Youth Inventory.
- Schedule post-operative diagnostic MRI of the brain (to assess lead placement prior to implantable pulse generator programming). A head CT will be obtained if there are MRI contraindications.

At the conclusion of this visit, the subject will be given an appointment card for the next study visit.

4.8. Visits 6 – 9 – Follow-up/Optimization of Programming

These visits begin approximately 3 weeks after Visit #5.

A study neurologist (with experience in programming DBS devices who has extensive experience working with patients with movement disorders undergoing DBS) in conjunction with one of the study psychiatrists will set initial stimulation parameters. As this procedure is experimental, the stimulation parameters will be modified empirically and individualized for each subject. However, attempts will be made to use typical clinical ranges for DBS of the thalamus (electrode voltage 1 – 5.0 V, pulse width 60-210 microseconds, and stimulation frequency 130 – 185 Hz (35). These numbers indicate the ranges and maxima for the stimulation parameters to be used in this protocol. These represent conservative values with respect to the safety of the stimulation, as indicated by the limits incorporated into the Medtronic programmer. The study neurologist experienced in programming in conjunction with one of the study psychiatrists will use TS symptom scales (especially the Severity Ratings section of the YGTSS, incorporating measures of tic frequency and intensity) to optimize the DBS programming at all subsequent follow-up visits. In situations of partial response as assessed over the previous week, the stimulation voltage intensity may be increased,

or the frequency and pulse width settings modified within the limits stated above to seek a more complete response. Any acute changes in OCD or ADHD symptoms, acute changes in depression or anxiety symptoms, and/or appearance of adverse events deemed likely to be related to DBS programming may prompt a reduction in stimulation voltage, change in stimulation contacts used, or alteration in frequency or pulse width.

At the time of initial programming, the subjects will receive additional literature as well as the appropriate patient controller device, which allows them to turn the stimulation on or off. The subjects will be instructed in its use and receive pocket cards and materials to carry with them.

The subject will come in for four further follow-up visits weekly after the initial programming session (Visit #6). The study neurologist experienced in programming in conjunction with one of the study psychiatrists will use TS symptom scales (especially YGTSS), acute changes in OCD or ADHD symptoms, acute changes in depression or anxiety symptoms, and/or appearance of adverse events deemed likely to be related to DBS to optimize programming at all subsequent follow-up visits.

The following assessments will be conducted:
- Programming Form
- New/changed adverse events
- Record changes in concomitant medications
- TS symptom scales (YGTSS, YBOCS, WHO ASRS)
- Ham-D, BAI, and YMRS for depression, anxiety, and/or mania symptoms (Beck Youth Inventory for ages 15-17)
- CSSS at alternating visits.
- Global Assessment of Function Scale (GAF)
- Neurocognitive battery (as per Visit #1)

At the conclusion of this visit, the subject will be given an appointment card for the next study visit.

4.9. **Visits 10 – 12: Follow-Up Visits**

These visits begin approximately 3 months after Visit #6.

The purpose of the follow-up visits is to monitor for symptom changes, report any complications and to optimize programming if necessary. Subjects will come in at 3 months after implantation of the neurostimulator and then every 3 months for Visits 11 and 12 (6 and 9 months after implantation of the neurostimulator, respectively). The study neurologist experienced in programming in conjunction with one of the study psychiatrists will use TS symptom scales (especially the YGTSS), acute changes in other comorbid conditions (OCD/ADHD), acute changes in depression or anxiety symptoms, and/or appearance of adverse events deemed likely to be related to DBS to optimize programming at all subsequent follow-up visits.

The following assessments will be conducted:
- Programming Form
- New/changed adverse events
- Record changes in concomitant medications
- TS symptom scales (YGTSS, YBOCS, WHO ASRS)

- Ham-D, BAI, YMRS (Beck Youth Inventory for ages 15-17)
- GAF
- CSSS at alternating visits.
- Neurocognitive battery (for Visit #11 as per Visit #1)

At the conclusion of this visit, the subject will be given an appointment card for the next study visit, which is the final study visit.

4.10. **Visit 13 – Study Completion (or Early Termination Visit)**

This visit is approximately 4 months after Visit #12.

The purpose of this last visit is to monitor for symptom changes, report any complications and to optimize programming if necessary. Subjects will come in at 4 months after the last visit (12 months after implantation of the neurostimulator). The study neurologist experienced in programming in conjunction with one of the study psychiatrists will use TS symptom scales (YGTSS, YBOCS, and the WHO Adult ADHD Self-Report Scale), acute changes in depression or anxiety symptoms, and appearance of adverse events deemed likely to be related to DBS to optimize programming at all subsequent follow-up visits.

The following assessments will be conducted at study completion (or if the subject is early terminated from the study for any reason):

- Programming Form
- New/changed adverse events
- Record changes in concomitant medications
- TS symptom scales (YGTSS, YBOCS, and the WHO ASRS)
- Ham-D, BAI, YMRS (Beck Youth Inventory for ages 15-17)
- GAF
- Neurocognitive battery (as per Visit #1)

At the conclusion of this visit, the subject will be discharged from the study and will continue standard clinical care for patients who undergo DBS procedures. The patient will continue to meet with the study physicians. If symptom improvement has been observed with DBS, the patient will continue standard of care for DBS. If symptom improvement has not been observed, the subject can opt to have the stimulation device turned off.

4.11. **Early Discontinuation/Treatment Failure**

Subjects may choose to discontinue study participation at any time, for any reason, specified or unspecified, and without prejudice. If a subject chooses to discontinue early after implantation of the DBS device, the investigator must request that the subject return to the clinic within 24 hours and complete the assessments for early termination described in Section 4.10. The Investigator will have the subject's DBS device turned off and request that the subject continue to come in for monitoring visits to complete safety assessments. Subjects who are determined to be treatment failures, as defined by having no improvement in tic symptoms (as scored with the YGTSS) will be offered the option to have the DBS device turned off after a period of 3 months to allow suitable time for appearance of clinical improvement. Subjects who experience a worsening of TS, OCD, ADHD, depression, or anxiety symptoms that persists for 4 weeks will have the device turned off. The Investigator must request that such subjects also return to the clinic

within 24 hours and complete the assessments for early termination described in Section 4.10 as well as continue to come in for monitoring visits to complete safety assessments.

All subjects must be educated that although the DBS device will be turned off in the event of discontinuation from the study, the DBS device will **not** be removed, as the risk of such a procedure outweighs any perceived benefits.

4.12. **Table of Visits and Testing**

Visit #	Approx. Week #	TS symptom scales	Other psych testing	Surgical procedures	Adverse event monitoring	IPG programming	Medication change monitoring	Urine tox
1	0	DSM-IV SCID, YGTSS,YBOCS, WHO ASRS	Ham-D, BAI,GAF, CSSS,YMRS,NCOG	NA	NA	NA	medications recorded	yes
2	2	DSM-IV SCID, YGTSS,YBOCS, WHO ASRS	Ham-D, BAI,GAF, YMRS	NA	NA	NA	yes	yes
3	4	YGTSS,YBOCS, WHO ASRS	Ham-D, BAI, CSSS,YMRS	NA	NA	NA	yes	yes
4	7	NA	NA	Implantation of DBS leads	yes	NA	NA	NA
5	8	YGTSS,YBOCS, WHO ASRS	Ham-D, BAI, YMRS	Implantation of IPG	yes	yes	yes	NA
6	11	YGTSS,YBOCS, WHO ASRS	Ham-D, BAI,GAF, CSSS,YMRS,NCOG	NA	yes	yes	yes	NA
7	12	YGTSS,YBOCS, WHO ASRS	Ham-D, BAI,GAF, YMRS,NCOG	NA	yes	yes	yes	NA
8	13	YGTSS,YBOCS, ADHD	Ham-D, BAI,GAF, CSSS,YMRS,NCOG	NA	yes	yes	yes	NA
9	14	YGTSS,YBOCS, WHO ASRS	Ham-D, BAI,GAF, YMRS,NCOG	NA	yes	yes	yes	NA
10	23	YGTSS,YBOCS, WHO ASRS	Ham-D, BAI,GAF, CSSS,YMRS	NA	yes	yes	yes	NA
11	35	YGTSS,YBOCS, WHO ASRS	Ham-D, BAI,GAF, YMRS,NCOG	NA	yes	yes	yes	NA
12	47	YGTSS,YBOCS, WHO ASRS	Ham-D, BAI,GAF, CSSS,YMRS	NA	yes	yes	yes	NA
13	62	YGTSS,YBOCS, WHO ASRS	Ham-D, BAI,GAF, YMRS,NCOG	NA	yes	yes	yes	NA

4.13. **Unscheduled Visits**

Subjects may telephone the study team to request additional visits if he/she experiences new adverse events. The subject will be asked to come to the study site within 24 hours (or to go their local emergency room if it is assessed to be serious by an Investigator).

The following assessments will be performed:

- New/changed adverse events

- Record changes in concomitant medications
- TS symptom scales (YGTSS, YBOCS, and the WHO ASRS)
- Ham-D, BAI, YMRS, and CSSS (Beck Youth Inventory for ages 15-17)

Unscheduled visits for assessment and treatment of potential DBS-related adverse events are allowed throughout the study.

4.14 **Long-Term Follow-Up Visits**

The purpose of the long-term follow-up visits is to monitor for additional symptom changes, report any complications and to optimize programming if necessary over the lifetime of the implanted system. Subjects will come in at roughly 6 month intervals for two years after Visit #13, and then annually after that. The study neurologist experienced in programming in conjunction with one of the study psychiatrists will use TS symptom scales (especially the YGTSS), acute changes in other comorbid conditions (OCD/ADHD), acute changes in depression or anxiety symptoms, and/or appearance of adverse events deemed likely to be related to DBS to optimize programming at all subsequent follow-up visits. These assessments will occur until the subject no longer wants to participate, or until the device is removed due to a complication or wish of the subject, or until the device generator depletes and the subject no longer wishes to have it replaced.

Replacements for the IPG will be performed when the cell is depleted as assessed during follow-up visits or for changes in symptoms. The first cell implanted at Visit #5 will be the Activa PC (standard cell). Either the Activa PC (standard cell) or the Activa RC (rechargeable system) will be offered at the times of IPG replacement subsequent to this, pending the subject's preference and willingness to participate in the recharging process. The RC system will be discussed with the subject particularly in cases where the lifetime of the prior IPG was less than 2 years.

The following assessments will be conducted:

- Programming Form
- New/changed adverse events
- Record changes in concomitant medications
- TS symptom scales (YGTSS, YBOCS, WHO ASRS)
- Ham-D, BAI, YMRS (Beck Youth Inventory for ages 15-17)
- GAF
- CSSS at alternating visits.
- Neurocognitive battery if suggested for any reason by one of the study neurologists or psychiatrists

4.15 **Covid19 Related Protocol Changes**

We are modifying our protocol (summarized below) to minimize risk to participants and study team members by limiting in-person interaction wherever possible.

Preoperative evaluation:

Please note that for this research study, all visits taking place related to placement and maintenance of this implanted neuromodulation system are covered under an FDA Investigational Device Exemption #G120131. Preoperative visits will take place via telemedicine when possible with both the referring neurologist at Johns Hopkins and the operative neurosurgeon. For the preoperative rating scales for the characterization of Tourette Syndrome, in person clinic visits with the multidisciplinary movement disorder team at Johns Hopkins will take place for evaluation. These in person visits will take place at the Johns Hopkins Outpatient Center (JHOC), and will follow current protocols for wearing masks and face shields in the clinic spaces. Evaluated subjects will also be required to wear masks. Similar procedures will be performed by the Neuropsychology Team in the Meyer 2 exam area for the required preoperative neuropsychological testing.

Post-operative management:

Postoperative surgical visits for suture/staple removal will take place at the JHOC under the current established protocols for seeing patients in person. Masks (patients and clinicians) will be worn at all times, and face shields when appropriate. The same protocol will be followed by the neurology and neuropsychological teams for device activation and initial programming, as well as follow up programming optimization visits, and Tourette Syndrome and neuropsychological rating scales. Similar precautions will be taken for visits related to maintenance of the implanted system, and for implantable pulse generator replacements due to battery depletion.

5. Inclusion/Exclusion Criteria

5.1. Study Population

The study group will consist of 10 patients with treatment-resistant Tourette Syndrome to undergo DBS of the thalamic Ce-Spv-Voi complex

5.2. Inclusion Criteria

1. Males and females who are ≥ 15 years of age. There is no strict age cutoff at the upper limit of inclusion, however subjects may meet the exclusion criteria based on medical contraindications to deep brain stimulation surgery (Points 3. and 6. under the **Exclusion Criteria**). For subjects in the age range of 15-24 years, an additional Ethics Committee consultation will be obtained prior to offering the subject the required screening visit. This is based on the revised screening criteria now proposed by Shrock, Mink, et al. on studies investigating DBS in TS (38). Additionally, for subjects in the age range of 15-20, a caregiver will be required to be present for all study visits.

2. Subject has a diagnosis of TS as determined by a review of medical records, discussion with referring psychiatrist as well as the DSM-IV criteria and videotaped assessment. This will include an assessment to determine the presence of psychogenic tics, embellishment, factitious symptoms, personality disorders and malingering.

3. Subject determined to be treatment-resistant for at least <u>one year</u> prior to the Screening Visit as demonstrated by clinical evidence (determined by review of medical records and discussion with referring

psychiatrist or neurologist) of persistent functionally impairing tics that have not responded to treatment with a minimum of three adequate regimens of medication including two failed trials of at least one typical neuroleptic and one atypical neuroleptic medication, along with one failed trial of a first tier medication as defined as follows (standard dosages for these trials are outlined in (1)):

a. Adequate trials of one non-neuroleptic medication including drugs from the following (first tier) list: clonidine, guanfacine, topiramate, baclofen, levetiracetam, and clonazepam (1). Trial failure is defined as demonstrated lack of efficacy or severe side effects.

b. Two adequate trials of at least one typical neuroleptic medication (pimozide, fluphenazine, haloperidol) and at least one atypical neuroleptic (risperidone, aripiprazole, ziprasidone, olanzapine, quetiapine). Trial failure is defined as demonstrated lack of efficacy or severe side effects.

4. A mandatory trial of behavioral interventions in an attempt to reduce the severity of the tics or comorbid symptoms must also be completed by the subject before offering participation in this trial. This may include habit reversal therapies, stress reduction therapies, or other behavioral therapies under investigation for tic suppression (36,37).

5. Subject has both significant vocal and motor tics with a tic subscale score of at least 35 on the YGTSS (Yale Global Tic Severity Scale) at all three Baseline Visits prior to undergoing surgery (20). For subjects with predominantly vocal tics (and minimal motor) causing significant problems this score requirement will be reduced to 18, similarly for subjects with predominantly motor tics (and minimal vocal) causing significant problems the required score will be 18 (38). A portion of the study team, including the surgeon and two neurologists, will determine by consensus which category the subject falls into and whether the tics are a significant problem.

6. All other aspects of the subject's care must be optimized during the preceding 6 months before admission to the study. This includes treatment for comorbid medical, neurological, and psychiatric disorders. Additionally, it includes psychological interventions for any ongoing psychosocial problems the subject may have during the preceding 6 months before study admission.

7. Subject must be ambulatory.

8. Females who are postmenopausal, physically incapable of childbearing, or practicing an acceptable method of birth control. Acceptable methods of birth control include surgical sterilization, hormonal contraceptives, or double-barrier methods (condom or diaphragm with a spermicidal agent or intrauterine device [IUD]). If practicing an acceptable method of birth control, a negative urine pregnancy test result has been obtained at baseline Visits 1 and 3.

9. Subject is determined by an independent psychiatrist with expertise in capacity assessments to have decision-making capacity to provide informed consent.

10. Subject is able to read English, understand and cooperate with study procedures, and has signed a written informed consent form prior to any study procedures.

5.3. Exclusion Criteria

1. Subject has a positive urine drug screen at any of the three Baseline Visits.

2. Subject had major surgery within three months prior to Baseline Visit 1 or has other surgery planned during the proposed study period.

3. Subject is determined by medical consultant to have medical contraindications to undergoing surgery.

4. Subject is pregnant or breast-feeding.

5. Subject has a history of alcohol or drug abuse within the past 6 months and/or dependence within the past year.

6. Subject has a medical illness/condition, and/or abnormal diagnostic finding that would interfere with the completion of the study, confound the results of the study, or pose risk to the patient.

7. Subject has an untreated or uncontrolled Axis I disorder or other major psychiatric disorder including major depression, bipolar disorder, or schizophrenia as determined by the screening psychiatrist.

8. Subject has either a current or past history of suicidal plan and/or intent.

9. Subject has a tic disorder or other movement disorder attributable to another medical, neurological, or psychiatric disorder other than Tourette Syndrome.

10. Subject has a drug-induced tic disorder.

11. Subject has significant psychosocial factors that might increase the risk of the DBS procedure or complicate recovery and outcome assessments. (Examples include – history of noncompliance with previous medical and psychosocial treatments, multiple failed medication treatments of inadequate dose or duration, a history of multiple other surgical procedures with poor outcome, unexplained medical history gaps, or pending lawsuits or other legal action.)

12. Subject has metal in the head or any other type of implanted stimulator (i.e. cardiac pacemaker, deep brain stimulator for a different disease, spinal cord stimulator, cochlear implant, vagus nerve stimulator, etc.).

13. Subject has participated in another investigational drug trial or therapeutic trial within 30 days of Baseline Visit 1.

14. Subject has a diagnosis of intellectual disability with documented IQ<70.

15. Subject has a neurological condition, or a history of traumatic brain injury associated with loss of consciousness of > 1 hour and/or intracranial/epidural/subdural bleeding.

6. Drugs/ Substances/ Devices

Deep Brain Stimulation Therapy (DBS) delivers electrical stimulation to areas in the brain and has been approved to help control symptoms of various movement disorders (e.g. DBS of the subthalamic nucleus in

Parkinson's disease or DBS of the thalamus in essential tremor). The surgery for PD or essential tremor patients places electrodes (plastic and metal tubes of diameter 1/16-1/32 inch) in the subthalamic nucleus or ventral intermediate nucleus of the thalamus as identified by radiologic and physiologic criteria. Once the electrodes are implanted, they will be connected to an implanted stimulator plus pulse generator (IPG). The implantable pulse generator powers the electrode. The DBS electrodes, and stimulator pulse generator (one device) are called the System. DBS is not approved for use in Tourette Syndrome. However, the use of DBS has expanded to psychiatric diseases such as treatment-resistant depression and obsessive-compulsive disorder and is currently in early phase studies in other psychiatric disorders.

The primary implantable pulse generators used in this study are derived from the Medtronic Activa deep brain stimulation system, including the PC and RC 2-channel pulse generator models. As of April 1st, 2021, Medtronic will no longer provide the Activa PC for new or replacement implantations, but will support the Percept model implantable pulse generator. New implantations for this protocol in Tourette Syndrome will also only utilize the Percept model pulse generator.

7. Study Statistics

7.1. Primary Outcome Variable – Efficacy

The primary outcome variable will be the clinical response of tic symptoms to treatment, as defined by a 40% decrease from baseline in the Yale Global Tic Severity Scale. The cutoff of 40% was chosen to be consistent with the lower end of improvements observed in previous drug trials treating TS when compared to placebo (1). An improvement in at least one the three participants is a potential indicator that DBS implantation in treatment refractory Tourette Syndrome can be pursued further.

7.2. Secondary Outcome Variables – Efficacy

Secondary efficacy variables will include mean change from baseline scores of the YBOCS and WHO Adult ADHD Self-Report Scale inventories. Response as defined by a 20% decrease from baseline will also be calculated.

7.3. Safety Analysis

Safety will be assessed by the recording the frequency and severity of adverse events, defined as any new symptom or worsening of a pre-existing symptom. Adverse events reported on case report forms will be mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percent of subjects reporting each event will be summarized during the study period. Incidence of adverse events by maximum reported severity will also be tabulated. Serious adverse events and adverse events leading to discontinuation will be displayed.

7.4. Statistical Plan

This is a pilot study looking at using DBS in 10 Tourette Syndrome patients.

7.5. Early Stopping Rules

DBS will be discontinued if the subject experiences a worsening of his tic or other Tourette symptoms (or OCD, ADHD, depression, or anxiety symptoms) without returning to baseline (prior to DBS implantation) within 4 weeks from the worsening of the symptoms. DBS will be discontinued if subjects experience suicidal ideation or mania that does not improve with turning off the stimulator. DBS will also be discontinued if neurologic symptoms including muscle contractions, flashing lights, electric jolting sensations, increase in dyskinesias will not improve with stimulator setting change and they are severe enough to interfere with patient daily functioning. Finally DBS will be discontinued if subjects are unable to tolerate the stimulator for any reason not foreseen by the investigator and that clearly interferes with subject's functioning.

Subjects will also be removed from the study for any significant adverse events that jeopardize patient safety. This includes any events related to the surgical procedure or subsequent DBS stimulation therapy. The entire study of 10 subjects will be stopped should the number of subjects meeting the above **Early Stopping Rules** reaches 3 at any point in the study. If this occurs before the full subject recruitment goal has been met, no further subjects will be recruited.

7.6. **Data Sharing**

De-identified information regarding the implanted subjects will be shared with the TAA International DBS Database (IRB#201600091) at the University of Florida Center for Movement Disorders & Neurorestoration in Gainesville, FL. Elements to be transferred, where available, include:
Year of birth;
Gender;
Ethnicity;
Age at onset;
Age at diagnosis;
Age at surgery;
Pre-operative psychiatric comorbidities;
Pre-operative medications;
Pre-operative outcome measures/severity ratings [depending on what you use, be specific here];
Surgical target & hardware implanted;
Post-operative lead location measurements;
Post-operative programming parameters;
Post-operative outcome measures/severity ratings [again, specific];
Information regarding Adverse Events (start date, end date, relevant medications and diagnostic findings, narrative summaries, etc.)

The information is being gathered in order to permit broader analysis of the trends and outcomes in DBS surgery for TS than is possible at any one institution. Collaborators to the project are registered with the UF Identity Management system and given secure 'Gatorlink' credentials which can be used to access the database for entry and review of data. The de-identified data, in an organized spreadsheet, may also be sent to the study team at the University of Florida for entry into the database.

8. Risks

8.1. Medical risks

The medical risks of this study are the same as for other types of DBS surgery: bleeding, stroke, paralysis, infection, and death. The risks of anesthesia include heart attack, arrythmia or allergic reaction. The risks associated with the System are failure of therapy, neurologic symptoms including muscle contractions, electric jolting sensations, speech alterations, and altered ability to think or remember. Most of these can be reversed by adjusting the stimulator. To be included in this protocol patients/their parents must sign a Hospital consent form listing these risks. Additionally this form will state that the FDA has not approved this indication for the use of the System, which is itself FDA approved. There may be side effects and discomforts that are not yet known.

8.2. Adverse events associated with DBS

There is a small but serious risk of intracranial hemorrhage with implantation of the lead, which is substantially lower than the risk associated with ablative procedures such as pallidotomy (39). A review of the literature estimated that rates of symptomatic and asymptomatic intracranial hemorrhage in DBS of the STN are ~ 2% and 1.2%, respectively (40) and infection occurs in ~ 2% of cases. The mortality rate for the procedure is below 1% and is mostly due to intracranial hemorrhage. One large multicenter report of 1,183 patients who received DBS reported a 30-day postoperative mortality rate of 0.4% (41). Other reported complications included hardware problems such as generator failure or lead breakage (6%—9/149), stimulation-induced side effects (3%—4/149), and behavioral changes (1%—2/149) (42). The infection rate is no higher than for other surgical procedures, but if it does occur, it can necessitate the explantation of the device or generator (43).

Deep brain stimulation can cause brain tissue damage if the stimulation charge density exceeds 30 $\mu C/cm^2$/phase. The stimulation settings used in this study (similar to the current FDA approved DBS indications) will not exceed this limit.

The accuracy of electrode placement in DBS implantation surgery is optimized by using a series of overlapping and independent targeting methods. First, the patients wear a rigid stereotactic head frame (Leksell Frame, Elekta AB, Stockholm) which defines a Cartesian stereotactic space within the fiducial volume of the frame. Patients undergo MRI head imaging (or CT imaging if there are MRI contraindications) immediately after frame placement. It is also possible to use post-frame placement CT images fused to a previously obtained MRI head series for targeting minimizing the time spent wearing the stereotactic frame during the imaging process. Stereotactic frames are fitted with fiducial markers which appear bright in standard MRI T1- or T2-weighted images, or radiopaque markers for CT scans. There are several commercially available software packages which then convert screen pixel location defined by a cursor to the Cartesian space defined by the frame (Leksell SurgiPlan, Elekta AB, Stockholm; FrameLink, Medtronic, Minneapolis). Either direct targeting of the target structure can be performed by placing the cursor over the targeted structure, or the target structure can be inferred by the relatively fixed positions of atlas-based brain landmarks such as the well-known anterior commissure – posterior commissure system. The final coordinates for the target are then set on the appropriate x, y, and z graduated markings built into the frame system.

As a check on the imaging derived target location, microelectrode recording will be performed, as in the treatment of movement disorders where the targets include the subthalamic nucleus, the globus pallidus interna, and subnuclei of the thalamus. These structures have well-known and well-defined extracellular electrophysiologic firing patterns. The surgeon will use these firing patterns to help in verifying the electrode tip location, and to help in deciding where the tip should be moved if the firing patterns are consistently different from the known target firing patterns. Additionally, stimulation currents are used

(passing through the microelectrode guide tube) and can aid in defining possible side effects due to the stimulation currents from the final implanted electrode and can guide the movement of the electrode on subsequent passes to optimize placement in the thalamus while minimizing sensory or motor side effects due to the applied stimulation.

Standard risk reduction efforts in the operating room will be implemented as in other surgical procedures. The federally mandated Safety Pause will be performed before skin incision, which includes patient verification, surgical site verification, and a team discussion of unusual case aspects. The equipment packs will be opened on the sterile field before skin incision to check for any sterility or operational issues. Intravenous antibiotics will be administered to the patient within 30 minutes of skin incision, followed by two postoperative doses for the stage of the procedure involving intracranial electrode placement. A single preoperative dose of antibiotics will be given within 30 minutes of skin incision for the implantation of the implantable pulse generator. Electrode placement will additionally be checked in the operating room using a fluoroscopic unit which has been draped into the field. A lateral fluoroscopic image will include the electrode tips and their location with respect to the frame fiducials showing the center of the frame coordinate system. Postoperative imaging will include an immediate head CT examination as the patient leaves the operating room, and a delayed MRI of the brain. Both scans are to verify final electrode location and to look for any perioperative complications (i.e. hemorrhage, lead migration / breakage).

8.3. Plans for reporting unanticipated problems or study deviations

The PI of the study will be responsible for reporting all adverse events to the IRB. Serious adverse events deemed to be associated with the study device (adverse device effect) will be reported to the IRB within 7 days. Any deaths will be reported within 24 hours.

Adverse device effects (ADEs) in this study are identified and categorized in a way patterned after the Code of Federal Regulations (21 CFR 812.3):

a. An adverse device effect (ADE) is any serious adverse effect on the health and/or safety or any life threatening problem or death caused by, or associated with the device and/or stimulation therapy if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3):

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

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

i. A preexisting medical condition
ii. A medication

Furthermore, AEs will be further categorized and identified as Surgical/Procedure Related, Device Related, Therapy Related, Disorder Related, or Other/Procedure Related. Examples of each of these categories may include (but are not limited to):

Surgical/Procedure Related – surgical site infection, perioperative mental status changes, perioperative confusional state or delirium, perioperative syncope, perioperative adverse drug reactions, cerebral hemorrhage, perioperative stroke, perioperative pulmonary embolism, etc.

Device Related – Lead fracture, lead migration, implantable pulse generator failure or abnormal function, skin erosion or delayed infection, etc.

Therapy Related – gait disturbance or balance disorder, confusional state or delirium not attributable to medication or other health problem, mental status changes not attributable to medication or other health problem, problems with speech, depression and suicidal ideation, induced dyskinesias, etc.

Other/Procedure Related – Falls or balance disorder, pneumonia, syncope, confusional state or delirium, mental status changes, depression and suicidal ideation, adverse drug reactions, etc.

Disorder Related – falls or balance disorder, gait disturbance, depression and suicidal ideation, etc.

The severity of AEs will be classified after the scheme of Follett et al. (44) – as serious adverse events (an event that poses substantial risk to the patient's health and is likely to require medical intervention or close follow-up), and moderate or severe adverse events (an event that may interfere with normal activity and lead to the consideration of medical intervention or close follow-up.

8.4. Disclosing reportable findings and parental notification

The following set of ground rules to use in terms of informing parents of the 15-17 year age range study subjects about concerning results from the psychiatric assessments, or revelations of high risk behaviors will be implemented in this study:

We assess for suicidal thoughts at multiple visits in the protocol (using the CSSS), if we are concerned about the child based on the answers to this assessment, the parents will be informed and a discussion will be had with the parents and the child to gain more information. Additional treatment providers will be contacted (child psychiatry) if the child does appear to be at risk of hurting himself/herself.

Assessments during the study visits also include questions concerning drug and alcohol use. This information will be kept private and not disclosed to the parent or authorities unless there are serious concerns about the child's safety or the safety of others. If the child provides study staff with information indicating that imminent harm to self and/or others is possible as a result of drug and alcohol use (for example, substance use while driving, binge behaviors, risky and unprotected sexual contact under the influence, etc.), then the parents will be informed.

Any information regarding child abuse, reportable communicable diseases, and any possible threats of harm to the subject or others (for example suicide and homicide) will be disclosed to the parent(s) or the appropriate authorities depending on the circumstance.

8.5. Legal risks (e.g. associated with breach of confidentiality)
N/A

8.6. Financial risks to the participants
There are no financial risks to the study's participants

9. Benefits

As this is a pilot study, the probable benefits for the participant and for society are unknown. However, if DBS of the thalamic Ce-Spv-Voi complex results in improvement in tic frequency or severity, this could result in an improvement in the quality of life of patients with treatment-refractory Tourette Syndrome. These patients face long term social stigma and difficulties with education and job attainment. A new therapeutic treatment option could result in improvements in social integration. Additionally, information about stimulation of the brain in patients with TS along with microelectrode recordings obtained during the surgical placement procedure may improve treatment for future patients.

10. Payment and Remuneration

No payment is scheduled for the patient's participation in this study.

11. Costs

Portions of this research study are supplied free of charge to the patient. These include the baseline physical examination, the baseline EKG, the baseline clinical laboratory tests, the urine toxicology screen, and the urine pregnancy test if needed. The subject and/or their health insurer is responsible for all other parts of the study as identified in the Johns Hopkins Prospective Reimbursement Analysis as performed by the Clinical Research Support Services Office. The Centers for Medicare and Medicaid Services has given us permission to bill Medicare Part A and Part B for these portions of the study.

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