SUMMARY OF SAFETY AND PROBABLE BENEFIT

Summary of Safety and Probable Benefit

I. General Information

Device Generic Name:	Implantable Multi-Programmable Quadripolar Deep Brain Stimulation System
Device Trade Name:	Medtronic Reclaim™ DBS Therapy for OCD
Applicant's Name/Address:	Medtronic, Inc. 710 Medtronic Parkway NE Minneapolis, MN 55432
Humanitarian Device Exemption (HDE) Number:	H050003
Humanitarian Use Designation (HUD)	05-0149
Date of Humanitarian Use Device Designation:	March 21, 2005
Date of Panel Recommendation:	None
Date of Good Manufacturing Practices Inspection:	December 14, 2007 and July 25, 2008
Date of Notice of Approval to Applicant:	February 19, 2009

II. Indications for Use

The Medtronic Reclaim DBS Therapy is indicated for bilateral stimulation of the anterior limb of the internal capsule, AIC, as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant obsessive compulsive disorder (OCD) in adult patients who have failed at least three selective serotonin reuptake inhibitors (SSRIs).

III. Contraindications

Implantation of a brain stimulation system for treatment of OCD is contraindicated for:

- Patients exposed to diathermy. Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (all now referred to as diathermy) on patients implanted with a neurostimulation system. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death. Diathermy is further prohibited because it can also damage the neurostimulation system components resulting in loss of therapy, requiring additional surgery for system explantation and

replacement. Injury or damage can occur during diathermy treatment whether the neurostimulation system is turned "on" or "off."

- Patients exposed to Magnetic Resonance Imaging (MRI). Performing MRI in the areas of or near the implanted DBS system components can cause tissue lesions from component heating, especially at the lead electrodes, resulting in serious and permanent injury including coma, paralysis or death.
- Patients who are unable to properly operate the brain stimulator.

IV. Warnings and Precautions

Refer to the Model 3391 DBS for OCD lead labeling for a complete list of warnings and precautions.

Electroconvulsive Therapy (ECT) – The safety of ECT in patients who have an implanted deep brain stimulation (DBS) system has not been established. Induced electrical currents may interfere with the intended stimulation or damage the neurostimulation system components resulting in loss of therapeutic effect, clinically significant undesirable stimulation effects, additional surgery for system explantation and replacement, or neurological injury.

Avoid Excessive Stimulation – There is a potential risk of brain tissue damage when stimulation parameters are set to high amplitudes and wide pulse widths. Parameter values that may be excessively high should only be programmed with due consideration of the warnings concerning charge density (all neurostimulator models) and charge imbalance (Model 7426 neurostimulator) described in "Programming the Neurostimulator" on page 71. The programmer displays a warning that displays when parameter values are chosen that may exceed the charge density limit (WARNING: CHARGE DENSITY MAY BE HIGH ENOUGH TO CAUSE TISSUE DAMAGE). If you are using a Model 3391 lead and having difficulty programming effective stimulation without receiving this warning, please see"Programming the Neurostimulator" on page 70 for more information on calculating safe stimulation parameters.

Somatic Psychiatric Therapies – The safety of somatic psychiatric therapies using equipment that generates electromagnetic interference (eg, transcranial magnetic stimulation, and vagus nerve stimulation) has not been established in patients who have an implanted deep brain stimulation (DBS) system.

Inadvertent Programming – If more than one neurostimulator is implanted, then the potential for unintentional programming changes to the other neurostimulator exists. If two neurostimulators are implanted, then they must be implanted at least 8 inches apart to minimize interference. Verify final programmed parameters by reviewing both devices at the conclusion of any programming session.

V. Device Description

The Reclaim™ DBS Therapy for OCD uses implantable neurostimulators, extensions, and leads to deliver electrical stimulation to the anterior limb of the internal capsule (AIC) of the brain. The device consists of a lead, a neurostimulator, and an extension that connects the lead to the neurostimulator. The Medtronic Model 3391 DBS Lead has been designed to stimulate the AIC. The Model 3391 DBS Lead for OCD is used with the previously approved Model 7426 Soletra or Model 7428 Kinetra Neurostimulator, Model 7482 Extension, and related DBS therapy accessories.

A description of each of the system components follows.

Model 3391 DBS™ Lead:
The DBS lead consists of a polyurethane protective sheath with four platinum/iridium electrodes near the tip of each lead that deliver stimulation to the target site. The leads are stereotactically introduced into the target and fixed at the skull with a burr hole cap and ring.

Model 7426 Soletra and Model 7428 Kinetra Neurostimulators:
The neurostimulator is implanted subcutaneously in the subclavicular or upper abdominal region. It is comprised of a battery and integrated circuits that are hermetically sealed within an oval-shaped titanium enclosure. The neurostimulator delivers electrical stimulation pulses with a variety of parameters, modes, and polarities. The electrical pulses are carried from the neurostimulator to an implanted deep brain stimulation lead by means of a lead extension. The stimulation parameters can be non-invasively adjusted to optimize control of the symptoms of OCD and minimize side effects using an external programmer. The neurostimulator is battery powered, and when the battery is depleted, it can be replaced surgically. The frequency of replacement is dependent upon the amount of time the neurostimulator is used each day and the stimulation parameters used.

Model 7482 Extension:
The extension is a set of wires within silicone tubing that connects the lead to the neurostimulator, providing an electrical path that allows stimulation to be delivered to the target site. The extension is subcutaneously passed from the scalp area, where it connects to the lead, through to the subclavicular area or upper abdominal region, where it connects to the neurostimulator.

Model 8840 N'Vision Clinician Programmer:
The Model 8840 N'Vision Programmer is used to program the neurostimulator via radio-frequency telemetry.

Model 8870 Application Card:
The Model 8870 Application Card is a plug-in card designed to control the specific functions of the Model 8840 N'Vision Clinician Programmer. It contains the necessary software to program the neurostimulator.

Model 7436 (Soletra) Access Review Therapy Controller and 7438 (Kinetra) Therapy Controller:
The therapy controller is designed for use by a patient or caregiver. Using the therapy controller, the patient or caregiver can turn therapy on or off, check whether the therapy is on or off, and check the condition of the neurostimulator's battery. The Model 7438

(Kinetra) Therapy Controller also allows adjustment of amplitude, pulse width, and rate within physician-prescribed limits by patients with implanted Kinetra neurostimulators.

VI. Alternative Practices and Procedures

There are two primary approaches to the treatment of OCD, pharmacotherapy and cognitive behavior therapy (CBT). Lack of therapeutic success with one approach leads to trials of the alternative approach or a combination of the two. A rarely used third therapy approach, appropriate for only the most severely afflicted and treatment resistant patients, is neurosurgical ablation of certain brain regions involved in mood and anxiety. The neurosurgical ablation procedures are irreversible in nature, and involve the destruction of specific volumes of brain tissue through various controlled means. Surgical procedures include cingulotomy, subcaudate tractotomy, limbic leucotomy which is a combination of the first two procedures and capsulotomy.

DBS therapy is an alternative to neurosurgical procedures, specifically anterior capsulotomy, for patients with chronic, severe OCD which has proven resistant to primary pharmacological and/or behavior therapy options.

VII. Marketing History

Reclaim™ DBS Therapy for OCD has not been commercialized to date. The Model 3391 DBS for OCD Lead has not been commercially distributed to date.

VIII. Potential Adverse Effects

A. Categories of Adverse Effects

Adverse events reported from 26 severe, treatment-resistant OCD patients treated with DBS at four collaborating centers, three in the US, and one in Europe are summarized below. There were a total of 347 adverse events reported in 26 of the 26 patients (100%). Twenty-three (23) of these events experienced by 12 patients (42.3%) were reported as serious adverse events, including one patient death.

These adverse events which include the serious adverse events identified above are categorized as follows:

- **Surgical/Procedure-Related** – associated with surgical implantation of the DBS system,
- **Device-Related** – caused by the implanted system,
- **Therapy-Related** – caused by the electrical stimulation of the nervous system while treating the subjects symptoms,
- **Disorder-Related** – an event that might reasonably be attributed to the patients' underlying disease state, concomitant medications or treatment regimens, or other co-morbid conditions.

Table 1 summarizes the adverse events by category reported for the 26 patient cohort by the four collaborating centers.

Table 1. Adverse Events by Category

	Events	Patients
Surgical/Procedure-Related	46	14 (53.8%)
Device-Related	5	5 (19.2%)
Therapy-Related	188	23 (88.5%)
Disorder-Related	108	24 (92.3%)
Total	**347**	**26 (100.0%)**

B. Serious Adverse Events

Table 2 summarizes the serious adverse events reported for the 26 patient cohort by the four collaborating centers. There were a total of 23 serious adverse events reported in 11 subjects (42.3%). All serious adverse events, excluding one death, were resolved. As noted in Table 2, not all events were considered to be related to the device.

One death in the 26 patients at the four collaborating centers was reported. The death was identified as being related to a pre-existing condition (cancer progression) in one patient and was not considered to be related to DBS therapy.

An additional death in a patient with OCD receiving DBS therapy was reported in the published literature. Abelson et al. (2005) reported one suicide in their study of four patients, and concluded that the suicide was not related to the DBS therapy. This death is not included in the summary (Table 1) since it was not reported directly and did not occur in the primary patient cohort, i.e. different target site in the brain.

Two instances of intracranial hemorrhage due to surgery were reported. One was asymptomatic and resolved without further consequence. The second resulted in an increase in apathy, which resolved with time. One subject suffered a single tonic-clonic seizure shortly after implantation of the leads. This subject has had no further seizures. There was one report of infection, which was treated and resolved.

Seven events of increased depression or suicidality and three instances of increased or fluctuating OCD symptoms were reported. Some of these reports occurred during periods when DBS therapy was actively on and several reports were associated with discontinuation of stimulation due to study design or battery depletion. One occurrence of hypomania and one of violent behavior requiring medical intervention were reported.

One subject was involved in a car accident and an incident of domestic disturbance. One occurrence of hypomania and one of violent behavior requiring medical intervention were reported. Two subjects had a broken lead or extension, which required surgical replacement. One compression fracture and one kidney infection occurred in subjects during the study period.

Table 2 summarizes the serious adverse events reported for the 26 patient cohort by the four collaborating centers.

Table 2. Serious Adverse Events

Type of Event	Events	Patients	Category
Suicidality/Increased Depression	7	5 (19.2%)	Disorder (3), Therapy (4)
Increased OCD/Fluctuating Results	3	3 (11.5%)	Therapy
Hemorrhage, Intracranial	2	2 (7.7%)	Surgical
Lead/Extension Failure	2	2 (7.7%)	Device
Aggression/Violent Behavior	1	1 (3.8%)	Disorder
Car Accident	1	1 (3.8%)	Disorder
Compression Fracture	1	1 (3.8%)	Disorder
Death	1	1 (3.8%)	Cancer Progression
Domestic Problems/Irritability	1	1 (3.8%)	Therapy
Hypomania	1	1 (3.8%)	Therapy
Infection	1	1 (3.8%)	Surgical
Pyelonephritis	1	1 (3.8%)	Disorder
Seizure, Post-operative	1	1 (3.8%)	Surgical
Total	**23**	**11 (42.3%)**	

C. Reported Adverse Events

Table 3 summarizes all adverse events reported for the 26 patient cohort by the four collaborating centers. Table 3 includes the Serious Adverse Events previously noted above. Again, not all events were considered related to the device.

Table 3. Reported Adverse Events

	Events	Patients
Surgical/Procedure-Related	**46**	**14 (53.8%)**
Pain or Discomfort at Incision / Implant Sites	21	12 (46.2%)
General Post-op Discomfort	5	3 (11.5%)
GI Symptoms Post-op	5	2 (7.7%)
Hemorrhage	2	2 (7.7%)
Infection	2	1 (3.8%)
Apathy	1	1 (3.8%)
Contact dermatitis	1	1 (3.8%)
Headaches	1	1 (3.8%)
Seizure	1	1 (3.8%)
Other	3	3 (11.5%)
Device-Related	**5**	**5 (19.2%)**
Broken lead or extension	2	2 (7.7%)

	Events	Patients
Erosion of system components through skin	1	1 (3.8%)
Sensation of shock during programming	1	1 (3.8%)
Switched off	1	1 (3.8%)
Therapy-Related	**188**	**23 (88.5%)**
Increased OCD symptoms	22	12 (46.2%)
Increased anxiety	19	11 (42.3%)
Insomnia	18	12 (46.2%)
Increased depression/suicidality	13	10 (38.5%)
Cognitive disturbance (clouding)	11	8 (30.8%)
Induced muscle contraction	10	7 (26.9%)
Hypomania	9	9 (34.6%)
Restlessness	8	3 (11.5%)
Stimulation induced parasthesia	7	6 (23.1%)
Induced sensation of taste/smell	7	5 (19.2%)
Irritability	6	5 (19.2%)
Weight gain	6	6 (23.1%)
Increased fatigue	5	4 (15.4%)
Upper respiratory infection	5	4 (15.4%)
Headaches	4	4 (15.4%)
Increased tics	4	1 (3.8%)
Dizziness	3	2 (7.7%)
GI Upset	3	3 (11.5%)
Decreased appetite	2	1 (3.8%)
Dry mouth	2	2 (7.7%)
Dysarthria	2	1 (3.8%)
Itching at surgical site(s)	2	2 (7.7%)
Nausea	2	2 (7.7%)
Sedation	2	2 (7.7%)
Urinary tract disturbance	2	1 (3.8%)
Weight loss	2	2 (7.7%)
Acne	1	1 (3.8%)
Cervical neck pain	1	1 (3.8%)
Congestion	1	1 (3.8%)
Edema	1	1 (3.8%)
IPG depletion	1	1 (3.8%)
Increased sleeping	1	1 (3.8%)
Induced sensation, IPG pocket	1	1 (3.8%)
Intermittent shocks/jolts	1	1 (3.8%)
Left kidney area pain	1	1 (3.8%)
Lethargy	1	1 (3.8%)
Sore throat	1	1 (3.8%)

	Events	Patients
Unequal pupils	1	1 (3.8%)
Disorder-Related	**108**	**24 (92.3%)**
Changes in mood, anxiety, or anger	16	10 (38.5%)
Gastrointestinal disturbances	11	9 (34.6%)
Insomnia	10	6 (23.1%)
Sedation	4	2 (7.7%)
Urinary tract disturbance	3	2 (7.7%)
Back pain	2	2 (7.7%)
Contact dermatitis	2	1 (3.8%)
Cough	2	1 (3.8%)
Disequilibrium	2	2 (7.7%)
Diverticulosis	2	1 (3.8%)
Restless limbs	2	2 (7.7%)
Tremor	2	2 (7.7%)
Abnormal blood sugar	1	1 (3.8%)
Adenomyosis	1	1 (3.8%)
Aggression/violent behavior	1	1 (3.8%)
Ankle fracture	1	1 (3.8%)
Attention/cognitive deficits	1	1 (3.8%)
Car accident	1	1 (3.8%)
Chronic cough	1	1 (3.8%)
Compression fracture	1	1 (3.8%)
Depersonalization	1	1 (3.8%)
Edema	1	1 (3.8%)
Facial numbness	1	1 (3.8%)
Fall	1	1 (3.8%)
Fatigue	1	1 (3.8%)
Fever	1	1 (3.8%)
Flu	1	1 (3.8%)
General sense of not feeling well	1	1 (3.8%)
Hair twirling	1	1 (3.8%)
Hematoma, subcutaneous (eye)	1	1 (3.8%)
Increased OCD symptoms	1	1 (3.8%)
Increased sexual interest	1	1 (3.8%)
Itching above eye	1	1 (3.8%)
Memory worsening	1	1 (3.8%)
Muscle cramps in neck	1	1 (3.8%)
Muscle rigidity	1	1 (3.8%)
Numbness in arm after coughing	1	1 (3.8%)
Nystagmus	1	1 (3.8%)
Oral paresthesia	1	1 (3.8%)
Paresis/numbness in hand	1	1 (3.8%)

	Events	Patients
Pneumonia	1	1 (3.8%)
Shortness of breath	1	1 (3.8%)
Sinus inflammation	1	1 (3.8%)
Social withdrawal	1	1 (3.8%)
Stomach pains	1	1 (3.8%)
Tennis elbow	1	1 (3.8%)
Twitching of nose	1	1 (3.8%)
Weight gain	1	1 (3.8%)
Weight loss	1	1 (3.8%)
Total	**347**	**26 (100.0%)**

D. Potential Adverse Effects

A summary of the adverse events that occurred in the prospective clinical trial used to support approval for the indications of Parkinson's disease and essential tremor is provided. This summary is limited to adverse events that would be expected with DBS in general, since the target of stimulation is different for those previously approved indications and the current OCD indication.

Safety data for the Parkinson's disease and essential tremor indication was provided for 160 patients. The rate of intracranial hemorrhage was 7.5%, device-related infection (10.6%); paresis/asthenia(10.0%); and hemiplegia/hemiparesis (8.1%). Stimulation related adverse events included sensory impairment, cognitive, speech/language, and neuropsychological changes. Device related adverse events included intermittent continuity, electromagnetic interference, lead breakage, infection, erosion, shock/jolt, dislodged, migration, normal battery failure, malfunction, current leak, wire breakage, kinked electrode, electrode problem, positioning difficulties, impedance low.

One patient experienced manic symptoms (manic reaction) and attention and cognitive deficits (thinking abnormal) concurrent with exposure to an electronic article surveillance (electromagnetic interference) device.

IX. Preclinical Studies

A. Previous Preclinical Studies

With the exception of the Model 3391 lead, all components of the Medtronic Deep Brain Stimulation for Obsessive Compulsive Disorder Therapy have been commercially approved as components of the Medtronic Activa® Tremor Control System (PMA P960009, PMA P960009/S3, PMA P960009/S9, and PMA P960009/S10) and Medtronic Activa Parkinson's Control Therapy (P960009/S7).

Therefore, the preclinical testing of these components provided in prior Medtronic Activa Tremor Control System PMAs is applicable to the Medtronic Deep Brain Stimulation for Obsessive Compulsive Disorder Therapy.

B. Additional Preclinical Studies

The Model 3391 DBS Lead represents minor design modifications from the approved Model 3387 DBS Lead. The modifications from the Model 3387 lead consist of increasing the length of each of the four electrodes from 1.5 mm to 3 mm and increasing the separation between electrodes from 1.5 mm to 4 mm. This configuration allows stimulation energy to be delivered throughout a cylinder of brain tissue of height 24 mm versus a cylinder of height 10.5 mm with the Model 3387 lead. Other than changes to electrode size and spacing, the Model 3391 lead uses the same lead design, materials of construction, manufacturing and sterilization processes, and packaging as the Model 3387 lead. Therefore, many of the preclinical testing was not required to be repeated for the Model 3391 lead.

The Medtronic Model 3391 DBS for OCD lead has undergone additional pre-clinical testing summarized below:

C. Design Verification Testing

Functional testing was performed using samples manufactured using designs, materials and processes representative of that planned for use for commercial manufacturing. Sample sizes were selected to meet a minimum 90% confidence at 90% reliability. The functional testing performed on the Model 3391 lead is summarized in Table 5.

Table 4. Design Verification Testing Summary

Test	Purpose	Acceptance Criteria	Result
DC Resistance	Compliance with electrical connection/conduction specifications.	DC resistance of each conductor: ≤ 200 Ω	All 22 leads met the acceptance criteria.
Initial Visual and Functional	Verify that leads meet visual and functional specifications after environmental exposures.	Samples shall be defect free, and meet physical specifications.	All 22 leads met the acceptance criteria.
10 Day Soak	Verify no adverse effects of immersion of lead in normal saline.	No adverse impact to functional and performance integrity.	All 22 leads subjected passed subsequent functional tests.
Dielectric Strength	Compliance with electrical connection/conduction specifications.	There should be a maximum of 2 milliamps leakage current in conduction pathways.	All 22 leads met the acceptance criteria.
AC Cross Circuit (Leakage) Impedance	Compliance with electrical connection/conduction specifications.	≥ 2 KΩ impedance between lead and extension. ≥ 5 KΩ impedance between each circuit and reference electrode.	Qualified by design similarity to previously tested product.
Separation Strength/Composite Pull	Compliance to design specification for force required to break electrical connections.	All current carrying connections have a separation force ≥ 0.75 lb	All 22 leads met the acceptance criteria.
Lead Body Flex	Compliance to design specifications for lead flex life.	No lead conductor failures through 100,000 flex cycles (Weibull B50).	All 22 leads met the acceptance criteria
Lead Implant	Verify ability to maintain a linear path during lead placement procedure.	Lead shall transverse 2.5 cm with a maximum deflection of 1 mm.	All 22 leads met the acceptance criteria.
Lead Column Buckling Stiffness	Compliance to design requirement for lead electrode end column stiffness.	Column stiffness shall be > 6 lb/in with stylet inserted.	All 22 leads met the acceptance criteria.
Contact Alignment/Crush (Torque)	Verify that the lead is fully functional after connection to extension with the torque wrench.	All circuits must align and maintain electrical continuity after insertion and tightening of setscrews to 3.5 -4.0 in-ozs.	All 22 leads met the acceptance criteria.
Lead/Extension Insertion/Withdrawal	Compliance to the design requirement for insertion and withdrawal force for lead and extension interface.	Electrical and mechanical functionality maintained after five insertion-withdrawal cycles. Insertion force ≤1.5 lbs, withdrawal force ≤ 1.0 lb.	Qualified by design similarity to previously tested product.
Lead Body Bending Stiffness	Compliance to the design requirement for lead body stiffness.	Bending stiffness ≤ 1.2 lbf	All 22 leads met the acceptance criteria
Lead Body Dynamic Crush Strength	Compliance to design requirements for lead body crush strength.	No functional damage following exposure to a minimum of 4 lbs compression force applied directly to the lead body.	All 22 leads met the acceptance criteria.

D. Packaging Validation

Functional testing performed demonstrated that the packaging assembly will protect the device and accessories from damage during storage and distribution. Test samples contained a Model 3391 lead, accessories and labeling/literature representative of that planned for use for commercial distribution. Each package was subjected to five (5) 100% ETO sterilization cycles and then exposed to environments the product may see during distribution and storage, including temperature and humidity extremes, two series of drop tests before and after package compression and vibration exposures. Visual inspection, dye penetration and ink smear tests of the 22 packages tested demonstrated compliance to design specifications.

E. Shelf Life

The minor changes in the Model 3391 lead design from currently approved DBS leads do not impact the shelf life of the sterile packaged DBS leads. The packaging system and sterilization process are the same. Therefore, the shelf life will be the same as that qualified for other DBS leads; four years from the date of sterilization.

F. Biocompatibility

The Model 3391 lead uses the same materials as the currently marketed Models 3387 and 3391 leads. A biological assessment of the materials used in the Model 3391 lead with potential for body tissue/fluid contact confirmed compliance with ISO 10993-1 for biological effect for use in this application.

G. EMI/EMC/MRI

The Model 3391 DBS Lead represents minor design modifications from the approved Model 3387 DBS Lead. The design modifications are limited to increased electrode size and spacing. Assessment of the designs indicated that the Model 3391 lead will have equivalent EMI/EMC performance compared to the approved Models 3387 and 3389 leads.

Due to the potential for severe adverse effects when DBS systems are exposed to MRI scans, MRI use is contraindicated for patients with DBS systems using the Model 3391 lead.

H. Animal Testing

Due to the extent of similarity of the Model 3391 lead to currently approved DBS leads in regards to design, materials of construction, handling characteristics, and implant procedure no additional animal testing was performed.

X. Clinical Studies

A. Overview of Clinical Data

The clinical data was collected prospectively at each of the four clinical sites. All centers studied patients with treatment-resistant OCD. Common inclusion criteria included:

- Treatment refractory OCD
- Moderate to severe OCD severity based on YBOCS
- Functional impairment due to OCD

- Disease duration at least 5 years (except UM)
- Adult age

Common patient exclusions include:

- Surgical contra-indications to DBS
- Abnormalities on MRI
- Pregnancy, or women of childbearing potential not using effective contraception
- Psychotic disorder
- Current or unstably remitted substance abuse
- Severe personality disorders
- Body dysmorphic disorder

All patients received stimulation to the anterior limb of the internal capsule with the Medtronic DBS system. Average stimulation parameters were voltage (7.7 μA), pulse width (262 μSec) and frequency (110 Hz.) All protocols used the Yale Brown Obsessive Compulsive Scale (YBOCS), a validated 10 item clinician administered assessment of OCD symptoms, the Hamilton Depression Scale (HAM-D) to assess depression, and the Clinical Global Impression (CGI) Scale to assess change in general patient status. Assessments were performed at baseline, 6 and 12 months and then yearly.

B. Patient Demographics

Results from 26 severe, treatment-resistant OCD patients treated with DBS at four collaborating centers, three in the US, and one in Europe are summarized below. All patients met stringent inclusion criteria including disease severity, YBOCS >30, treatment refractory with respect to medications and cognitive behavioral therapy, and symptom duration. Patient demographics are shown in Table 6 below.

Mean age for the patient cohort at time of implant was 37 years, with approximately equal numbers of males and females (53.8%/ 46.2%). Mean duration of symptoms for these patients averaged 22 years, demonstrating the long-standing, treatment-resistant nature of the disorder in this population. All patients had been treated with multiple trials of medications, and had also undergone cognitive behavioral therapy. A majority of the patients (88%) also reported a history of co-morbid depression (major depressive disorder [MDD]) associated with their severe OCD.

Table 5. Patient Demographics

Center /Patient	Age at Implant	Impant Dur.[1] (Months)	Gender (M/F)	Age at OCD Onset	Symptom Dur. (Years)	Secondary Diagnosis (Axis I / Axis II)	History of Depression	History of CBT
Butler Hospital								
BH1	32	53.5	M	10	22	MDD (single episode), OCPD	Y	Y
BH2[2]	40	51.5	F	16	24	MDD (hypomanic episode)	Y	Y
BH3	39	49.2	M	12	27	Dysthymia	Y	Y
BH4[2]	26	40.3	F	15	11	MDD	Y	Y
BH5	32	30.8	M	10	22	MDD	Y	Y
Cleviand Clinic								
CC1[3]	59	12.0	F	19	40	None.	N	Y
CC2	35	40.5	F	12	23	MDD	Y	Y
CC3	22	38.8	M	8	14	MDD, Shizophrenic Traits	Y	Y
CC4	23	34.2	M	7	16	MDD	Y	Y
CC5	45	18.8	M	19	26	None.	N	Y
University of Florida								
FL1	32	26.9	F	24	8	MDD (single episode)	Y	Y
FL2	50	21.0	M	34	16	MDD (recurrent)	Y	Y
FL3	38	17.5	M	22	16	MDD (recurrent, in remission)	Y	Y
FL4	32	8.2	M	10	22	MDD (in remission)	Y	Y
FL5	32	3.3	F	15	17	MDD (partial remission)	Y	Y
Letivan								
LV1[4]	35	15.0	M	12	23	MDD, Histrionic, Narcissistic	Y	Y
LV2	52	85.6	F	24	28	MDD, Generalized Anxiety Disorder	Y	Y
LV3	39	70.7	F	16	23	MDD, Panic Attacks, Dependent PD.	Y	Y
LV4[4]	35	41.0	M	12	23	MDD (Past Comorbid)	Y	Y
LV5	40	44.9	F	14	26	MDD (Past)	Y	Y
LV6	37	38.8	M	16	21	MDD (Comorbid)	Y	Y
LV7	39	27.8	F	15	24	MDD (Past)	Y	Y
LV8	40	27.5	M	14	26	MDD (Comorbid), Panic Attacks	Y	Y
LV9	23	10.4	M	12	11	MDD	Y	Y
LV10	30	5.3	F	9	21	None.	N	Y
LV11	57	3.5	F	16	41	MDD	Y	Y
Mean:	**37.1**	**31.4**	**M= 53.8% F = 46.2**	**15.1**	**22.0**	.	**Yes= 88.5% No= 11.5%**	**Yes= 100% No = 0%**
Min:	22.0	3.3		7	8			
Max:	59.0	85.6		34	41			

1. Number of implant months as per 07/01/2005.
2. Stimulators turned off at 12-months post-implant.
3. This patient died in January 2003 (12-months post-implant), from pneumonia and cancer, not related to the study.
4. Number of implant months at time DBS system explanted.

C. OCD Symptoms (YBOCS)

Table 7 shows the YBOCS scores, collected over a period of up to three years, for the patients treated with DBS at these four centers. The majority of these patients remained on concurrent stable medications.

Table 6. YBOCS Scores

Patient	Pre-Stimulation		1 Month	3 Months	6 Months	12 Months	12 Months (LOCF)[4]	24 Months	36 Months
	Baseline	Post-Op							
BH1	32	28	30	28	16	15	15	24	20
BH2	34	30	27	26	25	25	25	27	30
BH3	35	35	27	26	24	26	26	25	24
BH4	34	30	21	19	27	29	29	32	30
BH5	33	33	30	19	28	26	26	24	.
CC1	38	38	28	30	31	.	31	.	.
CC2	36	35	32	29	24	30	30	20	22
CC3[1]	35	34	30	31	28	30	30	18	18
CC4[1]	33	34	26	16	9	8	8	9	12
CC5[2]	36	36	29	26	27	20	20	21	.
FL1	37	21	36	18	14	26	26	12	.
FL2	31	35	37	28	29	29	29	.	.
FL3	33	28	35	26	31	7	7	.	.
FL4	31	30	36	35	29	.	29	.	.
FL5	32	26	30	20	.	.	20	.	.
LV1	38	.	.	30	33	31	31	.	.
LV2	33	.	25	20	14	25	25	21	21
LV3	30	.	17	12	14	16	16	11	9
LV4	38	.	23	22	18	22	22	22	26
LV5[3]	34	.	30	28	26	25	25	34	32
LV6	30	.	3	24	15	12	12	1	7
LV7	35	.	10	14	9	7	7	3	.
LV8	32	.	18	8	17	14	14	13	.
LV9	31	.	24	5	8	2	2	.	.
LV10	37	.	18	1	5	.	5	.	.
LV11	36	.	13	6	.	.	6	.	.
N	26	15	25	26	24	21	26	17	12
Average	**34.0**	**31.5**	**25.4**	**21.0**	**20.9**	**20.2**	**19.8**	**18.6**	**20.9**
Median	**34.0**	**33.0**	**27.0**	**23.0**	**24.0**	**25.0**	**23.5**	**21.0**	**21.5**
S.D.	(2.5)	(4.5)	(8.5)	(9.0)	(8.5)	(9.0)	(9.5)	(9.3)	(8.3)
Average % Chg.	.	**-7.1%**	**-24.7%**	**-37.9%**	**-38.6%**	**-40.7%**	**-41.8%**	**-45.4%**	**-38.7%**
Median % Chg.	.	**-2.9%**	**-21.2%**	**-32.6%**	**-32.4%**	**-29.7%**	**-33.6%**	**-42.1%**	**-36.9%**

1. Last follow-up for patients CC3 and CC4 occurred at 33 and 32 months, respectively. For analyses, the data is reported as the 36 month time-point.

2. Last follow-up for patient CC5 was at 19 months. For analyses, the data is reported as the 24 month time-point.

3. At the time of surgery, this patient was implanted with bilateral DBS electrodes in the anterior limbs of the internal capsule, and a second set of DBS electrodes in the dorsomedial thalamus, to investigate an alternative DBS target. At 27 months, the capsular electrodes were turned off, due to lack of therapeutic response, and the electrodes in the dorsomedial thalamus were turned on. The final data point for this patient (a non-responder) at 36 months is included in the intent-to-treat analysis.

4. Last observation carried forward (LOCF) conducted for 12-month time-point. Data for 5 patients (CC1, FL4, FL5, LV10, LV11) imputed using last measured YBOCS score prior to 12-month follow-up.

At 12 months, the average YBOCS score for the group (n=21) had decreased by an average of 40.7%, with a corresponding decrease of 45.4% for the cohort followed out to 24 months (n=17). Using a last observation carried forward (LOCF) analysis for all patients, the average YBOCS reduction was 41.8% at the 12 month time point. According to the Expert Consensus Panel of OCD (March et al,1997), a full responder is considered a subject who demonstrates a 35% reduction in their YBOCS score and a partial responder is a subject with a 25% reduction in their YBOCS score. An analysis of differences in prescribed medications between DBS responders and nonresponders found that patients who responded to DBS remained stable on their prescribed psychotropic drugs (-2.8% change) between baseline and last follow-up, while patients who were nonresponders, increased their psychotropic medications (15.4% increase).

Four of the 26 patients from the 4 collaborating centers discontinued deep brain stimulation. These patients, along with the one patient death, are listed in Table 7. None of these patients were reported as a YBOCS responder (based upon the 35% response criterion) in any prior analyses.

Three of the 5 patients discontinued DBS due to lack of effectiveness. One discontinued DBS because of the inability to achieve an effective level of treatment without adverse effects (hypomania). Two of these 5 patients elected to have their DBS system explanted and proceeded to undergo a capsulotomy.

Table 7. Patient Discontinuation

Patient	Event	Time of Event (Post-implant)	Reason for Therapy Termination	DBS System Explanted	Last Follow-up (Outcome Measures)
BH3[1]	Stimulators Turned Off	12 months	No change in OCD symptoms	N	36 months
BH4[1]	Stimulators Turned Off	12 months	No change in OCD symptoms	N	36 months
CC1	Death	12 months	Cancer	N	6 months
LV1	Capsulotomy	15 months	Lack of DBS effectiveness	Y	12 months
LV4	Capsulotomy	41 months	Inability to titrate DBS to effective level (between effective therapy and hypomania)	Y	36 months

[1] Data after therapy discontinuation included in outcome measures for intent-to-treat analyses.

As seen in Figure 1, in the subgroup of patients that met at least a partial clinical response criteria (as defined by >25% reduction on the YBOCS), the magnitude of improvement was greater than for all subjects.

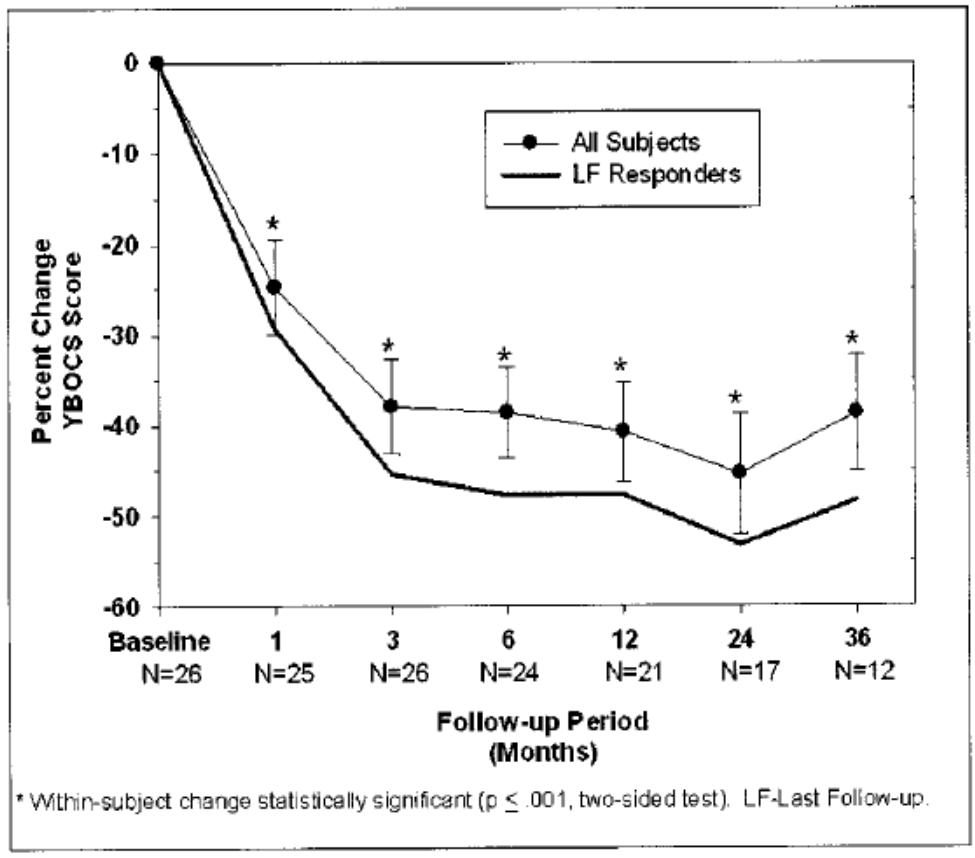

Figure 1. Average YBCOS Score following DBS Treatment

As seen in Table 8, at 12 months, 10 subjects met the 35% response criteria and an additional 4 met the 25% response criteria. A LOCF analysis at this time point, results in 13 of 26 patients meeting the 35% response level and 4 patients meeting the 25% level. Thus, at 12 months 67% of the patients met criteria for response and this level of response was sustained through the last follow-up visit.

Table 8. Responder Rates

		Non-Responders	Partial Responders	Full Responders	Full & Partial Responders
Time	No. of Patients	0 to < 25% Reduction	≥ 25% & < 35% Reduction	≥ 35% Reduction	> 25% Reduction
6 Months	24	9 (37.5%) [18.8%, 59.4%]	4 (16.7%) [4.7%, 37.4%]	11 (45.8%) [25.6%, 67.2%]	15 (62.5%) [40.6%, 81.2%]
12 Months	21	7 (33.3%) [14.6%, 57.0%]	4 (19.0%) [5.4%, 41.9%]	10 (47.6%) [25.7%, 70.2%]	14 (67.7%) [43.0%, 85.4%]
12 Months (LOCF)[a]	26	9 (34.9%) [17.2%, 55.7%]	4 (15.4%) [4.4%, 34.9%]	13 (50.0%) [29.9%, 70.1%]	17 (65.4%) [44.3%, 82.8%]
Last Follow-up	26	7 (26.9%) [11.6%, 47.8%]	3 (11.5%) [2.4%, 30.2%]	16 (61.5%) [40.6%, 79.8%]	19 (73.1%) [52.2%, 88.4%]

[a] Last observation carried forward (LOCF) conducted for 12-month time point. Data for 5 patients (CC1, FL4, FL5, LV10, LV11) imputed using last measured YBOCS score prior to 12-month follow-up.

The Expert Consensus Panel for Obsessive Compulsive Disorder (1997) has defined OCD severity using the YBOCS assessment as follows: mild 10-18, moderate 18-29, severe >30. As seen in Table 9, at baseline, 100% (26/26) of the patients enrolled into the study protocols at the 4 collaborating centers met the criteria for "severe" OCD (YBOCS >30). Results at 6 months, 12 months, 12 month LOCF and last FU, show that over 80% of the patients had decreased severity from severe at baseline to either mild or moderate. These changes in YBOCS scores reflect a reduction in symptom severity as defined by this clinical rating scale.

Table 9. OCD Severity Ratings

		Range of OCD Severity		
Time	No. of Patients	Mild (10-18)	Moderate (18-29)	Severe (30 or above)
Baseline	26	0 (0.0%)	0 (0.0%)	26 (100.0%)
6 Months	24	11 (45.8%)	10 (41.7%)	3 (12.5%)
12 Months	21	8 (38.1%)	10 (47.6%)	3 (14.3%)
12 Months (LOCF)[a]	26	10 (38.5%)	12 (46.2%)	4 (15.4%)
Last Follow-up	26	11 (42.3%)	10 (38.5%)	5 (19.2%)

[a]Last observation carried forward (LOCF) conducted for 12 month time point. Data for 5 patients (CC1, FL4, FL5, LV10, LV11) imputed using last measured YBOCS score prior to 12 month follow-up.

There are four subtypes of OCD according to the Leckman (1997) scheme. As seen in Table 10, subjects with the obsessions and checking subtype, had the best response, i.e. -74.0% (LOCF), as measured by the YBOCS. The majority of these subjects also had comorbid anxiety and depression which likewise improved during treatment. No subjects with hoarding as their primary subtype were included in the study.

Table 10 OCD, Depression and Anxiety Improvements by Subtype

OCD sub-type	N	YBOCS		HAM-D		HAM-A	
		Mean	SD	Mean	SD	Mean	SD
Hoarding	0	-	-	-	-	-	-
Cleanliness and washing	11	-31.9%	19.7%	-45.2%	33.1%	38.5%	33.1%
Obsessions and checking	6	-74.0%	19.7%	-77.4%	16.3%	-66.9%	33.4%
Symmetry and ordering	9	-42.9%	33.2%	-45.6%	31.8%	-52.8%	30.6%

In each of these subtype categories, there were patients that met the criteria for full response (n=5 for cleanliness and washing (45%), n=5 for symmetry and ordering (56%) and n=6 for obsessions and checking (100%).

Two of the 4 centers, Leuven and U. Fl. incorporated a randomized blinded period of stimulation into their study designs. As can be seen in Table 11, the YBOCS score improved by 62% when stimulation was on compared to 8% when stimulation was off.

Table 11 YBOCS Results of Randomized Blinded Stim Phase

STIM	N	YBOCS	Baseline (BL)	Period 1 (P1)	Diff (P1-BL)	%Chg (P1-BL
ON	9	Mean	34.3	13.1	-21.2	-62.1%
		SD	(3.2)	(8.6)	(8.2)	22.4%
OFF	7	Mean	32.7	30.1	-2.6	-8.3%
		SD	(2.2)	(11.7)	(11.1)	35.7%
P values[a]:			0.253	0.008	0.003	0.006

[a] Two -sample t-test assuming unequal variances (2 tailed).

D. Global Assessment of Function (GAF)

In conjunction with the YBOCS measures, three of the 4 centers also collected corresponding ratings of Global Assessment of Function (GAF), a measure of overall psychological, social and occupational functioning. At baseline, the majority of patients (20/21) had GAF scores ranging between 20 and 40, indicating severe disability. GAF scores improved over time for the vast majority of patients with the average score increasing from a baseline value of 34.8 (n=21) to 56.1 (n=20) at 6 months, 56.4 (n=18) at 12 months, and 59.0 (n=21) at last follow-up. An LOCF analysis at 12 months shows a similar level of improvement (mean=57.6) for all 21 patients. This improvement in GAF for the patient population is illustrated in Figure 2.

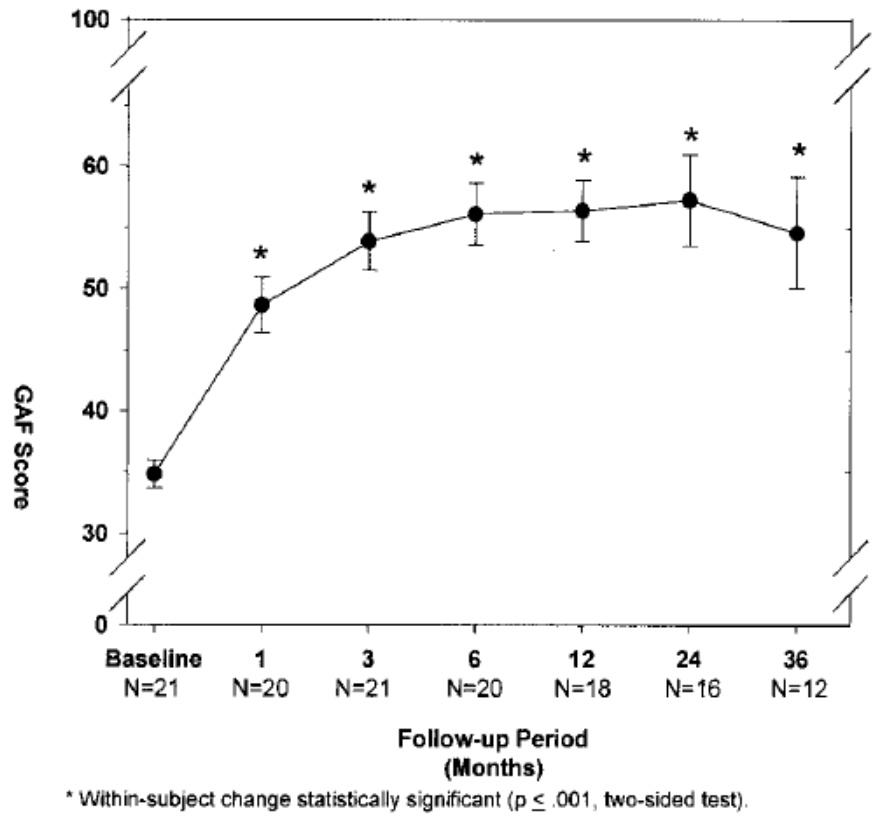

Figure 2. Average GAF Score following DBS Treatment

Table 12 shows the distribution of GAF scores at various time-points for the 21 patients. At baseline, 20 of 21 patients exhibited scores of 40 or less, while at last follow-up only 2 patients remained at this relatively low functional level. At 12 months (LOCF) and last FU, 48% and 62%, respectively, of the patients scored 51 or greater at last follow-up; no patients were able to achieve this degree of function at baseline. There was a progressive shift in the distribution of scores at baseline to levels of higher function over time following DBS treatment in this patient population.

Table 12. Distribution of GAF Scores

Functioning	Ratings	Number of Patients / % of Patients									
		Baseline		6 Months		12 Months		12 Months (LOCF)[a]		Last Follow-up	
Inability to function - all areas (judgment, thinking, mood)	21-30	7	33.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Major impairment in several areas (judgment, thinking, mood)	31-40	13	61.9%	0	0.0%	1	5.6%	1	4.8%	2	9.5%
Serious impairment (social, occupational, school)	41-50	1	4.8%	10	50.0%	9	50.0%	10	47.6%	6	28.6%
Moderate difficulty (social, occupational, school)	51-60	0	0.0%	3	15.0%	1	5.6%	1	4.8%	4	19.0%
Some difficulty (social, occupational, school)	61-70	0	0.0%	5	25.0%	6	33.3%	6	28.6%	6	28.6%
Slight impairment (social, occupational, school)	71-80	0	0.0%	2	10.0%	1	5.6%	3	14.3%	2	9.5%
Good functioning	81-90	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	4.8%
		21	100.0%	20	100.0%	18	100.0%	21	100.0%	21	100.0%

[a] Last observation carried forward (LOCF) conducted for 12-month time point. Data for 3 patients (CC1, LV10, LV11) imputed using last measured GAF score prior to 12-month follow-up.

Treating physicians also provided an impression of the overall, global condition of these patients after DBS therapy, including psychological, social, functional, occupational and quality of life considerations. Those impressions were reported on a modified Likert Scale, similar to the standard Pippard Postoperative Rating Scale using the 5-point scale shown in Table 13. Overall, the treating physicians reported that approximately 2/3 of the patients were much better following DBS therapy, compared to their pre-treatment condition.

Table 13. Clinical Global Outcome Ratings

Score	Rating	No. Patients	%
5	Much Better	17	65.4%
4	Slightly Better	5	19.2%
3	No change	4	15.4%
2	Slightly Worse	0	0.0%
1	Worse	0	0.0%
	COUNT:	**26**	100.0%

XI. Risk / Probable Benefit Analysis

Severe, intractable, treatment-resistant OCD is a devastating condition. The three main approaches to its treatment include medications, psychotherapy and neurosurgical ablation. Patients appropriate for neurosurgical therapies are severely symptomatic with long-standing illness. Surgical procedures include cingulotomy, subcaudate tractotomy, and limbic leucotomy which is a combination of the first two procedures and capsulotomy. Due to the destructive, irreversible nature of surgical ablation procedures, there is a significant risk associated with these procedures. The reported rate, type and

severity of adverse events from the various neurosurgical procedures varies. Frontal lobe deficit syndrome occurred in 30% of 116 capsulotomy cases (Herner, 1961.) Among subjects with capsulotomy for anxiety, 40% had adverse symptoms of mild severity and 13% of moderate severity. In addition, fatigue, emotional blunting, emotional incontinence, indifference, low initiative, disinhibition and impaired sense of judgement were reported (Herner, 1961 and Kullberg, 1977.) Kullberg noted that cingulotomy produced fewer adverse events, i.e. transient confusion and affective deficit in the immediate postoperative phase than capsulotomy. A comparison of conventional thermocapsulotomy to gamma radiation capsulotomy in OCD patients found that in the gamma radiation capsulotomy group there were no signs of postoperative confusion and disorientation (Rylander, 1979.) Postoperative seizures have been reported in 3% of patients by Herner (1961) and in 4% by Mindus (1991.)

DBS is an alternative to neurosurgical ablation for patients with chronic severe OCD who are resistant to medications and psychotherapy. Although there are a number of serious adverse events experienced by subjects treated with DBS, in the absence of therapy, chronic severe medically refractory OCD can be very disabling. Patients with treatment-resistant OCD have a high comorbidity of depression and anxiety, profound impairment in social and occupational functioning, and severe subjective distress. Suicidal ideation, suicide attempts and suicide have occurred in this population.

Risks associated with DBS therapy for OCD appear to be similar to the risks associated with the performance of stereotactic surgery and the implantation of DBS systems for currently approved indications (Parkinson's Disease and Essential Tremor). Many of these adverse events can be reduced or eliminated by adjusting the stimulation parameters. OCD patients appropriate for DBS therapy 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. In this context, the risks associated with DBS electrode implantation and stimulation, a reversible procedure (i.e. DBS is not intended to destroy neurological tissue), are justified and offer the patient a reasonable probability of benefit from the therapy. The reversible nature of DBS therapy also allows patients the opportunity to take advantage of any therapies that may be developed in the future and still allows the patient the option of having a surgical ablation procedure.

The clinical data provided on 26 treatment-resistant OCD patients at four centers, suggest that these subjects improved on the YBOCS score, a validated outcome measure for OCD as well as the global outcome measures. Taken together, FDA believes that the data suggest that DBS for the treatment of OCD is a reasonable alternative to subjects whose only remaining option is neurosurgical ablation.

Therefore, it is reasonable to conclude that the probable benefit to health from using the Reclaim™ DBS Therapy for OCD outweighs the risk of illness or injury when used in accordance with the Instructions for Use and when taking into account the probable risks and benefits of currently available alternative forms of treatment.

XII. Panel Recommendation

This HDE was not reviewed by an FDA advisory panel. The panel has previously reviewed other components of the device that is the subject of this HDE for the treatment of Parkinson's disease. This HDE does not raise any unanticipated safety issues. Therefore, it was determined that this application need not be submitted to the advisory panel.

XIII. CDRH Decision

CDRH has determined that, based on the data submitted in the HDE, that the Medtronic Reclaim® OCD Therapy will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on February 19, 2009.

XIV. Approval Specifications

Directions for use: See the Physician's Labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

XV. References

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