FDA Executive Summary

Prepared for the
March 3, 2014 meeting of the
FDA's Pediatric Advisory Committee

H020007

Medtronic Activa Neurostimulator for Dystonia Treatment

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I. INTRODUCTION

In accordance with the Pediatric Research Equity Act (PREA), this review provides a safety update based on the post-marketing experience with the use of the Medtronic Activa® Dystonia Therapy in pediatric patients since approval in 2003. The purpose of this review is to provide the Pediatric Advisory Committee (PAC) with post-marketing safety data so the committee can advise the Food and Drug Administration (FDA) on whether they have any new safety concerns and whether they believe that the HDE remains appropriately approved for pediatric use?

The Medtronic Activa® Dystonia Therapy system is indicated for unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above.

This memorandum summarizes the safety data regarding H020007 through the present day including pre-market clinical data, post-market medical device reporting (MDR) for adverse events, and peer-reviewed literature regarding safety data associated with the device.

II. DEVICE DESCRIPTION

The Medtronic Activa® Dystonia Therapy uses an implantable neurostimulator to deliver electrical stimulation to the internal globus pallidus (GPi) or subthalamic nucleus (STN) of the brain. The device consists of a lead, a neurostimulator, and an extension that connects the lead to the neurostimulator. The Medtronic Activa® Dystonia Therapy consists of two "kits" comprised of the individual medical device components that are required by an implanting physician.

The two kits are the Model 3307 and the Model 3309 Activa Dystonia Therapy kits. Their contents differ only by the model of DBS lead contained within each kit. The Activa® Dystonia Therapy kits include a Soletra Model 7426 Neurostimulator, a Model 7482 Extension, a Model 7452 Control Magnet, and either a Model 3387 (Model 3307 kit only) or Model 3389 (Model 3309 kit only) lead. Several associated products (listed below) are used in conjunction with the Activa® Dystonia Therapy kits but are not included in the kit. All contents of the model 3307 and 3309 Activa Dystonia Therapy kits and associated products have been approved by the FDA within prior Pre-Market Approval (PMA) submissions.

Since the original approval of the HDE in 2003, FDA has approved the use of newer components for the system, most recently in 2011. The original components remain approved. The following sections discuss the components and accessories that were originally approved, and those that have been updated, followed by description of components that have not been updated/modified

Neurostimulator

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. A connector assembly on the neurostimulator allows connection to the extension. The electrical pulses are carried from the neurostimulator to an implanted intracerebral lead by means of a lead extension.

Original Model 7426 Soletra Neurostimulator

The stimulation parameters can be non-invasively adjusted to optimize control of the symptoms of Dystonia and minimize side effects. The adjustments are made via radio-frequency communication using the Model 7432 Physician Programmer with the Model 8840 N'Vision 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. The neurostimulator case shields are manufactured of titanium with a Parylene coating. The connector assembly is manufactured of polyurethane with titanium setscrews. Material characterizations and toxicity testing have been previously performed on all materials in accordance with applicable standards.

Subsequently Approved Models 37601, 37602, 37603 (Activa PC and Activa SC)
Activa PC is a dual channel primary cell device. This non-rechargeable neurostimulator can provide stimulation to 1 or 2 leads (one in each hemisphere of the brain). Activa PC is designed for connection to the Model 37085 extension which has 15% extensibility for improved biomechanics. Patients currently implanted with a Model 7482A extension can achieve compatibility with an Activa PC with the use of the Model 64001 or 64002 adaptors

Activa SC is available in two models; Model 37602 and Model 37603 and is a single channel primary cell device providing stimulation to a single lead. The models are identical except for the connectors to allow compatibility with both DBS extensions; the Model 7482A (Activa SC Model 37602) and Model 37085 (Activa SC Model 37603) extensions. Patients currently implanted with Model 7482A extension may receive a replacement Activa SC Model 37602 device without an adaptor. New Activa SC patients may receive a Model 37603 device and utilize the Model 37085 extension.

The essential therapy delivery method is unchanged from the approved Soletra, (approved under P960009): Stimulation is delivered to an implanted lead, with a maximum of 4 electrodes per lead in either constant voltage or constant current mode. Rate is limited to 250 Hz, pulse width is limited to 450 μsec, amplitude is limited to 10.5 V (or 25.5 mA) and the charge density warning threshold is 30 μC/cm2/phase.

Figure 1. Activa SC Model 37602 and Model 37603

Figure 2. Activa PC Model 37601

Lead 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.

Original 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.

Subsequently-Approved Model 37085 Extension

The Activa SC INS (Model 37603) has 4 contacts which align with the 4 contacts of the 37085 extension. The Activa PC INS has 16 contacts (2x8). One 37085 extension can be used in each of the two bores of the Activa PC connector. The extension is subcutaneously passed from the scalp area, where it connects to the lead, through to the subclavicular area or upper abdominal region, where it connects to the neurostimulator.

The Universal Port Plug is intended for use in unilateral implants, where only one channel of a dual channel neurostimulator is used. It is supplied with the Extension.

The Model 37085 Extension is supplied with the same tunneling tools that are currently released for distribution with the approved Model 7482A Extension. The connector boots supplied with the Model 37085 Extension are identical to those approved for use with the Model 37083 and/or the Model 7482A Extension.

Patient Programmer

The therapy controller is designed for use by a patient or caregiver. Using the therapy controller, the patient or caregiver can turn therapy on or off, check whether the therapy is on or off, and check the condition of the neurostimulator's battery.

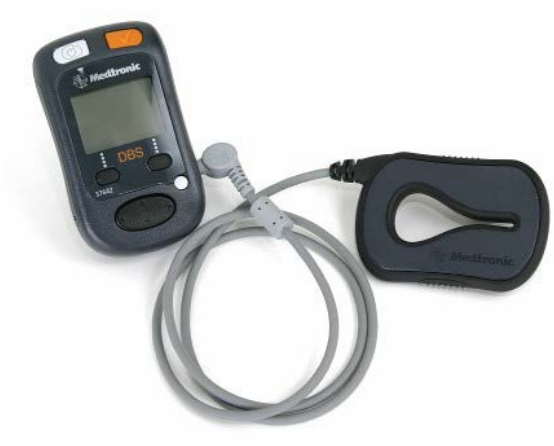
Original Model 7438 Therapy Controller

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.

Subsequently-approved Model 37642 Patient Programmer

The Model 37642 Patient Programmer is a non-sterile, battery-operated external device designed for patient use. The software application provides a user interface developed for DBS patient use, which includes a daily reminder to check INS battery status. Patients may use the programmer to turn the neurostimulator on and off, check the battery and adjust stimulation therapy, if this capability has been enabled by the physician.

The patient programmer communicates with the neurostimulator via RF communication. The programmer must be held directly over the implant to achieve synchronization or the external antenna may be positioned over the implant, allowing the patient to view the programmer screen while checking status or making stimulation parameter adjustments. All communication with the neurostimulator begins with synchronization, which sends the settings from the neurostimulator to the patient programmer.



Model 3625 Test Stimulator
The test stimulator is used for perioperative testing. Parameters that can be adjusted include amplitude, pulse width, rate, and electrode selection. The test stimulator enables the physician to evaluate the efficacy of neurostimulation for the patient, particularly in relation to lead position, during intraoperative testing.

Model 37022 External Neurostimulator
The Model 37022 ENS outputs are programmed via a telemetry link from the 8840 clinician programmer using the same 8870 software application card used to program the INS outputs. This limits available parameter ranges to only those that are approved for the INS to be implanted. In addition, the Model 37022 ENS can provide stimulation in either voltage or current mode, while the Model 3625 Test Stimulator output is limited to voltage mode.

Components/Accessories without newer models

Model 3387/Model 3389 DBS™ Leads
The DBS leads consist of a polyurethane protective sheath with four 1.5 mm platinum/iridium electrodes near the tip of each lead that deliver stimulation to the target site. Lead models include Model 3387, in which the 4 electrodes are spaced 1.5 mm apart and Model 3389, in which the electrodes are spaced 0.5 mm apart. The leads are stereotactically introduced into the target and fixed at the skull with a burr hole cap and ring.

Model 7452 Control Magnet
The control magnet allows the patient to turn stimulation on and off.

Model 7432 Clinician Programmer
The Model 7432 Physician Programmer consists of a printer, programmer, and programming head that communicates via telemetry to the neurostimulator. Clinicians use the programmer to adjust the neurostimulator stimulation parameters and to verify current settings.

Model 7460 MemoryMod Software Cartridge
The Model 7460 MemoryMod Software Cartridge is a plug-in cartridge designed to control the specific functions of the Model 7432 Clinician Programmer. It contains the necessary software to program the Soletra Neurostimulator.

Model 8840 N'Vision Clinician Programmer
The Model 8840 N'Vision Programmer is used with the Model 7432 Physician Programmer to program the neurostimulator.

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 (whether Soletra, Activa PC, or Activa SC).

Model 3353/3354 Lead Frame Kits
The lead frame kits (which are designed to fit Electa/Leksell and Radionics or Radionics-like stereotactic frames) are used to stabilize the lead in the insertion cannula during implantation.

Burr Hole Ring and Cap
The burr hole ring is constructed of nylon and the cap is made of silicone. The ring has ridges that hold it in place within the burr hole in the skull. Troughs are machined into the ring, and when the leads are inserted, the burr hole cap secures the lead in one of the troughs.

III. REGULATORY HISTORY AND APPROVED INDICATIONS FOR USE

The Activa System received designation as a Humanitarian Use Device (HUD Designation) on November 27, 2001 and on April 15, 2003, the HDE application was approved by the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration, Please note that post-approval studies were not a requirement associated with approval of H020007.

HDE Approved Indications for Use:
The Medtronic Activa Dystonia Therapy is indicated for unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above.

V. BACKGROUND – Thoracic Insuffiiency Syndrome and Alternative Practices

Outside of the Activa device, treatment of primary dystonia includes oral medications, injections of therapeutic agents directly into nerve or muscle tissue, and surgery. Medical therapy is largely determined by the specific diagnosis, based on the clinical categorization and etiology, and includes use of anticholinergics, muscle relaxants, antiepileptics, and dopamine replacement therapy. Alternative treatments include the injection of therapeutic agents leading to chemodenervation and neuromuscular blockade

Surgical treatment, only recommended for patients who fail to improve with either medication or injections, may include lesioning. Physical therapy also plays a supplementary role for some patients. Supportive therapy (e.g., counseling, etc.) can help some individuals' psychosocial adjustment to the disorder.

VI. CLINICAL DATA USED TO SUPPORT HDE APPROVAL (FOCUS ON SAFETY ISSUES

Available literature was used as the primary data set to support HDE approval and consisted of retrospective, single institution, unblinded case series that employed a variety of classification and rating scales to select patients and evaluate outcomes.

There were 201 patients represented in 34 manuscripts discussing specific case studies and outcomes. Patient gender for known cases included 83 females (83/201, 41%), 57 males (57/201, 28%), and 61 of unknown gender (61/201. 30%). In select case studies where age was reported at the time of first surgery, the mean age was 27.7 years (range: 5 to 78 years, N=91). Patient age classification at the time of first surgery included 21 children, 18 adolescents, 53 adults, and 109 of unknown age as shown in Table 1. Eighty-one percent (81%) of the pediatric patient population studied (N=21) was above age 7.

Table 1. Age Classification at Surgery in Literature (n=201)

Age Classification	**N**	**Average Age (yrs.)**
Pediatric (0-12 yrs.)	21	8.6
Adolescent (13-17 yrs.)	18	14.8
Adult (>18 yrs.)	53	39.9
Unknown	109	-

The majority type of dystonia experienced in these patients was generalized dystonia (65.2%) as shown in Table 2. There were 34 patients where the type of dystonia was unspecified.

Table 2. Type of Dystonia in Literature (n=201)

Type of Dystonia	**N**	**% (n=201)**
Generalized	131	65.2
Cervical	17	8.5
Hemidystonia	5	2.5
Multifocal	3	1.5

Segmental	8	4
Cervical (and truncal)	1	0.5

Focal	1	0.5
Dystonic Tremor	1	0.5
Unspecified	34	16.9

The follow-up experience in this literature ranged from 0.7 months to 132 months (Average: 12.1 months). Follow-up experience data was available on 191 of 201 patients. More than 50% of dystonic patients treated with deep brain stimulation participated in greater than 3 months of follow-up. The stimulation target was primarily the globus pallidus internus (bilateral GPi 71.2%, unilateral GPi 6.8%) as shown in Table 3.

Table 3. Stimulation Target in Literature (n=201)

Stimulation Target	**N**	**Percent (n=205)***
GPi, bilateral	146	71.2
GPi, unilateral	14	6.8
GPi, unspecified	8	3.9
Pallidal, bilateral	1	0.5
Pallidal, unspecified	5	2.4
STN, bilateral	15	7.3
VLp, bilateral posterior	7	3.4
VLp, unilateral posterior	6	2.9
Vim, unilateral	1	0.5
Internal capsule, thalamic interphases, bilateral	1	0.5
VPL thalamic nucleus, unilateral	1	0.5

* *There were 201 patients represented in the 34 manuscripts discussing specific case studies and outcomes. Four patients experienced multiple surgeries.*

Patient Outcome

Assessment of probable benefit from 3 publications describing more than 10 patients shows the following: Coubes et al.(2002a) reported 19 patients with generalized dystonia positive for the DYT1 mutation, with a clinical score improvement of 71% and functional score improvement of 63% following one year of therapy; improvement defined as the percent decrease between pre- and post-implant motor assessment scores (Burke-Fahn- Marsden Dystonia Rating Scale (BFM)). Vidaihet et al. (2002) reported 14 primary generalized dystonia patients (with at least 6 months follow up) treated with bilateral stimulation. Clinical scores were 56 $\pm$ 21 pre-operatively and 26 $\pm$ 16 postoperatively (BFM). Broggi et al. (2002) reported 10 primary dystonia patients. Eight of the 10 patients observed clinical improvement evaluated by BFM, ranging between 27 and 88% (up to 6 months follow up); improvement defined as the percent decrease between pre- and post-implant motor assessment scores.

Deep Brain Stimulation Therapy in Children & Adolescents

Eight manuscripts discuss specific outcomes in pediatric populations. In the largest series, Coubes et al. (2002a,b) treated dystonic children ($\leq$12 years, N=20) and adolescents (13 to 17 years, N=14) with

deep brain stimulation therapy. Clinical scores (BFM) in patients with generalized dystonia positive for the DYT1 mutation were 61 ± 23 pre-operatively and 21 ± 21 postoperatively (at 3 months), 11 ± 11 postoperatively (at 6 months), and 14 ± 17 postoperatively (at 12 months).

Safety Data

Thirty-four manuscripts on published studies to date were reviewed at the time of the HDE submission. The literature reviewed involving a total of 201 patients described the following adverse events:

- Hemiplegia/Hemiparesis
- Worsening of Motor Impairment (dysphagia)
- Sensory Impairment
- Speech/Language
- Subcutaneous Hemorrhage/Seroma
- Cerebral Spinal Fluid Abnormality
- General*
  - Infection
  - Erosion
  - Lead fractures
  - Hardware Breakage
  - IPG Failure
- Déjà vu corrected by surgically revised lead placement
- Irritating cough with stimulation ON

* *Includes adverse events related to the system components*

Potential Adverse Effects

Additionally, one may reasonably expect the risks associated with the use of the Activa system for the approved indications of Parkinson 's disease (PD) and Essential Tremor (ET) to be similar in treating dystonia. As described in the summary of safety and effectiveness data for a supplemental premarket approval application for bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic Activa Parkinson's Control Therapy indicated for adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication (P960009S007), a description of adverse events that may also be applicable for use with dystonia is provided from a prospective open label design study (Table 4).

Over the entire study duration, 12/160 patients (7.5%) had intracranial hemorrhage; 17/160 patients (10.6%) had device-related infection; 16 patients (10.0%) had paresis/asthenia; and 13/160 patients (8.1%) had hemiplegia/hemiparesis. The rate of stimulation-related adverse events was 51.9% (83/160 patients) and the rate of ongoing stimulation-related events was 22.5% (36/160 patients). The rate of serious stimulation- related adverse events was 9.4% (15/160) and the rate of ongoing serious stimulation related adverse events was 3.1% (5/160) patients. Ongoing serious stimulation-related adverse events included: worsening of motor impairment/PD symptoms (dyskinesia), sensory impairment (pain); and speech/language (dysarthria, hypophonia, and speech disorder). Other stimulation related adverse events included: worsening of motor impairment/PD symptoms (worse motor fluctuations, incoordination, abnormal gait, akinesia/bradykinesia, tremor, rigidity, myoclonus and dysphagia); sensory impairment (paresthesia, sensory disturbance, hypesthesia, hearing [tinnitus] and headache); speech/language (voice alteration); eye (visual disturbances [diplopia,

abnormal vision and visual field defect] and eye disorders [twitching]); cognitive (thinking abnormal, confusion, alteration of mentation [dizziness]); general (respiratory [laryngismus], musculo-skeletal [abnormal posture], gastrointestinal [vomiting], urogenital [urinary incontinence], metabolic/nutritional [weight loss], skin and appendages [sweating] and systemic [accidental injury]; sleep [somnolence and insomnia]; neuropsychological (psychiatric disturbances [manic reaction and neurosis]); general paresis/asthenia; internal system events (shock/jolt, positioning difficulties); cardiovascular (cerebrovascular accident); hemiplegia/hemiparesis (asthenia) and depression.

The rate of device-related adverse events was 36.9% (59/160 patients) and the rate of ongoing device-related events was 10.0% (16/160 patients). The rate of serious device- related adverse events was 17.5% (28/160 patients) and the rate of ongoing serious device-related adverse events was 6.3% (10/160 patients). Ongoing, serious device- related adverse events included: internal DBS system events (intermittent continuity, electromagnetic interference, and lead breakage); infection, worsening of motor impairment/PD symptoms (worse motor fluctuations, and incoordination) due to loss of effect; and skin and appendages (erosion). Other device-related adverse events included: internal DBS system events (shock/jolt, dislodged, migration, normal battery failure, malfunction, current leak, wire breakage, kinked electrode, electrode problem, positioning difficulties, impedance low); external system events (difficult to program, printer problem); sensory impairment (pain, sensory disturbance, paresthesia and headache); speech/language (hypophonia); skin and appendages (skin disorder); subcutaneous hemorrhage/seroma (seroma); paresis/asthenia; metabolic/nutritional (edema); and cerebral spinal fluid abnormality (pneumocephalus).

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.

Table 4. Summary of Adverse Events Reported in the Parkinson's Disease Clinical Trial

Adverse Event All Patients (n=160)				
Major Category	**# of Events (known serious)**	**Study Related**	**# (%) of Patients**	**95% CI****
Intracranial Hemorrhage*	13 (8)	13	12 (7.5)	3.4, 11.6
Adverse Event All Patients (n=160)				
Major Category	**# of Events (known serious)**	**Study Related**	**# (%) of Patients**	**95% CI****
Device-Related Infection*	32 (23)	31	17 (10.6)	5.9, 15.4
Infection with Explant*	15 (15)	15	9 (5.6)	2.1, 9.2
Infection without Explant*	17 (8)	16	12 (7.5)	3.4, 11.6
Paresis/Asthenia*	16 (1)	6	16 (10)	5.4, 14.7
Hemiplegia/Hemiparesis*	15 (8)	10	13 (8.1)	3.9, 12.4
Worsening of Motor Impairment/ PD Symptom*	357 (48)	130	110 (68.8)	61.6, 75.9

Dyskinesia*	131 (22)	64	60 (37.5)	30.0, 45.0
Worse Motor Fluctuations*	85 (15)	23	56 (35)	27.6, 42.4
Abnormal gait*	38 (4)	10	30 (18.8)	12.7, 24.8
Incoordination*	33 (3)	14	29 (18.1)	12.2, 24.1
Tremor*	22 (0)	4	18 (11.3)	6.4, 16.2
Akinesia/Bradykinesia*	20 (0)	9	19 (11.9)	6.9, 16.9
Dysphagia*	13 (3)	2	12 (7.5)	3.4, 11.6
Rigidity*	13 (1)	3	12 (7.5)	3.4, 11.6
Myoclonus	1 (0)	1	1 (0.6)	0, 1.9
Therapeutic Response, decreased	1 (0)	0	1 (0.6)	0, 1.9
Sensory Impairment*	148 (14)	59	79 (49.4)	41.6, 57.1
Pain*	71 (5)	15	50 (31.3)	24.1, 38.4
Paresthesia*	37 (1)	23	29 (18.1)	12.2, 24.1
Sensory Disturbance*	18 (2)	11	16 (10)	5.4, 14.7
Headache*	16 (4)	8	14 (8.8)	4.4, 13.1
Neuralgia	3 (2)	0	3 (1.9)	0, 4.0
Hearing*	2 (0)	1	2 (1.3)	0, 3.0
Neuropathy	1 (0)	1	1 (0.6)	0, 1.9
Cognitive*	142 (21)	61	72 (45)	37.3, 52.7
Confusion*	56 (5)	27	44 (27.5)	20.6, 34.4
Thinking abnormal*	39 (3)	16	33 (20.6)	14.4, 26.9
Hallucinations	15 (2)	1	11 (6.9)	3.0, 10.8
Alteration of Mentation*	16 (5)	9	14 (8.8)	4.4, 13.1
Amnesia*	9 (2)	6	8 (5.0)	1.6, 8.4
Delusions*	5 (4)	0	4 (2.5)	0, 4.9
Dementia	2 (0)	2	2 (1.3)	0, 3.0
DBS System*	93 (33)	80	57 (35.6)	28.2, 43.1
Internal*	86 (33)	74	55 (34.4)	27.0, 41.7
External*	7 (0)	6	6 (3.8)	0.8, 6.7
Speech/Language*	77 (15)	48	59 (36.9)	29.4, 44.4
Dysarthria*	47 (6)	32	42 (26.3)	19.4, 33.1
Speech/Language*	30 (9)	16	23 (14.4)	8.9, 19.8
Neuropsychological*	55 (18)	6	31 (19.4)	13.3, 26.0
Psychiatric Disturbances*	25 (8)	4	14 (8.8)	4.4, 13.1
Personality Disorder	12 (4)	1	9 (5.6)	2.1, 9.2
Hostility	6 (2)	0	5 (3.1)	0.4, 5.8
Manic Reaction*	5 (2)	2	3 (1.9)	0, 4.0

Adverse Event All Patients (n=160)				
Major Category	**# of Events (known serious)**	**Study Related**	**# (%) of Patients**	**95% CI****
Neurosis*	1 (0)	1	1 (0.6)	0, 1.9
Paranoid Reaction	1 (0)	0	1 (0.6)	0, 1.9
Anxiety*	25 (7)	2	20 (12.5)	7.4, 17.6

Apathy	4 (2)	0	4 (2.5)	0, 4.9
Suicide Attempt	1 (1)	0	1 (0.6)	0, 1.9
Depression*	41 (10)	4	35 (21.9)	15.5, 28.3
Sleep*	45 (1)	8	37 (23.1)	16.6, 29.7
Eye*	48 (6)	25	39 (24.4)	17.7, 31.0
Visual Disturbance*	33 (6)	20	30 (18.8)	12.7, 24.8
Eye Disorder*	10 (0)	5	9 (5.6)	2.1, 9.2
Eye Infection	5 (0)	0	4 (2.5)	0, 4.9
Subcutaneous Hemorrhage/Seroma*	15 (6)	10	14 (8.8)	4.4, 13.1
Convulsions	7 (6)	5	7 (4.4)	1.2, 7.5
Death	3 (3)	0	3 (1.9)	0, 4.0
Cerebral Spinal Fluid Abnormality	5 (1)	5	5 (3.1)	0.4, 5.8
General*	312 (52)	40	110 (68.8)	61.6, 75.9
Systemic*	75 (14)	7	49 (30.6)	23.5, 37.8
Gastrointestinal*	55 (5)	9	41 (25.6)	18.9, 32.4
Urogenital*	53 (7)	3	43 (26.9)	20.0, 33.7
Respiratory	43 (10)	8	30 (18.8)	12.7, 24.8
Metabolic/Nutritional*	36 (4)	6	29 (18.1)	12.2, 24.1
Musculo-Skeletal*	21 (7)	2	19 (11.9)	6.9, 16.9
Skin and Appendages*	25 (5)	5	22 (13.8)	8.4, 19.1
Ecchymosis	1 (0)	0	1 (0.6)	0, 1.9
Erosion*	3 (3)	2	3 (1.9)	0, 4.0
Infection, fungal	2 (0)	0	2 (1.3)	0, 3.0
Lymphedema	1 (0)	0	1 (0.6)	0, 1.9
Petechia	1 (0)	0	1 (0.6)	0, 1.9
Psoriasis	1 (1)	0	1 (0.6)	0, 1.9
Rash	7 (0)	0	7 (4.4)	1.2, 7.5
Skin Disorder	6 (1)	2	6 (3.8)	0.8, 6.7
Sweating*	3 (0)	1	3 (1.9)	0, 4.0
Ear	4 (0)	0	4 (2.5)	0, 4.9
Cardiovascular*	64 (14)	24	32 (20)	13.8, 26.2

* *Includes adverse events related to the system components.*

** *Note: Exact 95% confidence intervals were used when the # (%) of patients was 0 (0%) because the normal approximation to the binomial does not provide a confidence interval. In every other case, the normal approximation to the binomial was used to calculate confidence intervals.*

Rationale for HDE Approval - Risk Probable Benefit Analysis

Limited treatment strategies existed for chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis). The three main approaches to the treatment of primary dystonia include systemic pharmacological agents (oral medications), local pharmacological agents (injected directly into affected muscles or their nerve

supply), and destructive surgical or neurosurgical intervention. When local injection therapy is impractical or unsafe, and when systemic medications are not effective or produce unacceptable side effects, surgery may be considered. Surgical treatments of dystonia, including ablative therapies such as thalamotomies and pallidotomies, are irreversible, destructive procedures that can be associated with disabling complications. . Although there are a number of serious adverse events experienced by patients treated with deep brain stimulation, in the absence of therapy, chronic intractable dystonia can be very disabling and in some cases, progress to a life- threatening stage or constitute a major fixed handicap. When the age of dystonia occurs prior to the individual reaching their full adult size, the disease not only can affect normal psychosocial development (due to ostracization and/or prevention of normal peer relationships), but also cause irreparable damage to the skeletal system. As the body of the individual is contorted by the disease, the skeleton may be placed under constant severe stresses which may cause permanent disfigurement.

Risks associated with DBS therapy for dystonia appear to be similar to the risks associated with the performance of stereotactic surgery and the implantation of DBS systems for other approved indications (Parkinson's Disease and Essential Tremor), except for when used in either child or adolescent patient groups. These additional risks include the use of general anesthetic instead of local anesthesia during implantation, potential lead strains or fractures related to elongation of the trunk of the patient (due to normal growth) while the length of implanted conductor (from the neurostimulator to the burr hole) remains fixed, the risk of lead migration due to patient head growth resulting in ineffective stimulation and the added risk of children being engaged in active play and sports activities that could damage components of the implanted system. The risks of lead strain, fracture and migration can be minimized by evaluating the patient's implanted lead/extension assembly for sufficient strain relief at regular post-implant follow-up sessions and by considering the replacement of the extension with one of greater length during other elective surgery procedures, such as during the regular change out of neurostimulators that must occur because of battery depletion. In cases where lead tip displacement may occur due to cranial growth the lead tip migration may be accommodated through reprogramming due to the number and spacing of the electrode contacts.

Therefore, it was reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

VII. ANNUAL DISTRIBUTION NUMBER (ADN) AND US DEVICE DISTRIBUTION DATA

The Pediatric Medical Device Safety and Improvement Act of 2007 amended section 520(m) of the Food and Drug Administration Amendments Act and now allows HDEs indicated for pediatric use and approved on or after September 27, 2007, to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). The ADN is the number of individuals affected by the disease or condition per year (i.e., annual incidence) multiplied by the number of devices reasonably necessary to treat an individual. According to statute, the ADN cannot exceed 3,999. If the calculated ADN exceeds 3,999, FDA must restrict to the ADN to 3,999 based upon FDAAA legislation.

VIII. POSTMARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

Overview of Manufacturer and User Facility Device Experience (MAUDE) Database
Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MAUDE database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting, including
    - rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources.

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MAUDE data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MAUDE data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with the Medtronic Activa Neurostimulator for Dystonia Treatment
The Agency conducted queries of the MAUDE database and of the CDRH Ad Hoc Reporting System (CARS) on September 27, 2013 for all Medical Device Reports (MDRs) associated with the Medtronic Activa Neurostimulator for Dystonia Treatment with no date limitations set. The queries resulted in the identification of 274 unique MDR reports (270 by the manufacturer; 3 from user facilities; 1 from a voluntary reporter). Patient gender information was provided in 204 of the 270 reports of which 105 were female and 99 were male patients. Differentiation between adult and pediatric patients was able to be made in 198 of the 274 MDRs and it was found that there were 48 pediatric patients and 150 adult patients. The actual patient age for pediatric patients was able to be determined in 33 of the 48 pediatric patient MDRs. Pediatric patient age ranged from eight to 21 years of age. The average age of the known pediatric patients was 14.73 years.

The reporting country was available in 46 of the pediatric MDRs, and includes 41 MDRs from the United States and five from the United Kingdom.

Table 5 shows the top reported device and patient problem codes as provided in the MDRs identified as being associated with pediatric patients. These codes are useful in obtaining a general overview of what is being seen in the MDRs; however they do not provide the full picture of the events occurring.

Table 5. Top ten patient and device problem codes reported in MDRs for pediatric patients (n = 48).

Patient Problem	Number of MDRs*	Device Problem	Number of MDRs*
Decreased Therapeutic Response	15	High Impedance	10
Infection	6	Device Operates Differently Than Expected	8
Electric Shock	4	Migration of Device or Device Component	6
Pain	3	Inappropriate Shock	4
Unexpected Therapeutic Effects	3	Break	3
Cerebrovascular Accident	2	Device Displays Error Message	3
Impaired Healing	2	Battery Issue	2
Staphylococcus Aureus	2	Disconnection	2
Ambulation Difficulties	1	Electro-Magnetic Interference (EMI)	2
Chest Pain	1	Failure to Charge	2

* A single MDR may be associated with more than one problem.

In an effort to separate reports for events that occurred zero to 30 days post-implant from those that occurred 30 days post-implant, an analysis of the time to event (TTE) was conducted. The TTE was calculated based on implant and explant dates provided, date of event provided, and the event text for each report. The TTE was only able to be conclusively determined for 21 of the pediatric reports received. A breakdown of the reports received for these 21events for implants in place greater than and less than 30 days can be seen in Table 6. There were six reports in which it was confirmed that the event occurred between zero and 30 days post implantation and 15 reports in which the event occurred greater than 30 days post implantation.

Table 6. MDRs Received by Time to Event.

		Event Type	
Reported Problem	**MDR Count**	**Injury[1]**	**Malfunction[2]**
0 to 30 Days Post Implant, n=6			
Explant Due to Infection	2	2	0
Left Facial Weakness / Somnolence	1	1	0
Stroke During Implant	1	1	0
Cerebral Infarction Three Days Post Implant	1	1	0
Lead End Cap Unable to be Removed	1	0	1
Greater Than 30 Days Post Implant, n=15			
Worsening of Dystonia	3	2	1
Explant Due to Infection	2	2	0
Explant Due to Charging Issue	1	1	0
Replaced Due to Loss of Therapeutic Effect	1	1	0
Replaced Due to High Therapy Settings	1	0	1
Premature Battery Depletion / Return of Symptoms	1	1	0
Unexpected Shock	1	0	1
Replaced Due to Impedance Issue	1	1	0
Replaced Due to Broken Leads / Return of Symptoms	1	1	0
Lead Extensions Replaced Due to Fall	1	1	0
Explant Due to System Positioning	1	1	0
Explant Due to Charging Time	1	1	0
Total	**21**	**17**	**4**

[1] Serious Injury per regulatory definition (CFR803.3) includes an event that is life-threatening or results in permanent impairment of a body function or permanent damage to a body structure or necessitates medical or surgical intervention(s) to preclude permanent impairment of a body function or permanent damage to a body structure.

[2]A malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended; it is reportable when it is likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The 48 pediatric MDRs were individually reviewed to look for events identified as clinically significant or concerning (as requested by CDRH clinicians). A breakdown of the number of MDRs received for each specified event can be seen in Table 7.

Table 7. Reports received for specific clinical events*.

Event	Number of Reports
Return or Worsening of Symptoms	15
Explanted	9
Infection	7
Replaced	7
Cerebrovascular Accident	3
Procedure Related	2
Battery Issue	1
Revision Due to Growth	1

* A single MDR may be associated with more than one event.

Return or Worsening of Symptoms (n=15)
There are a variety of reasons cited for return of or worsening of patient symptoms. In the reports reviewed, these reasons include the device being turned off (purposely and accidentally, ages 12 and 19)[†], the battery reaching the end of life (normal depletion, age 16), electro-magnetic interference, and high impedances seen with the leads (ages 13, 13, 11, and 16).

Explanted (n=9)
Reports in which an explant was stated to have occurred are unique from reports of a replacement, as listed in Table 6 above. These reports do not give any indication that the device was replaced after explant. There were four reports which indicated devices were explanted due to infection (patient ages of 11, 12 and 21). The remaining five reports listed the reasons for removal as follows: improperly placed leads (age 13), patient unhappy with the charging time needed (age 14), migration of the battery (age 12), the device was no longer used (age 19), and unknown (age 12).

Infection (n=7)
There were two reports that identified an infection occurred, but did not provide any additional details about the infection (ages 21 and 10). Three additional reports indicated that the patient's infection was Staphylococcus Aureus (ages 11 and 12), with one report indicating the patient was treated with IV antibiotics (age 14). One report indicated that a lead eroded through the patient's skin and likely led to an infection. The last report stated that the patient had a throat infection, but that it was not related to the device in any way.

Replaced (n=7)
Three of the reports in which it was indicated that the device was replaced did not provide specific reasons for the replacement. There were two reports in which it was stated that the device was replaced due to the patient's loss of therapeutic effect with the device (age 16). The remaining two reports provided reasons of a short circuit condition (age 19) and the battery being at the end of its life (normal depletion, age 17) for the replacements.

Cerebrovascular Accident (CVA) (n=3)
One report states that the patient's dystonia was never completely controlled. It was indicated that approximately two months after implant the patient experienced a small CVA at the right caudate head. No further information was provided regarding the patient's status (age 13). The second report indicated that a patient experienced a cerebral infarction three days post implant. An MRI indicated that the infarct was a small focus of ischemia/infarction at the posterior aspect of the left caudate head with a small band of abnormal signal leading to the lead tract. It was stated that this may have been the result of a

disruption of a small artery. No further information was provided regarding the patient's status (age 8). The last report indicated that a patient experienced a stroke as well as a subdural hematoma during the implant surgery. It was not determined at the time if the stroke damaged the area that would have had dystonia implications. It was also stated that the patient went into a coma afterwards, but no additional information on patient status was provided. This report was received from a clinic to which the patient went sometime after the initial implant, which may indicate the patient is no longer in a coma.

Procedure Related (n=2)
Reports within the procedure related event subtype are defined to be issues that occurred during the initial implant procedure. The first report stated that a patient experienced a stroke as well as a subdural hematoma during the implant surgery. This report is the same as the third report described within the CVA subsection above. The second report stated that a patient experienced an asymptomatic perioperative hemorrhage. It is unknown if this was an intracranial hemorrhage. No further information was provided and this report cited a literature article (age 17).

Battery Issue (n=1)
The single report of a battery issue indicated that there was premature depletion of the battery. No other information was provided.

Revision Due to Growth (n=1)
This report indicated that a patient was implanted when he was nine, with the batteries in his abdomen, however the longest leads possible were not used at that time. The patient began experiencing high impedances with the device, which the physician attributed to growth of the patient. A revision surgery was done in which it was determined that the issue was with the lead extensions, which were replaced with newer stretch coil extensions.

[†]Age information is only provided where known.

Of note is that there were no MDRs received that mentioned patient depression or suicidal ideation. These types of events were indicated to be clinically relevant and have been found to occur in literature; however these events have not occurred in the MDR data reviewed to date.

<u>MDR Summary</u>
In summary, there have been 48 MDRs received for the Dystonia indication of the Medtronic Activa Neurostimulator in pediatric patients. MDRs related to a return or worsening of symptoms (loss of therapeutic effect) accounted for 31.25% of all the pediatric patient events reported. These types of reports are often indicative of an issue that can be resolved; however these events required a replacement or explant in three of the MDRs received. The labeling does address the issue of symptom return / worsening and these types of events are known to occur in other neurostimulators. Other patient problem types occurring within the MDRs have been noted to occur in either the device labeling or clinical summary. The top mechanical problem reported was high impedance (20.83% of reports), which is a condition seen at the lead / device connection. The labeling states that issues with open circuits (high impedance) can occur without warning and impedance issues are also known to occur in other neurostimulators. Other device / mechanical problem types occurring within the MDRs are either noted to occur in the device labeling or are known issues with neurostimulator devices in general.

IX. POSTMARKET DATA: POST-APPROVAL STUDIES

Post-approval studies were not a requirement associated with approval of H020007.

X. POSTMARKET DATA: LITERATURE REVIEW WITH FOCUS ON SAFETY DATA

The intent of this systematic literature review is to provide a broad examination of adverse events associated with the use of the Medtronic Activa neurostimulator. The events were generally grouped into several categories with little overlap with the exception of power/battery issues vs. revision, which frequently occur in tandem. The categories include: general device malfunction and adverse events (nearly all events), infections, effectiveness, electromagnetic interference (EMI), depression/suicide, power/battery life/battery failure, perioperative adverse events, and revisions.

The literature review was conducted to address the following questions:

1) What adverse events (safety) are reported in the literature for Medtronic neurostimulators in the treatment of movement disorders?
2) What is the safety of these devices in the target population of pediatrics treated for dystonia?

Methods:
A systematic search of the published peer-reviewed literature in the PubMed and EMBASE databases was conducted on November 26, 2013. The review team agreed upon the search terms prior to the conducting the search. The search strategy, inclusion and exclusion criteria are detailed below.

The search was conducted in the databases using the following search string:

(medtronic dystonia) OR (medtronic activa deep brain stimulation) OR (medtronic dbs) OR (medtronic activa) OR activa OR (dbs AND pediatric AND Dystonia)

The limits utilized were articles published in English since January 1, 2003 (approximate time frame of HDE approval to present). The rationale for limits was to query as widely as possible to maximize the number of relevant results. Collectively, our approach yielded 153 articles. Following several passes of the titles, abstracts and texts, 118 articles were excluded based on the following: duplicate article (n=10), no adverse events reported (n=8), non-research article (n=27), non-English (n=1), non-Medtronic device (n=1), non-human (n=31), IFUs do not include a movement disorder (n=9), non-systematic review (n=4), unable to access article (n=2), cohort captured elsewhere (n=1), and unrelated (n=24). The remaining thirty-five (35) articles were included in the final synthesis[1-35]. Data collection/abstraction was conducted in a predetermined format.

Results:
There were eight (8) case reports[4,12,13,15,23,25,29,34], twenty-two (22) observational studies[1-3,5-11,14,15,18-22,24,28], two (2) surveys[16,27], one systematic review[32], one (1) case series with systematic literature review[30], and one

(1) randomized controlled trial (RCT) [26]. Of the identified studies, fifteen (15) were based in the US[4,5,10,11,13,15,16,19,21-24,27-29], twelve (12) were based outside the US (OUS) [1-3,6-9,12,14,18,25,26], one (1) was multinational[17], and one (1) was not identified[20]. The sample sizes ranged from 1 to 4,553, with an average of 194 patients. Nineteen studies (19) had less than twenty-five (25) patients[4-8,10-13,15,18,20,21,23,25,29,33-35], ten (10) studies had twenty-five (25) to one hundred (100) patients[3,9,14,17,24,26-28,30,31], and five (5) studies had more than one hundred (100) patients[1,2,16,19,22]. Of the studies retained, thirteen (13) utilized a cohort solely of adults[4,7,11-15,17,21,23-25,29], eleven (11) had a mixed adult-pediatric cohort[2,3,10,18,19,22,26,27,31,35], two (2) did not report cohort age or age was not determined[20,28], one (1) was not reported but likely adults only[6], one (1) was not reported but likely a mixed adult-pediatric cohort [16], and only seven (7) had cohorts that utilized solely pediatric subjects[5,8,9,30,32-34]. Ages ranged from four (4) years of age to eighty (80) years of age.

Of the papers included in this review, nearly all utilized some Medtronic hardware or suspected Medtronic hardware (Medtronic provided financial support), although the device descriptions were limited for most studies. Some reported that a Medtronic internal pulse generator (IPG) was used, Medtronic leads, or other components. Many studies examined multiple device brands within their respective cohorts, and some utilized experimental devices in these cohorts. Two papers did not report this information or the hardware was not identified[23,28]

Studies including pediatrics only

Of particular interest for this review is dystonia in pediatric patients (less than 22 years of age). Limiting articles to those which utilized solely a cohort of pediatrics, included some Medtronic hardware, and had an indication for use including dystonia, resulted in the identification of three papers[5,8,9] Because these three papers provide the highest standard of evidence to understand the safety concerns related to the Medtronic Activa Dystonia Therapy in pediatrics with dystonia, these will be discussed briefly. Among the three pediatric only papers, the range of AEs in patients aged 2 to 20 was 27.8% to 43% (with the understanding that one event though multiple events can occur in the same patient). The most commonly observed adverse events in these articles were revision, infection, breakage, and battery failure and are discussed in further detail by each study.

Ghosh[5]: A US based retrospective single-site observational trial was conducted 2003-2010 in 8 pediatrics with a mean age of 14.1 ± 4.6 years (range: 2-15 years). The cohort was 88% male (7/8), 7 bilateral globus pallidus interus (GPi) DBS, and 1 unilateral GPi for hemi-dystonia. Mean follow-up time was 4.7 years (range: 0.5-8 years). The following malfunctions occurred (overall incidence was 37.5% of patients experienced ≥1 AE): 1 electrode dislocation, 1 breakage of extension cable, and 1 infection, each yielding a revision.

Kaminska[8]: A United Kingdom (UK) based prospective observational trial was conducted in 25 pediatrics (only some with dystonia) with a mean age of 11.1 years (range: 4.2-19 years) to examine the human factors of rechargeable IPGs. Follow-up was 10 months (range: 3-17 months). Data only included individuals with greater than three months of follow-up. For all 30 Activa devices implanted, good standards of device recharging were achieved primarily by caregivers (responsible for this requirement in 82% of cases). Overall, 43% of patients experienced more than one AE. Transient recharging problems were noted in 36% of cases. The etiology of these charging problems ranged from migration of hardware (n =3), problems with the recharger (n =2), and user problems (i.e. compliance, accidentally shutting off device) (n =5). In some cases the issues were resolved by hardware replacement (n =12) or training (n

=4). Four cases of seroma were observed postoperatively. Overall, 52% of the patients had a reported complication.

Lumsden[9]: A United Kingdom (UK) based observational study was conducted in 54 pediatrics with dystonia (n =13) with a mean age 11.1 years (range: 3.3-20 years) from June 2005 to May 2010 with an endpoint solely of battery failure. This study included only Medtronic Soletra and Kinetra IPGs. Of these patients, 15/54 (27.7%) required replacement of the IPG because of battery failure. The mean time to battery failure 24.5±2.9 months (range: 13-39 months).

Studies including adults and pediatrics

In papers that included both adult and pediatric patients, the data is not stratified on patient age; therefore it is not possible within the identified literature to provide detailed safety information by this subset.

Randomized controlled trial (RCT)

The sole RCT identified utilized a mixed age cohort that included pediatrics, presumed Medtronic hardware, and focused solely on dystonia[26]. This was a ten center multi-country European RCT with a mixed pediatric-adult population (n=38) and a follow-up of 5 years July, 2002 through May, 2004. Patients were 14-75 years old with idiopathic dystonia hallmarked by substantial disability refractory to drug therapy. Patients served as their own sham controls. Of the adverse events, 71 total were recorded (<6 months/acute: 19; 6 months-5years/chronic: 49). Serious adverse events included:

- infection: 7 total, 4 acute
- lead dislodgement: 4 total, 1 acute
- lead breakage: 4 chronic
- malfunction: 3 chronic
- ineffectiveness: 2 chronic
- cable fracture: 1 chronic
- cervical myelopathy: 1 chronic
- peripheral denervation surgery: 1 chronic
- attempted suicide: 1 chronic

General Device Malfunction and Adverse Events

Numerous adverse events were observed in the overall group of thirty-five (35) papers. AEs describing technical failures were reported that included 40 cases of 'technical dysfunction' at least 4 of which specifically required revision [1,3]. One paper noted technical dysfunctions immediately after implantation 'seems' higher in Activa PC and Activa RC, which have extension leads[1]. Stimulator malfunction (n =3) was reported[26]. Additionally, the following malfunctions were reported:

- Short circuits: 23/595 [1,4]
- Disconnected contacts: 8/591[1]
- Kinked lead: 1/4[4]
- Notched lead wire was identified:1/4[4].
- Wire failure with open circuit requiring revision: 1/4 [4]
- Broken lead wire after a traumatic fall required revision: 1/4[4]

Battery charging was problematic in nine patients n=9[7,8], and resolved in two with training n=2[8]. IPG rotation caused charging problems in one patient n=1[15]. Spontaneous adapter migration occurred in 8% of cases in one study[8]. Targeting/localization errors were described in 83% of perioperative patients in one study n=35/42[11], and 13% or 6/46 in another study[24]. In a study following up 215 patients to determine the number of emergency room (ER) visits required, 60 patients (26.5% of overall cohort) required ER visits for decline in mental status (13), neurological problems (123), infections and hardware problems (63), orthopedic issues (24), and unspecified medical issues (16)[19]

Infections

Infections were reported in nine articles. Infections at IPG site (n=12) and at the lead extender hardware (n=2), device related infection (n=2), and device related infection following an end of life revision (n=1)[22] were reported. Other papers described infections in 4.5 % to and 12.5% of patients [3,6] 36.8% of patients had a subcutaneous infection[26], incision site infections in 4.3%[24], infections/skin erosions in 8% [8], 8% of implanted devices became infected[33], and 9.4% of patients had secondary infection of the stimulation system[31]. There was one infection in a patient who received a replacement IPG at end of device life[22]. Scalp/burrhole infections occurred in one study (n=3)[30]. One study reported that no infections occurred[21].

EMI

Electromagnetic interference (EMI) was reported in 2 articles. EMI occurred disabling the devices n=20[2] (3 were from a theft detector, 4 at airport security gate, 3 from a loudspeaker, 1 from voice memory, 1 by a mobile phone, 2 from a dentist visit, 1 from an ECG, 1 lightning rod, 1 electric welder and 2 from high voltage lines and 1 other). One case report described that an IPG prevented collection of an ECG signal because it interfered and could not be stopped from firing in an acute ER cardiac situation[12].

Depression/ Suicide

Overall, two of thirty-five papers reported patient depression or suicidal ideation (n=2) [25,26]. Volkmann et al. reported suicidal ideation 6 months post-operatively in a patient whose age was not reported. A second paper noted that on testing of stimulation effects in a 63 year old female, at follow-up, device activation caused transient reproducible and severe depression while the device was on)[25].

Power/Battery Life /Battery Failures

Power and battery concerns were reported in nine articles. The range of battery life was from 4 to 93 months with a mean life of 2 to 3 years. One paper reported a mean battery life 3.1 years in the following models: Medtronic Itrel 2, Itrel 3, Soletra, or Kinetra [3]. Another paper solely evaluating Medtronic Activa RCs, it was reported that battery life was lower than manufacturer claims with 19/22 (86.3%) requiring a charge every 3 days and 10/22 (45.5%) requiring a daily charge[8]. A study utilizing Medtronic Restore Ultra and Activa RC described that there was a problem with recharging stimulators because of "poor contact" in 7/9 (77.7%)[7]. A paper reported 15/54 (27.7%) required revision and replacement for battery failure at a mean 24.5±2.9 months (range: 13-39 months); however, none of these revisions were among the Activa devices included in the study [9]. A study utilizing Medtronic Kinetra and Soletra IPGs described battery survival at 24 months at 64% with a mean time to replacement (n =14 replacements) at 2.42 years[10]. Another study whose cohort only included battery failures gave a mean survival rate of 37.47 months for the Medtronic Activa Soletra device (range: 4-93 months) [17]. A reorientation of a Medtronic Activa RC IPG caused inappropriate undercharging in only onedevice[15]. Sillay et al. (2008) described 208 "end of life" IPG replacements /revisions and 30 lead replacements, "that did not involve exposure of the IPG"[22]. Finally, a Medtronic funded study described a revision for battery replacement not classified as an adverse event because it was within a typical lifespan in an unspecified device

model[26]. Unexplained switching off of the stimulator occurred in a study which examined the Medtronic Kinetra and Soletra devices (n=6)[30].

Perioperative adverse events (<30 Days)
Perioperative adverse events were assessed in ten articles. These kinds of adverse events included a surgical site (IPG) painful to the touch (n=1)[7], peri-operative hemorrhage (n=3) across two studies[10,24], a lead 'pushed down' during anchorage (n=1)[21], peripheral denervation (n=1)[26], and postoperative confusion (n=1)[26]. Device component mistargeting and device component migration was identified as previously specified above. A single paper reported stroke leading to death one month after IPG implant (n=1) [27]. One additional death was reported in a pediatric patient on the table for a revision. The patient suffered heart failure and was subsequently identified to have multi-organ failure[34]. A death was also described within a systematic review citing Allbright 2006 where the infection of hardware led to baclofen withdrawal and subsequent patient death[32]. A multifocal left brain hemisphere stroke was reported in an adult patient 2 days post-surgery[35]. A case of venous embolus was identified in 1/22 patients. [33]A systematic review cited five non-device related deaths (cited Fisher 2010)[32].

Revisions
Numerous papers described revisions for reasons detailed above that spanned end of life battery failure to serious adverse events like lead breakage. Fourteen papers reported revisions with rates ranging from 0.67% to 100% (case reports). Of these, the proportions of revisions included4/591 (0.67%)[1], 1/46 (2.17%)[24], 1/24 (4.1%)[21], 1/21 (4.8%)[11], 14/54 (27.7%)[9], 3/8 (37.5%)[5], 2/3 (66%)[4], 1/1 (100%)[12,15], and 3/3 (100%)[29]. The Ondo paper which examined a cohort consisting only of battery failures described revisions in 122/122 (100%) patients[17]. Yu et al. (2009) reported three infections following revisions to add parallel leads to alleviate a refractory tremors [29]. Device revisions (n=2) were reported following lead fractures[34]. Haridas et al. (2011) reported that of the 43 implanted leads, 21% were replaced in the first year[33]. One paper had probable revisions without providing specific details on the frequency and outcomes[26].

Conclusions Based on Literature Review
Despite their strengths, the highlighted articles had several limitations[5,8,9]. The study by Ghosh was limited because it is a retrospective study from a single site with a very small sample size. One patient had their procedure done at a different institution from the remainder of the cohort prior to joining the trial. This article did not report p-values for improvements, though the values are stated to be significant in the abstract[5]. The study by Kaminska did not specifically examine safety in the patients as a primary endpoint, and therefore has limited utility in this analysis. While the article by Lumsden is the main source on battery issues, it does not provide a strong safety assessment[9].

The use of the device is not without risk of adverse events and there are some peri-operative and acute postoperative events. Follow up periods were generally limited to peri-operative or acute (<30 days) and resultantly, some adverse events e.g. revision or depression are very likely to be underreported. Because only three out of thirty-five assessed papers specifically discussed dystonia strictly in pediatrics, the literature is limited in providing generalizable safety information for this population.

XI. REFERENCES

1. Allert N, Markou M, Miskiewicz AA, Nolden L, Karbe H. Electrode dysfunctions in patients with deep brain stimulation: a clinical retrospective study. *Acta Neurochir (Wien).* Dec 2011;153(12):2343-2349.

2. Blomstedt P, Jabre M, Bejjani BP, Koskinen LO. Electromagnetic environmental influences on implanted deep brain stimulators. *Neuromodulation.* Oct 2006;9(4):262-269.

3. Cif L, Vasques X, Gonzalez V, et al. Long-term follow-up of DYT1 dystonia patients treated by deep brain stimulation: an open-label study. *Mov Disord.* Feb 15 2010;25(3):289-299.

4. Farris S, Vitek J, Giroux ML. Deep brain stimulation hardware complications: the role of electrode impedance and current measurements. *Mov Disord.* Apr 15 2008;23(5):755-760.

5. Ghosh PS, Machado AG, Deogaonkar M, Ghosh D. Deep brain stimulation in children with dystonia: experience from a tertiary care center. *Pediatr Neurosurg.* 2012;48(3):146-151.

6. Gillies MJ, Joint C, Forrow B, Fletcher C, Green AL, Aziz TZ. Rechargeable vs. nonrechargeable internal pulse generators in the management of dystonia. *Neuromodulation.* May-Jun 2013;16(3):226-229; discussion 229.

7. Harries AM, Major S, Sandhu M, Honey CR. Rechargeable internal neural stimulators--is there a problem with efficacy? *Neuromodulation.* May-Jun 2012;15(3):214-217; discussion 217-218.

8. Kaminska M, Lumsden DE, Ashkan K, Malik I, Selway R, Lin JP. Rechargeable deep brain stimulators in the management of paediatric dystonia: well tolerated with a low complication rate. *Stereotact Funct Neurosurg.* 2012;90(4):233-239.

9. Lumsden DE, Kaminska M, Tustin K, et al. Battery life following pallidal deep brain stimulation (DBS) in children and young people with severe primary and secondary dystonia. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery.* Jul 2012;28(7):1091-1097.

10. Markun LC, Starr PA, Air EL, Marks WJ, Jr., Volz MM, Ostrem JL. Shorter disease duration correlates with improved long-term deep brain stimulation outcomes in young-onset DYT1 dystonia. *Neurosurgery.* Aug 2012;71(2):325-330.

11. McClelland S, 3rd, Ford B, Senatus PB, et al. Typical variations of subthalamic electrode location do not predict limb motor function improvement in Parkinson's disease. *J Clin Neurosci.* Jun 2009;16(6):771-778; discussion 779.

12. Mindermann T, Maurer D. Delayed diagnosis of myocardial infarction due to deep brain stimulation. *Acta Neurochir (Wien).* Sep 2013;155(9):1679-1680.

13. Nazzaro JM, Lyons KE, Pahwa R, Ridings LW. The importance of testing deep brain stimulation lead impedances before final lead implantation. *Surg Neurol Int.* 2011;2:131.

14. Nilsson MH, Jarnlo GB, Rehncrona S. Functional balance performance in patients with Parkinson's disease after long-term treatment with subthalamic nucleus high-frequency stimulation. *Parkinsonism Relat Disord.* 2008;14(4):291-297.

15. Ondo W, Hewgley T, Almaguer M. Interesting complication of the Medtronic Activa RC impulse pulse generator. *Mov Disord.* Feb 2012;27(2):333-334.

16. Ondo WG, Bronte-Stewart H, Group DBSS. The North American survey of placement and adjustment strategies for deep brain stimulation. *Stereotact Funct Neurosurg.* 2005;83(4):142-147.
17. Ondo WG, Meilak C, Vuong KD. Predictors of battery life for the Activa Soletra 7426 Neurostimulator. *Parkinsonism Relat Disord.* May 2007;13(4):240-242.
18. Pinsker MO, Volkmann J, Falk D, et al. Electrode implantation for deep brain stimulation in dystonia: a fast spin-echo inversion-recovery sequence technique for direct stereotactic targeting of the GPI. *Zentralbl Neurochir.* May 2008;69(2):71-75.
19. Resnick AS, Foote KD, Rodriguez RL, et al. The number and nature of emergency department encounters in patients with deep brain stimulators. *J Neurol.* Jan 2010;257(1):122-131.
20. Sauner D, Runge M, Poggenborg J, et al. Multimodal localization of electrodes in deep brain stimulation: comparison of stereotactic CT and MRI with teleradiography. *Stereotact Funct Neurosurg.* 2010;88(4):253-258.
21. Shahlaie K, Larson PS, Starr PA. Intraoperative computed tomography for deep brain stimulation surgery: technique and accuracy assessment. *Neurosurgery.* Mar 2011;68(1 Suppl Operative):114-124; discussion 124.
22. Sillay KA, Larson PS, Starr PA. Deep brain stimulator hardware-related infections: incidence and management in a large series. *Neurosurgery.* Feb 2008;62(2):360-366; discussion 366-367.
23. St Martin MB, Hirsch BE. Cochlear implantation in a patient with bilateral deep brain stimulators. *Laryngoscope.* Jan 2007;117(1):183-185.
24. Starr PA, Martin AJ, Ostrem JL, Talke P, Levesque N, Larson PS. Subthalamic nucleus deep brain stimulator placement using high-field interventional magnetic resonance imaging and a skull-mounted aiming device: technique and application accuracy. *Journal of neurosurgery.* Mar 2010;112(3):479-490.
25. Tommasi G, Lanotte M, Albert U, et al. Transient acute depressive state induced by subthalamic region stimulation. *J Neurol Sci.* Oct 15 2008;273(1-2):135-138.
26. Volkmann J, Wolters A, Kupsch A, et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. *Lancet Neurol.* Dec 2012;11(12):1029-1038.
27. Waln O, Jimenez-Shahed J. Rechargeable Deep Brain Stimulation Implantable Pulse Generators in Movement Disorders: Patient Satisfaction and Conversion Parameters. *Neuromodulation.* Sep 24 2013.
28. Wharen RE, Jr., Putzke JD, Uitti RJ. Deep brain stimulation lead fixation: a comparative study of the Navigus and Medtronic burr hole fixation device. *Clin Neurol Neurosurg.* Aug 2005;107(5):393-395.
29. Yu H, Hedera P, Fang J, Davis TL, Konrad PE. Confined stimulation using dual thalamic deep brain stimulation leads rescues refractory essential tremor: report of three cases. *Stereotact Funct Neurosurg.* 2009;87(5):309-313.
30. Borggraefe I, Mehrkens JH, Telegravciska M, Berweck S, Botzel K, Heinen F. Bilateral pallidal stimulation in children and adolescents with primary generalized dystonia--report of six patients and literature-based analysis of predictive outcomes variables. *Brain & development.* Mar 2010;32(3):223-228.
31. Cif L, El Fertit H, Vayssiere N, et al. Treatment of dystonic syndromes by chronic electrical stimulation of the internal globus pallidus. *Journal of neurosurgical sciences.* Mar 2003;47(1):52-55.

32. DiFrancesco MF, Halpern CH, Hurtig HH, Baltuch GH, Heuer GG. Pediatric indications for deep brain stimulation. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery.* Oct 2012;28(10):1701-1714.

33. Haridas A, Tagliati M, Osborn I, et al. Pallidal deep brain stimulation for primary dystonia in children. *Neurosurgery.* Mar 2011;68(3):738-743; discussion 743.

34. Miyagi Y, Koike Y. Tolerance of early pallidal stimulation in pediatric generalized dystonia. *Journal of neurosurgery. Pediatrics.* Nov 2013;12(5):476-482.

35. Starr PA, Turner RS, Rau G, et al. Microelectrode-guided implantation of deep brain stimulators into the globus pallidus internus for dystonia: techniques, electrode locations, and outcomes. *Journal of neurosurgery.* Apr 2006;104(4):488-501.