SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Implantable multi-programmable deep brain stimulation system
Device Trade Name:	Medtronic DBS Therapy for Dystonia (including Activa™, Percept™ and SenSight™ devices)
Device Procode:	SGS
Applicant's Name and Address:	Medtronic, Inc. Medtronic Neuromodulation 7000 Central Ave., N.E. Minneapolis, MN 55432
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P960009/S482
Date of FDA Notice of Approval:	November 22, 2025

Medtronic's Deep Brain Stimulator (DBS) System was approved for the following indications for use:

- P960009 approved on July 31, 1997: Unilateral thalamic stimulation of the ventral intermediate nucleus (VIM) using Medtronic DBS Therapy for Tremor is indicated for the suppression of tremor in the upper extremity. The system is intended for patients who are diagnosed with essential tremor or parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.

- P960009/S7 approved on January 14, 2002 (Modified in P960009/S229 approved on November 18, 2015): Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Parkinson's Disease is indicated for adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's disease of at least 4 years' duration that are not adequately controlled with medication, including motor complications of recent onset (from 4 months to 3 years) or motor complications of longer-standing duration.

- P960009/S219 approved on April 27, 2018: Bilateral stimulation of the anterior nucleus of the thalamus (ANT) using the Medtronic DBS System for Epilepsy is

indicated as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures.

The SSEDs to support the indication are available on the CDRH website and are incorporated by reference here:

https://www.accessdata.fda.gov/cdrh_docs/pdf/P960009B.pdf
https://www.accessdata.fda.gov/cdrh_docs/pdf/P960009S007B.pdf
https://www.accessdata.fda.gov/cdrh_docs/pdf/P960009S219B.pdf

The current supplement (S482) was submitted to expand the indication for the Medtronic DBS System to aid in the management of chronic, intractable (oral and/or injectable medication refractory) primary dystonia symptoms for the Indications for Use specifically stated below.

II. INDICATIONS FOR USE

The Activa™, Percept™ and SenSight™ Deep Brain Stimulation Therapy System is indicated for bilateral stimulation of the internal globus pallidus (GPi) using Medtronic DBS Therapy for Dystonia as an aid in the management of chronic, intractable (oral and/or injectable medication refractory) primary dystonia, including:

- generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis) in adult patients; and
- generalized dystonia in pediatric patients twelve years of age or above.

III. CONTRAINDICATIONS

General DBS contraindications
Implantation of a deep brain stimulation (DBS) system is contraindicated for these situations:

Diathermy - 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 can also damage the neurostimulation system components, resulting in loss of therapy and requiring additional surgery for system explantation and replacement. Patients should be advised to inform all their health care professionals that they should not be exposed to diathermy treatment.

Injury to the patient or damage to the device can occur during diathermy treatment when:

- the neurostimulation system is turned on or off.
- diathermy is used anywhere on the body—not just at the location of the neurostimulation system.
- diathermy delivers heat or no heat.
- any component of the neurostimulation system (lead, extension, neurostimulator) remains in the body.

Certain magnetic resonance imaging (MRI) procedures - Use of a full body transmit radio frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area is contraindicated for patients with the following implanted DBS systems or system components:

- Activa SC Model 37602 Neurostimulator
- Model 64001 and Model 64002 pocket adaptors implanted with any DBS system

Tissue lesions from component heating, especially at the lead electrodes, resulting in serious and permanent injury including coma, paralysis, or death, can occur if a contraindicated MRI scan is performed on a patient with any of these DBS systems.

Refer to the MRI guidelines for Medtronic deep brain stimulation systems Instructions for use manual associated with this product for comprehensive safety information and instructions.

Patients unable to operate patient devices - Patients who are unable, or do not have the necessary assistance, to properly operate the patient control device (e.g., patient programmer, therapy access controller) or a charging system (applicable to rechargeable DBS Systems only) should not use this device.

Transcranial magnetic stimulation (TMS) - Contraindicated for use in patients with an implanted DBS System.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Medtronic DBS System for Dystonia labeling.

V. DEVICE DESCRIPTION

Medtronic DBS Therapy for Dystonia uses an implantable multi-programmable neurostimulation system to deliver electrical stimulation to the internal globus pallidus (GPi) of the brain. Refer to Figure 1 for a representation of a DBS system. The major components of a DBS system include:

- Leads and Extensions – Conducts electrical stimulation to the GPi as part of a DBS system. The extension connects the lead to the neurostimulator. In some cases, a pocket adaptor is also used to connect the extension to the neurostimulator
- Implantable Neurostimulator (INS) – Generates electrical current that is conducted through DBS extensions and leads to the distal lead electrodes.
- Burr Hole Device – Used to anchor the lead to the skull.
- Clinician Programmer – Used by the clinician to configure and maintain the patient's therapy through adjustment of the available therapy parameters (amplitude, rate, pulse width, cycling, electrode configuration, etc.) and the creation of programs which consist of a specific set of values for each of the therapy parameters.
- Patient Programmer – Used by the patient to maintain their therapy within parameters configured by the clinician.
- Patient Recharger – Used by the patient to charge the battery of a rechargeable INS. A plug-in charger recharges the patient recharger.

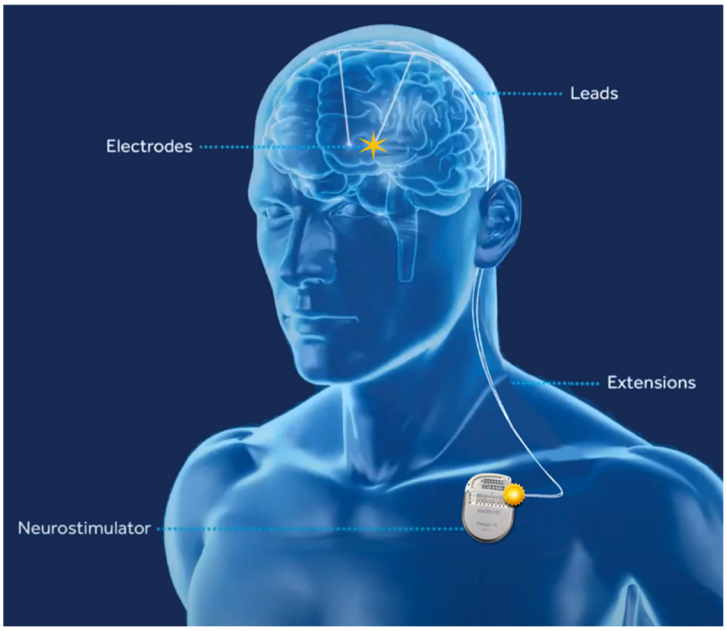

Figure 1. Representation of a Bilateral DBS System

Medtronic DBS system components within the scope of this submission have been approved by FDA through the initial submission and supplements to PMA P960009. Table 1 lists the system components and associated document control numbers for their market approval. There are no changes proposed for these devices; the only changes proposed are to the labeling concerning the indication for use.

Table 1. Medtronic DBS System Components

Component		Model	FDA Submission Number	FDA Approval or Clearance Date
Implantable	Neurostimulators	7426 Soletra Neurostimulator*	P960009/S009	March 21, 2000
		37601 Activa PC Neurostimulator*	P960009/S052	April 07, 2009
		37602 Activa SC Neurostimulator 37603 Activa SC Neurostimulator	P960009/S092	January 26, 2011
		B35200 Percept PC INS	P960009/S361	June 24, 2020
		B35300 Percept RC INS	P960009/S438	January 08, 2024
	Leads	3387S DBS Lead Kit* 3389S DBS Lead Kit*	P960009/S036	March 2, 2006
		B33005 SenSight Directional Lead Kit B33015 SenSight Directional Lead Kit	P960009/S391	May 25, 2021
	Extensions	7482 / 7482A DBS Extension*	P960009/S010	April 12, 2000
		37085 Extension Kit*	P960009/S051	March 27, 2009
		7483 DBS Extension* 37086 Extension Kit	P960009/S134	February 3, 2012
		B34000 SenSight Extension Kit	P960009/S391	May 25, 2021
	Implantable accessories	3550-25 Boots Accessory Kit	P960009/S026	October 31, 2002
		64001 Pocket Adapter (1 x 4) 64002 Pocket Adapter (2 x 4)	P960009/S067	June 8, 2009
		B31060 Connector Plug	P960009/S361	June 24, 2020

Component		Model	FDA Submission Number	FDA Approval or Clearance Date
		B31000 Burr Hole Device B31020 SenSight Lead Cap Kit B31061 SenSight Connector Plug B32000 SenSight Burr Hole Device Kit	P960009/S391	May 25, 2021
External	Implant accessories	3550-05 Percutaneous Extension Kit	P960009	July 31, 1997
		3550-67 Screening Cable 3550-68 Screening Cable 37022 External Neurostimulator	P960009/S051	March 27, 2009
		3550-45 Torque Wrench Accessory Kit	P960009/R017	January 25, 2010
		B31010 SenSight Depth Stop and Cranial Tunneler Kit B31040 SenSight Lead Test Cable Kit B31050 SenSight Extension Test Cable Kit	P960009/S391	May 25, 2021
	Clinician accessories	8840 N'Vision Clinician Programmer 8870 Software Application Card	P960009/S025	October 31, 2002
		8880T2 Communicator A610 DBS Clinician Programmer Application	P960009/S304	May 26, 2018
	Patient accessories	37092 External Antenna 37642 Patient Programmer	P960009/S051	March 27, 2009
		A620 DBS Patient Programmer Application TH90 Handset and Communicator Package Kit	P960009/S333	July 3, 2019
		TH91 Handset and Communicator Package Kit	P960009/S361	June 24, 2020
		A90300 Recharger Application Software CD9000 Charging Dock	P960009/S365	June 25, 2020
		RS6230 DBS Recharging System	P960009/S438	January 08, 2024

Component		Model	FDA Submission Number	FDA Approval or Clearance Date
		WR9230 Wireless Recharger		

* Model is no longer sold, however electronic labeling (eManuals) is available on the Medtronic Manual Library website (www.medtronic.com/manuals).

VI. ALTERNATIVE PRACTICE AND PROCEDURES

There are several other alternatives for the correction of dystonia, including oral medications, botulinum toxin, and lesioning procedures. In patients with generalized and focal isolated dystonia syndromes, anticholinergic medications have proved useful. Levodopa is effective in some patients with dopa-responsive dystonia parkinsonism. Baclofen, carbamazepine, and benzodiazepines are other agents that have been used in the treatment of dystonia either alone or in combination.[1] Botulinum toxin (BoNT) is often of limited interest in general dystonia due to the need for repeated injections covering multiple body areas. However, BoNT is the first line of treatment for patients with blepharospasm and cervical dystonia (spasmodic torticollis). Lesioning procedures (thalamotomies and pallidotomies) have been used for treatment but were discouraged in the 2006 EFNS/MDS-ES guidelines[2] due to their high risk of side effects, and the absence of new data maintained this decision in the EFNS 2011 update.[3]

VII. MARKETING HISTORY

The Medtronic DBS Therapy for Dystonia system was approved in the US through a Humanitarian Device Exemption (HDE) under H020007 on April 15, 2003, for the following 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."

The Summary of Safety and Probable Benefit can be found at: https://www.accessdata.fda.gov/cdrh_docs/pdf2/H020007B.pdf.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device as identified in device labeling. One may reasonably expect the risks associated with the use of the DBS system for the approved indications of Parkinson's disease (PD) and Essential Tremor (ET) to be similar in treating dystonia in adults. Additional considerations for pediatric patients that may alter potential adverse effects on

health include smaller size with ongoing physical growth, age-related differences in neurocognitive development, and continued behavioral maturation.

Risks (potential adverse events) related to the lead, extension, or neurostimulator implant, explant, or revision procedures:

- Immediate intracranial hemorrhage or cerebral infarction which could be symptomatic, or which could result in temporary or permanent neurological injury or death
- Asymptomatic intracerebral hemorrhage or ischemia related to the DBS lead implant identified through postoperative imaging
- Complications related to anesthesia, including allergic reaction, hypotension, nausea and vomiting, headache, and other symptoms
- Complications or effects related to the device implantation or removal procedure, including lead insertion or removal difficulty, failure of the burr hole ring and cap, mechanical or electrical complications of the device, lead(s) not within target requiring replacement
- Complications or effects related to the tunneling procedure, including injury to nerve tissue (such as the spinal accessory nerve), vascular injury that may result in prolonged hospitalization, and tunneling through unintended anatomy (such as in between the ribs and entering the thoracic cavity)
- Cerebrospinal fluid leakage (also called CSF fistula)
- Pneumocephalus
- New onset seizures associated with the lead implant procedure
- General medical complications such as deep vein thrombosis, postoperative fever, and general postoperative discomfort

Risks (potential adverse events) after implantation of the lead(s), extension(s), or neurostimulator(s):

- Delayed intracranial hemorrhage or cerebral infarction which could be symptomatic, or which could result in temporary or permanent neurological injury or death
- Complications of the incision/surgical site, including inflammation, lack of healing, wound dehiscence, transient or persistent pain, seroma, or hematoma
- Infection of the incision/surgical site that could result in sepsis
- Meningitis, encephalitis, or brain abscess resulting from infection involving the brain and/or central nervous system
- Focal edema localized to the area around the lead
- Aseptic intraparenchymal cyst formation around the distal lead tip that may occur weeks to months after implant and may present as new neurological symptoms. Surgical removal of the lead may reduce the size of the cyst and the neurological symptoms caused by cyst formation.
- Erosion of the skin at the lead, extension, or neurostimulator site
- Migration or dislodgement of the lead, extension, or neurostimulator

- Lead, extension, or neurostimulator device complications, including lead or extension fracture, neurostimulator malfunction, neurostimulator setscrews not adequately tightened, and high impedance
- Fibrosis (including tightening, tethering, or bowstringing) at the extension or neurostimulator site may develop weeks to years after implant. It can be associated with pain, disfigurement, limited head mobility, and may require surgical intervention.
- Neurological symptoms, new or exacerbation of existing symptoms which might be transient or permanent, including:

    - vision disorders: diplopia, oculomotor difficulties, or other visual field disorders.
    - speech and swallowing disorders: dysphagia, dysarthria, dysphasia, drooling.
    - motor coordination and balance disorders: akinesia, "freezing," bradykinesia, dyskinesia, paresis, asthenia, muscle spasms/rigidity, tremor, loss of balance/coordination, gait disorder, dizziness, involuntary movements, tics, chorea, dystonia, facial muscle or limb partial paralysis.
    - sensory disturbances: paresthesia, hypoesthesia, burning sensation, headache.
    - mentation impairment: attention or cognitive deficits, dysgraphia, memory disturbances, confusion, somnolence, lethargy.
    - sleep disorders: insomnia, abnormal dreams.
    - déjà vu.

- Psychiatric and behavioral disorders, new or exacerbation of existing symptoms that might be transient or permanent, including:

    - new onset or worsening depression, suicidal ideation, suicide attempt, suicide.
    - anxiety, panic, restlessness.
    - irritability, anger, aggression, agitation.
    - changes or fluctuations in mood, apathy, fatigue.
    - other behavioral manifestations: changes in eating behaviors, obsessive-compulsive disorder, abnormal behavior.
    - hyperactivity or euphoria (hypomania).
    - psychosis, delusions, hallucinations, delirium, disinhibition, perseveration, abnormal thinking.

- New onset seizures during ongoing therapy
- Allergic or immune system response to the implanted materials
- Gastrointestinal disturbances
- Cough associated with DBS
- Transient uncomfortable stimulation (jolting or shocking sensation)
- Lack of effective therapy or loss of therapeutic effect
- Weight gain or loss

In addition to the adverse events related to DBS therapy, the following potential adverse events can occur with DBS Therapy for Dystonia.

Risks (potential adverse events) after implantation of the lead(s), extension(s), or neurostimulator(s):

- Hemiplegia or hemiparesis

Note: Pediatric patients may have increased risks of infections, device-related complications (for example, hardware breakage), revisions, and explants compared to adults due to continued growth, increased physical activity, and potential for longer duration of use.

Patient brain development: The impact of DBS on overall cognitive and neurological development and behavioral changes in pediatric patients is unknown.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

All components of the Medtronic DBS System for Dystonia are commercially approved as part of PMA P960009 and supplements. The preclinical testing of these components provided in the relevant PMA/PMA supplements is also applicable to the Medtronic DBS System for Dystonia. Table 1 lists the system components and associated document control numbers for their market approval. There are no physical changes proposed for these devices.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

These data were the basis for the PMA approval decision. A summary of the clinical data is presented below.

A. Study Design

1. Data Sources

The applicant employed information from multiple data sources to establish a reasonable assurance of safety and effectiveness of the Medtronic DBS Therapy system in the US as an aid in the management of chronic, intractable (oral and/or injectable medication refractory) primary dystonia, including:

- generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis) in adult patients
- generalized dystonia in pediatric patients twelve years of age and above.

These data sources included an analysis of a subset of clinical data purchased from a published randomized controlled trial (RCT) by Kupsch (2006)[4] and its long-term follow-up study by Volkmann (2012),[5] collectively referred to as the "Investigator Study"[6] in this document; an additional RCT conducted by Volkmann (2014)[7]; a meta-analysis of published literature; and data from the Medtronic Product Surveillance Registry (PSR).

Specially, the following clinical data sources were used:

- Study Specific Data
  The applicant performed an analysis on a subset of clinical data from a RCT that was published in Kupsch (2006).[4] The sponsor purchased the actual clinical data for 30 out of 40 studied patients directly from the authors and performed analysis of that data. Follow-up data from the same study that was published in Volkmann (2012)[5] was also used. This data is referred to as the Investigator Study.[6] The Investigator Study[6] was used to support the safety and effectiveness of bilateral GPi DBS in primary generalized and segmental dystonia in adults. The corresponding data in the primary generalized dystonia are also considered as supportive evidence for bilateral GPi DBS in primary generalized dystonia in pediatric patients 12 years of age or above.

  A RCT Study from Volkmann (2014)[7] was used to support the safety and effectiveness of bilateral GPi DBS in primary cervical dystonia in adults.

- Meta Analysis from Systematic Literature Review
  The systematic literature review involved a comprehensive search of the MEDLINE and Embase databases, as well as PubMed ahead-of-print and in-process records, over a more than 10-year period covering November 1, 2012, through August 31, 2024. It also included a key RCT by Kupsch (2006)[4] and its long-term follow-up,[5] both published outside this period. Other relevant studies were found by cross-referencing, with an emphasis on evidence related to particular dystonia types. The focus was on primary data sources for bilateral GPi DBS in adult patients with primary generalized, segmental, and cervical dystonia, without other neurological features or pathological abnormalities and in pediatric patients 12 years of age or above with primary generalized dystonia, without other neurological features or pathological abnormalities. Published studies were included in the analysis if at least 80% of the study population aligned with the indication or individual patient data could be extracted for analysis.

- Medtronic Product Surveillance Registry (PSR)

Real-world data from the PSR is summarized for patients receiving Medtronic DBS Therapy for primary dystonia. The PSR is a prospective, non-randomized, multi-center, global registry that enrolls patients on a rolling basis without specified limits on the number of patients or end dates. Patients from active PSR sites worldwide are followed prospectively in alignment with routine care practices throughout the lifetime of their devices or until they exit the registry. These data were mainly used to support safety.

2. Study Objectives

- *Safety Objectives*
  The overall safety objective was to summarize current safety information for Medtronic DBS Therapy for Dystonia through analysis of current data from the systematic review of published scientific literature and the PSR. The analysis focused on the following therapy-relevant safety events which are already labeled as potential risks associated with DBS-related surgical procedures or with use of DBS therapy after implantation, and are commonly reported in published scientific literature for DBS Therapy for Movement Disorders:

  - Hemorrhage (cerebral or intracranial, symptomatic or asymptomatic)
  - Infection
  - Device complications (lead migration, device failures, etc.)
  - Suicide and suicide attempt

  The rates of therapy-relevant safety events were pooled separately for adult and pediatric populations and summarized using descriptive statistics. Surgical interventions including system revision (e.g., device repositioning or replacement) and complete system explant were summarized.

- *Effectiveness Objectives*
  The overall effectiveness objective was to characterize the clinical benefits related to reduction in movement symptoms. The effectiveness of the Medtronic DBS Dystonia system was demonstrated through analysis of Study Specific Data and results from a meta-analysis of the systematic review of published scientific literature. The average Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor score was used in the analysis for primary generalized dystonia in both adults and pediatric patients 12 years of age or above and segmental dystonia in adults. The average Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity score was used in the analysis for primary cervical dystonia in adults. The European Quality of Life 5-Dimension Questionnaire (EQ-5D) information at baseline and follow-up in the PSR was used in the analysis for health-related quality of life for all types of dystonia in adults.

3. Study Design: Study Specific Data

The Investigator Study[6] provided the main evidence to support the GPi DBS therapy in primary generalized dystonia in adults. The study contains a subset of data purchased by Medtronic from the study published in Kupsch (2006).[4] Data from long-term follow-up were also used from the study published in Volkmann (2012).[5] The main purpose of the analysis was to demonstrate the safety and effectiveness of bilateral GPi DBS in patients with primary generalized or segmental dystonia who were oral and/or injectable medication refractory. The Kupsch (2006)[4] study includes 40 patients (full study cohort), of which only 30 patients signed an Informed Consent Form agreeing to have their data released to Medtronic (MDT). As such, the results and associated conclusions from the Study Specific Data contain data from only those 30 patients. The study in Kupsch (2006)[4] was not sponsored by Medtronic.

Kupsch (2006)[4] RCT Study

Kupsch (2006)[4] was a two arm, double-blind, randomized and placebo-controlled study to demonstrate the safety and effectiveness of GPi stimulation in subjects with primary generalized or segmental idiopathic dystonia who were severely handicapped, in spite of optimal conservative therapy. Patients were randomized in a 1:1 manner to receive either neurostimulation or sham stimulation for the 3-month blinded phase. The subjects in both groups were given the same operation to implant stimulation electrodes in the GPi. During a 3-month follow-up period, the neurostimulation group was administered effective pallidum stimulation (frequency 130 Hz; pulse width 120 μs; amplitude 0.5 V below adverse event threshold). In the sham stimulation group, the stimulator was set at 0 volts (V) so that there would be only placebo or apparent stimulation for 3 months. Drug therapy was freely adjusted to the subjects' requirements in both groups. The groups were unblinded after 3 months and the stimulation system in the sham stimulation group was then switched to the same parameters as the neurostimulation group. This was followed by an open follow-up observation phase, with subsequent final evaluation (in comparison to the pre-operative status of both groups) after 6 months of continuous pallidum stimulation. After 6 months of follow-up, patients were assessed annually for 5 years in Volkmann (2012)[5] for the long-term device effect.

Study Population

The intended study population was subjects with idiopathic segmental, multifocal or generalized dystonia who benefit inadequately from drug treatment and who are seriously handicapped by the disease.

There were 8 study centers participating in the study, 7 centers in Germany and 1 center in Austria. The centers were chosen based on their experience with DBS Therapy. To participate, a center must have successfully treated 8 subjects with DBS Therapy, at least 2 with the target Globus Pallidus internus (GPi). In

addition, centers were required to have a projected implant rate of 10 patients per year.

Inclusion Criteria

- Presence of idiopathic multifocal segmental or generalized dystonia
- Duration of disease > 5 years
- Age between 14 and 75 years
- Relevant handicap in daily life, in spite of optimal drug therapy
- Presence of subject's written informed consent
- For adolescents between 14 and 18 years: additional written consent from parent or guardian

Exclusion Criteria

- Mattis Score < 120
- Beck depression inventory (BDI) > 25
- Prior stereotactic brain operations
- Marked cerebral atrophy
- Raised bleeding tendency
- Reduced resistance to infection
- Relevant cerebrovascular disease
- Psychiatric disease which could impair cooperation in the study
- Other contraindications

Study Device

Table 2 below describes the Medtronic DBS System components used in the Kupsch (2006)[4] study.

Table 2. Description of Dystonia DBS System Components

Device Component	Model
Neurostimulator	Model 7424 Itrel II Neurostimulator Model 7428 Kinetra Neurostimulator
DBS Leads	Model 3387 DBS Lead Model 3389 DBS Lead
Extensions	Model 7482/7483 DBS Extension Model 37085/37086 DBS Extension with Universal Port Plug
Accessories	Model 8840 N'Vision Clinician Programmer Model 8870 N'Vision Application Card Model 7438 Access Review Therapy Controller Model 7436 Access Therapy Controller Model 37642 Patient Programmer w/ optional 37092 antenna Models 64001 and 64002 Pocket Adaptor

Statistical Analysis

In Kupsch (2006)[4], the primary null hypothesis was an outcome of no significant difference in the change in the BFMDRS movement score (an average of the two scores recorded by observers who were unaware of the group assignments) from baseline to 3 months between patients receiving active neurostimulation and those receiving sham stimulation. Sample Size: 40 patients were needed to provide the study with 90% power to detect a 25% difference between treatment groups while allowing for an overall dropout rate of 10%, with a 5% probability of a type I error on the basis of a two-sided Mann–Whitney test. Data from all patients who underwent randomization were analyzed; missing values were imputed with the last observation carried forward.

Because not all patients were reconsented for use by Medtronic, only 30 of the 40 implanted patients are available for analysis. If the original power calculation was redone using the number of patients reconsented in each group (17 active and 13 sham), the estimated power for the primary analysis of the study remains over 80%. This reinforces the fact that 30 patients are sufficient to show significant benefit with this therapy. In the Investigator Study,[6] missing values were not imputed with the last observation carried forward. The analyses include only those patients who were reconsented for use by Medtronic.

Analyses by Dystonia Type
Analysis of effectiveness was completed by dystonia type. This analysis represents data from 18 patients with generalized dystonia and 11 patients with segmental dystonia. One additional patient with multifocal dystonia is excluded from this subgroup analysis.

Safety Objectives

- Systematic recording of the side-effects and adverse events.
- To characterize adverse events (AEs) for all subjects, including a tabulation of the profiles of the neurostimulation and sham stimulation group subjects through the 3-month blinded phase.

Primary Objectives
To demonstrate that the improvement in the movement score in the Burke-Fahn-Marsden-Dystonia-Rating-Scale (BFMDRS) for subjects in the DBS treatment group (neurostimulation) is greater than for subjects in the control group (sham stimulation) after 3 months of therapy.

The primary endpoint was a change from baseline to three months in severity of symptoms assessed with the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) movement score. Data from all of the investigational sites (30/40 patients) were pooled for analysis.

Secondary endpoints included the effect of neurostimulation on activities of daily living, the disability score on the BFMDRS, and quality of life (as assessed

with the SF-36).

The Kupsch (2006)[4] trial is registered with ClinicalTrials.gov, number NCT00142259.

Volkmann (2012)[5]

Volkmann (2012)[5] assessed the safety and effectiveness of bilateral GPi DBS in patients with primary generalized or segmental dystonia prospectively followed up for 5 years in the Kupsch (2006)[4] trial. 38 patients agreed to be followed up annually after the activation of neurostimulation, including assessments of dystonia severity, pain, disability, and quality of life. The primary endpoint of the 5-year follow-up study extension was the change in dystonia severity at 3 years and 5 years as assessed by open-label ratings of the BFMDRS motor score compared with the preoperative baseline and the 6-month visit. The primary endpoint was analyzed on an intention-to-treat basis.

Volkmann J (2014)[7]

Volkmann (2014)[7] was used as evidence to support the Medtronic DBS Dystonia system in bilateral GPi DBS therapy in primary cervical dystonia. Volkmann (2014)[7] used a similar study design as that in Kupsch (2006).[4] In brief, Volkmann (2014)[7] is a two-arm, double-blind, randomized, and placebo-controlled study design to demonstrate the safety and effectiveness of bilateral GPi DBS stimulation in patients with medication-refractory cervical dystonia.

Eligibility Criteria:

Aged 18–75 years, disease duration ≥3 years, TWSTRS severity score ≥15 points. 62 Patients were enrolled from 10 academic centers in Germany, Norway, and Austria.

Protocol

Patients were randomized in a 1:1 manner to receive either neurostimulation or sham (amplitude 0 V) stimulation by computer-generated randomization lists with randomly permuted block lengths stratified by center. All patients, masked to treatment assignment, were implanted with a DBS device and received their assigned treatment for 3 months, during which the neurostimulation group was administered pallidum stimulation (frequency 180 Hz; pulse width 120 μs; amplitude 0.5 V below adverse event threshold). In the sham stimulation group, the stimulator was set at 0 volts (V) so that there would be only placebo or apparent stimulation for 3 months. Drug therapy was freely adjusted to the subjects' requirements in both groups. The groups were unblinded after 3 months and the stimulation system in the sham stimulation group was then switched to the same parameters as the neurostimulation group. This was followed by an open follow-up observation phase, with subsequent final evaluation (in comparison to the pre-operative status of both groups) after 6 months of continuous pallidum

stimulation, i.e. 6 months post-operatively in the neurostimulation group and 9 months postoperatively in the sham stimulation group.

Statistical Analysis:
The primary null hypothesis was an outcome of no difference in the change of the TWSTRS severity score (mean of the two observer-blinded scores) from baseline to 3 months between patients receiving active neurostimulation and those receiving sham stimulation. It was estimated that a sample size of 60 patients, i.e., 30 per group, would power the study at 80% with a 5% probability of a type I error (two-sided Mann-Whitney U test of the primary null hypothesis). This design allows detection of a 20% difference between treatment groups with respect to the primary outcome criterion (percentage change in TWSTRS severity score) assuming a standard deviation (SD) of 25%, while making provision for an overall dropout rate of 10%. The primary endpoint was the change in the TWSTRS severity score from baseline to 3 months, assessed by two masked dystonia experts using standardized videos, analyzed by intention to treat. The key secondary outcome included change in TWSTRS disability. TWSTRS total score was one of the exploratory effectiveness endpoints.

This trial is registered with ClinicalTrials.gov, number NCT00148889.

4. Study Design: Meta-Analyses of Literature

Safety
A meta-analysis was conducted to evaluate rates of therapy-relevant safety events (excluding suicide and suicide attempt because of no reported occurrence in the patient populations evaluated), system revisions, and explants in adult patients based on the type of dystonia and in pediatric patients 12 years of age or above with primary generalized dystonia. Additionally, the analysis was conducted to compare these rates between adult and pediatric patients 12 years of age or above with primary generalized dystonia.

To avoid the possibility that the quantities estimated with different study designs (e.g., randomized controlled trials, prospective studies, retrospective studies/case controls) may not represent the same target of inference (e.g., estimates from randomized trials may be for unconditional treatment effects, while estimates from observational studies may represent treatment effects conditional on covariates), meta-analyses of safety were also conducted in both adult and pediatric patients with primary dystonia stratified by study designs.

Effectiveness
The meta-analysis was conducted to evaluate effectiveness outcomes in adult patients with primary generalized, segmental and cervical dystonia, and in pediatric patients with primary generalized dystonia. Additionally, a comparative analysis was conducted to evaluate differences in adults versus pediatric patients 12 years of age or above with primary generalized dystonia.

To avoid the possibility that the quantities estimated with different study designs may not represent the same target of inference, meta-analyses of effectiveness outcomes in both adult and pediatric patients were also conducted with different types of dystonia stratified by study design. Only one RCT for each dystonia type was included in the meta-analysis; therefore, only point estimate was provided for the RCT.

Data Extraction

- For safety outcomes, the proportion of patients with safety events was extracted from the publication or calculated by dividing the reported number of events by the number of patients enrolled in the study. If the authors specifically stated a type of event did not occur the rates were reported as 0 (0%). If the authors did not comment on a type of event, not reported (NR) is shown.
- For effectiveness outcomes, the average Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor score was used in the analysis for generalized dystonia and segmental dystonia. The average Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity score was used in the analysis for cervical dystonia.

Statistical Methods

Meta-analysis of dystonia effectiveness and safety were implemented using random-effects modeling with inverse variance weighting. All analyses were completed using the 'meta' package in R software which enabled the use of both fixed-effect and random effects models, depending on the level of heterogeneity observed among the studies. The random effects model was preferred in cases of significant heterogeneity, quantified using the I^2 statistic and Cochran's Q-test. The precision of pooled estimates was represented by 95% confidence intervals, ensuring a comprehensive understanding of variability within and across studies.[8,9]

- Safety assessment**:** The pooled proportions of therapy-relevant safety events were calculated separately for each dystonia type with the *metaprop* function from the 'meta' package in R. The individual proportion from each study was logit transformed before being pooled for overall proportion estimation. A continuity correction of 0.5 was applied to studies with zero events. Confidence intervals for individual studies used the Clopper-Pearson method, and random-effects models accounted for between-study heterogeneity.[10,11]

- Effectiveness assessment**:** Dystonia rating scale improvement (BFMDRS and TWSTRS) was measured as percentage change from baseline for effectiveness assessment. The pooled effect sizes were derived using the *metagen* function from the 'meta' package in R. Standard errors were computed from reported or imputed standard deviations to reflect score variability accurately. Confidence intervals were calculated using standard normal critical values to quantify estimate precision.

All safety and effectiveness meta-analyses were also conducted with stratification by study designs (e.g., randomized controlled trials, prospective studies, retrospective studies/case controls) to avoid the possibility that the quantities estimated with different study designs may not represent the same target of inference. Within each stratum, a random-effects model (REML estimator with Hartung–Knapp adjustment) was applied to appropriately account for between-study variability across study designs. When only a single study was available for a design stratum, the individual study was estimated and 95% confidence interval along with a narrative discussion of precision and risk of bias.

Subgroup analyses of adult vs pediatric were performed using stratified meta-analysis based on patient population (adult vs pediatric) by utilizing the option of subgroup in *metaprop* function in R. Differences were statistically tested using the Chi-square (χ^2) test for group differences, with significance defined as $p < 0.05$.[8–10,12]

5. Study Design: Product Surveillance Registry (PSR)

The PSR (the Registry) is sponsored by Medtronic and is comprised of a global network of hospitals, clinics and clinicians from which "real-world" product safety and patient clinical outcome information is generated. The purpose of the Registry is to provide continuing evaluation and periodic reporting of safety and effectiveness of market-released products for their intended use.

The PSR is a prospective, non-randomized, multi-center, global registry allowing new products to be easily added following market release. Patients are enrolled on a rolling basis without specified limits on the number of patients or end dates. Patients from all geographies where there are active PSR sites are followed prospectively in accordance with the routine care practices over the lifetime of their devices or upon exit from the registry. In addition to event collection, patients enrolled under the PSR protocol collect quality of life (EQ-5D) data at baseline and follow-up. The EQ-5D scoring generates an index score, with higher scores representing better health-related quality of life.

The primary objective of the PSR is continuing evaluation of safety and effectiveness of Medtronic market-released products for their intended use. Patients are followed prospectively for events related to the device, procedure, and/or therapy, as well as negative changes in behavior from baseline (e.g., depression, suicidal ideation). Events are further categorized as product performance events (PPE) or non-PPE.

The registry began as the Implantable Systems Performance Registry (ISPR) and started collecting data on deep brain stimulation (DBS) patients in 2009. Medtronic has continually worked to develop systems and processes to monitor product performance following market release more effectively and launched the

global Product Surveillance Registry (PSR) in 2011. This analysis represents the data collected through October 31, 2022.

The PSR is registered with ClinicalTrials.gov, number NCT01524276.

Data Collection
Patients were identified as receiving DBS for the treatment of dystonia if they met the following criteria:

- Primary purpose for device use is for symptomatic dystonia treatment
- Patients were consented
- Patients were implanted with a DBS system

Events that occurred on or after implant are included in the analysis. All device/therapy/procedure related adverse events are included in the adverse event summaries. All device events are included in the device event summaries, regardless of the associated device (i.e., neurostimulator, lead, extension).

Patients were categorized as Pediatric (21 years of age or less) or Adult (older than 21 years of age).

B. Safety and Effectiveness Results

Safety and effectiveness outcomes are presented separately for primary generalized, segmental, and cervical dystonia in adult patients (> 21 years) and for primary generalized dystonia in pediatric patients (≥ 12 years of age but ≤ 21 years of age). These categorizations are based on the dystonia type and average age reported in each publication or age of patients enrolled in the PSR registry.

1. Safety Results

Safety outcomes are presented separately for primary generalized, segmental, and cervical dystonia for adult patients and for pediatric patients 12 years of age or above. Comparisons of therapy-relevant safety events between adult and pediatric patients with primary generalized dystonia by study designs are also provided below to add more detailed information on the safety profile of bilateral GPi DBS for primary generalized dystonia treatment in pediatric patients 12 years of age or above.

- Safety Outcomes for Bilateral GPi DBS in Adult Patients

Primary Generalized Dystonia

Study Specific Data
The analysis of safety of bilateral GPi DBS for the treatment of primary generalized dystonia in adult patients was based on data from 18 patients with generalized dystonia in the Investigator Study[6]. A summary of adverse events (AEs) is presented in Table 3 below. During the randomization period, a total

of seven events were reported in 4 patients (neurostimulation: 2/9 and sham stimulation: 2/9) with generalized dystonia. Of the 7 events, two (neurostimulation: 1/9 and sham stimulation: 1/9) were considered serious adverse events (SAEs). During the randomization period, a total of two adverse device events (ADEs) were reported in 2 patients (neurostimulation: 1/9 and sham stimulation: 1/9) with generalized dystonia. The overall adverse event and serious adverse event occurrence rates were 22.2% and 11.1% in the 3-month blinded phase in the DBS group, and 72.2% and 55.6% in the open label phase, respectively.

Table 3. Adverse Event Summary – Generalized Dystonia in Adults

	Blinded Phase				**Open Label Phase**	
	Neurostimulation		**Sham Stimulation**		**All Patients**	
Event Type	**Events**	**Patients % (n/N)**	**Events**	**Patients % (n/N)**	**Events**	**Patients % (n/N)**
All Events	4	22.2% (2/9)	3	22.2% (2/9)	29	72.2% (13/18)
By seriousness						
SAE	1	11.1% (1/9)	1	11.1% (1/9)	23	55.6% (10/18)
Non-SAE	1	11.1% (1/9)	1	11.1% (1/9)	5	22.2% (4/18)
Not assessed	2	22.2% (2/9)	1	11.1% (1/9)	1	5.6% (1/18)
By relatedness						
ADE	1	11.1% (1/9)	1	11.1% (1/9)	20	61.1% (11/18)
Non-ADE	1	11.1% (1/9)	1	11.1% (1/9)	7	27.8% (5/18)
Not assessed	2	22.2% (2/9)	1	11.1% (1/9)	2	11.1% (2/18)

Adverse events with missing date will be classified as blinded phase.

Adverse events from baseline to 5 years are summarized in Table 4 below.

Table 4. Adverse Event Summary – Baseline to 5 years

	Serious		**Non-Serious**		**Not assessed**		**Total**	
Event Type	**Events**	**Patients (%) with an Event**	**Events**	**Patients (%) with an Event**	**Events**	**Patients (%) with an Event**	**Events**	**Patients (%) with an Event**
Loss of effect	5	27.8% (5/18)	0	0% (0/18)	0	0% (0/18)	5	27.8% (5/18)
Subcutaneous infection	5	16.7% (3/18)	0	0% (0/18)	0	0% (0/18)	5	16.7% (3/18)
No stimulation	4	22.2% (4/18)	2	5.6% (1/18)	1	5.6% (1/18)	7	27.8% (5/18)
Dystonia	3	11.1% (2/18)	1	5.6% (1/18)	0	0% (0/18)	4	16.7% (3/18)
Other	3	16.7% (3/18)	1	5.6% (1/18)	0	0% (0/18)	4	16.7% (3/18)
Dysarthria	2	11.1% (2/18)	0	0% (0/18)	0	0% (0/18)	2	11.1% (2/18)
Electrode fracture	1	5.6% (1/18)	0	0% (0/18)	0	0% (0/18)	1	5.6% (1/18)
Sensory disturbances	1	5.6% (1/18)	1	5.6% (1/18)	0	0% (0/18)	2	11.1% (2/18)
Stimulator malfunction	1	5.6% (1/18)	0	0% (0/18)	0	0% (0/18)	1	5.6% (1/18)
NA	0	0% (0/18)	0	0% (0/18)	3	16.7% (3/18)	3	16.7% (3/18)

	Serious		Non-Serious		Not assessed		Total	
Event Type	**Events**	**Patients (%) with an Event**	**Events**	**Patients (%) with an Event**	**Events**	**Patients (%) with an Event**	**Events**	**Patients (%) with an Event**
Facial weakness	0	0% (0/18)	1	5.6% (1/18)	0	0% (0/18)	1	5.6% (1/18)
Interrupted stimulation	0	0% (0/18)	1	5.6% (1/18)	0	0% (0/18)	1	5.6% (1/18)
Total	25	55.6% (10/18)	7	33.3% (6/18)	4	16.7% (3/18)	36	72.2% (13/18)

NA = Not available.

Safety Outcomes from the Publications

In addition to the Investigator Study,[6] the analysis of safety of bilateral GPi DBS for the treatment of primary generalized dystonia in adult patients also includes data from 6 publications representing a total of 173 patients contributing safety outcomes. These 6 publications consist of 3 prospective studies,[13–15] and 3 retrospective studies.[16–18]

Among the publications for generalized dystonia, dystonia severity was characterized by severe or marked disability, impaired function in performance of activities of daily living, or poor symptom control in spite of medical management.[6,13,14,16–19] Average age at surgery ranged from 22 to 38 years.[6,14–18] Duration of generalized dystonia before surgery ranged from 8 to 22 years.[6,14–16,18]

Across six other published studies, the reported incidence rates for AE and SAE ranged from 25% to 58%,[14–18] and 8 to 18%,[14–16,18] respectively, over a follow-up period spanning 6 months to 7 years of follow-up in adult patients with generalized dystonia.

Table 5 lists the reported occurrence of one or more therapy-relevant safety events in adult patients with generalized dystonia in each publication.

Table 5. Therapy-Relevant Safety Events in Adult Patients with GPi DBS for Generalized Dystonia[a]

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	Symptomatic ICH (n, %)	Asymptomatic ICH (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Device revisions (n, %)	Explants (n, %)
RCT (n=1)										
Investigator-Sponsored Clinical Study[6]	18	DBS: 38.2 ± 12.9 Sham: 38.1 ± 8.7	6 mos. - 5 yrs.	0 (0%)	0 (0%)	3/18 (16.7%)	11/18 (61.1%)	NR	10/18 (55.6%)	4/18 (22.2%: 2 subcutaneous infections, 1 dystonia, 1 loss of effect)
Prospective Studies (n=3)										
Coubes (2004)[13]	12	NR	42.1 ±14.8 mos.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NR	NR
Valldeoriola (2010)[14]	24	30 ± 14	12 mos.	1/24 (4.2%)	NR	1/24 (4.2%)	1/24 (4.2%: 1 fracture of the cable)	NR	1/24 (4.2%: 1 fracture of the cable)	2/24 (8.3%: 1 infection, 1 skin allergic reaction)
Vidailhet (2007)[15]	17	36.3[b] (range: 22-53)	3 yrs.	NR	NR	1/17 (5.9%)	2/17 (11.8%: 1 lead fractures)	NR	1/17 (5.9%: 1 lead fracture)	1/17 (5.9%: 1 infection)
Retrospective Studies (n=3)										
Fitzgerald (2014)[16]	60	33.5	5 yrs.	NR	NR	8/60 (13.3%)	11/60 (18.3%, 6 lead revisions due to suboptimal placement, 3 lead fracture, 1 lead erosion, 1 wound granuloma)	NR	8/60 (33.3%; 6 lead revisions, 2 extensions and INS replaced due to infection)	7/60 (11.7%; 7 device removals due to infection)
Isaias (2009)[17]	30	28 ± 17	Up to 8 yrs.	0 (0%)	0 (0%)	4/30 (13.3%)	6/30 (20%: 2 fractured extension cables, 1 scalp erosion, 1 IPG malfunction, 2 lack of benefit)	NR	6/30 (20%)	NR
Sobstyl (2014)[18b]	12	DYT-1 positive: 21.7 DYT-1 negative: 23.1	Up to 5 yrs.	0 (0%)	0 (0%)	NR	7/12 (58.3%, 7 pts. total: 4 electrode breakages, 2 unexpected rapid battery depletions, 2 erosions, 1 suboptimal lead position, 1 seroma)	NR	7/12 (58.3%)	NR

[a] If the authors specifically stated a type of event did not occur the rates were reported as 0 (0%). If the authors did not comment on a type of event, not reported (NR) is shown.

[b] Estimated from individual patient data reported in the publication

Table 6 summarizes overall results of the meta-analysis of therapy-relevant safety outcomes in adult patients with GPi DBS for Generalized Dystonia using a random effects model.

For adult patients with generalized dystonia, device complications (22%), infections (12%), and intracerebral hemorrhage (symptomatic: 3%, asymptomatic: 0%) are the main therapy-related safety events. Device revisions (19%) and explants (13%) are the most common other safety events. These rates are based on pooled data from multiple publications.
Device complications and revisions are the most frequent safety events, followed by infections. Symptomatic and asymptomatic intracerebral hemorrhage (ICH) are less common. Substantial heterogeneity was observed for both device complication rates and device revision rates. The reasons for the variability may be multifactorial and influenced by experience gained over time with DBS implant surgery and differences in reporting device complications and revisions.

Table 6. Pooled Therapy-Relevant Safety Event Rates in adult patients with GPi DBS for Generalized Dystonia using Random Effects Model

Safety Event	Pooled Event Rate (95% CI)	No. of Publications	References
Therapy-Relevant Safety Events			
Device complications	22% (10-44%)	7	[6,13–18]
Infection	12% (8-18%)	6	[6,13–17]
Symptomatic ICH	3% (1-9%)	5	[6,13,14,17,18]
Asymptomatic ICH	0% (0-26%)	4	[6,13,17,18]
Other Safety Events			
Device revisions	19% (8-40%)	6	[6,14–18]
Explants	13% (8-20%)	4	[6,14–16]

Primary Segmental Dystonia of the Head and Neck

Study Specific Data
The analysis of safety of bilateral GPi DBS for the treatment of primary segmental dystonia in adult patients was based on data from 11 patients with primary segmental dystonia in the Investigator Study[6].

The analysis of safety of bilateral GPi DBS for the treatment of primary generalized dystonia in adult patients was based on data from 11 patients with segmental dystonia in the Investigator Study[6]. A summary of AEs is presented in Table 7 below. There were nine events reported in 7 patients (neurostimulation: 4/7 and sham stimulation: 3/4) with segmental dystonia, and four were considered SAEs in three patients (neurostimulation: 2/7 and sham stimulation: 1/4). During the open label phase after 6 months of continuous stimulation, 16 AEs were reported in 8 (72.7%) patients with segmental dystonia. During the randomization period, five ADEs were

reported in 4 patients (neurostimulation: 3/7 and sham stimulation: 1/4) with segmental dystonia. The overall AE and SAE occurrence rates were reported as 57.1% and 28.6% in the 3-month blinded phase in the DBS group, and 72.7% and 63.6% in the open label phase, respectively.

Table 7. Adverse Event Summary – Segmental Dystonia in Adults

Event Type	Blinded Phase				Open Label Phase	
	Neurostimulation		Sham Stimulation		All Patients	
	Events	Patients % (n/N)	Events	Patients % (n/N)	Events	Patients % (n/N)
All Events	6	57.1% (4/7)	3	75.0% (3/4)	16	72.7% (8/11)
By seriousness						
SAE	3	28.6% (2/7)	1	25.0% (1/4)	12	63.6% (7/11)
Non-SAE	2	28.6% (2/7)	0	0 % (0 /4)	3	27.3% (3/11)
Not assessed	1	14.3% (1/7)	2	50.0% (2/4)	1	9.1% (1/11)
By relatedness						
ADE	4	42.9% (3/7)	1	25.0% (1/4)	13	54.5% (6/11)
Non-ADE	1	14.3% (1/7)	0	0 % (0 /4)	2	18.2% (2/11)
Not assessed	1	14.3% (1/7)	2	50.0% (2/4)	1	9.1% (1/11)

Adverse events with missing date will be classified as blinded phase.

Adverse events from baseline to 5 years are summarized in Table 8 below.

Table 8. Adverse Event Summary - Baseline to 5 years- Segmental Dystonia

Event Type	Serious		Non-Serious		Not assessed		Total	
	Events	Patients (%) with an Event	Events	Patients (%) with an Event	Events	Patients (%) with an Event	Events	Patients (%) with an Event
Dysarthria	6	18.2% (2/11)	3	27.3% (3/11)	0	0% (0/11)	9	45.5% (5/11)
Loss of effect	2	18.2% (2/11)	1	9.1% (1/11)	0	0% (0/11)	3	27.3% (3/11)
Other	2	18.2% (2/11)	1	9.1% (1/11)	0	0% (0/11)	3	18.2% (2/11)
Depression	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
Dystonia	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
Electrode fracture	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
Gait disturbances	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
Interrupted stimulation	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
Stimulator malfunction	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
NA	0	0% (0/11)	0	0% (0/11)	3	27.3% (3/11)	3	27.3% (3/11)
Rebound	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)	1	9.1% (1/11)

Event Type	Serious		Non-Serious		Not assessed		Total	
	Events	Patients (%) with an Event	Events	Patients (%) with an Event	Events	Patients (%) with an Event	Events	Patients (%) with an Event
Total	16	72.7% (8/11)	5	45.5% (5/11)	4	36.4% (4/11)	25	90.9% (10/11)

NA = Not available.

Safety Outcomes from the Publications

In addition to the Investigator Study,[6] the analysis of safety of bilateral GPi DBS for the treatment of segmental dystonia in adult patients also includes data from 8 published studies with a total of 101 patients contributing safety outcomes. The 8 publications consist of 2 prospective studies[20,21] and 6 retrospective studies.[22–27]

Among the publications for segmental dystonia, severity was characterized by severe symptoms, marked disability or functional impairment, or failed or discontinued medications or botulinum neurotoxin due to no or slight effect.[6,20–27] Average age at surgery ranged from 47 to 67 years.[6,20–27] Duration of segmental dystonia before surgery ranged from 3 to 20 years.[6,20–27]

Across eight other published studies, the reported incidence rates for AE and SAE are 8.3% to 100%,[20–26] and 0 to 25%,[26,27] respectively, over a follow-up period of 6 months to 5.6 years in adult patients with segmental dystonia of the head and neck.

Table 9 lists the reported occurrence of one or more therapy-relevant safety events in adult patients with GPi DBS for segmental dystonia in each publication.

Table 9. Therapy-Relevant Safety Events in Adult Patients with GPi DBS for Segmental Dystonia[a]

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	Symptomatic ICH (n, %)	Asymptomatic ICH (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Device revisions (n, %)	Explants (n, %)
RCT (n=1)										
Investigator-Sponsored Clinical Study[6]	11	DBS: 51.3 ± 12.8 Sham: 50.8 ± 15.3	5 yrs.	0 (0%)	0 (0%)	0 (0%)	6/11 (54.5%)	NR	6/11 (54.5%)	1/11 (9.1%)
Prospective Studies (n=2)										
Blahak (2008)[20]	10	57.4 ± 15.0	17 mos.	0 (0%)	0 (0%)	0 (0%)	1/10 (10%: 1 small superficial skin granuloma above the stimulation lead)	NR	0 (0%)	0 (0%)
Ostrem (2007)[21]	6	62.6	6 mos.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Retrospective Studies (n=6)										
Fu (2024)[22]	23	52.4 ± 7.4	38.3 mos.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NR	NR	NR
Horisawa (2019)[23]	16	51.4	66.6 ± 40.7 mos. (range 13–150)	NR	NR	1/16 (6.3%)	1/16 (13.5%, 1 lead breakage)	NR	NR	1/16 (6.3%: 1 infection and lead breakage in same patient)
Reese (2011)[24]	12	64.5 ± 4.4	38.8 ± 21.7 mos.	0 (0%)	0 (0%)	1/12 (8.3%)	0 (0%)	NR	1/12 (8.3%: 1 infection)	NR
Ren (2022)[25]	13	46.9 ± 7.2	36.6 ± 11.0 mos. (range 18–55)	0 (0%)	0 (0%)	1/13 (7.7%)	NR	NR	1/13 (7.7%: 1 pouch position changed after infection)	NR
Sharma (2020)[26]	4	66.5 (range 54 – 79)[b]	1 yr.	1/4 (25%)	NR	1/4 (25%)	1/4 (25%: 1 lead fracture)	NR	NR	1/4 (25%: 1 infection & lead fracture)
Tian (2021)[27]	6	61.2 (range 53 – 71)[b]	43.7	0 (0%)	0 (0%)	0 (0%)	NR	NR	NR	NR

[a] If the authors specifically stated a type of event did not occur the rates were reported as 0 (0%). If the authors did not comment on a type of event, not reported (NR) is shown.

[b] Estimated from individual patient data reported in the publication

Table 10 summarizes overall results of the meta-analysis of therapy-relevant safety outcomes in adult patients with GPi DBS for segmental dystonia using a random effects model.

For adult patients with segmental dystonia, device complications (13%), infections (7%), and intracerebral hemorrhage (symptomatic: 6%, asymptomatic: 4%) are the main therapy-related safety events. Device revisions (14%) and explants (9%) are the most common other safety events. These rates are based on pooled data from multiple publications.

High heterogeneity was observed in device complications and device revision rates, likely influenced by clinical factors such as surgical experience and reporting practices.

Table 10. Pooled Therapy-Relevant Safety Event Rates in Adult Patients with GPi DBS for Segmental Dystonia Using Random Effects Model

Safety Event	Pooled Event Rate (95% CI)	No. of Publications	References
Therapy-Relevant Safety Events			
Device complications	13% (4-32%)	7	6,20–24,26
Infection	7% (3-15%)	9	6,20–27
Symptomatic ICH	6% (2-15%)	8	6,20–22,24–27
Asymptomatic ICH	4% (2-12%)	7	6,20–22,24,25,27
Other Safety Events			
Device revisions	14% (4-41%)	5	6,20,21,24,25
Explants	9% (3-22%)	5	6,20,21,23,26

Cervical Dystonia

Study Specific Data

The analysis of safety of bilateral GPi DBS for the treatment of primary cervical dystonia in adult patients was based on primary source data from 62 patients with cervical dystonia in the Volkmann (2014)[7] RCT. The neurostimulation group reported 5 SAEs (16%, 5/32) compared to 11 SAEs (37%, 11/30) in the sham group, with 69% (11/16) resolving without sequelae (Table 11).

Table 11. Adverse Event Summary for Cervical Dystonia in Adults (Volkmann 2014)

Event Type	Open Label Phase					
	Neurostimulation (n=32)		Sham Stimulation (n=30)		All Patients (n=62)	
	Events	Patients % (n/N)	Events	Patients % (n/N)	Events	Patients % (n/N)
SAE	5	15.6% (5/32)	11	36.7% (11/30)	16	25.8% (16/62)

Event Type	Open Label Phase					
	Neurostimulation (n=32)		Sham Stimulation (n=30)		All Patients (n=62)	
	Events	Patients % (n/N)	Events	Patients % (n/N)	Events	Patients % (n/N)
Non-SAE (AEs)	21	65.6% (21/32)	20	66.7% (20 /30)	41	66.1% (41/62)

Safety Outcomes from the Publications

In addition to Volkmann (2014)[7], the analysis of safety of bilateral GPi DBS for the treatment of cervical dystonia in adult patients also include data from 8 published studies with a total of 183 patients contributing safety outcomes. Among the publications on cervical dystonia, 7 studies[28–34] reported average age at surgery in the 50s to low 60s. [7] Two studies[35,36] reported an average age of surgery in the 40s, 1 study[26] in the low 70s and 1 study[37] did not report age at surgery. Volkmann (2014)[7] reported a duration of disease of 15 years. Duration of disease trended shorter in 6 studies[28,30,31,35–37] published since 2015, ranging from 3 to 6 years. One study[26] published in 2020 had a disease duration of 17 years before surgery.

Across nine other published studies, the reported incidence rates for AE and SAE were 3.8% to 80%[26,28–30,32–35] and 0 to 14.3%,[26,28,29,35,38] respectively, over a follow-up period of 1 year to 10 years in adult patients with cervical dystonia.

Table 12 lists the reported occurrence of one or more therapy-relevant safety events in adult dystonia patients with GPi DBS for cervical dystonia in each publication.

Table 12.Therapy-Relevant Safety Events in Adult Patients with GPi DBS for Cervical Dystonia[a]

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	ICH (symptomatic) (n, %)	ICH (asymptomatic) (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Device revisions (n, %)	Explants (n, %)
RCT of GPi for Cervical Dystonia (n=1)										
Volkmann (2014)[7]	62	DBS: 57.1 ± 9.82 Sham: 56.6 ± 11.33	6 mos.	1/62 (1.6%, 1 hemiparesis or stroke)	NR	3/62 (4.8%)	5/62 (8.1%, 1 tethering of extension cable, 2 electrode dislocations, 1 electrode misplacement, 1 IPG dislocation)	NR	2/62 (3.2%): 2 surgical exchange of device components	1/62 (1.6%)
Prospective Study of GPi for Cervical Dystonia (n=1)										
Walsh RA (2013)[34]	10	55.5 ± 12.8	7.8 yrs. (range 4.9–10.7)	NR	NR	2/10 (20%)	1/10 (10%, 1 suboptimal lead placement)	NR	4/10 (40%): 2 lead removals, 1 lead replacement, 1 lead repositioned	1/10 (10%): 1 infection
Retrospective Studies of GPi for Cervical Dystonia (n=7)										
Chung M (2015)[28]	25	52.2 ± 9.6	19.9 ± 11.5 mos.	2/25 (8.0%)	NR	1/25 (4.0%)	2/25 (8.0%, 1 electrode reposition, 1 extension line revision)	NR	2/25 (8.0%): 1 electrode reposition, 1 extension line revision	NR
Contarino MF (2014)[29]	15	56.5 ± 14.8 (range: 29-77)	2.3 ± 0.9 mos. (range 1–4)	1/15 (7%)	NR	NR	5/15 (33%, 1 tight extension, 1 painful moving IPG, 1 lead fracture and contralateral lead migration, 1 electrode fixation replacement, 1 electrode repositioning)	NR	5/15 (33%): 1 tight extension, 1 painful moving IPG, 1 lead fracture and contralateral lead migration, 1 electrode fixation replacement, 1 electrode repositioning	NR
Cui Z (2022)[35]	53	44.79 ± 12.88	40.49 ± 19.82 mos.	2/53 (3.8%)	NR	NR	0 (0%)	NR	NR	NR
Jacksch C (2022)[32]	15	61.5	10 yrs.	NR	NR	1/15 (6.7%)	2/15 (13.3%, 2 cable tractions)	NR	3/15 (20.0%): 2 revisions for cable traction, 1 pulse generator replacement for infection	NR

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	ICH (symptomatic) (n, %)	ICH (asymptomatic) (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Device revisions (n, %)	Explants (n, %)
Sharma (2020)[26]	7	72.6 ± 16.5 (range: 51-98)[b]	1 yr.	1/7 (14.3%)	NR	NR	1/7 (14.3%: 1 tethering of extension wire)	NR	NR	NR
Wang X (2020)[36]	23	41.13 ± 13.49 (range: 16-70)	19.04 ± 16.30 mos. (range 3–74)	0/23 (0%)	0/23 (0%)	NR	NR	NR	0/23 (0%)	NR
Witt JL (2013)[33]	28	56.0 ± 10.4 (range: 33-70)	33.7 ± 25.0 mos. (range 4–97)	NR	3/28 (10.7%)	1/28 (3.6%)	2/28 (7.1%, 2 suboptimal lead placement)	NR	3/28 (10.7%): 2 lead replacement, 1 system reimplantation	1/28 (3.6%)

[a]If the authors specifically stated a type of event did not occur; the rates were reported as 0 (0%). If the authors did not comment on a type of event, not reported (NR) is shown.

[b] Estimated from individual patient data reported in the publication

Table 13 summarizes overall results of the meta-analysis of therapy-relevant safety outcomes in adult patients with GPi DBS for cervical dystonia using a random effects model.

For adult patients with cervical dystonia, device complications (11%), infections (7%), and intracerebral hemorrhage (symptomatic: 5%) are the main therapy-related safety events. Device revisions (14%) and explants (4%) are the most common other safety events. The event rates are based on pooled data from multiple publications, providing robust estimates for these outcomes.

Device complications and revisions are the most frequent safety events in cervical dystonia for adult patients with moderate to high heterogeneity, likely influenced by clinical factors such as surgical experience and reporting practices.

Table 13. Pooled Therapy-Related Safety Event Rates in Adult Patients with GPi DBS for Cervical Dystonia Using Random Effects Model

Safety Event	Pooled Event Rate (95% CI)	No. of Publications	References
Therapy-Relevant Safety Events			
Device complications	11% (6-19%)	8	[7,26,28,29,32–35]
Infection	7% (3-13%)	5	[7,28,32–34]
Symptomatic ICH	5% (2-10%)	6	[7,26,28,29,35,36]
Asymptomatic ICH	NR	NA	NA
Other Safety Events			
Device revisions	14% (6-28%)	7	[7,28,29,32–34,36]
Explants	4% (1-11%)	3	[7,33,34]

- Safety Outcomes for Bilateral GPi DBS in Pediatric Population with Primary Generalized Dystonia

  The analysis of safety of GPi DBS for the treatment of primary generalized dystonia in pediatric patients 12 years of age or above was based on data from 12 publications evaluating 202 pediatric patients contributing safety outcomes. The published studies consist of 4 prospective[13,15,39,40] and 8 retrospective studies.[41–48]

  The published studies compared reasonably well in baseline patient characteristics. Most pediatric patients in these studies received bilateral GPi DBS for primary generalized dystonia. Dystonia severity was characterized as severe or significant disability or impairment in daily activities despite medical management.[13,15,39–41,43,46–48] Average age at surgery ranged from 10

to 17 years.[15,39–43,45–48] Duration of dystonia symptoms before surgery ranged from 3 to 10 years.[15,39–48]

Across 12 published studies, the reported incidence rates for AE and SAE were 0% to 100%[13,15,39–43,45–48] and 0 to 60%,[15,40,41,43] respectively, over a follow-up period of 6 months to 10 years in pediatric patients with generalized dystonia.

Table 14 lists the reported occurrence of one or more therapy-relevant safety events in pediatric dystonia patients with GPi DBS for generalized dystonia in each publication.

Table 14. Therapy-Relevant Safety Events in Pediatric Populations with GPi DBS Generalized Dystonia[a]

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	ICH (symptomatic) (n, %)	ICH (asymptomatic) (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Revisions (n, %)	Explants (n, %)
Prospective Studies (n=4)										
Borggraefe (2010)[39]	24	14.2 ± 3.4 (range: 9-20)	12.0 ± 4.8 mos.	NR	NR	3/24 (12.5%)	9/24 (37.5%: 6 unexplained switching off the stimulator, 2 electrode migration, 1 cable perforation)	NR	4/24 (16.7%: 3 exchanges of electrodes for infection, 1 abdominal pouch revision)	NR
Coubes (2004)[13]	19	≤ 17	42.1 ±14.8 mos.	0 (0%)	0 (0%)	1/19 (5.3%)	NR	NR	1/19 (5.3%)	NR
Starr (2014)[40]	6	10.2 (range: 7-13) [b]	12 mos.	0 (0%)	0 (0%)	NR	1/6 (16.7%: 1 open circuit on lead)	NR	NR	NR
Vidailhet (2007)[15]	5	17.2 (range: 15-19) [b]	3 yrs.	NR	NR	NR	NR	NR	NR	NR
Retrospective Studies (n=8)										
Ghosh (2012)[41]	6	13.2 (range: 8-21) [b]	5.8 ± 1.4 yrs. (range 4–8) primary dystonia)	0 (0%)	0 (0%)	0 (0%)	2/6 (33.3%: 1 electrode dislocation, 1 extension breakage)	NR	2/6 (33.3%: 1 electrode dislocation, 1 extension breakage)	NR
Haridas (2011)[42]	22	13.4 ± 2.7 (range: 9-21)	2 yrs.	0 (0%)	0 (0%)	3/22 (13.6%)	5/22 (22.7%: 2 desire to improve clinical response, 1 lead fracture, 1 extension cable fracture, 1 suboptimal lead position)	NR	8/22 (36.4%: 3 infections, 2 desire to improve clinical response, 1 lead fracture, 1 suboptimal lead position, 1 extension cable fracture)	NR
Krause (2016)[43]	8	12.5 ± 3.5 (range: 7-17)	58.5 ± 18.0 mos. (range 20–156)	NR	NR	NR	2/8 (25%: 1 IPG dislocation, 1 electrode revision)	NR	2/8 (25%; 1 IPG dislocation, 1 bilateral	NR

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	ICH (symptomatic) (n, %)	ICH (asymptomatic) (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Revisions (n, %)	Explants (n, %)
									electrode revision)	
Lumsden (2013)[44]	70 (63 after excluding 7 patients)	12.8 (range: 4.6-17.5) [b]	12 mos.	NR	NR	5/70 (7.1%)	NR	NR	NR	5/70 (7.1%; removal of part of the implanted stimulating system within first 6 mos. following surgery)
Markun (2012)[45]	14	15.5 ± 5.7 (range: 10-27)	32.2±17.9 (7-77) mos.	NR	1/14 (7.1%)	NR	3/14 (21.4%: 2 lead extender fractures, 1 lead repositioning)	NR	3/14 (21.4%: 2 lead extender fractures, 1 lead repositioning)	NR
Marotta (2020)[48]	9	16.0 (range: 14-17)	13 mos.	NR	1/9 (11.1%)	NR	0 (0%)	NR	0 (0%)	0 (0%)
Petrossian MT (2013)[46]	8	13.3 range: (9-17)[b]	50.8 mos. (median 52.5 mos., range 16–84)	0 (0%)	0 (0%)	2/8 (25%)	2/8 (25%: 2 lead fractures)	NR	0 (0%)	1/8 (12.5%: 1 infection)
Ramezani Ghamsari M (2021)[47]	11	14.72 ± 3.71 (range: 9-20)	8.5 ± 6.9 yrs. (range 7–10)	NR	NR	0 (0%)	0 (0%)	NR	NR	NR

[a]If the authors specifically stated a type of event did not occur; the rates were reported as 0 (0%). If the authors did not comment on a type of event, not reported (NR) is shown.

[b] Estimated from individual patient data reported in the publication

Table 15 summarizes overall results of the meta-analysis of therapy-relevant safety outcomes in pediatric patients with GPi DBS for generalized dystonia using a random effects model.

For pediatric patients with generalized dystonia, device complications (26%), infections (16%), and intracerebral hemorrhage (symptomatic: 4%, asymptomatic: 6%) are the main therapy-related safety events. Device revisions (21%) and explants (20%) are the most common other safety events. The event rates are based on pooled data from multiple publications, providing robust estimates for these outcomes.

Device complications, device revisions, and explants are the most frequent safety events in pediatric patients. Clinical factors (e.g., surgical experience, reporting practices) may drive this the high device-related events.

Table 15. Pooled Therapy-Relative Safety Event Rates in Pediatric Patients with GPi DBS for Generalized Dystonia Using Random Effects Model

Safety Event	Pooled Event Rate (95% CI)	No. of Publications	References
Therapy-Relevant Safety Events			
Device complications	26% (18-35%)	9	39–43,45–48
Infection	16% (9-25%)	7	13,39,41,42,44,46,47
Symptomatic ICH	4% (1-14%)	5	13,40–42,46
Asymptomatic ICH	6% (2-14%)	7	13,40–42,45,46,48
Other Safety Events			
Device revisions	21% (13-22%)	8	13,39,41–43,45,46,48
Explants	20% (7-43%)	3	44,46,48

- Comparison of Therapy-Relevant Safety Events Between Adult and Pediatric Patients with Generalized Dystonia by Study Designs

  A safety meta-analysis compared adult and pediatric patients with generalized dystonia using prospective and retrospective studies, as no randomized trials existed for pediatric patients. There were no RCTs included in the pediatric analysis; therefore, the safety meta-analysis for adult vs pediatrics by study design is limited to prospective and retrospective studies only. Summary of safety events by study design comparing adult and pediatric patients with primary generalized dystonia is provided below.

  Device Complications

  Figure 2 presents a forest plot and detailed comparison of device complication rates between adult and pediatric patients with generalized dystonia by study design, with data pooled from the prospective studies (a) and retrospective studies (b) using a random effects model.

Prospective Studies: Using a random effects model, the pooled device complication rate was 7% (95% CI: 3–19%) for adult patients and 34% (95% CI: 19–53%) for pediatric patients, with no heterogeneity among studies. The combined device complication rate across both dystonia types was 14% (95% CI: 5–34%), with high heterogeneity across both groups (p=0.0502).

Retrospective Studies: Using a random effects model, the pooled device complication rate was 30% (95% CI: 4–83%) for adult patients and 21% (95% CI: 14–32%) for pediatric patients. No heterogeneity was observed in pediatric studies, but high heterogeneity was observed in adult studies (I^2 = 75.7%, τ^2 = 0.6925, p=0.0165). The combined device complication rate was 24% (95% CI: 16–35%), with low heterogeneity across both groups (p=0.2083).

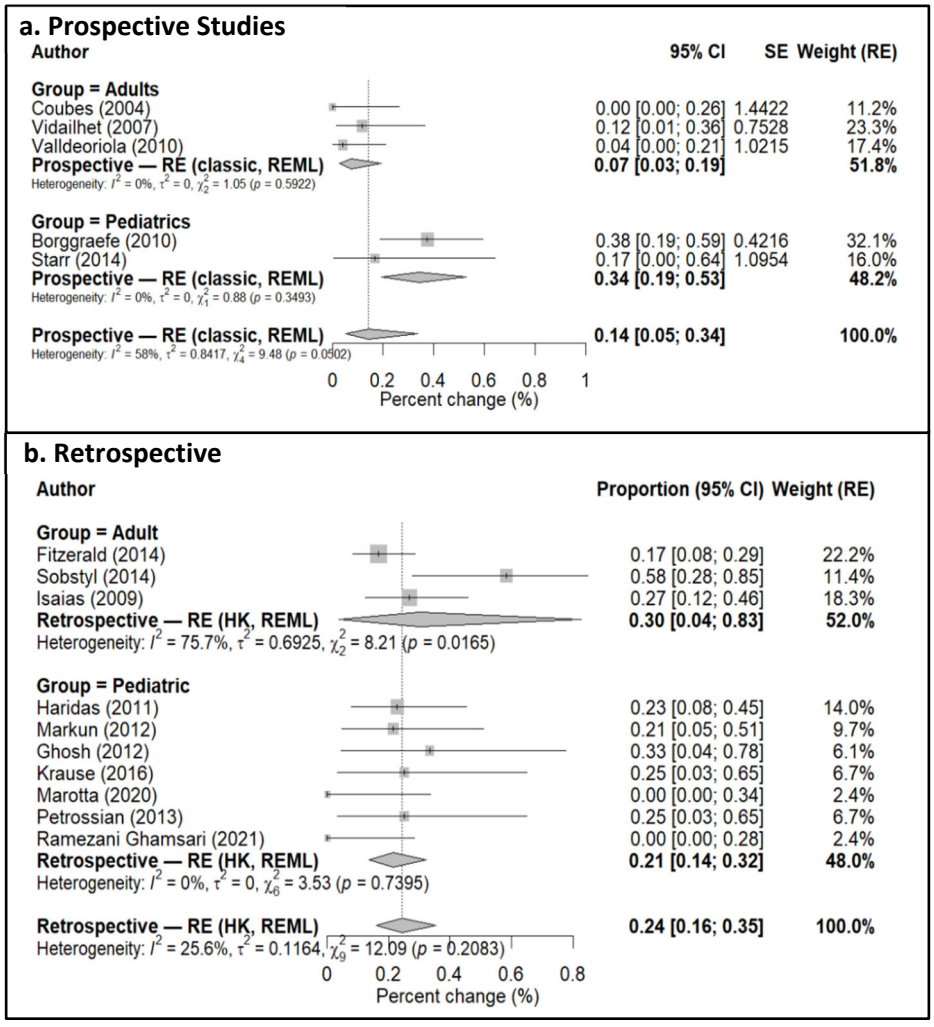

Figure 2. Forest Plot of Device Complication Rates in Adult and Pediatric Patients with Generalized Dystonia by Study Designs, a) Prospective, b) Retrospective.

Infection

Figure 3Figure 3 presents a forest plot and detailed comparison of device infection rates between adult and pediatric patients with generalized dystonia by study design, with data pooled from the prospective studies (a) and retrospective studies (b) using a random effects model.

Prospective Studies: Using a random effects model, the pooled infection rate was 5% (95% CI: 1–15%) for adult patients and 10% (95% CI: 4–24%) for pediatric patients, with no heterogeneity among studies. The combined infection rate for both dystonia types was 7% (95% CI: 3–15%) with no heterogeneity across both groups (p=0.7992).

Retrospective Studies: Using a random effects model, the pooled infection rate was 15% (95% CI: 9–23%) for adult patients and 19% (95% CI: 11–32%) for pediatric patients, with no heterogeneity among studies. The combined infection rate was 16% (95% CI: 11–24%), with no heterogeneity across both groups (p=0.6158).

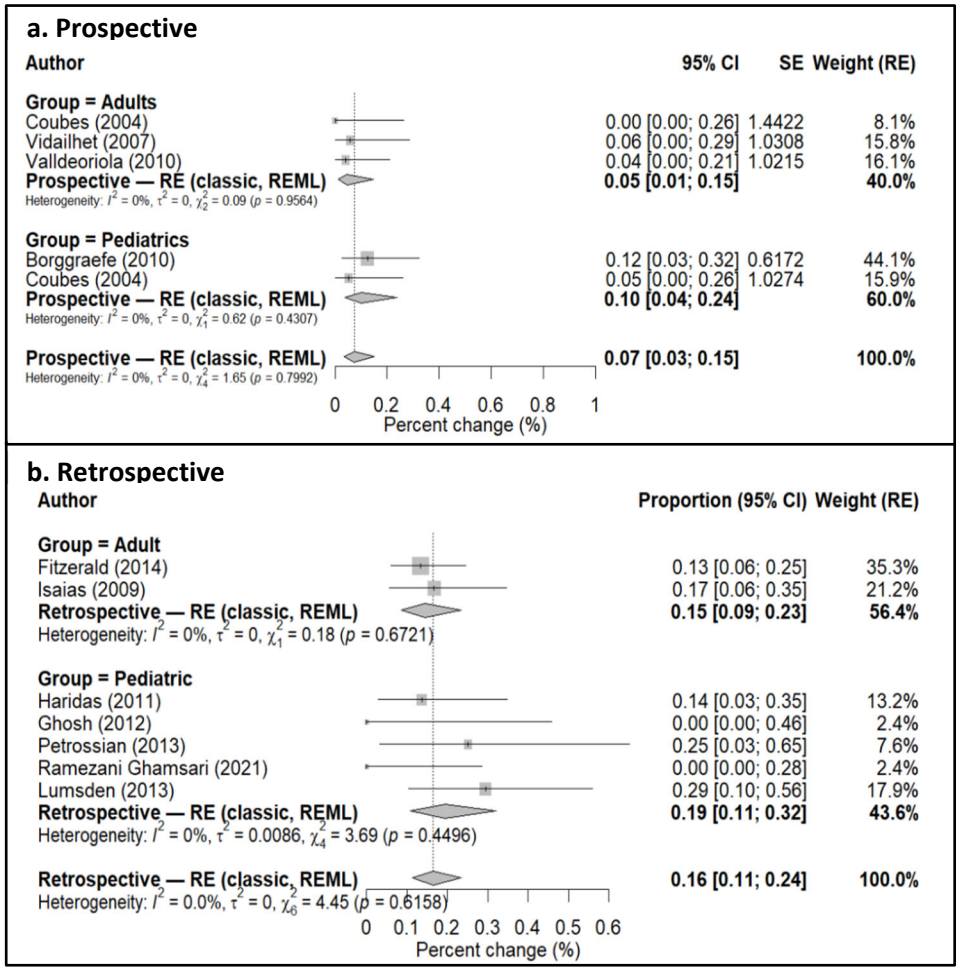

Figure 3. Forest Plot of Infection Rates in Adult and Pediatric Patients with Generalized Dystonia by Study Design, a) Prospective, b) Retrospective.

Symptomatic ICH

Figure 4 presents a forest plot and detailed comparison of symptomatic ICH rates between adult and pediatric patients with generalized dystonia by study design, with data pooled from the prospective studies (a) and retrospective studies (b) using random effects model.

Prospective Studies: Using a random effects model, the pooled symptomatic ICH rate was 4% (95% CI: 1–18%) for adult patients and 4% (95% CI: 1–25%) for pediatric patients, with no heterogeneity among studies. The combined symptomatic ICH rate was 4% (95% CI: 1–13%) with no heterogeneity across both groups (p=0.9619).

Retrospective Studies: Using a random effects model, the pooled symptomatic ICH rate was 2% (95% CI: 0–16%) for adult patients and 4% (95% CI: 1–19%) for pediatric patients, with no heterogeneity among studies. The combined symptomatic ICH rate was 3% (95% CI: 1–11%) with no heterogeneity across both groups (p=0.9378).

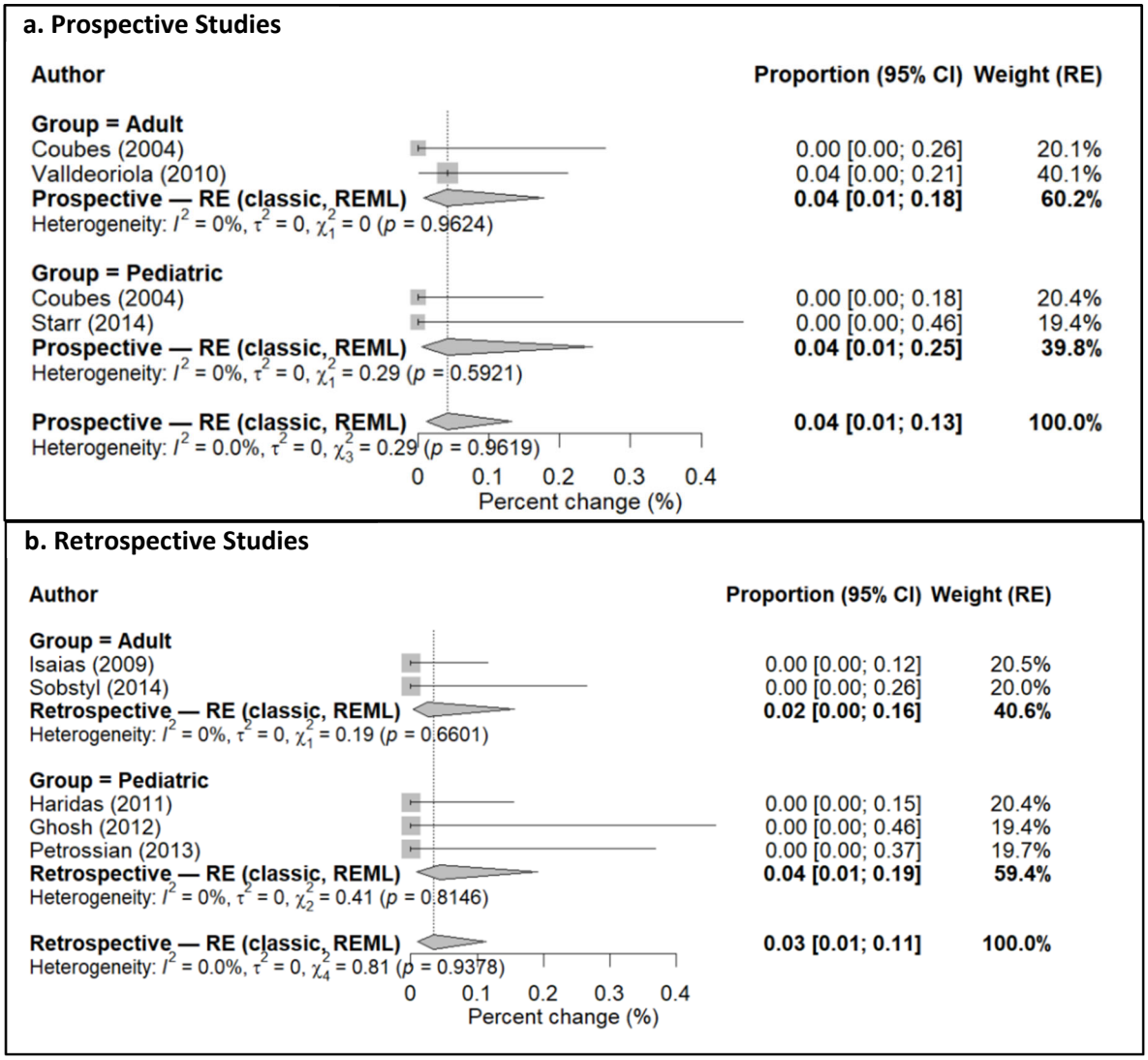

Figure 4. Forest Plot of Symptomatic Intracranial Hemorrhage Rates in Adult and Pediatric Patients with Generalized Dystonia by Study Design, a) Prospective, b) Retrospective.

Asymptomatic ICH

Figure 5 presents a forest plot and detailed comparison of asymptomatic ICH rates between adult and pediatric patients with generalized dystonia by study design, with data pooled from the prospective studies (a) and retrospective studies (b) using random effects model.

Prospective Studies: Only one prospective study in the adult cohort reported on asymptomatic ICH rates. The point estimate of asymptomatic ICH rate in this study for adult patients was 0% (95% CI: 0–26%) and the pooled estimate of asymptomatic ICH rate for two studies for pediatric patients was 4% (95% CI: 1–25%), with no heterogeneity among studies.

The combined asymptomatic ICH rate was 4% (95% CI: 1–18%) with no heterogeneity across both groups (p=0.8652).

Retrospective Studies: Using a random effects model, the pooled asymptomatic ICH rate was 2% (95% CI: 0–16%) for adult patients and 7% (95% CI: 2–17%) for pediatric patients, with no heterogeneity among studies. The combined asymptomatic ICH rate was 5% (95% CI: 2–13%) with no heterogeneity across both groups (p=0.9261).

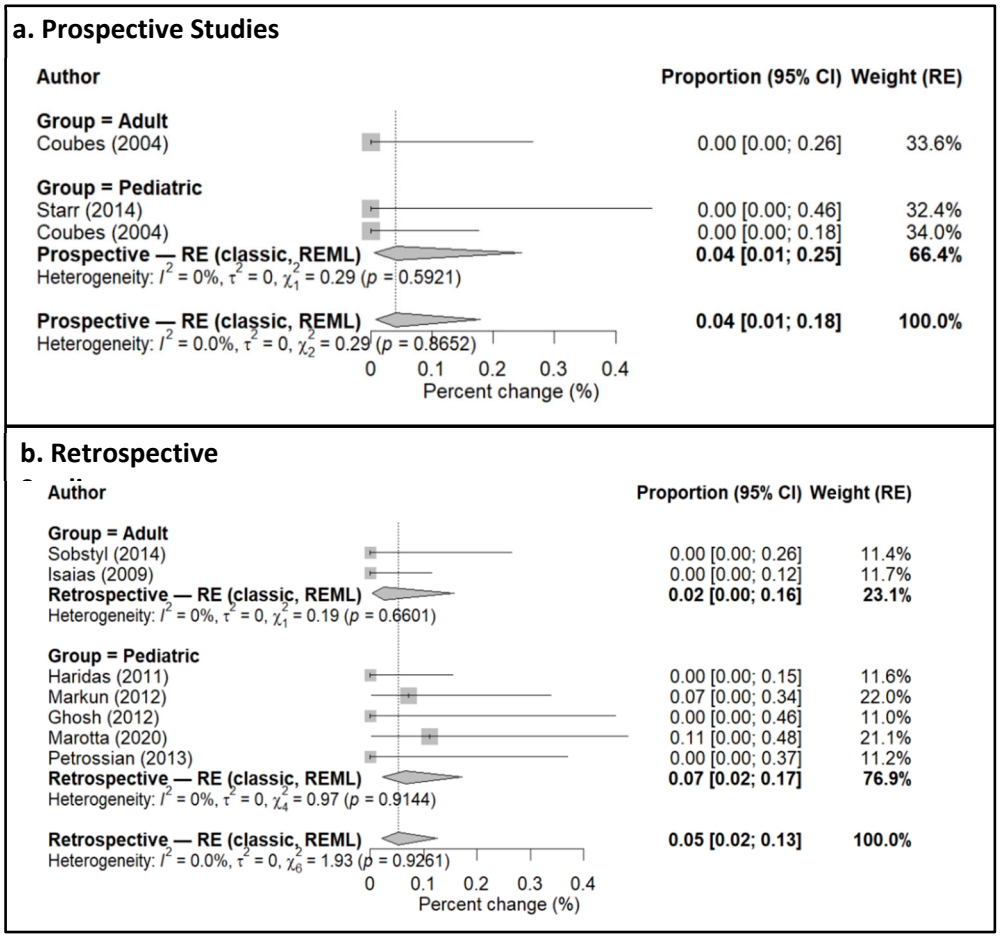

Figure 5. Forest Plot of Asymptomatic Intracranial Hemorrhage Rates in Adult and Pediatric Patients with Generalized Dystonia by Study Design, a) Prospective, b) Retrospective.

Device Revisions

Figure 6 presents a forest plot and detailed comparison of device revision rates between adult and pediatric patients with generalized dystonia by study design, with data pooled from the prospective studies (a) and retrospective studies (b) using a random effects model.

Prospective Studies: Using a random effects model, the pooled device revision rate was 5% (95% CI: 1–18%) for adult patients and 12% (95%

CI: 4–30%) for pediatric patients, with no heterogeneity among studies. The combined device revision rate was 9% (95% CI: 4–20%) with no heterogeneity across both groups (p=0.4303).

Retrospective Studies: Using a random effects model, the pooled device revision rate was 26% (95% CI: 2–86%) for adult patients and 27% (95% CI: 15–44%) for pediatric patients. Substantial heterogeneity was observed in included studies for adult patients (I^2 = 80.2%, τ^2 = 1.0284, p=0.0064) but no heterogeneity was observed among pediatric studies. The combined device revision rate was 24% (95% CI: 14–39%) with moderate heterogeneity across both groups (p=0.0535), primarily driven by the substantial heterogeneity observed in adult patients.

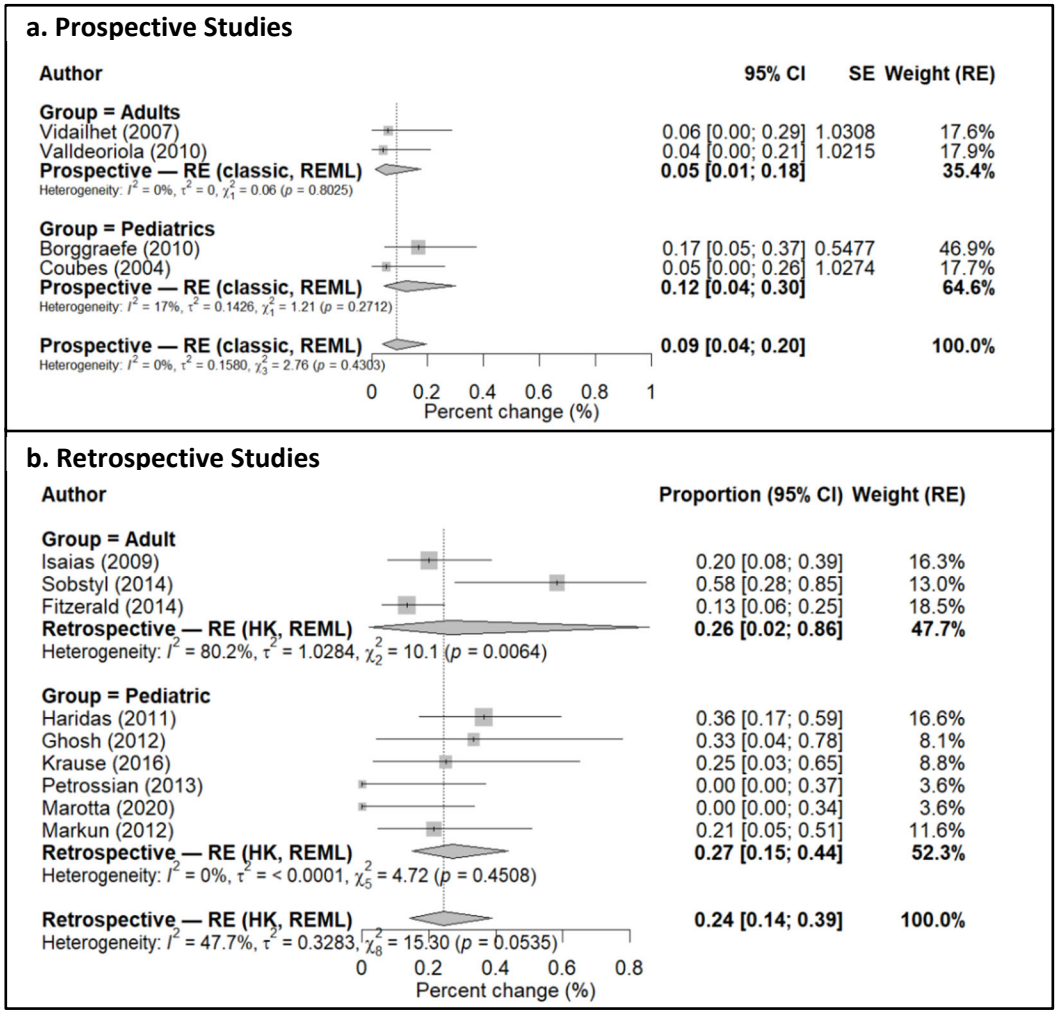

Figure 6. Forest Plot of Device Revision Rates in Adult and Pediatric Patients with Generalized Dystonia by Study Design, a) Prospective, b) Retrospective.

Explants

Figure 7 presents a forest plot and detailed comparison of explant rates between adult and pediatric patients with generalized dystonia by study design using a random effects model. No explant rate was reported from the included studies for pediatric patients in prospective studies; therefore, data pooled from the retrospective studies only is presented for explants. Only one study presented the explant rate for adult patients, and the point estimate for explant rate was 12% (95% CI: 5–23%). The pooled estimate from three studies for pediatric patients was 20% (95% CI: 7–43%), with low heterogeneity among studies. The combined explant rate was 16% (95% CI: 8–29%), with low heterogeneity across both groups (p=0.2795).

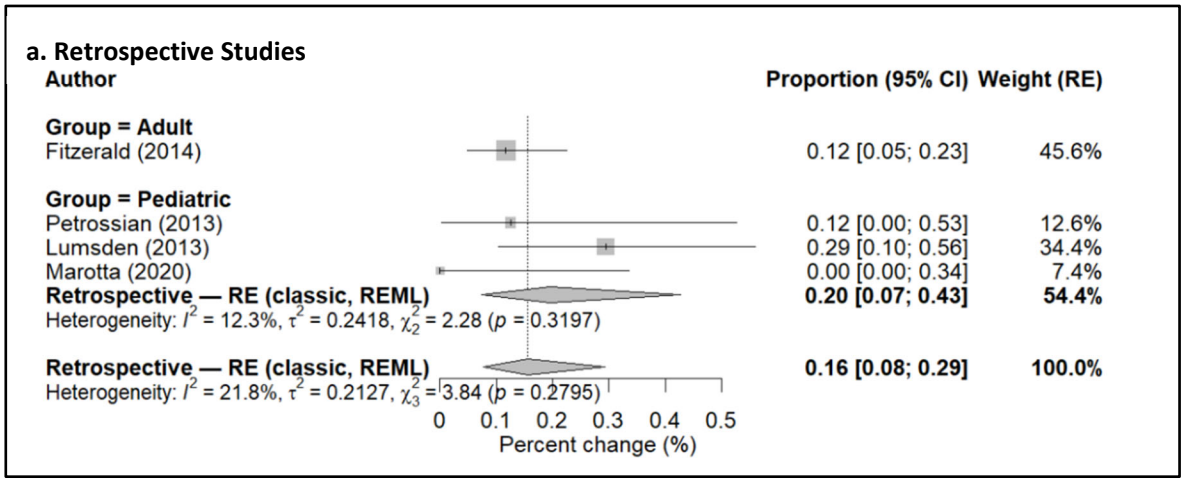

Figure 7. Forest Plot of Explant Rates in Adult and Pediatric Patients with Generalized Dystonia in Retrospective Studies

- Product Surveillance Registry (PSR)

  The PSR began collecting data on DBS patients in 2009. Safety data was available for 308 DBS patients with primary dystonia from 12 different countries enrolled in the registry. This analysis represents the data collected between 2009 and October 31, 2022. The majority of dystonia patients were adult (279/308; 90.6%). There were 27 (27/308; 8.8%) pediatric patients and two patients with missing age information.

  The majority of patients (250/273, 91.6%) had leads implanted in the GPi region with bilateral stimulation (255/273, 93.4%). Mean ages of adult and pediatric patients are 53 ± 14.4 years (range 22-88 years) and 16 ± 3.9 years (range 8-21 years), respectively. The average duration of device exposure for implanted dystonia patients was 38.2 ± 32.6 months for adults and 35.9 ± 30.9 months for pediatric patients.

  Adverse Event Summary

Events currently collected include all events that appear or worsen during the registry and are a result of implanted or external components (device related), implant or modification procedures (procedure related), or stimulation therapy (therapy related).

There were 166 adverse events (AEs) reported in 87 (28.2%) of the 308 dystonia patients. Within these adverse events, 58 were considered serious and occurred in 39 (12.7%) dystonia patients. By age group, serious adverse events (SAEs) occurred in 3 of 27 (11.1%) pediatric patients and 36 of 279 (12.9%) adult patients (Table 16). The 2 patients with unknown age did not experience any SAEs. The 58 SAEs by System Organ Class (SOC) are summarized in Table 17.

Table 16. Adverse Event and Serious Adverse Event Summary

Age Group	Number at risk	Adverse Events			Serious Adverse Events		
		Number of AEs	Patients with AEs	% of patients with AEs	Number of SAEs	Patients with SAEs	% of patients with SAEs
Adult	279	156	78	28.0%	54	36	12.9%
Pediatric	27	8	7	25.9%	4	3	11.1%
Unknown	2	2	2	100.0%	0	0	0.0%
Total	**308**	**166**	**87**	**28.2%**	**58**	**39**	**12.7%**

Table 17. Serious Adverse Event Summary by System Organ Class (SOC) and Preferred Term (PT)

Adverse Event SOC and PT	Adult (N = 279)	Pediatric (N = 27)	Total* (N = 308)
All Adverse Events	**54 (36, 12.9%)**	**4 (3, 11.1%)**	**58 (39, 12.7%)**
Infections and infestations	**14 (9, 3.2%)**	**1 (1, 3.7%)**	**15 (10, 3.2%)**
Medical Device Site Infection	8 (4, 1.4%)	1 (1, 3.7%)	9 (5, 1.6%)
Wound Infection	4 (4, 1.4%)	0 (0, 0.0%)	4 (4, 1.3%)
Meningitis Bacterial	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Staphylococcal Infection	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Psychiatric disorders	**1 (1, 0.4%)**	**1 (1, 3.7%)**	**2 (2, 0.6%)**
Aggression	0 (0, 0.0%)	1 (1, 3.7%)	1 (1, 0.3%)
Depression	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Nervous system disorders	**18 (13, 4.7%)**	**0 (0, 0.0%)**	**18 (13, 4.2%)**
Dystonia	10 (7, 2.5%)	0 (0, 0.0%)	10 (7, 2.3%)
Dyskinesia	2 (2, 0.7%)	0 (0, 0.0%)	2 (2, 0.6%)
Basal Ganglia Haemorrhage	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)

Adverse Event SOC and PT	Adult (N = 279)	Pediatric (N = 27)	Total* (N = 308)
Cerebral Haemorrhage	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Cerebrovascular Accident	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Generalized Tonic-Clonic Seizure	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Haemorrhage Intracranial	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Spinal Cord Disorder	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Gastrointestinal disorders	**1 (1, 0.4%)**	**0 (0, 0.0%)**	**1 (1, 0.3%)**
Dysphagia	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Skin and subcutaneous tissue disorders	**1 (1, 0.4%)**	**0 (0, 0.0%)**	**1 (1, 0.3%)**
Blister	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Musculoskeletal and connective tissue disorders	**4 (3, 1.1%)**	**0 (0, 0.0%)**	**4 (3, 1.0%)**
Muscle Tightness	3 (2, 0.7%)	0 (0, 0.0%)	3 (2, 0.6%)
Neck Pain	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Renal and urinary disorders	**1 (1, 0.4%)**	**0 (0, 0.0%)**	**1 (1, 0.3%)**
Acute Kidney Injury	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
General disorders and administration site conditions	**8 (7, 2.5%)**	**0 (0, 0.0%)**	**8 (7, 2.3%)**
Medical Device Site Pain	4 (4, 1.4%)	0 (0, 0.0%)	4 (4, 1.3%)
Medical Device Site Fistula	2 (1, 0.4%)	0 (0, 0.0%)	2 (1, 0.3%)
Gait Disturbance	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Medical Device Site Discomfort	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Injury, poisoning and procedural complications	**4 (4, 1.4%)**	**1 (1, 3.7%)**	**5 (5, 1.6%)**
Wound Dehiscence	1 (1, 0.4%)	1 (1, 3.7%)	2 (2, 0.6%)
Pneumocephalus	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Seroma	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Subdural Haematoma	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Product issues	**2 (2, 0.7%)**	**1 (1, 3.7%)**	**3 (3, 1.0%)**
Device Extrusion	1 (1, 0.4%)	1 (1, 3.7%)	2 (2, 0.6%)
Device Lead Damage	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)

Note: Sum of patients experiencing each event may not add to total as patients may have experienced more than 1 event. SOC = MedDRA System Organ Class. PT = MedDRA Preferred Term.
*Two patients with unknown age

Device Event Summary

Device events (DE) could be related to the neurostimulator, lead, extension, and/or external device (such as the recharger). Product performance-related events (PPE) are a subset of device events determined to be product performance-related and may or may not be related to a corresponding adverse event.

There were 53 device events (DEs) reported in 37 (37/308; 12.0%) patients, including 11.8% (33/279) in adult patients and 11.1% (3/27) in pediatric patients. Of the 53 DEs, 38 were product performance-related events that occurred in 30 (30/308; 9.7%) dystonia patients, including 9.3% (26/279) in adult patients and 11.1% (3/27) in pediatric patients (Table 18). The 37 PPEs for adult and pediatric patients are summarized in Table 23 by MedDRA Preferred Term. One patient of unknown age with an event (neurostimulator unable to recharge) with one PPE is not included within Table 19.

Table 18. Device Event Summary

Age Group	Number at risk	All Device Events			Product Performance-Related Events		
		Number of DEs	Patients with DEs	% of patients with DEs	Number of PPEs	Patients with PPEs	% of patients with PPEs
Adult	279	49	33	11.8%	34	26	9.3%
Pediatric	27	3	3	11.1%	3	3	11.1%
Unknown	2	1	1	50.0%	1	1	50.0%
Total	**308**	**53**	**37**	**12.0%**	**38**	**30**	**9.7%**

Table 19. Product Performance Events Summary[a]

Device Event	Adults N=279			Pediatric N=27		
	No. of Events	No. of Patients	% of Patients	No. of Events	No. of Patients	% of Patients
High Impedance[b]	13	11	3.9%	0	0	0.0%
Extension Migration	5	4	1.4%	0	0	0.0%
Lead Migration/Dislodgement[b]	5	4	1.4%	0	0	0.0%
Device Malfunction	3	3	1.1%	0	0	0.0%
Low Impedance[b]	2	2	0.7%	1	1	3.7%
Neurostimulator Unable to Recharge	1	1	0.4%	1	1	3.7%
Lead Fracture	2	2	0.7%	0	0	0.0%
Device Connection Issue	1	1	0.4%	0	0	0.0%
Device Electrical Finding	1	1	0.4%	0	0	0.0%
Device End of Life	1	1	0.4%	0	0	0.0%
Medical Device Complication[c]	0	0	0.0%	1	1	3.7%
Total	**34**	**26**	**9.3%**	**3**	**3**	**11.1%**

Device Event	Adults N=279			Pediatric N=27		
	No. of Events	No. of Patients	% of Patients	No. of Events	No. of Patients	% of Patients

[a] One patient with unknown age with an event (neurostimulator unable to recharge) is not presented in this table.
[b] One event each of High Impedance, Lead Migration/Dislodgement, and Low Impedance was serious without a corresponding clinical diagnosis (i.e., AE) reported on the Event CRF. Because no AE was reported, these events are not included in the SAE summaries. The high impedance event was serious due to in- patient or prolonged hospitalization and medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function. The lead migration/dislodgement and low impedance events were serious due to medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
[c] Reported as "Suspicion of heating of the antenna 5 minutes after starting the first recharge"

System Modifications

A system modification is any change to the implanted DBS system following the initial implant within the registry. This includes explant with or without replacement, repositioning, the addition of another extension and/or lead, or any other type of surgical intervention on the system. Overall, 29.5% (91/308) of dystonia patients had at least one system modification procedure (Table 20).

Out of the 91 patients with at least one system modification, 72.5% (66/91) experienced their system modification due to battery depletion without an event, 5.5% (5/91) experienced their system modification due to battery depletion with an event, and 35.2% (32/91) experienced their system modification due to an event. Patients may have experienced separate system modifications due to battery depletion and due to an event.

Overall, 25.9% (7/27) of pediatric dystonia patients had at least one system modification procedure. Table 21 below shows the reasons for all system modifications.

Within adult patients, 2.2% (6/279) had a permanent neurostimulator explant, and within pediatric patients, 3.7% (1/27) had a permanent neurostimulator explant.

Table 20. System Modifications Summary

Age Category	Number of Patients	% of Patients
Adult (N=279)	84	30.1%
Pediatric (N=27)	7	25.9%
***Total (N=308)**	**91**	**29.5%**
*2 patients with unknown age		

Table 21. Reasons for System Modifications

Age category	Modification Reason	Number of procedures	Number of patients with a system modification
Adult	Battery depletion	105	62

Age category	Modification Reason	Number of procedures	Number of patients with a system modification
Adult	Battery depletion; Event	6	5
Adult	Event	56	31
Adult	Other	5	3
Adult	**Total**	**172**	**84**
Pediatric	Battery depletion	4	4
Pediatric	Event	1	1
Pediatric	Other	2	2
Pediatric	**Total**	**7**	**7**

Patient Deaths

All deaths were collected regardless of their relatedness to the device, implant procedure, and/or therapy. There were 15 deaths: 12 deaths occurred in adult patients and 3 deaths occurred in pediatric patients. Twelve deaths in adult patients were attributed to cardiac arrest (1), heart attack/heart failure (2), Huntington's Chorea (1), advanced dystonia (1), liver cancer (1), and unknown causes (6). Three deaths in pediatric patients were attributed to respiratory system infection (1), worsened dystonia (1), and unknown cause (1). Eleven of the deaths were reported as not related to the device or procedure. Four deaths due to unknown causes had an unknown relationship to the device or procedure. None of these deaths were reported as a direct result of a product performance event.

2. Effectiveness Results

Effectiveness outcomes comprised changes in average BFMDRS motor scores for generalized and segmental (head and neck) dystonia and average TWSTRS severity scores for cervical dystonia. Outcomes are presented separately for primary generalized, segmental (head and neck), and cervical dystonia for adult patients, and pediatric patients 12 years of age or above with primary generalized dystonia. Comparisons of effectiveness outcomes between adult and pediatric patients with primary generalized dystonia by study designs are also included to provide additional information on the effectiveness of bilateral GPi DBS in pediatric patients 12 years of age or above with primary generalized dystonia.

Effectiveness Outcomes in Adult Population

- Generalized Dystonia

  The analysis of effectiveness of bilateral GPi DBS for the treatment of primary generalized dystonia in adult patients was based on data from the Investigator Study[6] and 5 publications (3 prospective and 2 retrospective) representing a total of 130 patients contributing device effectiveness outcomes. The highest level of available evidence is the Investigator Study,[6] a

subset data of 30 patients (18 with generalized dystonia, 11 with segmental dystonia, one additional patient with multifocal dystonia is excluded from this subgroup analysis) from the Kupsch (2006)[4] RCT study and its long-term follow up study by Volkmann (2012)[5].

Study Specific Data

The Investigator Study[6] included 18 patients with generalized dystonia, randomly assigned 9 patients to neurostimulation group and 9 to the sham stimulation group. Baseline characteristics were similar between the neurostimulation group and the sham stimulation group. During the randomization period, the BFMDRS motor score improved significantly in the neurostimulation group compared to the sham stimulation group (42.3% vs 2.5%; p=0.005). During the open-label phase, the BFMDRS motor score was improved by 50.1% at 6 months (n=18), 69.9% at 3 years (n=16) and 60.8% at 5 years (n=12), compared to baseline. Similar results were reported in the published article from the same clinical study with the full study cohort (n=40), where the motor score was improved by 44.8% at 6 months (n=24), 70.6% at 3 years (n=20) and 67.0% at 5 years (n=20), compared with baseline.[5]

Similar improvement was also observed for BFMDRS disability score, 35.6% for the neurostimulation group compared to 7.1% for the sham stimulation group at 3 months (p=0.005). The improvement in BFMDRS disability score as compared to baseline was significant and sustained at the 5-year follow-up for patients.

Table 22 and Table 23 present the BFMDRS motor score and the BFMDRS disability score by each follow-up for generalized dystonia.

Table 22. BFMDRS Motor Score Improvement by Visit for Generalized Dystonia

			BFMDRS Movement Score		**Change from baseline**			
BFMDRS (Movement)	**Range of possible scores**	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
Total	0 – 120	Baseline (Neurostimulation)	9	61.4 ± 27.5	9	NA	NA	NA
		Baseline (Sham Stimulation)	9	50.0 ± 29.1	9	NA	NA	NA
		3 Month (Neurostimulation)	9	32.7 ± 18.3	9	-28.7 ± 22.2	-42.3 ± 24.8	0.005[a]
		3 Month (Sham Stimulation)	8	52.0 ± 27.8	8	-0.5 ± 7.7	2.5 ± 23.2	
		6 Month	18	27.8 ± 20.9	18	-27.9 ± 17.7	-50.1 ± 22.0	<0.001[b]
		1 Year	12	27.5 ± 24.3	12	-29.0 ± 14.4	-55.6 ± 25.2	<0.001[b]
		2 Year	16	25.5 ± 22.7	16	-29.9 ± 18.1	-57.2 ± 25.6	<0.001[b]
		3 Year	16	19.3 ± 20.8	16	-37.0 ± 19.3	-69.9 ± 20.1	<0.001[b]
		4 Year	13	21.1 ± 22.1	13	-34.4 ± 24.6	-63.9 ± 24.2	<0.001[b]

			BFMDRS Movement Score		Change from baseline			
BFMDRS (Movement)	**Range of possible scores**	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
		5 Year	12	25.5 ± 22.2	12	-35.4 ± 21.3	-60.8 ± 25.7	<0.001[b]

[a] Two-sided Mann-Whitney Test
[b] Two-sided Wilcoxon signed-rank Test

Table 23. BFMDRS Disability Score Improvement by Visit for Generalized Dystonia

			BFMDRS Disability Score		Change from baseline			
BFMDRS (Disability)	**Range of possible scores**	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
Total	0 - 30	Baseline (Neurostimulation)	9	14.1 ± 6.1	9	NA	NA	NA
		Baseline (Sham Stimulation)	9	12.0 ± 7.2	9	NA	NA	NA
		3 Month (Neurostimulation)	9	9.6 ± 6.0	9	-4.6 ± 2.6	-35.6 ± 22.1	0.005[a]
		3 Month (Sham Stimulation)	8	11.0 ± 7.4	8	-0.9 ± 0.8	-7.1 ± 8.3	
		6 Month	18	8.3 ± 6.6	18	-4.8 ± 3.7	-40.8 ± 25.8	<0.001[b]
		1 Year	11	9.6 ± 8.0	11	-4.9 ± 4.1	-40.0 ± 31.2	0.008[b]
		2 Year	15	7.7 ± 6.9	15	-5.6 ± 5.1	-46.0 ± 28.1	<0.001[b]
		3 Year	14	8.6 ± 7.4	14	-5.1 ± 3.9	-42.4 ± 25.1	<0.001[b]
		4 Year	13	7.8 ± 7.3	13	-5.2 ± 4.7	-43.1 ± 30.5	0.002[b]
		5 Year	12	8.8 ± 7.3	12	-5.7 ± 3.8	-44.8 ± 28.3	0.002[b]

[a] Two-sided Mann-Whitney Test
[b] Two-sided Wilcoxon signed-rank Test

Effectiveness Outcome from the Publications

In addition to the Investigator Study,[6] the analysis of effectiveness of bilateral GPi DBS for the treatment of primary generalized dystonia in adult patients also includes data from 5 published studies with a total of 118 patients contributing effectiveness outcomes. The 5 publications consist of 3 prospective studies and 2 retrospective studies. These six (6) studies for primary dystonia in adult patients include 130 patients with follow-ups ranging from 1 year to 7 years; and average baseline BFMDRS motor scores range from 44 to 61 out of a possible score of 120.

Across five other published studies, the average improvement in BFMDRS motor scores ranged from 43.5% to 79.6% at 1 year,[6,13–17] 49.9% to 82.5% at 2 years,[6,13,16,17] and 56.4% to 85.5% at 3 years.[6,15,17]

Table 24 below reports effectiveness outcomes from the six publications (1 RCT, 3 prospective, and 2 retrospective studies) on adult patients with GPi DBS for generalized dystonia.

Table 24. BFMDRS Motor Scores at the Latest Follow-up in Adult Patients with GPi DBS for Generalized Dystonia

Publication	Study Type	Age at Surgery	BFMDRS Motor Score				p-value
			Last Follow-up (years)	N*	Baseline Score	% Improvement ± SD	
Investigator-sponsored study[6]	RCT	38.2 ± 12.9	5.0	12	DBS: 61.4 ± 27.5 Sham:50.0 ± 29.1	60.80±25.7 %	<0.01
Coubes (2004)[13]	Prospective	NR	2.0	12	57.9 ± 28.5	70.10±23.6%	0.0003
Valldeoriola (2010)[14]	Prospective (blinded)	30 ± 14	1.0	24	46.4 ± 21.4	50.22±NR%	<0.05
**Vidailhet (2007)[15]	Prospective	36.3 ± 9.8	3.0	17	48.4	56.40±25.2%	NR
Fitzgerald (2014)[16]	Retrospective	33.5	5.0	60	NR	49.80±NR%	<0.001
Isaias (2009)[49]	Retrospective	28 ± 17	7.0	5	44 ± 23.3	82.00±16.8%	0.068

* Sample size indicates the number of patients with data available at the most recent follow-up.
**data estimated from the individual patient data

A meta-analysis was conducted, comprising of 130 patients with follow-ups ranging from 1 year to 7 years. Figure 8 presents a forest plot of BFMDRS motor scores at the latest follow-up for generalized dystonia in adult patients, with data pooled from the selected studies. The pooled BFMDRS motor scores improvement calculated using the random effects model was 60.51% (95% CI: 50.69-70.32%) and 56.02% (95% CI: 51.89–60.15%) under the common effect model. High heterogeneity was observed among the included studies (I^2 = 77.2%, τ^2 = 114.1195, p=0.0005).

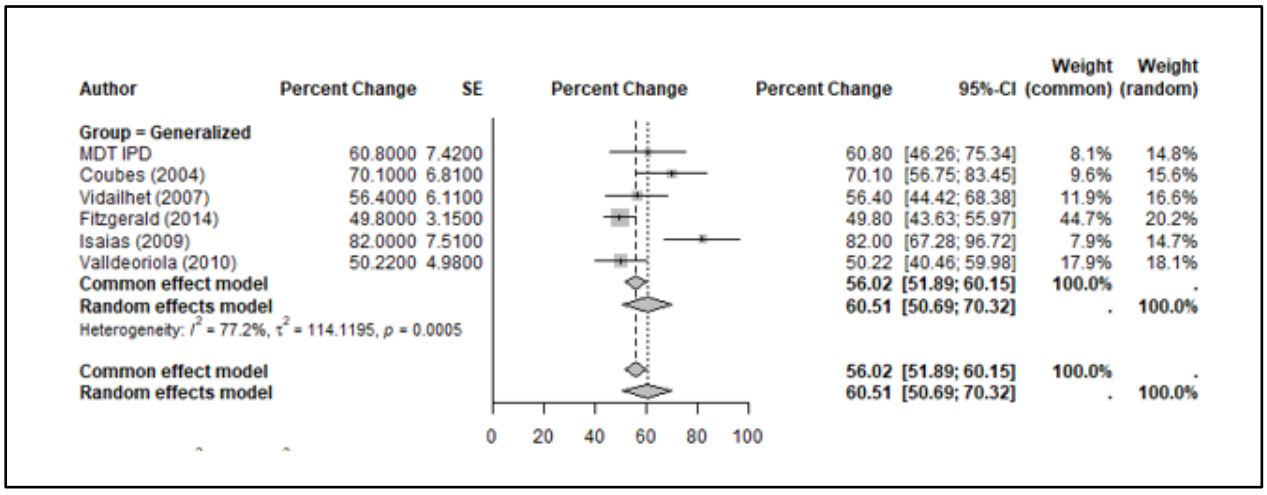

Figure 8. Forest Plot of Percent Improvement in BFMDRS Motor Scores in Adult Patients with Generalized Dystonia at the Latest Follow-up Reported in Each Study

Meta-analysis Stratified by Study Designs on Generalized Dystonia in Adult Patients

To address the possibility that effect estimates from different study designs may not represent the same inferential target, a meta-analysis of effectiveness outcomes by study designs in adult patients was conducted for generalized dystonia, focusing on the BFMDRS (Burke-Fahn-Marsden Dystonia Rating Scale) motor score improvements measured by standardized scales across various study designs. Only one RCT was included in the meta-analysis; therefore, only the point estimate was provided for the RCT.

Figure 9 presents forest plots of the BFMDRS motor score at the latest follow-up in adult patients with GPi DBS for generalized dystonia, with data pooled from the prospective studies (a), retrospective studies (b), and RCTs (c). The pooled BFMDRS motor score improvement for the three prospective studies was 58.08% (95% CI: 33.02% - 83.13%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure 9a). In comparison, the pooled BFMDRS motor score improvement for the two retrospective studies was 65.18% (95% CI: 33.65% - 96.70%), indicated in Figure 9b). There was only one RCT study, and the point estimate is 60.80% with a 95% CI of 46.26% - 75.34%, shown in Figure 9c). Each study contributes roughly equally to the overall results. Notably, the retrospective studies demonstrated greater heterogeneity ($I^2 = 93.6\%$, $\tau^2 = 485.2587$, $p < 0.0001$) than the prospective studies ($I^2 = 64.1\%$, $\tau^2 = 64.3561$, $p = 0.0615$).

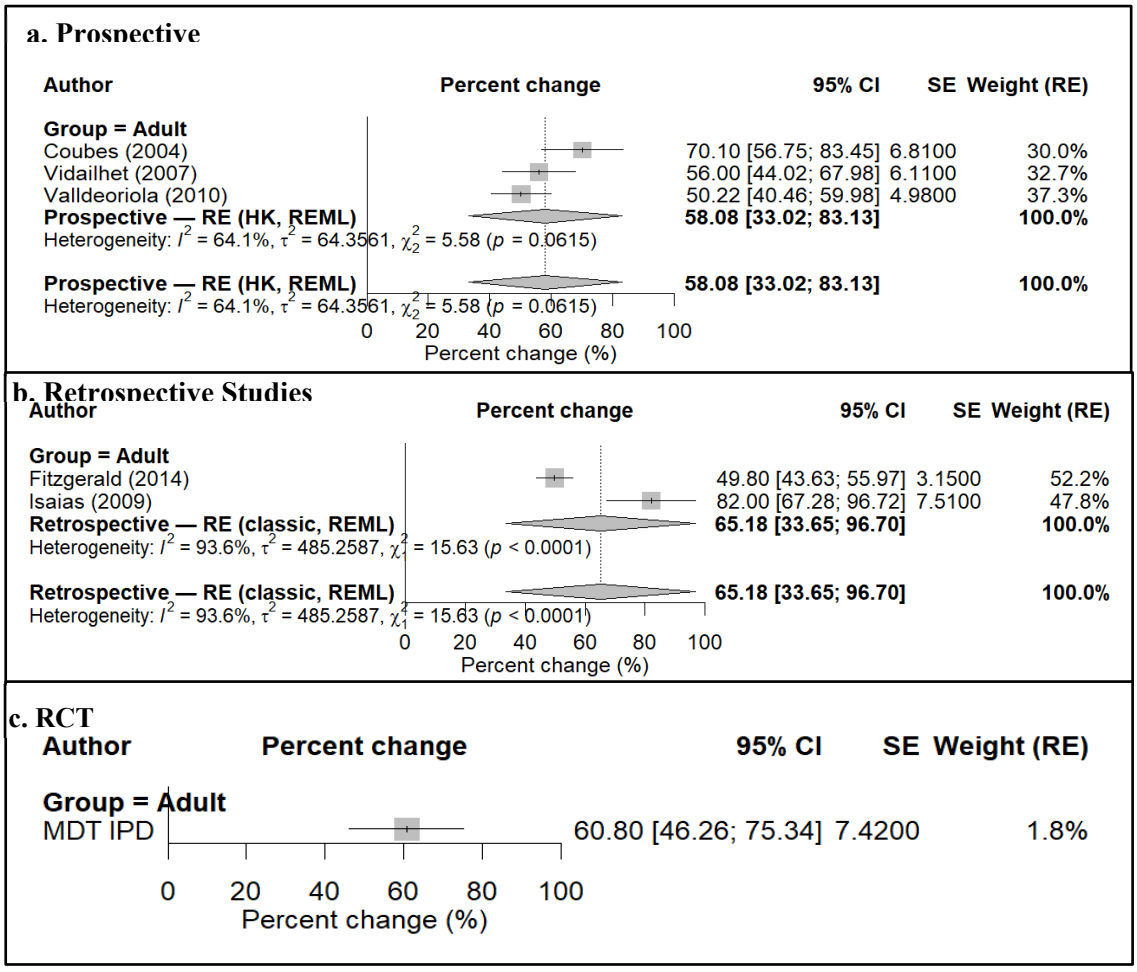

Figure 9. Forest Plots of Percent Improvement in BFMDRS Motor Scores in Adult Patients with GPi DBS for Generalized Dystonia at the Latest Follow-up by Study Designs, a) Prospective, b) Retrospective, c) RCTs.

- Segmental Dystonia of the Head and Neck

  The analysis of effectiveness of bilateral GPi DBS for the treatment of primary segmental dystonia of the head and neck in adult patients includes data from the Investigator Study[6] and 8 published studies with a total of 94 patients contributing effectiveness outcomes. The highest level of available evidence is the Kupsch (2006)[4] study, the Investigator Study,[6] and a subset of data from the Kupsch (2006)[4] and Volkmann (2012) [5] studies.

  Study Specific Data

  The Investigator Study[6] included 11 patients with segmental dystonia, randomly assigned 7 patients to neurostimulation group and 4 to the sham stimulation group. Baseline characteristics were similar between the neurostimulation group and the sham stimulation group. During the randomization period, the BFMDRS motor score improved significantly in the

neurostimulation group compared to the sham stimulation group (61.2% vs 0.9%; p=0.011). During the open-label phase, the BFMDRS motor score was improved by 60.0% at 6 months (n=11), 64.5% at 3 years (n=8), and 59.6% at 5 years (n=5), compared to baseline. Similar results were reported in the published article from the same clinical study with the full study cohort (n=40), where the motor score was improved by 54.5% (n=16) at 6 months, 60.5% (n=11) at 3 years, and 49.4% (n=12) at 5 years, compared with baseline.[5]

Similar improvement was also observed for BFMDRS disability score, 60.3% for the neurostimulation group compared to 8.3% for the sham stimulation group at 3 months (p=0.021). The improvement in BFMDRS disability score as compared to baseline was significant and sustained at the 5-year follow-up but improvement was not statistically significant beyond 6 months.

Table 25 and Table 26 present the BFMDRS motor score and the BFMDRS disability score by each follow-up for segmental dystonia.

Table 25. BFMDRS Motor Score Improvement by Visit for Segmental Dystonia

			BFMDRS Movement Score		Change from baseline			
BFMDRS (Movement)	**Range of possible scores**	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
Total	0 – 120	Baseline (Neurostimulation)	7	27.7 ± 16.2	7	NA	NA	NA
		Baseline (Sham Stimulation)	4	18.5 ± 6.9	4	NA	NA	NA
		3 Month (Neurostimulation)	7	11.6 ± 9.2	7	-16.1 ± 8.2	-61.2 ± 13.6	0.011[a]
		3 Month (Sham Stimulation)	4	18.1 ± 6.1	4	-0.4 ± 2.3	-0.9 ± 9.4	
		6 Month	11	9.5 ± 7.2	11	-14.9 ± 12.0	-60.0 ± 28.7	<0.001[b]
		1 Year	8	6.7 ± 5.9	8	-16.4 ± 12.6	-71.6 ± 20.3	0.008[b]
		2 Year	7	11.3 ± 11.5	7	-17.7 ± 15.4	-62.3 ± 33.2	0.016[b]
		3 Year	8	10.5 ± 9.9	8	-16.8 ± 11.5	-64.5 ± 23.6	0.008[b]
		4 Year	7	9.4 ± 9.3	7	-19.1 ± 11.6	-70.6 ± 22.5	0.016[b]
		5 Year	5	12.5 ± 9.1	5	-18.8 ± 14.0	-59.6 ± 24.4	0.063[b]

[a] Two-sided Mann-Whitney Test
[b] Two-sided Wilcoxon signed-rank Test

Table 26. BFMDRS Disability Score Improvement by Visit for Segmental Dystonia

			BFMDRS Disability Score		Change from baseline			
BFMDRS (Disability)	**Range of possible scores**	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
Total	0 - 30	Baseline (Neurostimulation)	7	6.7 ± 3.4	7	NA	NA	NA

			BFMDRS Disability Score		Change from baseline			
BFMDRS (Disability)	**Range of possible scores**	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
		Baseline (Sham Stimulation)	4	4.3 ± 1.3	4	NA	NA	NA
		3 Month (Neurostimulation)	7	2.6 ± 2.1	7	-4.1 ± 2.9	-60.3 ± 23.8	0.021[a]
		3 Month (Sham Stimulation)	4	3.8 ± 0.5	4	-0.5 ± 1.0	-8.3 ± 16.7	
		6 Month	8	3.3 ± 1.3	8	-2.3 ± 1.7	-38.6 ± 11.6	0.008[b]
		1 Year	7	2.6 ± 2.4	7	-2.1 ± 2.6	-45.8 ± 37.7	0.109[b]
		2 Year	6	5.7 ± 3.5	6	-0.8 ± 2.6	-11.9 ± 49.9	0.688[b]
		3 Year	7	5.1 ± 3.4	7	-1.0 ± 2.9	-13.9 ± 61.4	0.375[b]
		4 Year	5	5.0 ± 3.5	5	-2.0 ± 3.5	-21.1 ± 72.3	0.375[b]
		5 Year	4	4.5 ± 4.4	4	-2.8 ± 2.6	-42.7 ± 37.3	0.250[b]

[a] Two-sided Mann-Whitney Test
[b] Two-sided Wilcoxon signed-rank Test

Effectiveness Outcome from Publications

In addition to the Investigator Study,[6] the analysis of effectiveness of bilateral GPi DBS for the treatment of primary segmental dystonia in adult patients also includes data from 8 published studies with a total of 89 patients contributing effectiveness outcomes. The 8 publications consist of 2 prospective studies and 6 retrospective studies. A total of nine (9) studies were included for segmental dystonia in adult patients with follow-up ranging from 0.5 year to 5.6 years. Average baseline BFMDRS motor scores for segmental dystonia ranged from 13 to 37 out of a possible score of 120, which trends lower than baseline scores for generalized dystonia (range of 44 to 61) due to fewer body regions affected by symptoms.

Across eight other published studies, the average improvement in BFMDRS motor scores ranged from 45% to 72% at 3 to 8 months,[20–25] and 53% to 72% at 2 to 4 years.[22,24,25,27]

Table 27 below reports effectiveness outcomes from the Investigator Study[6] and eight (8) publications (2 prospective and 6 retrospective studies) on adult patients with segmental dystonia.

Table 27. Summary of Studies of Bilateral GPi DBS for Segmental Dystonia in Adult Patients

Publication	Study Type	Age at Surgery in years Mean±SD	BFMDRS Motor Score				
			Last Follow-up (years)	N*	Baseline Score Mean±SD	% improvement Mean±SD	p-value
Investigator-sponsored study[6]	RCT	51.3 ± 12.8	5.0	5	DBS: 27.7 ± 16.2 Sham: 18.5 ± 6.9	59.60±24.4%	0.063
Blahak (2008)[20]	Prospective	57.4 ± 15.0	0.6	10	37.3 ± 20.1	60.00±NR%	<0.01
Ostrem (2007)[21]	Prospective	62.2	0.5	6	22.0 ± 8.3	72.00± NR %	<0.028
Fu (2024) [22]	Retrospective	52.4 ± 7.4	3.2	23	13.1 ± 5.3	58.30±NR%	NR
Horisawa (2019)[23]	Retrospective	51.4**	5.6	16	15.5	58.90±38.1%	<0.001
Reese (2011)[24]	Retrospective	64.5 ± 4.4	3.2	11	21.4 ± 3.2	53.00± NR %	<0.001
Ren (2022)[25]	Retrospective	46.9 ± 7.2	3.1	13	16.3 ± 2.4	54.60± NR %	NR
Sharma (2020)[26]	Retrospective	66.5**	1.0	4	17.8**	65.00±12.0%	<0.05
Tian (2021)[27]	Retrospective	61.2**	3.6	6	22.6**	71.70±3.6%	NR

* Sample size indicates the number of patients with data available at the most recent follow-up.
** Estimated from individual patient data reported in the publication

A meta-analysis was conducted, comprising of 94 patients with follow-ups ranging from 0.5 year to 5.6 years. Figure 10 presents a forest plot of BFMDRS motor scores at the latest follow-up for segmental dystonia in adult patients, with data pooled from the selected studies. The pooled BFMDRS motor score improvement calculated using the random effects model was 62.03% (95% CI: 56.56–67.51%) and 67.42% (95% CI: 65.07–69.76%) under the common effect model. High heterogeneity was observed among the included studies ($I^2 = 74.3\%$, $\tau^2 = 37.3580$, $p=0.0001$).

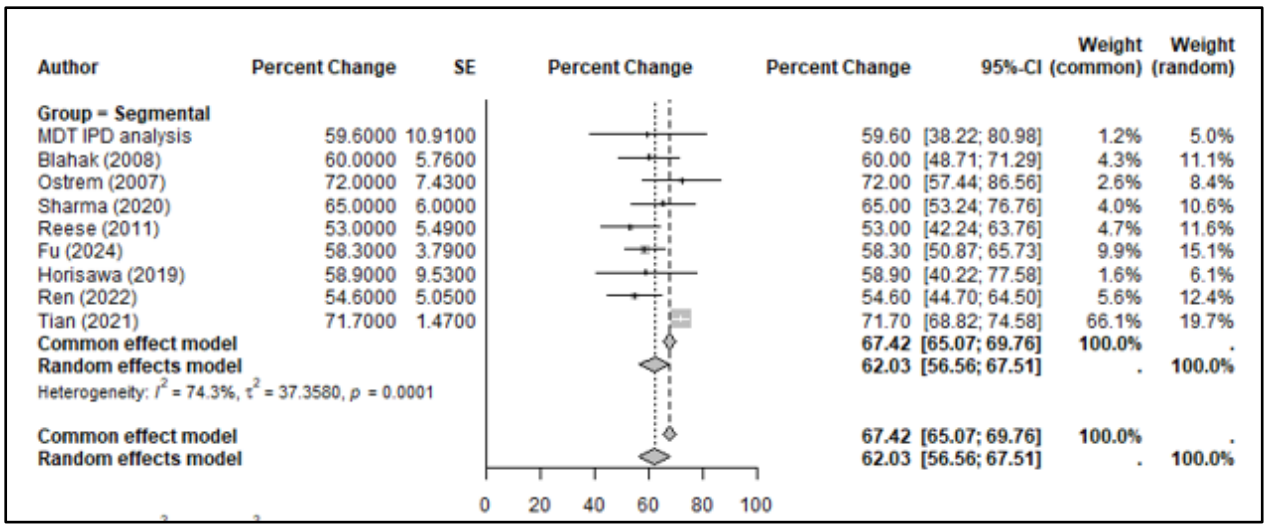

Figure 10. Forest Plot of Percent Improvement in BFMDRS Motor Scores in Adult Patients with GPi DBS for Segmental Dystonia at the Latest Follow-up Reported in Each Study

Meta-analysis Stratified by Study Designs on Segmental Dystonia of Head and Neck in Adult Patients

A meta-analysis of effectiveness outcomes by study design in adult patients was conducted for segmental dystonia, focusing on the BFMDRS (Burke-Fahn-Marsden Dystonia Rating Scale) motor score improvements measured by standardized scales across various study designs. Only one RCT was included in the meta-analysis; therefore, only the point estimate was provided for the RCT.

Figure 11 presents forest plots of the BFMDRS motor score at the latest follow-up for segmental dystonia in adult patients, with data pooled from the prospective studies (a), retrospective studies (b) and RCTs (c). The pooled BFMDRS motor score improvement for the two prospective studies was 65.08% (95% CI: 53.46% - 76.70%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure 11a). In comparison, the pooled BFMDRS motor score improvement for the six retrospective studies was 61.15% (95% CI: 53.11% - 69.20%), indicated in Figure 11b). There was only one RCT study, and the point estimate is 59.60% with a 95% CI of 45.80% - 73.40%, shown in Figure 11c). Notably, the retrospective studies demonstrated greater heterogeneity (I^2 = 82.5%, τ^2 = 48.5080, $p < 0.0001$) than the prospective studies (I^2 = 38.6%, τ^2 = 27.8087, $p = 0.2018$) but heterogeneity in prospective studies was not statistically significant.

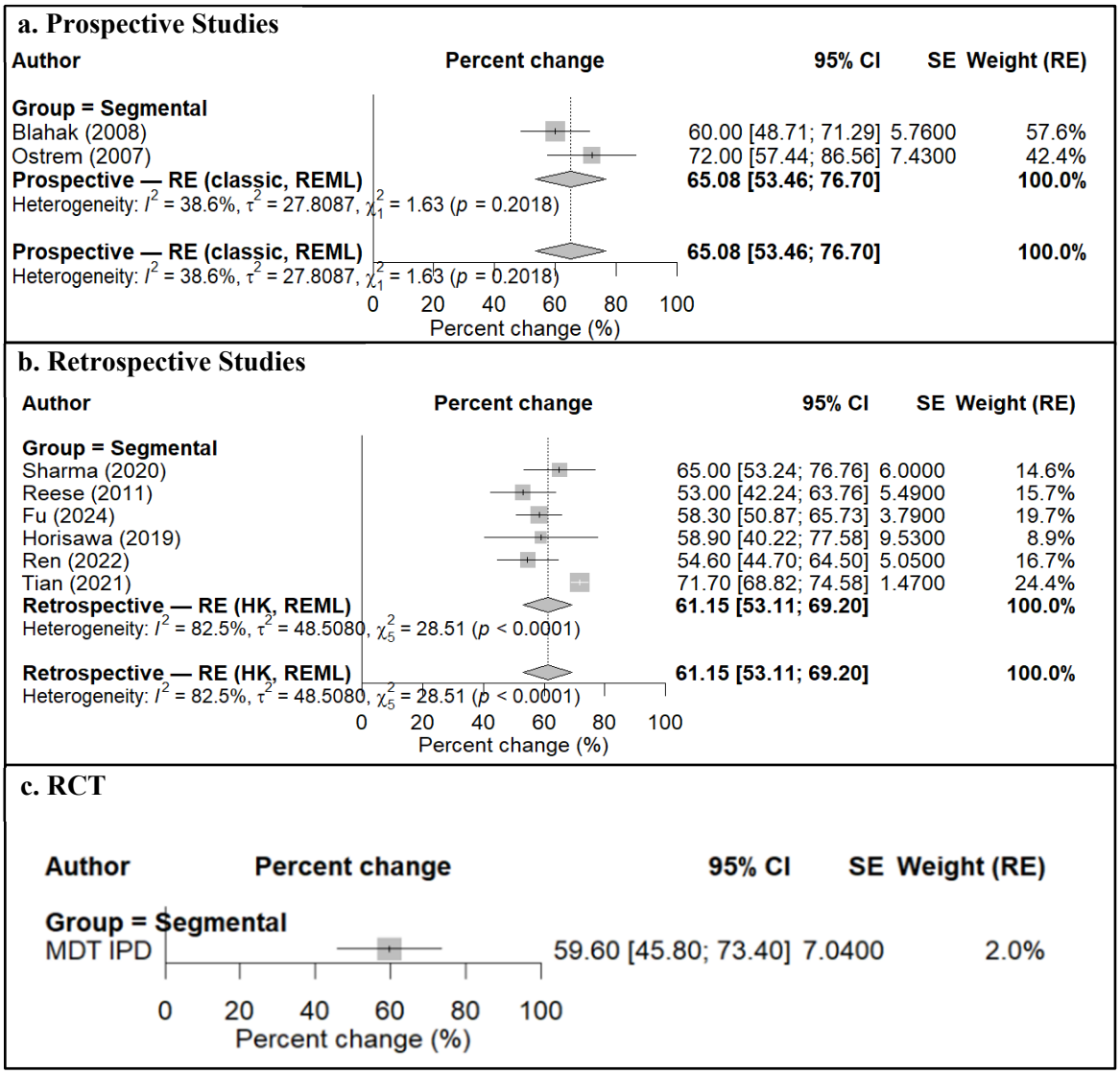

Figure 11. Forest Plots of Percent Improvement in BFMDRS Motor Scores in Adult Patients with GPi DBS for Segmental Dystonia at the Latest Follow-up by Study Designs, a) Prospective, b) Retrospective, c) RCTs.

- Cervical Dystonia
  The analysis of effectiveness of bilateral GPi DBS for the treatment of primary cervical dystonia in adult patients includes data from the Volkmann (2014)[7] study and 9 published studies with a total of 245 patients contributing effectiveness outcomes. The 10 publications consist of 1 RCT, 1 prospective study, and 8 retrospective studies. The highest level of available evidence is from the Volkmann (2014)[7] study.

Effectiveness Results from the Volkmann (2014) Study

The study randomized 62 patients to DBS (n=32) or sham-stimulation (n=30). The study population was approximately 57 years of age in both groups (57.1 ± 9.82 years for DBS and 56.6 ± 11.33 years for sham) with similar disease duration (14.9 ± 7.95 years for DBS and 14.8 ± 6.41 years for sham). The average baseline TWSTRS total score was 48.7 which represents motor impairment and associated disability. The average baseline TWSTRS severity score was 19.9 ± 3.7 for the DBS group and 20.9 ± 3.3 for the sham stimulation group. Three months after randomization, dystonia severity improved by 5.1 ± 5.1 points (26% improvement; 95% CI 3.5 to 7.0) in the DBS group compared with 1.3 ± 2.4 points in sham stimulation group (6% improvement; 95% CI 0.4 to 2.2) (p=0.0024; Table 28).

Analysis of secondary outcomes showed that the TWSTRS disability score improved by 5.6±5.6 points in the DBS group compared with 1.8 ± 3.8 points in the sham stimulation group (p=0.007). Additionally, the Bain Tremor Score improved by 2.0 ± 2.3 points in the DBS group compared with 0.4 ± 2.1 points in the sham stimulation group (p=0.02). There were no significant differences between treatment groups in the TWSTRS pain score or the Craniocervical Dystonia Questionnaire, a quality of life measurement.

After all patients had received six months of DBS, there were highly significant improvements in all of the secondary outcomes compared with baseline (p<0.0001). The TWSTRS severity score improved by a mean of 5.8 ± 5.31 points (28%), TWSTRS disability score by 46%, TWSTRS pain score by 51%, Bain Tremor Score by 66%, and Craniocervical Dystonia Questionnaire by 28%.

Table 28. Summary of TWSTRS Severity and Disability Scores (Volkmann 2014)[7]

		TWSTRS Score		Change from baseline			
Range of possible scores	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
TWSTRS Severity Score							
0 – 35	Baseline (Neurostimulation)	32	19.9 ± 3.7	32	NA	NA	NA
	Baseline (Sham Stimulation)	30	20.9 ± 3.3	30	NA	NA	NA
	3 Month (Neurostimulation)	32	14.7 ± 5.0	32	−5.1 ± 5.1	-26%	0.0024
	3 Month (Sham Stimulation)	30	19.6 ± 3.9	30	−1.3 ± 2.4	-6%	
	6 Months	62	14.6 ± 5.18	62	-5.8 ± 5.31	-28%	<0.0001
TWSTRS Disability Score							
0 – 20	Baseline (Neurostimulation)	32	13.8 ± 5.3	32	NA	NA	NA
	Baseline (Sham Stimulation)	30	15.7 ± 5.1	30	NA	NA	NA
	3 Month (Neurostimulation)	32	8.1 ± 5.7	32	−5.6 ± 5.6	-41%	0.007
	3 Month (Sham Stimulation)	30	13.9 ± 6.1	30	−1.8 ± 3.8	-11%	
	6 Months	62	8.1 ± 6.28	62	-6.7 ± 7.26	-46%	<0.0001

Effectiveness Outcome from Publications

In addition to Volkmann (2014),[7] the analysis of effectiveness of bilateral GPi DBS for the treatment of primary cervical dystonia in adult patients also includes data from 9 published studies with a total of 183 patients contributing effectiveness outcomes. The 9 publications consist of 1 prospective study and 8 retrospective studies. These ten (10) studies were included for cervical dystonia in adult patients with follow-up ranging from 0.5 year to 7.8 years. Average baseline TWSTRS severity scores ranged from 16 to 23 in 8 studies.[36,38,43–47]

Across nine other published studies, the average improvement in TWSTRS severity scores ranged from 29% to 75%[26,28,30–34,36,37] at follow-up time points ranging from 3 months to 7.8 years. These values trended higher than the average improvement of 28% in Volkmann (2014)[7] which may have been impacted by the short follow-up of 6 months.

Table 29 below reports effectiveness outcomes from the nine (9) other publications (1 prospective and 8 retrospective studies) in adult patients with cervical dystonia.

Table 29. Summary of Studies of Bilateral GPi DBS for Cervical Dystonia in Adult Patients

Publication	Study Type	Age at Surgery in years Mean±SD	TWSTRS Severity Score				
			Last Follow-up (years)	N*	Baseline Score Mean±SD	% improvement Mean±SD	p-value
Volkmann (2014)[7]	RCT	DBS: 57.1 ± 9.82 Sham: 56.6 ± 11.3	0.5	62	DBS: 19.9 ± 3.7 Sham: 20.9 ± 3.3	28.00±NR%	0.0001
Walsh (2013)[34]	Prospective	55.5 ± 12.8	7.8	10	21.5 ± 4.6	51.40±27.7%	<0.05
Chung (2015)[28]	Retrospective	52.2 ± 9.6	1.7	21	11.8 ± 2.1	62.40±18.5%	NR
Chung (2016)[37]	Retrospective	NR	1.6	4 (Phasic)	20.8 ± 5.1	75.00±NR%	0.008
				8 (Tonic)		67.00±NR%	
Cui (2022)[35]	Retrospective	44.79 ± 12.88	3.4	53	NR	61.08±NR%	0.000
Honaken (2021)[30]	Retrospective	50.1±7.3	2.8	12	15.8 ± 7.6	67.00±39.0%	<0.001
Huh (2019)[31]	Retrospective	51.7±10.2	4.4	4 (AM)	AM: 19	73.10±4.7%	NR
				13 (UM)	UM: 23	51.60±5.6%	
Sharma (2020)[26]	Retrospective	72.6 ± 16.5**	1.0	7	20.0 ± 6.0**	75.30±19.6%	NR
Wang (2020)[36]	Retrospective	41.13 ± 13.49	1.6	23	22.52 ± 3.78	48.75±33.7%	<0.001

Publication	Study Type	Age at Surgery in years Mean±SD	TWSTRS Severity Score				
			Last Follow-up (years)	N*	Baseline Score Mean±SD	% improvement Mean±SD	p-value
Witt (2013)[33]	Retrospective	56.0 ± 10.4	2.8	28	22 ± 4.18	50.80±27.6%	<0.0001

* Sample size indicates the number of patients with data available at the most recent follow-up.
** Estimated from individual patient data reported in the publication

A meta-analysis was conducted, comprising of 245 patients with follow-ups ranging from 0.5 year to 7.8 years. Figure 12 presents a forest plot of BFMDRS motor scores at the latest follow-up for cervical dystonia in adult patients, with data pooled from the selected studies.

The pooled TWSTRS severity score improvement calculated using the random effects model was 58.32% (95% CI: 50.04–66.61%) and 55.25% (95% CI: 53.28–57.21%) under the common effect model. High heterogeneity was observed among the included studies (I^2 = 93.6%, τ^2 = 173.7703, p<0.0001).

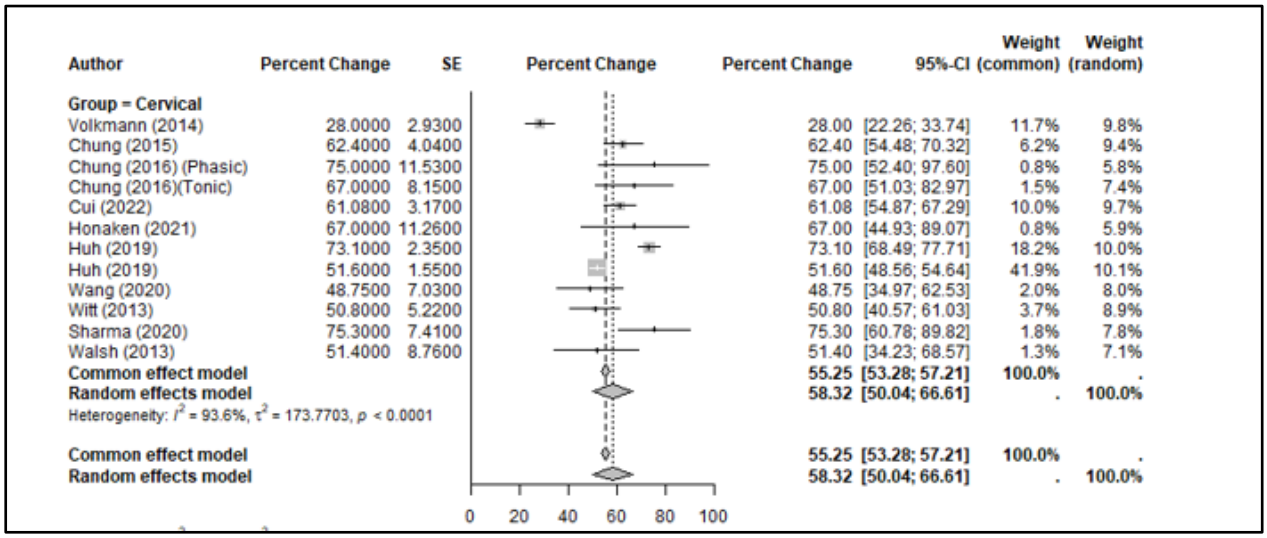

Figure 12. Forest Plot of Percent Improvement in TWSTRS Severity Scores in Adult Patients with GPi DBS for Cervical Dystonia at the Latest Follow-up Reported in Each Study

Meta-analysis Stratified by Study Designs on Cervical Dystonia in Adult Patients

A meta-analysis of effectiveness outcomes by study designs in adult patients was conducted for cervical dystonia, focusing on the TWSTRS severity score improvements measured by standardized scales across various study designs. Only one RCT was included in the meta-analysis; therefore, only the point estimate was provided for the RCT.

Figure 13 presents forest plots of the TWSTRS severity score at the latest follow-up for cervical dystonia in adult patients, with data presented from the prospective study (a), retrospective studies (b), and RCT (c).

There was only one prospective study, and the point estimate is 51.40% with a 95% CI of 34.23-68.57% (Figure 13a). The pooled TWSTRS severity score improvement for the eight retrospective studies was 62.04% (95% CI: 54.93% - 69.15%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure 13b). There was only one RCT study, and the point estimate is 28.00% with a 95% CI of 22.26% - 33.74%, shown in Figure 13c). The retrospective studies demonstrated substantial heterogeneity ($I^2 = 88\%$, $\tau^2 = 70.8406$, $p < 0.0001$).

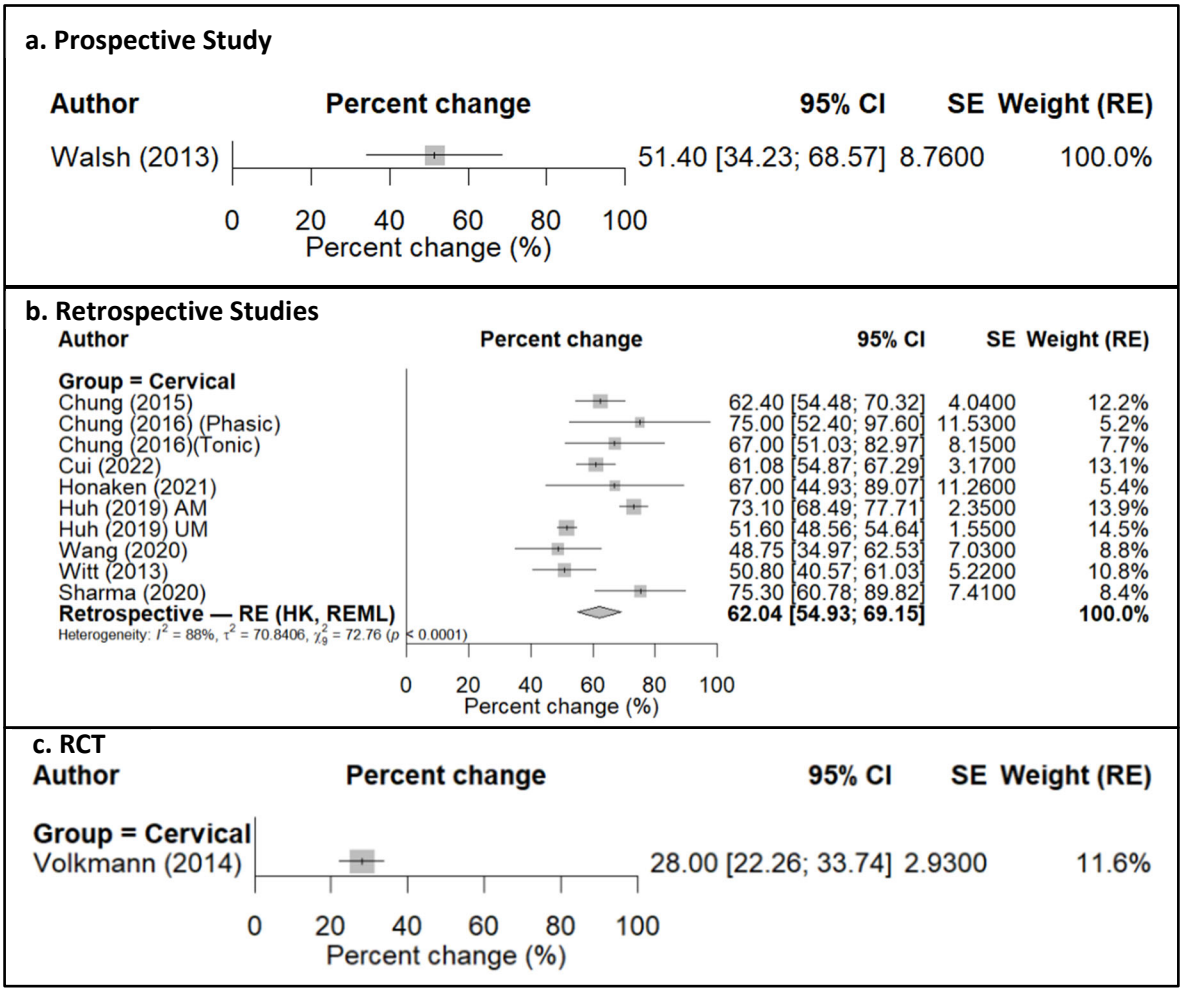

Figure 13. Forest Plots of Percent Improvement in TWSTRS Severity Scores in Adult Patients with Cervical Dystonia at the Latest Follow-up by Study Design, a) Prospective, b) Retrospective, c) RCT.

- Effectiveness Outcomes in Pediatric Population (12 years of age or above) with Primary Generalized Dystonia

Effectiveness Outcome from Publications

There are no RCTs and few large case series evaluating DBS for a pediatric population 12 years of age or above with Primary Generalized Dystonia. The dataset for this population is derived from 4 prospective[13,15,39,40] and 7 retrospectives[41–46,48] studies comprised of 143 patients for effectiveness analysis. Average age at surgery ranged from 10 to 17 years.[15,39–43,45–48,50] Duration of dystonia symptoms before surgery ranged from 3 to 10 years.[15,39–43,45–48,50]

Overall, improvements in average BFMDRS motor scores across all included studies ranged from 35% to 82% at 6 months,[13,41,46,48,50] 54% to 85% at 1 year,[13,15,39–43,45,48,50] 64% to 93% at 2 years,[13,42,45] and 43% to 94% when assessed at 2.7 years and beyond.[15,41–43,45,46]

Table 30 below reports effectiveness outcomes from the 11 publications (4 prospective and 7 retrospective studies) on pediatric patients with generalized dystonia.

Table 30. Summary of Studies of Bilateral GPi DBS for Generalized Dystonia in Pediatric Patients

Publication	Study Type	Age at Surgery in years Mean±SD	BFMDRS Motor Score				
			Last Follow-up (years)	N*	Baseline Score Mean±SD	% improvement Mean±SD	p-value
Borggraefe (2010)[39]	Prospective	14.2 ± 3.4	1.0	44	56.9 ± 22.7	63.70±31.7%	<0.001
Coubes (2004)[13]	Prospective	≤ 17	2.0	19	59.8 ± 25.8	84.70±13.6%	<0.0001
Starr (2014)[40]	Prospective	10.2**	1.0	5	42.9**	82.40±20.6%	NR
Vidailhet (2007)[15]	Prospective	17.2**	3.0	5	38.4	63.60±37.6%	NR
Haridas (2011)[42]	Retrospective	13.4 ± 2.7	3.0	11	39.9 ± 19.5	94.00±NR%	0.003
Ghosh (2012)[41]	Retrospective	13.2**	5.8	6	55 ± 33.2	62.60±16.4%	NR
Krause (2016)[43]	Retrospective	12.5 ± 3.5	4.9	8	45.4±7.5	42.90±11.6%	NR
Lumsden (2013)[44]	Retrospective	12.8**	1.0	14	57.0	62.20±NR%	0.001
Markun (2012)[45]	Retrospective	15.5 ± 5.7	2.7	14	54.6 ± 22.9	70.30±NR%	<0.001
Marotta (2020)[48]	Retrospective	16.0	1.0	9	48	82.00±NR%	NR

Publication	Study Type	Age at Surgery in years Mean±SD	BFMDRS Motor Score				
			Last Follow-up (years)	N*	Baseline Score Mean±SD	% improvement Mean±SD	p-value
Petrossian (2013)[46]	Retrospective	13.3**	4.0	8	45.6*	78.30±23.0%	NR

* Sample size indicates the number of patients with data available at the most recent follow-up.
** Estimated from individual patient data reported in the publication

A total of 11 studies comprised of 143 pediatric patients were included for generalized dystonia with follow up ranging from 1 year to 5.8 years. Figure 14 presents a forest plot of the BFMDRS motor score at the latest follow-up for generalized dystonia in pediatric patients, with data pooled from the selected studies.

The pooled BFMDRS motor score improvement calculated was 71.46% (95% CI: 62.28–80.63%) under the random effects model and 70.90% (95% CI: 67.69–74.12%) under the common effect model. High heterogeneity was observed among the selected studies ($I^2 = 89.1\%$, $\tau^2 = 192.4010$, $p < 0.0001$).

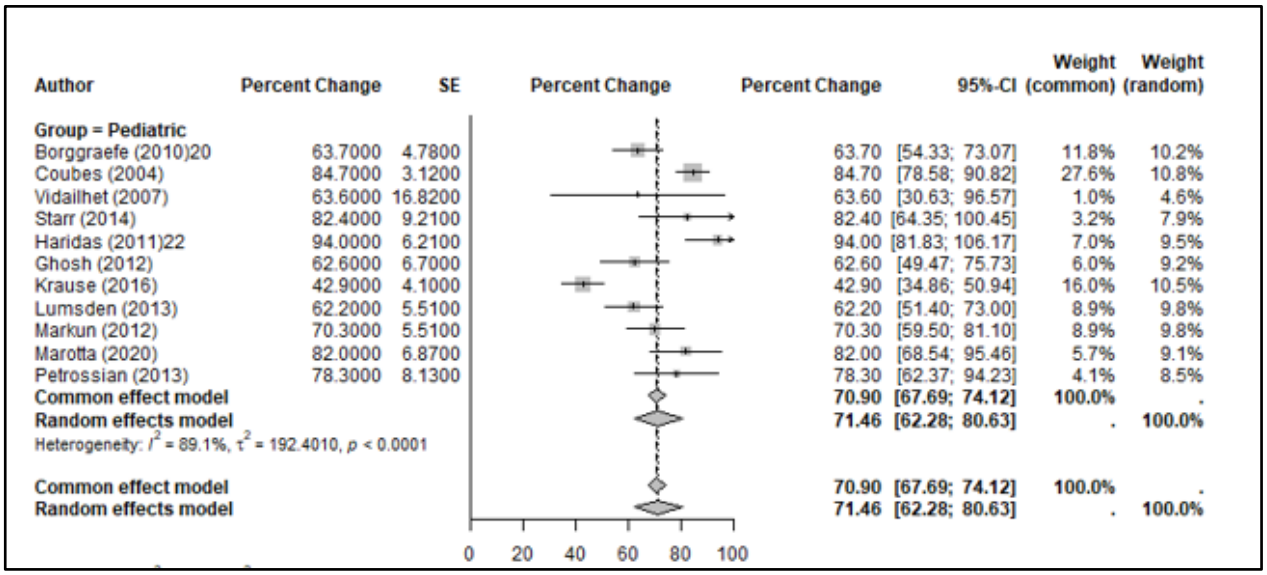

Figure 14. Forest Plot of Percent Improvement in BFMDRS Motor Scores in Pediatric Patients with GPi DBS for Generalized Dystonia at the Latest Follow-up Reported in Each Study

Meta-analysis Stratified by Study Designs on Generalized Dystonia in Pediatric Patients 12 years of age or above

A meta-analysis of effectiveness outcomes by study designs was conducted in pediatric patients with generalized dystonia, focusing on the BFMDRS motor improvements measured by standardized scales across various study designs. Figure 15 presents forest plots of the BFMDRS motor score at the latest follow-up for generalized dystonia in pediatric patients, with data pooled from

the prospective studies (a) and retrospective studies (b). No RCT was reported in the pediatric patient population.

The pooled BFMDRS motor score improvement for the four prospective studies was 75.24% (95% CI: 56.85% - 93.62%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure 15a). In comparison, the pooled BFMDRS motor score improvement for the seven retrospective studies was 69.85% (95% CI: 54.34% - 85.37%), indicated in Figure 15b). Notably, the retrospective studies demonstrated greater heterogeneity (I^2 = 90.2%, τ^2 = 251.9920, p < 0.0001) than the prospective studies (I^2 = 79.3%, τ^2 = 104.4817, p=0.0023).

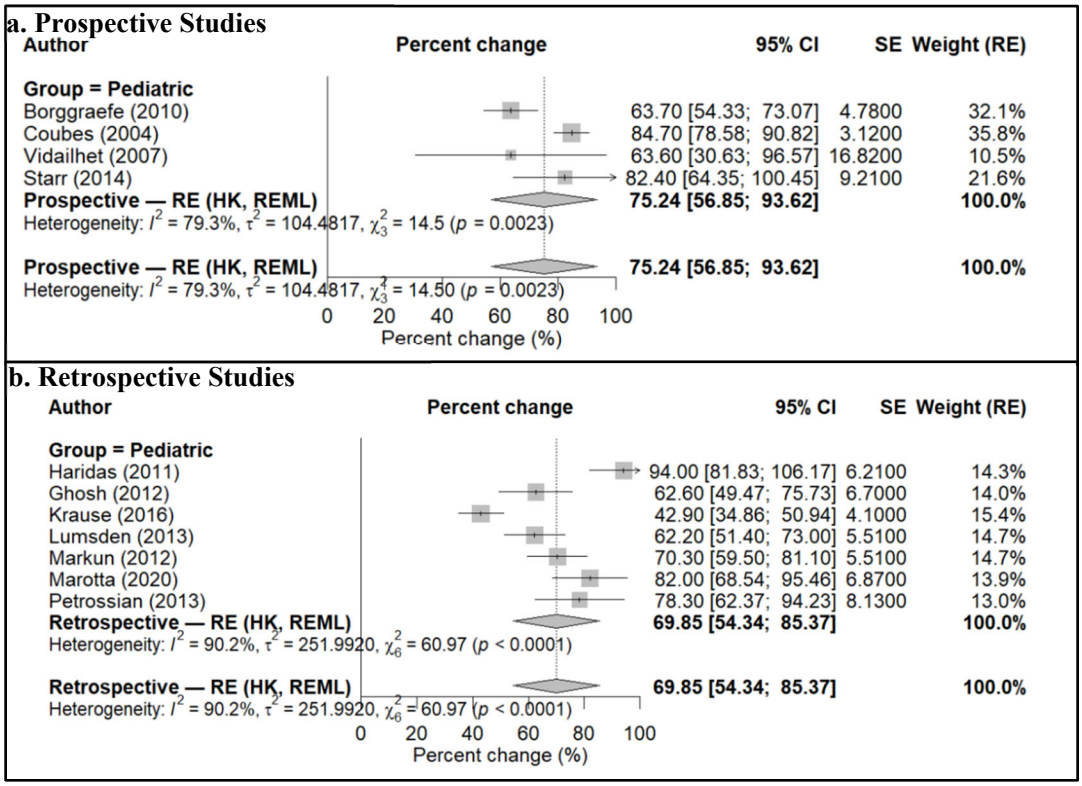

Figure 15. Forest Plots of Percent Improvement in BFMDRS Motor Scores in Pediatric Patients with Generalized Dystonia at the Latest Follow-up by Study Designs, a) Prospective, b) Retrospective.

Comparative Analysis of Adult vs Pediatric with Generalized Dystonia at Last Follow-up

A comparative meta-analysis was conducted using the random effects model to evaluate percent improvement in BFMDRS motor scores in adult patients and pediatric patients with generalized dystonia.

Average age at surgery in pediatric patients ranged from 10 to 17 years[15,39–43,45–48,50] and 22 to 38 years for adult patients.[6,14–18] Duration of generalized dystonia before surgery ranged from 8 to 22 years.[6,14–16,18] Duration of dystonia symptoms before surgery ranged from 3 to 10 years in pediatric patients[15,39–43,45–48,50] and 8 to 22 years for adult patients.[6,14–16,18] Average baseline BFMDRS motor scores across the data sources ranged from 38 to 60 out of a possible score of 120,[13,15,39–43,45–48,50] which is comparable to the range of 42 to 64 reported in the adult population.[6,13–15,17,18]

Figure 16 presents a forest plot and detailed comparison of BFMDRS scores between adult and pediatric patients with generalized dystonia at last follow-up, with data pooled from multiple studies. Six studies involving a total of 130 patients were analyzed in the adult population, and 11 studies with a total of 143 patients were included in the pediatric patient population. The effectiveness data used in the analysis are listed Table 24 for adult patients and Table 30 for pediatric patients with generalized dystonia.

The pooled BFMDRS motor scores improvement for adult patients with generalized dystonia was 60.51% (95% CI: 50.69-70.32%) and 71.46% (95% CI: 62.28–80.63%) for pediatric patients under the random effects model. The overall pooled BFMDRS motor scores improvement across both patient populations was 67.58% (95% CI: 60.41-74.76%).

There was high heterogeneity within both the adult and pediatric patient groups. This phenomenon has been reported in the published literature in adult populations. Heterogeneity also has been reported in pediatric studies. For example, Borggraefe (2010)[39] evaluated effectiveness outcomes by DYT1 status. Patients testing positive for DYT1 had significantly greater improvement than patients testing negative for DYT1. Markun (2012)[45] reported that patients without fixed orthopedic deformities at baseline had significantly greater improvement than patients with fixed deformities. Additionally, shorter duration of disease at time of surgery was also associated with better outcomes.[45]

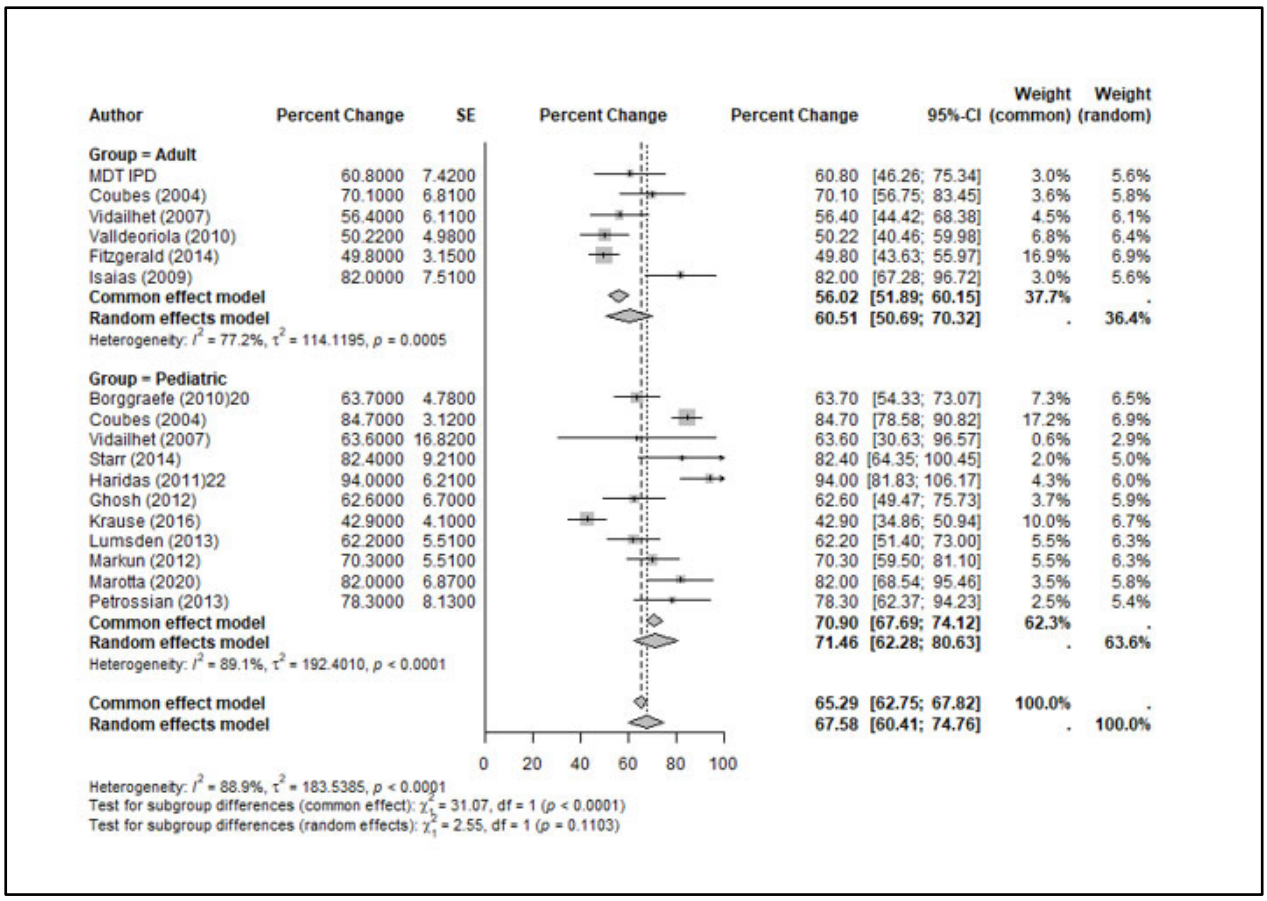

Figure 16. Forest Plot of Percent Improvement in BFMDRS Motor Scores in Adult vs Pediatric Patients with Generalized Dystonia at the Last Follow-Up

Impact of DBS on Cognitive Function in Pediatric Patients

The impact of DBS on overall cognitive function in pediatric patients remains unknown. Evidence from two small retrospective studies suggests that DBS does not adversely affect cognitive function in pediatric patients. These studies, involving a total of 22 pediatric patients followed for approximately one year, focused on the effects of GPi DBS on cognition. Marotta (2020)[48] studied nine patients, six with primary dystonia and three with secondary dystonia, over 13 months. Cognitive function, assessed using the Wechsler Intelligence Scale for Children, showed no deterioration. Additionally, two patients implanted with directional electrodes demonstrated mild improvements in executive functions. Owen (2015)[51] studied 13 children with primary dystonia with at least one year follow up and found that cognitive scores remained stable or improved in 10 patients, while three patients experienced score deterioration, possibly influenced by fatigue or distractions during testing. The authors concluded that cognition remained stable within this small cohort.

However, other scientific articles[52–54] identified 11 cognitive-related adverse events, including cognitive deficits or worsening (3), depression (2), psychiatric comorbidity (2), aggression (1), agitation (1), anxiety (1), and low mood (abulia and ebullience) (1). Kaminska (2017)[52] reported complications in 129 pediatric patients with various forms of dystonia, average age 10.8 years and at least six months of follow-up. One patient experienced low mood (abulia and ebullience), which was considered an intolerable side effect of stimulation; DBS was discontinued for this patient. Koy (2019)[53] studied 72 pediatric patients with dystonia over 4.6 years, including 16 with isolated inherited or idiopathic dystonia. In the perioperative period, one reversible case of agitation was linked to anesthesia. Long-term, two transient psychiatric events were associated with stimulation, and one reversible cognitive decline was unrelated to DBS. Xu (2020)[54] retrospectively studied nine pediatric patients (mean age 15.9) over 10 years, reporting cognitive deficits, depression, and anxiety as adverse events; some symptoms improved with stimulation adjustment, though details were unspecified.

Additional analysis of the PSR adverse events related to cognition, mood, and behavior included only one specific AE in one pediatric patient after 6 years of device use. This patient experienced a serious adverse event of aggression and was treated with medication.

The above data is limited by small sample sizes, insufficient long-term follow-up, and lack of RCT studies available to systematically investigate the impact of DBS on overall cognitive, neurological, and behavioral development in pediatric patients.

- Quality of Life Outcomes

Product Surveillance Registry

Patients enrolled under the current PSR protocol report quality of life (EQ-5D) data at baseline and follow-up, with changes summarized in Table 31. The change in EQ-5D score was calculated from baseline to the 6- or 12- and 24-month visits.

A total of 132 therapy-naïve adult dystonia patients and 13 pediatric dystonia patients had EQ-5D assessments at both baseline and follow-up. In adults, EQ-5D scores showed statistically significant improvement at all follow-up visits ($p<0.05$) at 6, 12, and 24 months. For pediatric patients, statistical testing was not performed due to the small sample size.

Table 31. Change in EQ-5D Index from Baseline to Follow-up in Therapy-Naïve Dystonia Patients

Visit	N	Baseline mean ± SD	Follow-up mean ± SD	Change mean ± SD	P-Value
Adult Patient Population					
6 Month	71	0.588 ± 0.237	0.725 ± 0.211	0.139 ± 0.283	<0.001
12 Month	65	0.601 ± 0.234	0.711 ± 0.254	0.110 ± 0.321	0.010
24 Month	52	0.608 ± 0.270	0.757 ± 0.219	0.149 ± 0.307	0.002
Pediatric Patient Population					
6 Month	10	0.451 ± 0.348	0.658 ± 0.242	0.207 ± 0.236	NA[b]
12 Month	7	0.411 ± 0.290	0.643 ± 0.252	0.232 ± 0.435	NA[b]
24 Month	8	0.480 ± 0.336	0.804 ± 0.197	0.323 ± 0.316	NA[b]
[b] p-values are not reported due to small sample size					

Systematic Literature Review: Quality of Life

A total of seven publications reported quality of life (QoL) data related to GPi DBS. Three secondary prospective publications following the Kupsch (2006)[4] RCT demonstrated sustained QoL improvements in adults with generalized and segmental dystonia, showing 10.6 point improvement in the SF-36 physical component at six months and five years.[5,55] At 10 years of follow-up compared to baseline, the same patient group showed significant improvements in pain (Visual Analog Scale: 4.6 ± 2.7 to 3.1 ± 2.4, P = 0.007). In cervical dystonia, Volkmann (2014)[7] found no significant QoL differences at three months between DBS and sham stimulation groups but noted a significant 28% improvement in CDQ-24 scores by six months (mean reduction of 19.4 points, P<0.0001).

Four other studies assessed QoL in adult and pediatric populations:

- Valldeoriola (2010)[14]: In 22 adults with generalized dystonia, SF-36 physical scores improved from 36.08 to 62.37 (P<0.01) at one year, alongside EQ-5D and pain scale improvements.
- Blahak (2008)[20]: Adult patients with segmental dystonia experienced a 40% and 51% increase in SF-36 scores at 7.5 and 17 months, respectively. Similar improvements were observed in the physical and mental health summary subscores.
- Vidailhet (2007)[15]: Adult and pediatric patients with generalized dystonia exhibited sustained SF-36 improvements in general health, physical functioning, and pain over three years (P≤0.05).
- Starr (2014)[40]: Six pediatric patients with generalized dystonia showed a 52.6% QoL improvement (SF-36) at 12 months (P=0.027).

Prospective studies represented the highest level of available clinical evidence. GPi DBS in adults with generalized and segmental dystonia demonstrated a 10.6 point improvement in the SF-36 physical component at six months, which was sustained to five years.[5,55] QoL improvements are accompanied by significant improvements in pain, anxiety, and depression.[56] A small prospective study of DBS in pediatric patients showed an approximate 52.6% improvement in total SF-36 scores at 12 months.[40] Additionally, evidence from other retrospective studies favors a positive impact of DBS on QoL.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation.

The applicant employed information from multiple data sources as part of their marketing application. These data sources included an analysis of a subset of clinical data purchased from a published randomized controlled trial (RCT) by Kupsch (2006) and its long-term follow-up study by Volkmann (2012),[5] collectively referred to as the "Investigator Study" in this document; an additional RCT conducted by Volkmann (2014); a meta-analysis of published literature; and data from the Medtronic Product Surveillance Registry (PSR).

The ability to provide financial disclosure for participating investigators by the applicant is limited because Medtronic was not the sponsor per 21 CFR part 812 of the published clinical studies. However, the broader definition of 'sponsor of the covered clinical study' under 21 CFR part 54 would classify Medtronic as supporting a potential covered clinical study reported in the published literature. A summary of financial disclosure information related to the RCT data is provided in Table 32 below.

Table 32. Financial disclosure information – RCT Data

Author, *Journal* (Year)	**Financial disclosure information**
Kupsch, *N Engl J Med* (2006) Information also applies to the Investigator-Study	Financial support of the study included an unrestricted research grant from Medtronic, by a grant from the German Ministry of Research and Technology, and by grants from the universities involved in the study. Medtronic was not involved with the conduct of this study. The publication reports, *"The authors vouch for the completeness and veracity of the data and data analyses. The study sponsors were not involved in the design or execution of the trial, data analysis, or reporting of the trial results."*
Volkmann, *Lancet Neurol* (2012)	Financial support of the study included an unrestricted research grant from Medtronic and funding from the universities involved and from the German Ministry of Research and Technology. Medtronic was not involved with the conduct of this study. This publication was based on long-term data collected from subjects enrolled in the RCT published by Kupsch (2006).[4] The publication reports, *"The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding*

Author, *Journal* (Year)	Financial disclosure information
	author had full access to all the data in the study and had final responsibility for the decision to submit for publication."
Volkmann, *Lancet Neurol* (2014)	Financial support of the study included an unrestricted research grant from Medtronic and funding from the universities involved. A medical writer for proofreading and editing the manuscript was funded by Julius Maximilians University, Würzburg, Germany. Medtronic was not involved with the conduct of this study. The publication reports, *"The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the statistical report (and source data on request) and vouch for the completeness and veracity of the data and data analyses. The writing committee had final responsibility for the decision to submit the paper for publication.*

As the sponsor of the PSR, the applicant did not collect financial disclosure information from participating investigators at the initiation of the study. Financial disclosure forms are available for participating sites for the past three years, and no conflicts have been identified.

None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable

XIII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurological Devices panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Deep Brain Stimulation (DBS) targeting the globus pallidus internus (GPi) is an established therapy for primary dystonia. Effectiveness was assessed using standardized scales to assess dystonia severity: Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) for generalized/segmental dystonia and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) for cervical dystonia.

- **Primary Generalized Dystonia in Adult Patients:**
  The analysis included 6 studies of 130 patients with primary generalized dystonia to evaluate effectiveness at the last follow-up (1 RCT, 3 prospective studies, and 2 retrospective studies). Among the publications for generalized dystonia, dystonia

severity was characterized by severe or marked disability, impaired function in performance of activities of daily living or poor symptom control despite medical management. The highest level of available clinical evidence is the Investigator Study,[6] which included 18 generalized dystonia subjects from the Kupsch (2006)[4] RCT and Volkmann (2012) study.[5] The BFMDRS motor score improved significantly by 42.3% in the neurostimulation group (n=9), compared to worsening by 2.5% in the sham stimulation group (n=8) at 3 months (p=0.005*)*.[6]

Across five other published studies, the average improvement in BFMDRS motor scores ranged from 43.5% to 79.6% at 1 year,[6,13–17] 49.9% to 82.5% at 2 years,[6,13,16,17] and 56.4% to 85.5% at 3 years.[6,15,17]

Meta-analysis of the Investigator Study and published literature showed a pooled rate of improvement in BFMDRS motor scores of 60.51% (95% CI: 50.69-70.32%) in 130 patients across the 6 total studies at follow-up time points ranging from 1 to 7 years with high heterogeneity. Similar pooled improvement rates were seen when the meta-analysis was stratified by study designs (i.e., RCT, prospective, and retrospective studies.)

- **Primary Segmental Dystonia of the Head and Neck in Adult Patients:**
  The analysis included 94 adult patients with segmental dystonia to evaluate effectiveness at the last follow-up (1 RCT, 2 prospective, and 6 retrospective studies). Among the publications for segmental dystonia, severity was characterized by severe symptoms, marked disability or functional impairment, or failed or discontinued medications or botulinum neurotoxin due to no or slight effect. The highest level of available evidence is the Investigator Study,[6] which included 11 subjects with segmental dystonia of the head and neck from the Kupsch RCT[4] and Volkmann (2012)[5] study. The BFMDRS motor improved significantly by 61.2% in the neurostimulation group (n=7), compared to 0.9% in the sham stimulation group (n=4) at 3 months (p = 0.011). There were significant improvements in motor scores at each follow-up through 4 years (70.6%) (n=7), however, a comparable improvement at 5 years (59.6%) was not statistically significant likely due to small sample size (n=5).

  Across eight other published studies, the average improvement in BFMDRS motor scores ranged from 45% to 72% at 3 to 8 months,[20–25] and 53% to 72% at 2 to 4 years.[22,24,25,27]

  Meta-analysis of the Investigator Study [6] and published literature showed a pooled rate of improvement in BFMDRS motor scores of 62.03% (95% CI: 56.56-67.51%) in 94 patients across the 9 total studies at follow-up time points ranging from 6 months to 5.6 years with high heterogeneity. Similar pooled improvement rates were seen when the meta-analysis was stratified by study design (i.e., RCT, prospective, and retrospective studies.)

- **Primary Cervical Dystonia in Adult Patients:**

The analysis included 245 adult patients with cervical dystonia to evaluate effectiveness at the last follow-up (1 RCT, 1 prospective, 8 retrospective studies). The highest level of available clinical evidence is the Volkmann (2014)[7] RCT for cervical dystonia in 62 patients. The TWSTRS severity score improved by 5.1 ± 5.1 points (26% improvement) in the neurostimulation group (n=32) compared to 1.3 ± 2.4 points (6% improvement) in the sham stimulation group (n=30) at 3 months (p=0.0024.). Significant differences between the neurostimulation group and the sham stimulation group were also observed in the TWSTRS disability score (41% vs. 11% improvement, p=0.007)) at 3 months. The scores were maintained after 6 months of follow-up in the open-label phase (28% improvement in TWSTRS severity and 46% in TWSTRS disability score, p<0.0001).

Across nine other published studies, the average improvement in TWSTRS severity scores ranged from 29% to 75%[26,28,30–34,36,37] at follow-up time points ranging from 3 months to 7.8 years. These values trended higher than the average improvement of 28% in Volkmann (2014)[7] which may have been impacted by the short follow-up of 6 months.

Meta-analysis of the published literature showed a pooled improvement in TWSTRS severity score of 58.32% (95% CI: 50.04–66.61%) in 245 adult patients across the 10 total studies at follow-up time points ranging from 6 months to 7.8 years with high heterogeneity. The improvement rates were higher for the pooled retrospective studies (62.04%) compared to the point estimate for the one prospective study (51.4%) and the one RCT (28.0%) when stratified by study design.

Bilateral GPi DBS showed a more modest improvement in the RCT trial for primary cervical dystonia (TWSTRS severity score improved 26% at 3 months in the Volkmann (2014)[7] study). However, the overall improvements from the published literature and meta-analysis offer additional supportive evidence of effectiveness and appear reasonably comparable between cervical and generalized and segmental dystonia, although formal statistical comparison was not conducted. In addition, while primary cervical dystonia is classified as a focal dystonia when symptoms are isolated to the neck muscles, cervical dystonia may also present as a component of a more widespread segmental or generalized dystonia. Given this symptomatic overlap, the demonstrated effectiveness of bilateral GPi DBS in primary generalized and segmental dystonia of the head and neck was considered when evaluating the potential effectiveness of bilateral GPi DBS for primary cervical dystonia that remains inadequately controlled by oral and/or injectable medications.

- **Primary Generalized Dystonia in Pediatric Patients (12 years of age or above):**
  There were no RCTs and few large case series evaluating DBS for pediatric dystonia. The analysis included 143 pediatric patients with primary generalized dystonia to evaluate effectiveness at the last follow-up (0 RCTs, 4 prospective, and 7 retrospective studies). The data sources compared reasonably well in baseline patient

characteristics. Average age at surgery ranged from 10 to 17 years, and duration of dystonia symptoms before surgery ranged from 3 to 10 years.

Overall, improvements in average BFMDRS motor scores across all included studies ranged from 35% to 82% at 6 months,[13,41,46,48,50] 54% to 85% at 1 year,[13,15,39–43,45,48,50] 64% to 93% at 2 years,[13,42,45] and 43% to 94% when assessed at 2.7 years and beyond.[15,41–43,45,46]

Meta-analysis showed a pooled improvement in BFMDRS motor score of 71.46% (95% CI: 62.28–80.63%) in 143 pediatric patients across the 11 total studies at follow-up time points ranging from 1.0 to 5.8 years with high heterogeneity. Similar pooled improvement rates were seen when the meta-analysis was stratified by study design (75.24% in prospective compared to 69.85% in retrospective studies.)

Additional comparative meta-analyses of percent improvement in BFMDRS motor scores at last follow-up between adult and pediatric patients with primary generalized dystonia was conducted using the random effects model. Pooled rates of percent improvements in BFMDRS motor scores were 60.51% for adult patients with follow-up ranging from 1 to 7 years and 71.46% for pediatric patients with follow-up ranging from 1 to 5.8 years, with no significant difference between the two groups and high heterogeneity.

In summary, the data from these studies demonstrated the effectiveness of Medtronic DBS Therapy for Dystonia targeting the GPi as an aid in the management of chronic, intractable (oral and/or injectable medication refractory) primary dystonia, including generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis) in adult patients, and generalized dystonia in pediatric patients twelve years of age and above.

B. Safety Conclusions

- **Primary Generalized Dystonia in Adult Patients:**
  The analysis included 173 patients with generalized dystonia to evaluate safety, including 18 patients in the Investigator Study and 155 patients in 6 published literature studies (3 prospective and 3 retrospective studies). The Investigator Study[6] reported overall adverse event and serious adverse event occurrence rates of 22.2% and 11.1% in the 3-month blinded phase, and 72.2% and 55.6% in the open label 5 year follow-up phase, respectively. Therapy-related safety events during the 5-year follow-up phase of the Investigator Study included: device complications (61.1%), device revisions (55.6%), explants (22.2%), infections (16.7%), and intracranial hemorrhage (symptomatic: 0%, asymptomatic: 0%).

  Across six other published studies, the reported incidence rates for AE and SAE ranged from 25% to 58%,[14–18] and 8 to 18%,[14–16,18] respectively, over follow-up periods spanning 6 months to 7 years in adult patients with generalized dystonia.

Meta-analysis of therapy-relevant safety events across the 7 total studies showed that device complications (22%), revisions (19%), and explants (13%) were the most frequent safety events, followed by infections (12%). Intracerebral hemorrhage (symptomatic: 3% and asymptomatic: 0%) was less common. Substantial heterogeneity was observed for both device complication rates and device revision rates, which could be multifactorial and are likely influenced by clinical factors such as surgical experience and reporting practices.

- **Primary Segmental Dystonia of the Head and Neck in Adult Patients**
  The analysis included 101 patients with segmental dystonia to evaluate safety, including 11 patients in the Investigator Study and 90 patients in 8 published literature studies (2 prospective and 6 retrospective studies). The Investigator Study[6] reported overall AE and SAE occurrence rates of 57.1% and 28.6% in the 3-month blinded phase, and 72.7% and 63.6% in the open label phase through five years, respectively. Therapy-related safety events during the 5-year follow-up phase of the Investigator Study included: device complications (54.5%), device revisions (54.5%), explants (9.1%). infections (0%), and intracranial hemorrhages (symptomatic: 0%, asymptomatic: 0%).

  Across eight other published studies, the reported incidence rates for AE and SAE 8.3% to 100%,[20–26] and 0 to 25%,[26,27] respectively, over follow-up periods ranging from 6 months to 5.6 years in adult patients with segmental dystonia of the head and neck.

  Meta-analysis of therapy-relevant safety events across the 9 total studies showed similar trends in segmental dystonia compared to generalized dystonia: device complications (13%), revisions (14%), explants (9%), infections (7%), and intracranial hemorrhages (symptomatic: 6%, asymptomatic: 4%). High heterogeneity was observed for both device complication rates and device revision rates, likely influenced by clinical factors such as surgical experience and reporting practices.

- **Primary Cervical Dystonia in Adult Patients:**
  The safety analysis included 238 patients with cervical dystonia from 9 published literature studies (1 RCT, 1 prospective, and 7 retrospective studies). The Volkmann (2014)[7] RCT reported 5 SAEs (16%, 5/32) in the neurostimulation group compared to 11 SAEs (37%, 11/30) in the sham group, with 69% (11/16) resolving without sequelae. Most SAEs within 6 months of follow-up were related to surgery, device or stimulation, and resolved without sequelae. Therapy-related safety event rates included device complications (8.1%), device revisions (3.2%), explants (1.6%), infections (4.8%), and intracranial hemorrhages (symptomatic: 1.6%, asymptomatic: NR).

  Across 8 other published studies, the reported incidence rates for AE and SAE were 3.8% to 80%[26,28–30,32–35] and 0 to 14.3%,[26,28,29,35,38] respectively, over follow-up periods ranging from 1 to 10 years in adult patients with cervical dystonia.

Meta-analysis of therapy-relevant safety events across 9 total studies explants in adult patients with cervical dystonia showed device complications (11%), device revisions (14%), explants (4%), infections (7%), and intracranial hemorrhages (symptomatic: 5%, asymptomatic: NR) with moderate to high heterogeneity for device complications and device revision rates.

- **Primary Generalized Dystonia in Pediatric Patients (12 years of age or above):** There are no RCTs and few large case series evaluating DBS for pediatric dystonia. The safety analysis included 202 pediatric patients with generalized dystonia from 12 published literature studies (4 prospective and 8 retrospective studies) with an average follow-up ranging from 6 months to 10 years.

  Across 12 published studies, the reported incidence rates for AE and SAE were 0% to 100%[13,15,39–43,45–48] and 0 to 60%,[15,40,41,43] respectively, over follow-up periods ranging from 6 months to 10 years in pediatric patients with generalized dystonia.

  Meta-analysis of therapy-relevant safety events for pediatric patients with generalized dystonia showed device complications (26%), device revisions (21%), explants (20%), infections (16%), and intracerebral hemorrhages (symptomatic: 4%, asymptomatic: 6%).

- **Safety Conclusions from Medtronic Product Surveillance Registry Data (PSR):** In addition to published literature, safety was analyzed using Medtronic PSR data. The safety analysis included 308 patients with primary dystonia, including 279 adults (90.6%) with a mean age of 53 ± 14.4 years and 27 pediatric patients (8.8%) with a mean age of 16 ± 3.9 years. Average duration of device exposure was 38.2 ± 32.6 months for adults and 35.9 ± 30.9 months for pediatric patients. A total of 166 adverse events (related to device, therapy, or procedure) were recorded in 87 patients (28.2%). Serious adverse events occurred in 39 patients (12.7%), including 3 pediatric and 36 adult patients. Notable SAEs included intracranial hemorrhage (1.0% adults, 0% pediatric), infections (3.2% adults, 3.7% pediatric), procedural complications (1.4% adults, 3.7% pediatric), and psychiatric disorders (0.4% adults, 3.7% pediatric). Product performance events occurred in 9.3% of adults and 11.1% of pediatric patients. System explants occurred in 2.2% (6/279) of adult dystonia patients and 3.7% (1/27) of pediatric patients for various reasons including, infection, battery depletion, programming needs, or device protrusion. Fifteen deaths occurred in 12 adults and 3 pediatric patients. Although no deaths were directly attributed to a product performance event, four deaths were due to unknown causes with an unknown relationship to the device or procedure. There were no reported suicides or suicide attempts.

In summary, the clinical evidence compiled from the randomized controlled trials (the Investigator Study [6]) and Volkmann (2014),[7] systematic review of published scientific literature, and the Medtronic PSR is consistent with the known risks in other FDA approved indications for DBS and supports the overall safety profile of Medtronic DBS Therapy for Dystonia stimulating the GPi in adult patients with primary dystonia,

including generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis), and in pediatric patients with generalized dystonia twelve years of age and above.

C. Benefit-Risk Determination

Benefits:
The probable benefits of the device are based on data provided in this application to support PMA approval as described above.

Primary Generalized and Segmental Dystonia of the Head and Neck in Adult Patients:
Data to support the benefits of bilateral GPi DBS as an effective intervention for primary generalized and segmental dystonia in adults include the Investigator Study,[6] which demonstrated improvement in BFMDRS motor score by 42.3% in the neurostimulation group compared to worsening by 2.5% in the sham stimulation group in generalized dystonia and 61.2% in the neurostimulation group compared to 0.9% in the sham stimulation group in segmental dystonia at 3 months after DBS. Improvements in motor scores were maintained at follow-up intervals up to 5 years. Meta-analyses of GPi DBS including 130 patients with primary generalized dystonia across 6 studies and 94 patients with segmental dystonia across 9 studies demonstrated consistent results, with motor score improvements of 60.51% for generalized dystonia and 62.03% for segmental dystonia over follow-up periods ranging from 1 to 7 years and 6 months to 5.6 years, respectively.

Primary Cervical Dystonia in Adult Patients
Data to support the benefits of bilateral GPi DBS as an effective intervention for primary cervical dystonia in adults include the RCT by Volkmann (2014)[7], which demonstrated improvement in TWSTRS severity score by 26% in the neurostimulation group compared to 6% in the sham stimulation group at 3 months and 28% at 6 months after DBS. Improvements were also noted in TWSTRS disability scores. A meta-analysis of GPi DBS including 245 patients with primary cervical dystonia across 10 studies found a pooled improvement in TWSTRS severity of 58.32% over follow-up periods ranging from 6 months to 7.8 years.

Primary Generalized Dystonia in Pediatric Patients 12 years of age or above:
Data to support the benefits of bilateral GPi DBS as an effective intervention for primary generalized dystonia in pediatric patients include a meta-analysis of GPi DBS including 143 pediatric patients with primary generalized dystonia across 11 studies, which found a pooled improvement in BFMDRS motor scores of 71.46% over follow-up periods ranging from 1 to 5.8 years.

Comparative analysis by Medtronic revealed pooled motor score improvements of 71.46% in pediatric patients versus 60.51% in adults, albeit with high heterogeneity.

Risks:
The probable risks of the device are based on data provided in this application to support PMA approval as described above.

Data to support the safety of bilateral GPi DBS for primary generalized, segmental (head and neck), and cervical dystonia in adult patients and primary generalized dystonia in pediatric patients ages 12 and above include AEs, SAEs, and therapy-relevant safety events reported in the Investigator Study for adult generalized and segmental dystonia, the Volkmann (2014)[7] RCT for adult cervical dystonia, and meta-analyses of therapy-relevant safety event rates reported in published literature studies for each type of dystonia.

The Investigator Study reported the overall AE and SAE occurrence rates as 22.2% and 11.1% in the 3-month blinded phase in the DBS group, and 72.2% and 55.6% in the open label phase, respectively, in adult patients with generalized dystonia. Therapy-relevant safety events over 5 years for adult generalized dystonia included: device complications 61.1%, device revisions 55.6%, explants 22.2%, infections 16.7%, and symptomatic intracranial hemorrhages 0%. The Investigator Study reported the overall AE and SAE occurrence rates as 57.1% and 28.6% in the 3-month blinded phase in the DBS group, and 72.7% and 63.6% in the open label phase, respectively, in adult patients with segmental dystonia of the head and neck. Therapy-related safety events over 5 years for adult segmental dystonia included: device complications (54.5%), device revisions (54.5%), explants (9.1%). infections (0%), and intracranial hemorrhage (symptomatic: 0%, asymptomatic: 0%). The Volkmann (2014)[7] RCT reported 16% SAEs in neurostimulation group compared to 37% in the sham group, with 69% resolving without sequelae. Most SAEs within 6 months of follow-up were related to surgery, device or stimulation, and resolved without sequelae. Therapy-related safety event rates included device complications (8.1%), device revisions (3.2%), and explants (1.6%). infections (4.8%), intracranial hemorrhage (symptomatic: 1.6%, asymptomatic: NR).

Meta-analyses of therapy-relevant safety events showed device complication rates of 22% in adult generalized, 13% in adult segmental, 11% in adult cervical, and 26% in pediatric generalized dystonia. Device revision rates were 19% in adult generalized, 14% in adult segmental, 14% in adult cervical, and 21% in pediatric generalized dystonia. Explant rates were 13% in adult generalized, 9% in adult segmental, 4% in adult cervical, and 20% in pediatric generalized dystonia. Infection rates were 12% in adult generalized, 7% in adult segmental, 7% in adult cervical, and 16% in pediatric generalized dystonia. Intracranial hemorrhages were less common (≤6%) across all groups.

While device-related safety event rates in the meta-analyses appear higher in pediatric patients with generalized dystonia compared to adult patients with generalized dystonia, the rates were more comparable to the Investigator Study[6] of adult generalized dystonia, with similar rates of explants (20% vs 22.2%) and infections (16% vs 16.7%) and lower rates of device complications (26% vs 61.1%) and revisions (21% vs 55.6%) over a 5 year follow-up period, although formal statistical analysis was not conducted.

Additional data to support the safety of bilateral GPi DBS for primary generalized, segmental (head and neck), and cervical dystonia in adult patients and primary generalized dystonia in pediatric patients ages 12 and above include data from the Medtronic Product Surveillance Registry including 308 patients with primary dystonia (279 adult, 27 pediatric) with an average device exposure of approximately 3 years. Adverse events occurred in 28.2% of patients, with serious adverse events occurring in 12.9% of adults and 11.1% of pediatric patients. Notable SAEs included intracranial hemorrhage (1.0% adults, 0% pediatric), infections (3.2% adults, 3.7% pediatric), and procedural complications (1.4% adults, 3.7% pediatric). System explants occurred in 2.2% of adults and 3.7% of pediatric patients.

Additional factors considered in determining probable risks and benefits for the Medtronic DBS Therapy for Dystonia System included:

- Limited alternative treatments are available for chronic, intractable (oral and/or injectable medication refractory) primary dystonia that is often progressive and can lead to contractures and severe disability.
- Patients may accept higher surgical and device-related risks to achieve symptom relief when facing severe, intractable (oral and/or injectable medication refractory) dystonia.
- For pediatric patients 12 years of age or above with severe, intractable (oral and/or injectable medication refractory) primary generalized dystonia, early DBS intervention may help prevent or minimize the progression of secondary musculoskeletal complications, including joint contractures and fixed postural deformities that can significantly impact long-term functional outcomes.
- By 12 years of age or above, the basic anatomical structures targeted in DBS, e.g., the GPi, have largely reached adult-like organization and size, and patients can typically tolerate the surgical procedures and device implantation similarly to adults.
- Limiting pediatric indication to ages 12 and above allows patients to have sufficient time to carefully monitor symptom development and have the opportunity to better participate in treatment decisions.
- Adequate risk mitigation strategies can be implemented through patient selection, monitoring, and management of potential stimulation-related adverse events. Device labeling includes specific warnings and precautions to enable these mitigations.

Patient Perspective:
This submission did not include specific information on patient perspectives for this device.

Overall, the data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The probable benefit to health from the use of the device outweighs the probable risk of injury or illness from such use.

D. Overall Conclusion

The evidence presented in this application supports the reasonable assurance of effectiveness of this device when used in accordance with the indications for use. The Investigator Study[6] showed clinical meaningful improvements in BFMDRS motor scores for both generalized and segmental dystonia with sustained benefits through 5 years, supported by the meta-analysis showing consistent pooled BFMDRS motor scores improvement based on published literature. While the Volkmann (2014)[7] RCT showed more modest improvements in BFMDRS for patients with cervical dystonia, the meta-analysis showed higher pooled improvement over longer follow-up periods. For generalized dystonia in pediatric patients twelve years of age or above, meta-analysis data demonstrated pooled BFMDRS motor score improvements; descriptively, these improvements appeared comparable to those reported in adult populations.

The evidence presented in this application supports the reasonable assurance of safety of this device when used in accordance with the indications for use. While device-related complications, including infections, revisions, and explants, appeared numerically higher in pediatric patients at 12 years of age or above with primary generalized dystonia compared to adults with primary generalized dystonia based on the meta-analysis data, these rates were similar to those reported in the Investigator Study for adults with generalized dystonia. Although pediatric patients may experience a higher incidence of device-related safety events and long-term neurodevelopmental effects remain unknown, risks can be mitigated through careful patient selection, clinical monitoring, and device labeling.

In conclusion, the data in this application support that the probable benefits of using the Medtronic DBS Therapy for Dystonia outweigh the probable risks for bilateral stimulation of the internal globus pallidus (GPi) as an aid in the management of chronic, intractable (oral and/or injectable medication refractory) primary dystonia, including:

- generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis) in adult patients, and
- generalized dystonia in pediatric patients twelve years of age and above.

E. Limitations of the Study

Limitations of Results from RCT Studies

Data derived from the two randomized studies included the following limitations:

- Medication adjustments were allowed as needed with limited analyses of the impact to treatment outcomes. While treatment success with DBS possibly could be confounded by changes in medication, patients resort to surgical interventions such as DBS because of refractory dystonia symptoms or poorly tolerated side effects of medication.

- The following could affect the generalizability of results:
  - The duration of the randomized period was short.
  - Small sample size.
  - Open-label design of follow-up reports, which may result in an overestimation of the treatment effect.
  - There have been no randomized studies to evaluate the use of GPi DBS for pediatric patients twelve to 21 years of age.

Data derived from the systematic literature review included the following limitations:

- Meta-analyses of published literature revealed substantial heterogeneity. Substantial heterogeneity in the meta-analyses suggests publication bias and may underestimate risks of DBS and overestimate treatment success. The sources of heterogeneity include:

  - Studies differed in research methods and scientific rigor in terms of variable study designs, patient selection criteria, sample sizes, duration of follow-up, and reporting of safety and effectiveness outcomes.
  - DBS programming parameters with different stimulation settings, optimization protocols, and follow-up programming approaches.
  - Outcome measures with varying rater training, and measurement timing.
  - Follow-up durations with substantial variation ranging from 6 months (Volkmann 2014,[7] Ostrem 2007) to over 10 years (Walsh 2013: 4.9-10.7 years; Jacksch 2022: 10 years; Ramezani Ghamsari 2021: 7-10 years) across studies, with most studies falling between 1-5 years of follow-up.
  - Variability in defining and reporting adverse events in publications limits the accuracy of safety information that can be extracted from the published literature. The published literature provides limited access to primary source data such as individual dystonia motor scores and detailed adverse event descriptions. In the absence of primary source data, analyses of associated variables (e.g., body distribution and etiology of dystonia, baseline symptom scores, relevant co-morbidities, etc.) are not possible. While some published reports of studies of DBS to treat dystonia symptoms provided covariate analyses, data included in these publications do not allow for verification of the analyses.

Data derived from Medtronic Product Surveillance Registry (PSR) included the following limitations

- The PSR was primarily used to provide device safety information. Patient disposition information in the PSR indicates high lost-to-follow-up (LTFU) rates (20.5%, 52.9%, 61.4%, and 68.2% for years 2-5, respectively), which likely results in underreporting of adverse events and serious adverse events and introduces bias in adverse event and serious adverse event rate assessments. The significant missing data due to LTFU also can impact the reliability of treatment effect assessment. PSRs may preferentially

capture data from patients who remain in care, potentially missing safety events that lead to treatment discontinuation or loss to follow-up.

- The PSR registry does not collect data for covariates (e.g., medical history, patient and clinical characteristics) that may affect the post-device exposure outcomes. The covariates can be used in multiple variable analysis or stratified analysis to establish association between covariates and outcomes or to adjust/control for potential confounding bias. This limitation can potentially impact the accuracy and reliability of the real world evidence (RWE) based on the registry data due to potential confounding bias.

XV. CDRH DECISION

CDRH issued an approval order on November 22, 2025.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVII. REFERENCES

1. Albanese A, Giovanni MD, Lalli S. Dystonia: diagnosis and management. *Eur J Neurol*. 2019;26(1):5-17. doi:10.1111/ene.13762

2. Albanese A, Barnes M, Bhatia K, et al. A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES Task Force. *European journal of neurology*. 2006;13(5):433-444. doi:10.1111/j.1468-1331.2006.01537.x

3. Albanese A, Asmus F, Bhatia KP, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. *Eur J Neurol*. 2011;18(1):5-18. doi:10.1111/j.1468-1331.2010.03042.x

4. Kupsch A, Benecke R, Müller J, et al. Pallidal Deep-Brain Stimulation in Primary Generalized or Segmental Dystonia. *N Engl J Med*. 2006;355(19):1978-1990. doi:10.1056/NEJMoa063618

5. 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*. 2012;11(12):1029-1038. doi:10.1016/S1474-4422(12)70257-0

6. Medtronic. Investigator sponsored Dystonia Clinical Study Report 2024.

7. Volkmann J, Mueller J, Deuschl G, et al. Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. *Lancet Neurol*. 2014;13(9):875-884. doi:10.1016/S1474-4422(14)70143-7

8. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557

9. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

10. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods*. 2010;1(2):97-111. doi:10.1002/jrsm.12

11. Dettori JR, Norvell DC, Chapman JR. Fixed-Effect vs Random-Effects Models for Meta-Analysis: 3 Points to Consider. *Glob Spine J*. 2022;12(7):1624-1626. doi:10.1177/21925682221110527

12. Deeks JJ, Higgins JP, Altman DG. Cochrane Handbook for Systematic Reviews of Interventions. 2010:243-296. doi:10.1002/9780470712184.ch9

13. Coubes P, Cif L, Fertit HE, et al. Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results. *J Neurosurg*. 2004;101(2):189-194. doi:10.3171/jns.2004.101.2.0189

14. Valldeoriola F, Regidor I, Minguez-Castellanos A, et al. Efficacy and safety of pallidal stimulation in primary dystonia: results of the Spanish multicentric study. *J Neurol, Neurosurg Psychiatry*. 2010;81(1):65. doi:10.1136/jnnp.2009.174342

15. Vidailhet M, Vercueil L, Houeto JL, et al. Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. *Lancet Neurol*. 2007;6(3):223-229. doi:10.1016/s1474-4422(07)70035-2

16. FitzGerald JJ, Rosendal F, Pennington N de, et al. Long-term outcome of deep brain stimulation in generalised dystonia: a series of 60 cases. *J Neurol, Neurosurg Psychiatry*. 2014;85(12):1371. doi:10.1136/jnnp-2013-306833

17. Isaias IU, Alterman RL, Tagliati M. Deep Brain Stimulation for Primary Generalized Dystonia: Long-term Outcomes. *Arch Neurol*. 2009;66(4):465-470. doi:10.1001/archneurol.2009.20

18. Sobstyl M, Kmiec T, Zabek M, Szczaluba K, Mossakowski Z. Long-term outcomes of bilateral pallidal stimulation for primary generalised dystonia. *Clinical neurology and neurosurgery*. 2014;126(0303-8467):82-87. doi:10.1016/j.clineuro.2014.08.027

19. Vidailhet M, Vercueil L, Houeto JL, et al. Bilateral Deep-Brain Stimulation of the Globus Pallidus in Primary Generalized Dystonia. *N Engl J Med*. 2005;352(5):459-467. doi:10.1056/nejmoa042187

20. Blahak C, Wöhrle JC, Capelle HH, et al. Health-related quality of life in segmental dystonia is improved by bilateral pallidal stimulation. *J Neurol*. 2008;255(2):178-182. doi:10.1007/s00415-008-0614-3

21. Ostrem JL, Marks WJ, Volz MM, Heath SL, Starr PA. Pallidal deep brain stimulation in patients with cranial–cervical dystonia (Meige syndrome). *Mov Disord*. 2007;22(13):1885-1891. doi:10.1002/mds.21580

22. Fu S, Yang Z, He X, et al. Long-term Efficacy of Bilateral Globus Pallidus Stimulation in the Treatment of Meige Syndrome. *Neuromodulation: Technol Neural Interface*. 2024;28(3):532-544. doi:10.1016/j.neurom.2024.02.002

23. Horisawa S, Ochiai T, Goto S, et al. Long-term outcome of pallidal stimulation for Meige syndrome. *J Neurosurg*. 2019;130(1):84-89. doi:10.3171/2017.7.JNS17323

24. Reese R, Gruber D, Schoenecker T, et al. Long-term clinical outcome in meige syndrome treated with internal pallidum deep brain stimulation. *Mov Disord*. 2011;26(4):691-698. doi:10.1002/mds.23549

25. Ren H, Wen R, Wang W, et al. *Long-Term Efficacy of GPi DBS for Craniofacial Dystonia: A Retrospective Report of 13 Cases*.; 2022:673-682. doi:10.1007/s10143-021-01584-4

26. Sharma VD, Bezchlibnyk YB, Isbaine F, et al. Clinical outcomes of pallidal deep brain stimulation for dystonia implanted using intraoperative MRI. *J Neurosurg*. 2020;133(5):1582-1594. doi:10.3171/2019.6.JNS19548

27. Tian H, Xiong N, Xiong N, et al. Similar Long-Term Clinical Outcomes of Deep Brain Stimulation with Different Electrode Targets for Primary Meige Syndrome: One Institution's Experience of 17 Cases. *Neuromodulation : journal of the International Neuromodulation Society*. 2021;24(2):300-306. doi:10.1111/ner.13304

28. Chung M, Han I, Chung SS, Jang DK, Huh R. Effectiveness of selective peripheral denervation in combination with pallidal deep brain stimulation for the treatment of cervical dystonia. *Acta Neurochir*. 2015;157(3):435-442. doi:10.1007/s00701-014-2291-6

29. Contarino MF, Munckhof PVD, Tijssen MAJ, et al. Selective peripheral denervation: comparison with pallidal stimulation and literature review. *J Neurol*. 2014;261(2):300-308. doi:10.1007/s00415-013-7188-4

30. Honkanen EA, Korpela J, Pekkonen E, Kaasinen V, Reich MM, Joutsa J. Reappearance of Symptoms after GPi-DBS Discontinuation in Cervical Dystonia. *Mov Disord Clin Pr*. 2021;8(3):406-411. doi:10.1002/mdc3.13162

31. Huh R, Chung M. Range of voluntary neck motility predicts outcome of pallidal DBS for cervical dystonia. *Acta Neurochir*. 2019;161(12):2491-2498. doi:10.1007/s00701-019-04076-z

32. Jacksch C, Zeuner K, Helmers A, Witt K, Deuschl G, Paschen S. Long-term efficacy with deep brain stimulation of the globus pallidus internus in cervical dystonia: a retrospective monocentric study. *Neurological research and practice*. 2022;4(1):48. doi:10.1186/s42466-022-00214-8

33. Witt JL, Moro E, Ash RS, et al. Predictive factors of outcome in primary cervical dystonia following pallidal deep brain stimulation. *Mov Disord*. 2013;28(10):1451-1455. doi:10.1002/mds.25560

34. Walsh RA, Sidiropoulos C, Lozano AM, et al. Bilateral pallidal stimulation in cervical dystonia: blinded evidence of benefit beyond 5 years. *Brain*. 2013;136(3):761-769. doi:10.1093/brain/awt009

35. Cui Z, Chen T, Wang J, et al. The Long-Term Efficacy, Prognostic Factors, Safety, and Hospitalization Costs Following Denervation and Myotomy of the Affected Muscles and Deep Brain Stimulation in 94 Patients with Spasmodic Torticollis. *Brain sciences*. 2022;12(7). doi:10.3390/brainsci12070881

36. Wang X, Mao Z, Ling Z, Yu X. Predictive factors for outcome of pallidal deep brain stimulation in cervical dystonia. *Clin Neurol Neurosurg*. 2020;192(0303-8467):105720. doi:10.1016/j.clineuro.2020.105720

37. Chung M, Huh R. Different clinical course of pallidal deep brain stimulation for phasic- and tonic-type cervical dystonia. *Acta Neurochir*. 2016;158(1):171-180. doi:10.1007/s00701-015-2646-7

38. Wang X, Mao Z, Cui Z, et al. Predictive factors for long-term clinical outcomes of deep brain stimulation in the treatment of primary Meige syndrome. *J Neurosurg*. 2020;132(5):1367-1375. doi:10.3171/2019.1.JNS182555

39. Borggraefe I, Mehrkens JH, Telegravciska M, Berweck S, Bötzel 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 Dev*. 2010;32(3):223-228. doi:10.1016/j.braindev.2009.03.010

40. Starr P, Markun L, Larson P, Volz M, Martin A, Ostrem J. Interventional MRI-guided deep brain stimulation in pediatric dystonia: first experience with the ClearPoint system. *Journal of neurosurgery Pediatrics*. 2014;14(4):400-408. doi:10.3171/2014.6.PEDS13605

41. 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. doi:10.1159/000345830

42. Haridas A, Tagliati M, Osborn I, et al. Pallidal deep brain stimulation for primary dystonia in children. *Neurosurgery*. 2011;68(3):738-743. doi:10.1227/NEU.0b013e3182077396

43. Krause P, Lauritsch K, Lipp A, et al. Long-term results of deep brain stimulation in a cohort of eight children with isolated dystonia. *J Neurol*. 2016;263(11):2319-2326. doi:10.1007/s00415-016-8253-6

44. Lumsden D, Kaminska M, Gimeno H, et al. Proportion of life lived with dystonia inversely correlates with response to pallidal deep brain stimulation in both primary and secondary childhood dystonia. *Developmental medicine and child neurology*. 2013;55(6):567-574. doi:10.1111/dmcn.12117

45. Markun L, Starr P, Air E, Jr MW, Volz M, Ostrem J. Shorter disease duration correlates with improved long-term deep brain stimulation outcomes in young-onset DYT1 dystonia. *Neurosurgery*. 2012;71(2):325-330. doi:10.1227/NEU.0b013e318258e21b

46. Petrossian MT, Paul LR, Multhaupt-Buell TJ, et al. Pallidal deep brain stimulation for dystonia: a case series: Clinical article. *J Neurosurg: Pediatr*. 2013;12(6):582-587. doi:10.3171/2013.8.PEDS13134

47. Ramezani GM, Ghourchian S, Emamikhah M, et al. Long term follow-up results of deep brain stimulation of the Globus pallidus interna in pediatric patients with DYT1-positive dystonia. *Clinical neurology and neurosurgery*. 2021;201(0303-8467):106449. doi:10.1016/j.clineuro.2020.106449

48. Marotta R. Motor and cognitive functions in children with generalized dystonia after pallidal deep brain stimulation. *Acta Med Mediterr*. 2020;36(3):1873-1879. doi:10.19193/0393-6384_2020_3_293

49. Isaias I, Alterman R, Tagliati M. Outcome predictors of pallidal stimulation in patients with primary dystonia: the role of disease duration. *Brain : a journal of neurology*. 2008;131(Pt 7):1895-1902. doi:10.1093/brain/awn120

50. Lumsden D, Ashmore J, Charles-Edwards G, Selway R, Lin J, Ashkan K. Observation and modeling of deep brain stimulation electrode depth in the pallidal target of the developing brain. *World neurosurgery*. 2015;83(4):438-446. doi:10.1016/j.wneu.2015.01.012

51. Owen T, Gimeno H, Selway R, Lin J. Cognitive function in children with primary dystonia before and after deep brain stimulation. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2015;19(1):48-55. doi:10.1016/j.ejpn.2014.09.004

52. Kaminska M, Perides S, Lumsden D, et al. Complications of Deep Brain Stimulation (DBS) for dystonia in children - The challenges and 10 year experience in a large paediatric cohort. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2017;21(1):168-175. doi:10.1016/j.ejpn.2016.07.024

53. Koy A, Bockhorn N, Kuhn A, et al. Adverse events associated with deep brain stimulation in patients with childhood-onset dystonia. *Brain stimulation*. 2019;12(5):1111-1120. doi:10.1016/j.brs.2019.04.003

54. Xu W, Li H, Zhang C, Sun B, Wu Y, Li D. Subthalamic Nucleus Stimulation in Pediatric Isolated Dystonia: A 10-Year Follow-up. *The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques*. 2020;47(3):328-335. doi:10.1017/cjn.2020.32

55. Mueller J, Skogseid I, Benecke R, et al. Pallidal deep brain stimulation improves quality of life in segmental and generalized dystonia: results from a prospective, randomized sham-controlled trial. *Movement disorders : official journal of the Movement Disorder Society*. 2008;23(1):131-134. doi:10.1002/mds.21783

56. Krause P, Mahlknecht P, Skogseid IM, et al. Long-Term Outcomes on Pallidal Neurostimulation for Dystonia: A Controlled, Prospective 10-Year Follow-Up. *Mov Disord*. 2025;40(6):1098-1111. doi:10.1002/mds.30130