FDA Executive Summary

Prepared for the
Spring 2023 review by the
FDA's Pediatric Advisory Committee

Medtronic Activa Neurostimulator for Dystonia Treatment
H020007

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INTRODUCTION

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

The Medtronic Activa® Dystonia Therapy system is indicated for unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above. Other Medtronic device models have been approved under the dystonia therapy in pediatric patients' indication for use HDE H020007. For the purposes of this document, Medtronic Activa® Dystonia Therapy describes any device model approved under this HDE (H020007).

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

At this time, in review of the safety and effectiveness data, FDA believes the HDE remains appropriately approved for pediatric use.

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

Section 520(m)(6)(A)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. The Medtronic Activa Dystonia Therapy Kits are composed of only the neurostimulator if used for neurostimulator replacement or include the neurostimulator, extension, lead, and controller for implantation of the entire system. Therefore, the number of kits implanted provides a reasonable representation of the number of individuals treated with the device. No Medtronic Activa Dystonia Kits were sold in the US in the year 2022 (see below). The ADN of 8,000 has not been exceeded in 2022.

Medtronic Dystonia Kit Number	**Number of Kits Sold**
3307	0
3309	0
3310	0
3317	0
3319	0
3320	0

3330	0
3337	0
3339	0
33TH17	0
33TH19	0
33TH37	0
33TH39	0
33TH40	0
33TH47	0
33TH49	0
33TH57	0
33TH59	0
Total	**0**

cut-off date: December 31, 2022

Number of dystonia devices implanted and active implants (in use) in the calendar year 2022	
#devices implanted	466
#active implants	3783
#implants in pediatric patients in the year	55
#active implants in pediatric patients in the year	444

cut-off date: December 31, 2022

III. POSTMARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

Overview of the MDR Database

Each year, the FDA receives over 1.4 million MDRs of suspected device-associated deaths, serious injuries, and malfunctions. The database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers, and device user facilities) and voluntary reporters such as health care professionals, patients, and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

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

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

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

MDRs Associated with the Medtronic Activa Neurostimulator for Dystonia Treatment

The Agency searched the MDR database to identify reports associated with the Medtronic Activa Neurostimulator for Dystonia Treatment entered between September 28, 2021 and September 27, 2022. The reports entered during this timeframe are related to devices implanted between March 18, 2005 and September 7, 2022. The search resulted in the identification of 191 MDRs. For the purpose of this MDR analysis, these 191 MDRs will be referred to as the 2023 PAC data. The majority of the MDRs were submitted by the manufacturer (N= 189 MDRs) and two were submitted by voluntary reporter. Patient gender information was reported in 184 of the MDRs of which 107 were female and 77 were male patients. The event types by age category are presented in Tables 1a,1b, and 1c. And the number of MDRs in PAC data sets by PAC year are displayed graphically in Chart 1.

Table 1a. Event types by age category for MDRs included in the 2015, 2016, and 2017 PAC data sets.

	2015 PAC				2016 PAC				2017 PAC			
Event Type	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**
Malfunction	19 (13.9)	91 (66.9)	26 (19.1)	**136**	22 (15.1)	101 (69.6)	22 (15.1)	**145**	27 (15.9)	107 (63.3)	35 (20.7)	**169**
Injury	22 (15.2)	84 (58.3)	38 (26.3)	**144**	34 (18.3)	122 (65.9)	29 (15.6)	**185**	31 (20.1)	90 (58.4)	33 (21.4)	**154**
Death	1 (50)	1 (50)	0 (0)	**2**	0 (0)	0 (0)	3 (100)	**3**	0 (0)	1 (100)	0 (0)	**1**
Total	**42 (14.8)**	**176 (62.4)**	**64 (22.6)**	**282**	**56 (16.8)**	**223 (66.9)**	**54 (16.2)**	**333**	**58 (17.9)**	**198 (61.1)**	**68 (20.9)**	**324**

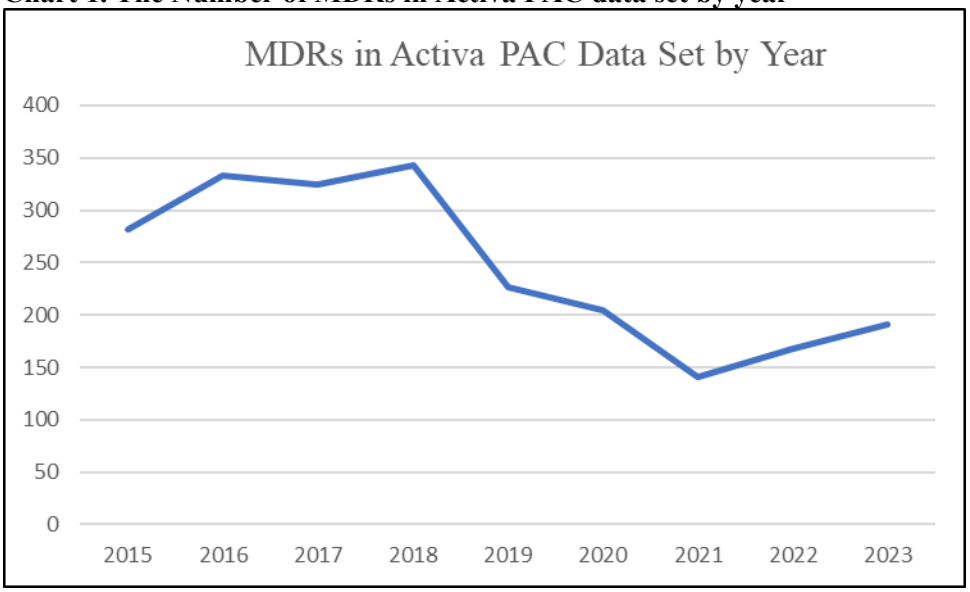
Table 1b. Event types by age category for MDRs included in the 2018, 2019, and 2020 PAC data sets.

	2018 PAC				2019 PAC				2020 PAC			
Event Type	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**
Malfunction	29 (15.5)	136 (72.7)	22 (11.7)	**187**	22 (16.2)	102 (75.5)	11 (8.1)	**135**	24 (18.6)	98 (75.9)	7 (5.4)	**129**
Injury	18 (12.1)	102 (68.9)	28 (18.9)	**148**	19 (21.3)	56 (62.9)	14 (15.7)	**89**	20 (26.6)	47 (62.6)	8 (10.6)	**75**
Death	6 (75)	2 (25)	0 (0)	**8**	0 (0)	3 (100)	0 (0)	**3**	0 (0)	0 (0)	0 (0)	**0**
Total	**53 (15.4)**	**240 (69.9)**	**50 (14.5)**	**343**	**41 (18)**	**161 (70.9)**	**25 (11)**	**227**	**44 (21.5)**	**145 (71)**	**15 (7.3)**	**204**

Table 1c. Event types by age category for MDRs included in the 2021, 2022, and 2023 PAC data sets.

	2021 PAC				2022 PAC				2023 PAC			
Event Type	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**
Malfunction	9 (12)	50 (66.6)	16 (21.3)	**75**	8 (8.8)	56 (61.5)	27 (29.7)	**91**	20 (19.6)	50 (49.0)	32 (31.4)	**102**
Injury	10 (15.1)	37 (56)	19 (28.7)	**66**	10 (13)	36 (46.8)	31 (40.2)	**77**	13 (14.6)	46 (51.7)	30 (33.7)	**89**
Death	0 (0)	0 (0)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	**0**
Total	**19 (13.4)**	**87 (61.7)**	**35 (24.8)**	**141**	**18 (10.7)**	**92 (54.7)**	**58 (34.5)**	**168**	**33 (17.3)**	**96 (50.2)**	**62 (32.5)**	**191**

Chart 1. The Number of MDRs in Activa PAC data set by year



Patient age was available in 129 MDRs, which included 33 pediatric reports and 96 adult reports. The patient age was unknown in 62 reports. The number of MDRs that originated in the United Stated (US) and outside of the US (OUS) for the 2023 PAC data is presented by age category in Table 2. The majority of MDRs originated from within the US.

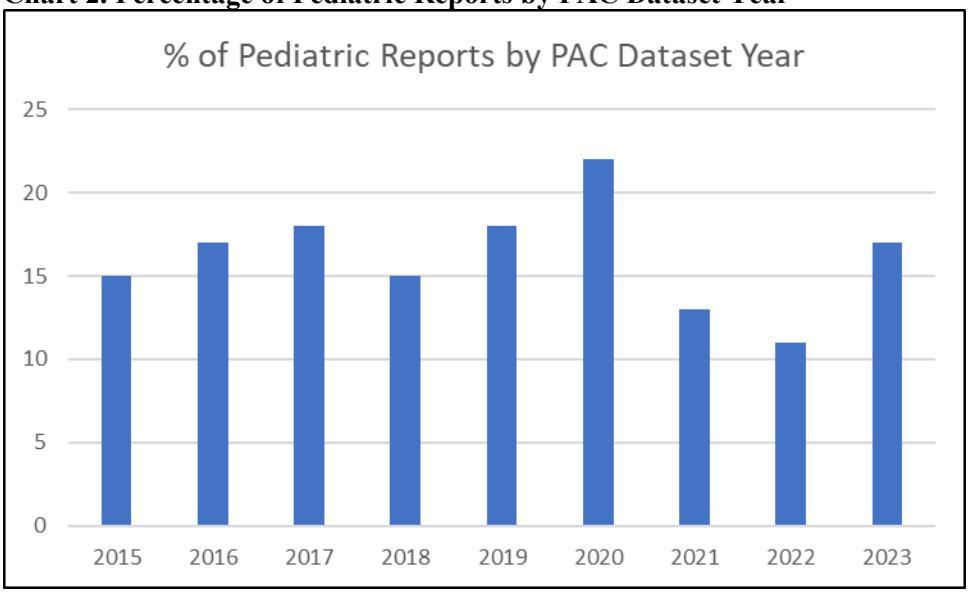
Table 2. The Number of US and OUS MDRs by age category in the 2023 PAC data set

Reporter Country	Pediatric	Adult	Unknown	Total
US	30	88	53	171
OUS	3	7	8	18
Unknown	0	1	1	2
Total	33	96	62	191

Pediatric MDR Review

The reporting country for the majority of Pediatric MDRs was the United States (N= 30 MDRs) and 3 MDRs were reported Outside the United States. Within the pediatric reports, 11 MDRs were associated with female patients, 22 MDRs were associated with male patients. Pediatric patient age ranged from 6 to 19 years of age. The average age of the patients in the pediatric reports was 14.7 years. The percentages of pediatric reports within PAC data sets reviewed annually between the 2015 and 2023 datasets ranged from 11% and 22% (See Chart 2)

Chart 2. Percentage of Pediatric Reports by PAC Dataset Year



Time to Event (TTE) for Pediatric MDRs

In an effort to separate reports for events that occurred zero to 30 days post-implant from those that occurred greater than 30 days post-implant, an analysis of the TTE was conducted on the pediatric MDRs. The TTE was calculated based on implant date provided and date of event provided for each report. The TTE was conclusively calculated for 26 of the 33 pediatric reports received. Reported problems and event

types for pediatric MDRs by TTE are presented in Tables 3 and 4. The range of TTE was from 0 to 2210 days with an average of 717 days and median of 596 days.

There were only 2 reports in which the event occurred between zero- and 30-days post-implant procedure and 24 reports in which the event occurred greater than 30 days post-implant procedure. Of note, one event occurring >30 days after implant reportedly occurred on day 32 and was a report of infection at the IPG site and explant of the device components.

Table 3. Reported problems and event types for pediatric MDRs* in the 2023 PAC data set with TTE ≤ 30 days (n=2)

Reported Problem	Injury	Malfunction
Device explanted	0	1
Impedance issue	0	1
Battery charging issue	0	1
Infection	0	0
Discomfort	0	0
Lead break/fracture	0	0
Worsening symptoms	0	0
Electromagnetic Interference	0	0

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

Table 4. Reported problems and event types for pediatric MDRs* in the 2023 PAC data set with TTE > 30 days (n=24)

Reported Problem	Injury	Malfunction
Impedance issue	5	10
Battery charging issue	3	9
Device explanted	9	1
Worsening symptoms	2	5
Discomfort	4	0
Infection	3	0
Lead break/fracture	2	0
Electromagnetic Interference	0	1

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

All pediatric reports were individually reviewed to identify events that were previously determined to be clinically significant or concerning by CDRH clinicians with input from previous PAC panel members, and to be consistent with prior MDR analyses. The specific adverse events are presented in Table 5 and explained in detail in the appropriate subsections below by the number of unique events. Please note that more than one contributing factor may have been associated with each of the events presented in Table 5.

Table 5. Clinically concerning pediatric reports* in the 2023 PAC data set

Adverse Event	MDR Report Count	Number of Unique events
Battery/Charging issue	13	9
Device explanted	12	10
Device replaced	9	7
Return or worsening of symptoms	7	5
Infection	3	3
Lead break/fracture	2	1
Potential electromagnetic interference	1	1
Cognitive issue	0	0
Stroke	0	0

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

- *Battery/Charging Issues (N=13 MDRs, 9 unique events):* Reports of battery/charging issues described resolved, unresolved, and unknown outcomes:
  - Resolved (N= 4 unique events)
    - Overdischarge (N= 1) for an unreported reason that was resolved with a Physician Recharge Mode action
    - Recharge positioning difficulty (N= 1) due to patient movement
    - Electromagnetic interference (N= 1) that was resolved with removal of the suspected EMI source
    - Rapid decrease in level of charge (N= 1) which was resolved with replacement of the device
  - Unresolved (N= 3 unique events)
    - Patient not charging the device due to non-use (N= 2)
    - Impedance issue (N= 1)
  - Unknown (N= 2 unique events)
    - Impedance issue (N= 1)
    - Increase in dystonia symptoms when battery charge level drops (N= 1)

- *Device Explant (N= 12 MDRs, 10 unique events) and Device Replacement (N= 9 MDRs, 7 unique events):*
  - 3 unique events were associated with explant without replacement described as impedance issue (N= 1) and infection (N= 2)
  - 7 unique events note explant and replacement and were associated with
    - Impedance issue (N= 3)
    - Bent lead (N= 1)
    - Infection (N= 1)
    - Suspected lead migration (N= 1)
    - Rapid decrease in charge level (N= 1)

- *Return or Worsening of Dystonia Symptoms (N= 7 MDRs, 5 unique events):* Reports of Worsening of Dystonia Symptoms described resolved, unresolved, and unknown outcomes:
  - Resolved (N= 2 unique events)
    - Excessive contractions, worsened dystonia, spasms, and impaired chewing as well as low impedance (N= 1) that resolved with reprogramming
    - Difficulty walking and a device communication issue (N= 1) that was

resolved by re-programming
    - Unresolved (N= 2 unique events)
        - Increase in dystonia when battery charge level drops (N= 1)
        - Worsening dystonia symptoms and fluctuating impedance (N= 1)
    - Unknown (N= 1 unique event)
        - Motor symptoms no longer relieved and high impedance

- *Infection (N= 3 MDRs, 3 unique events):*
    - Incision site infections (N= 2 unique events) with one removed 32 days post implant and one removed 285 days post implant.
    - Infection that did not note the infection site but noted explant and replacement with a time to event of 100 days (N= 1 unique event)

- *Lead break/fracture (N= 2 MDRs, 1 unique event):* One unique event described impedance issues and pain due to a bent lead. The issue was resolved with device replacement.

- *Potential Electromagnetic Interference (N= 1 MDR, 1 unique event):* Electromagnetic interference (N= 1) that was resolved with removal of the suspected EMI source described as *"…ipg "off" without turning it off. Environmental factors include patient was using bi-pap mask. There was no troubleshooting performed. Patient will discontinue use of mask. The issue was resolved*."

MDR Conclusions

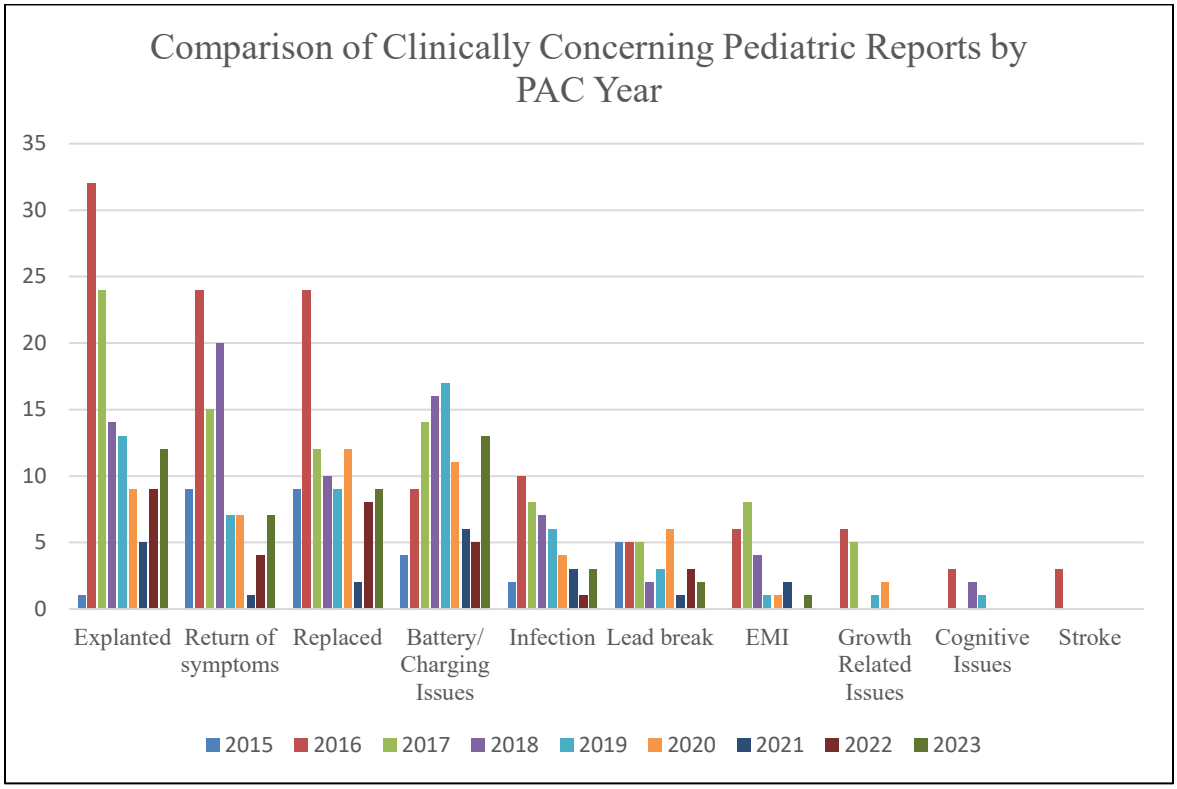
A total of 33 MDRs, reporting 26 unique events, were associated with use of the Dystonia indication of the Medtronic Activa® Dystonia Therapy system in pediatric patients. Device explant/replacement was the most frequently reported pediatric patient problem. The labeling does address the issue and these events are known to occur with use of other neurostimulators. Other reported patient problems are noted in either the device labeling and/or clinical summary.

The most frequently reported device problem was battery/charging issues associated with device problems of overdischarge, EMI, and impedance. These device problems stated in the MDRs are noted in the device labeling or are known device issues with neurostimulator devices in general.

No MDRs associated with pediatric death were reported within the 2023 PAC data.

No new patient or device problems were identified in the 2023 PAC data when compared to PAC data from previous years. The most frequently reported clinically significant or concerning pediatric reports by PAC year are presented in Chart 3. There were no cognitive issues reported in the PAC datasets, and stroke has only been reported in the 2016 dataset thus far.

Chart 3. Comparison of the number of clinically concerning pediatric reports* for 2015 – 2023 PAC data sets



* A single report may be associated with more than one type of adverse event.

IV. POSTMARKET LITERATURE REVIEW: SAFETY DATA

Purpose

The objective of this systematic literature review is to provide an update of post-market safety/adverse events (AEs) associated with the use of the Medtronic Activa neurostimulator. This is an update on the systematic assessment of published literature since the 2022 PAC meeting.

Specifically, the systematic review was conducted to address the following question:

- What is the safety of Medtronic Activa neurostimulator device for the treatment of dystonia in the pediatric population?

Methods

A literature search was conducted using the same search criteria applied in previous presentations to the PAC:

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

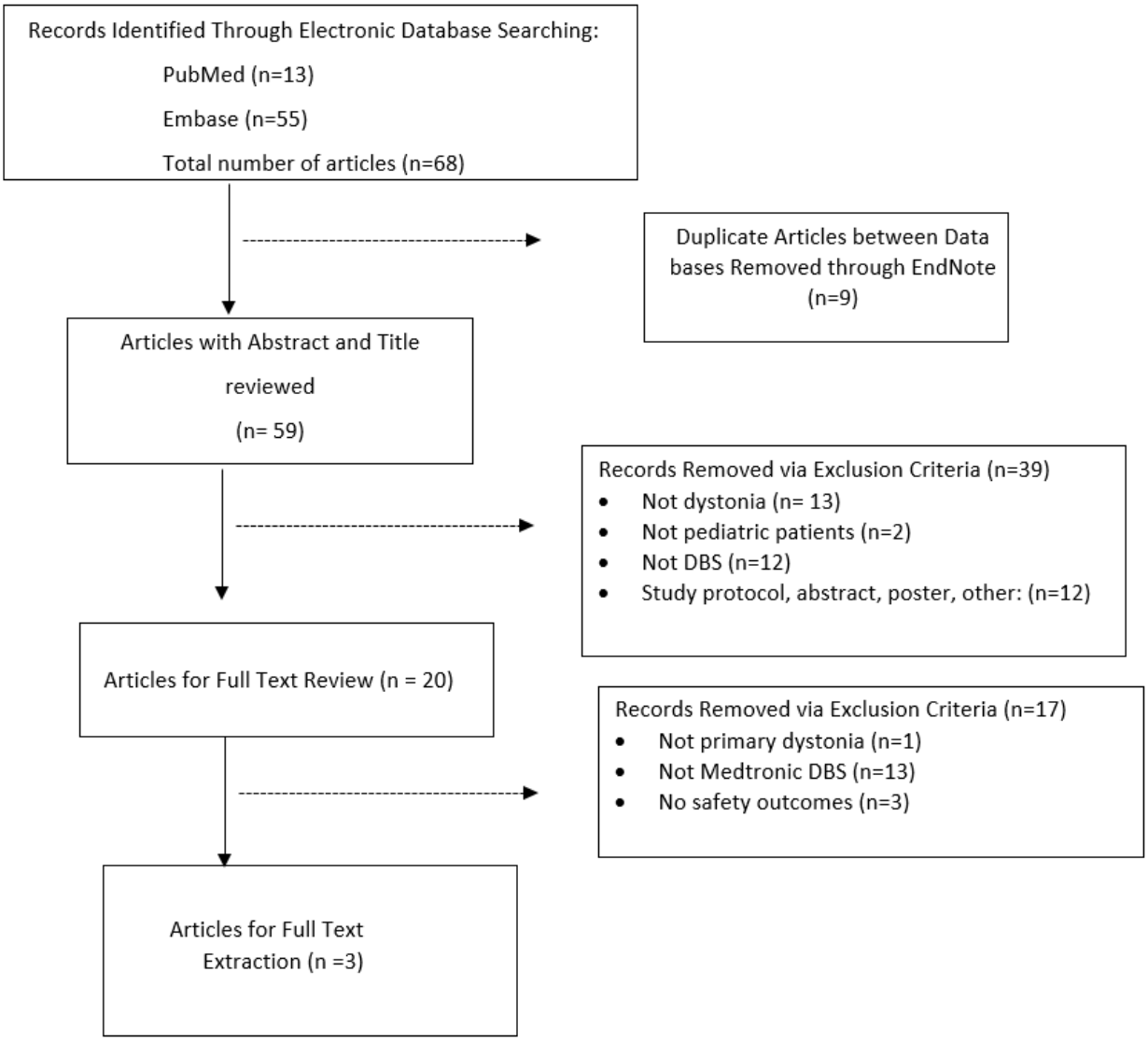
The search was limited to PubMed and EMBASE databases for the period between November 7, 2021 and November 6, 2022 (dates included). The following inclusion and exclusion criteria were used (Table 6):

Table 6.

PICOTS	Inclusion Criteria	Exclusion Criteria
Population	Children aged 7 to <22 with chronic, intractable primary dystonia, including generalized and/or segmental dystonia, hemi-dystonia, and cervical dystonia (torticollis)	Non-pediatric or combined (pediatric and adult) population where pediatric and adult subjects are not analyzed separately Not a primary dystonia (secondary or acquired)
Intervention	Medtronic Activa® Dystonia Therapy system (both on- and off-label use)	No use of Medtronic device or unknown device
Comparison	• Other active treatments or standard of care (e.g., medications, occupational/physical therapy, speech therapy, surgery) • No comparison group	No exclusion
Outcomes	Safety 1. New safety concerns not listed at time of HDE approval 2. Known/anticipated safety concerns • Hemiplegia/Hemiparesis • Worsening of Motor Impairment • Dysphagia • Sensory Impairment • Speech/Language • Subcutaneous Hemorrhage/Seroma • Cerebral Spinal Fluid Abnormality • General* o Infection o Erosion o Lead fractures o Hardware Breakage o IPG Failure • Déjà vu corrected by surgically revised lead placement • Irritating cough with stimulation ON * Includes adverse events related to the system components	Studies will be excluded if they do not report safety outcomes

	3. Other AEs e.g. those similar to AEs recorded with Activa systems approved for Parkinson 's disease and Essential Tremor (see appendix)	
Timing	Any	No exclusion
Setting	US and OUS	No exclusion
Study Design	• Randomized controlled trials • Cohort studies (prospective/retrospective) • Case-control studies • Cross-sectional studies • Case series and case reports • Systematic literature reviews (SLRs), meta-analyses	Laboratory studies, animal studies, economic and cost-effectiveness analyses SLRs and meta-analyses for which all included references were published prior to November 6, 2021
Language	Articles published in English	Non-English Language
Publication dates	November 7, 2021 to November 6, 2022	Published outside of date range

Figure. 1. Article Retrieval and Selection



A total of 20 full-text articles were reviewed for eligibility. Of these, three articles were identified for inclusion[1-3].

The three included articles consisted of two case series from China[1]and Egypt[2] and one retrospective cohort study from Italy[3]. The included studies enrolled between one and seven pediatric patients with primary dystonia, for an overall total of ten pediatric patients treated with a Medtronic DBS device. Duration of follow-up after DBS range from one to six years. The pediatric patients ranged in age from 7 to 20 years of age and included seven males and three females. Below are summaries the findings of the individual studies. Full study details are described in Table 7 (Evidence Table).

Results

Liu et al 2022[1] is a case series that describes three cases of Chinese patients who had shown severe and progressive dystonia in the absence of epilepsy since early childhood. One of the three pediatric patients, a 17-year-old male diagnosed with generalized dystonia, underwent globus pallidus internes [GPi] deep brain stimulation implantation with the Medtronic 3387 implant. The other two patients received DBS with non-Medtronic devices and therefore were not eligible for inclusion in this report. The article reported that no adverse events, such as post-operative complications or mortalities, occurred among the three patients.

Shalash et al 2022[2] is a case series which included a total of 3 patients, two pediatric patients and one adult. The two pediatric patients were a 20-year-old female and one 15-year-old male with generalized truncal dystonia that received bilateral GPI-DBS with Activa PC. One adverse event was reported; transient choking that improved by reprogramming experienced by the 15-year-old male.

Mandarano et al 2022[3] is a retrospective cohort study to assess motor and non-motor outcomes in pediatric onset refractory dystonia due to static or progressive brain disorders in a cohort of patients with DBS treatment duration of greater than 12 months. A total of nine patients were included in the study; however, two were adults and not eligible for inclusion in this report. The seven pediatric patients included in the study were implanted with a Medtronic DBS device (model not specified). Two adverse advents were reported among two of the seven pediatric patients. In one case, at bipolar mode over 3 Volt, DBS was associated with reversible deterioration in swallowing, and in one patient, the post-surgical course was complicated by the development of a cutaneous fistula. There were no adverse events reported among the remaining five pediatric patients.

The evidence derived from this systematic literature review has some limitations that need to be considered when interpreting the findings. This systematic literature review resulted in the identification of two case series and one retrospective study. Such evidence is not of the highest quality as compared to evidence from controlled trials and may be subject to potential biases and confounding. For example, the retrospective nature of the studies can introduce biases on the assessment of exposure to the device and/or outcomes, and there is also potential for bias introduced by loss to follow-up. Differences in length of follow-up among patients and studies may also influence the observed safety outcomes.

Table 7. Evidence Table

Reference, Country, Study Design, Purpose, Conflict of Interest	Study size	Eligible Patients*	Age, Sex Dystonia type	Device(s) Manufacturer/ Model	Follow-up	Adverse Events
Liu et al 2022[1] Country: China Study design: Case series Purpose: to explore diagnostic and therapeutic strategies for GNA01-associated movement disorders. Conflict of Interest: none	3	1	17- year- old male with generalized dystonia	Medtronic 3387	24 months	No post-operative complications or morbidities occurred.
Shalash et al 2022[2] Country: Egypt Study design: Case series Purpose: to report the experience of treating 3 patients (1 adult and 2 pediatric) with idiopathic generalized dystonia, with predominant mobile truncal dystonia by bilateral GPi-DBS Conflict of Interest: none	3	2	Patient 1: 20-year-old female with generalized dystonia Patient 2: 15- year-old male with generalized dystonia	Medtronic Activa PC	6 years and 1.5 years	Patient 2 experienced transient choking that improved by reprogramming.
Mandarano et al 2022[3] Country: Italy Study design: retrospective cohort Purpose: retrospective analysis of motor and non-motor outcomes in pediatric onset refractory dystonia due to static or progressive brain disorders in a cohort of patients with a DBS treatment duration ≥12 months. Conflict of Interest: none	9	7	Patient 1: 7-year-old male Patient 2: 11 -year-old male Patient 3: 11 -year-old male Patient 4: 7 -year-old female Patient 5: 10 -year-old male Patient 6: 10 -year-old female Patient 7: 21 -year-old male Pediatric onset refractory dystonia due to static or progressive brain disorders	Medtronic stimulator (model not specified)	12 months	Patient 1: reversible dysphagia Patient 2: none Patient 3: Cutaneous fistula on the surgical wound Patient 4: none Patient 5: none Patient 6: none Patient 7: none

*Patients aged 7 to <22 years having undergone DBS treatment with a Medtronic DBS device.

Literature Review Conclusions

The published, peer-reviewed clinical evidence considering use of a Medtronic DBS device published between November 7, 2021 and November 6, 2022 was limited to one small retrospective cohort study and two case series with an overall very small number of patients (n=15), ten of which were pediatric patients treated with a Medtronic DBS device and eligible for inclusion in this report.

Out of the ten pediatric patients treated with a Medtronic DBS device, three adverse events were reported: transient choking (n=1), reversible dysphagia (n=1), and a cutaneous fistula on the surgical wound (n=1). The current literature review reflects the safety profile of the Medtronic DBS device, when used in pediatric patients, and has not changed from that of the previous reviews. There were no new safety events identified.

SUMMARY

FDA's Review Team has identified no new safety concerns compared to what was known/anticipated at the time of HDE approval in 2003. Based on the available data, and taking into account the probable benefits and risks, FDA concludes that the HDE remains appropriately approved for pediatric use. FDA will continue routine surveillance including MDR and literature reviews. FDA will provide focused updated safety and use data to the PAC in 2024.

FDA will continue surveillance and will report the following to the PAC in 2024:

- Annual distribution number

- Literature review
- MDR review

V. References of Included Papers:

1. Liu, Y., et al., Both subthalamic and pallidal deep brain stimulation are effective for GNAO1-associated dystonia: three case reports and a literature review. Therapeutic Advances in Neurological Disorders, 2022. 15.

2. Shalash, A., et al., Outcome of pallidal stimulation of idiopathic generalized dystonia with predominant mobile truncal dystonia: case report. International Journal of Neuroscience, 2022. 132(5): p. 429-433.

3. Mandarano, R., et al., Deep Brain Stimulation in childhood-onset dystonia due to brain pathology. A long-term study. Eur J Paediatr Neurol, 2022. 37: p. 62-67.

References of Not Included Papers:

1. Abel M, Pfister R, Hussein I, et al. Deep Brain Stimulation in KMT2B-Related Dystonia: Case Report and Review of the Literature With Special Emphasis on Dysarthria and Speech. Frontiers in Neurology. 2021;12.

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