FDA Executive Summary

Prepared for the
Spring 2024 review by the
FDA's Pediatric Advisory Committee

Medtronic Activa Neurostimulator for Dystonia Treatment
H020007

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I. 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 2023 (see below). The ADN of 8,000 has not been exceeded in 2023.

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

Data timeframe: January 1, 2023 - December 31, 2023

Number of dystonia devices implanted and active implants (in use) in the calendar year 2023	
#devices implanted	508
#active implants	4079
#implants in pediatric patients in the year	76
#active implants in pediatric patients in the year	440

Data timeframe: January 1, 2023 - December 31, 2023

III. POST-MARKET 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 post-market 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, 2022 and September 27, 2023. The reports entered during this timeframe are related to devices implanted between February 24, 2010 and June 28, 2023. The search resulted in the identification of 196 MDRs. For the purpose of this MDR analysis, these 196 MDRs will be referred to as the 2024 PAC data. All of the MDRs were submitted by the manufacturer (N= 196 MDRs). Patient gender information was reported in 154 of the MDRs of which 94 were female and 60 were male patients. The event types by age category are presented in Tables 1a, 1b, and 1c. 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, 2017, and 2018 PAC data sets.

	2015 PAC				2016 PAC				2017 PAC				2018 PAC			
Event Type	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**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**	29 (15.5)	136 (72.7)	22 (11.7)	**187**
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**	18 (12.1)	102 (68.9)	28 (18.9)	**148**
Death	1 (50)	1 (50)	0 (0)	**2**	0 (0)	0 (0)	3 (100)	**3**	0 (0)	1 (100)	0 (0)	**1**	6 (75)	2 (25)	0 (0)	**8**
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**	**53 (15.4)**	**240 (69.9)**	**50 (14.5)**	**343**

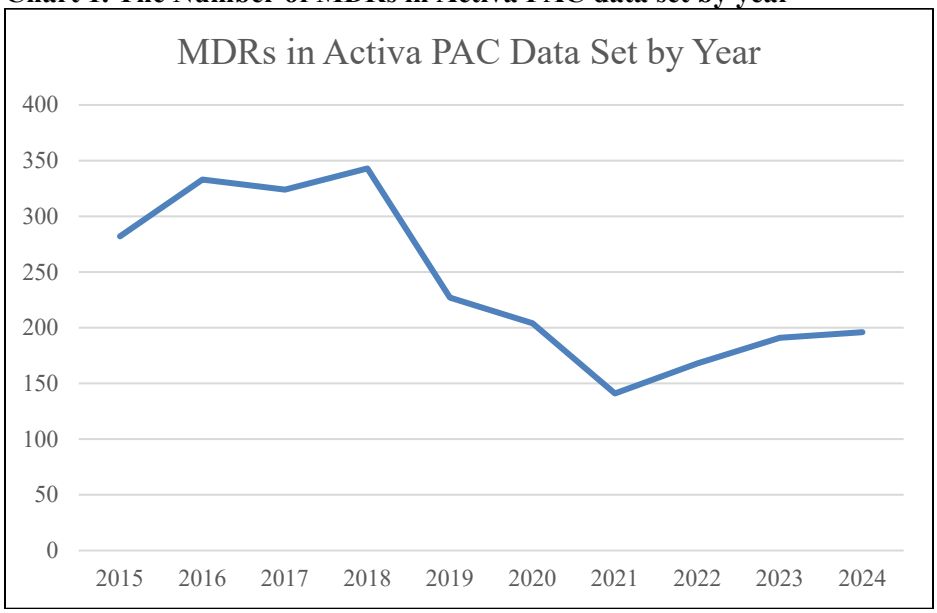
Table 1b. Event types by age category for MDRs included in the 2019, 2020, 2021, and 2022 PAC data sets.

	2019 PAC				2020 PAC				2021 PAC				2022 PAC			
Event Type	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**
Malfunction	22 (16.2)	102 (75.5)	11 (8.1)	**135**	24 (18.6)	98 (75.9)	7 (5.4)	**129**	9 (12)	50 (66.6)	16 (21.3)	**75**	8 (8.8)	56 (61.5)	27 (29.7)	**91**
Injury	19 (21.3)	56 (62.9)	14 (15.7)	**89**	20 (26.6)	47 (62.6)	8 (10.6)	**75**	10 (15.1)	37 (56)	19 (28.7)	**66**	10 (13)	36 (46.8)	31 (40.2)	**77**
Death	0 (0)	3 (100)	0 (0)	**3**	0 (0)	0 (0)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	**0**
Total	**41 (18)**	**161 (70.9)**	**25 (11)**	227	**44 (21.5)**	**145 (71)**	**15 (7.3)**	204	**19 (13.4)**	**87 (61.7)**	**35 (24.8)**	141	**18 (10.7)**	**92 (54.7)**	**58 (34.5)**	168

Table 1c. Event types by age category for MDRs included in the 2023 and 2024 PAC data sets.

	2023 PAC				2024 PAC			
Event Type	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**
Malfunction	20 (19.6)	50 (49.0)	32 (31.4)	**102**	12 (9.6)	58 (46.7)	54 (43.5)	**124**
Injury	13 (14.6)	46 (51.7)	30 (33.7)	**89**	11 (15.2)	32 (44.4)	29 (40.2)	**72**
Death	0 (0)	0 (0)	0 (0)	**0**	0 (0)	0 (0)	0 (0)	**0**
Total	**33 (17.3)**	**96 (50.2)**	**62 (32.5)**	**191**	**23 (11.7)**	**90 (45.9)**	**83 (42.3)**	**196**

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



Patient age was available in 113 MDRs, which included 23 pediatric reports and 90 adult reports. The patient age was unknown in 83 reports. The number of MDRs that originated in the United Stated (US)

and outside of the US (OUS) for the 2024 PAC data is presented by age category in Table 2. The majority of MDRs originated from within the US.

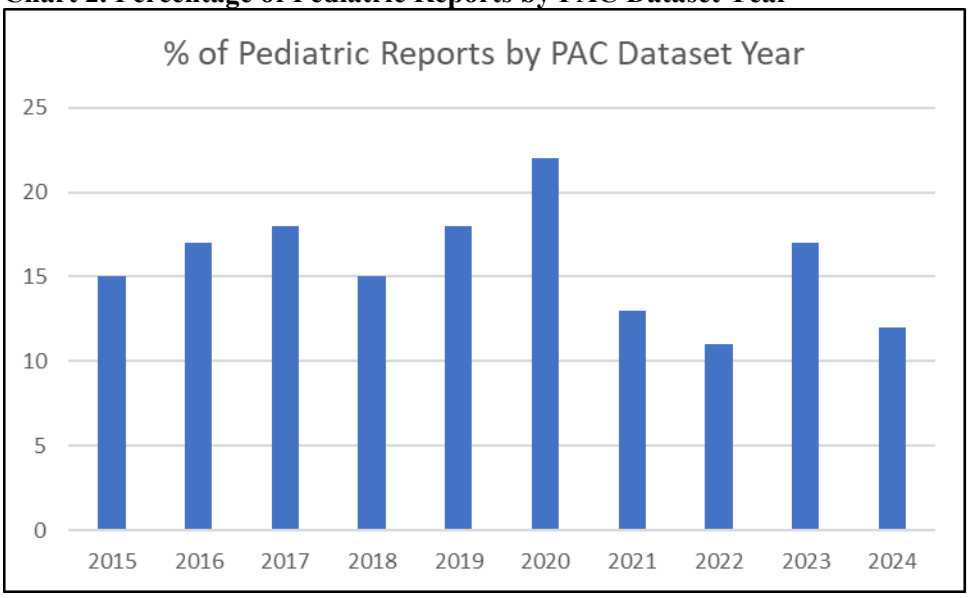
Table 2. The Number of US and OUS MDRs by age category in the 2024 PAC data set

Reporter Country	Pediatric	Adult	Unknown	Total
US	18	79	44	141
OUS	5	10	38	53
Unknown	0	1	1	2
Total	23	90	83	196

Pediatric MDR Review (N= 23)

The reporting country for the majority of Pediatric MDRs was the United States (N= 18 MDRs) and 5 MDRs were reported from outside the United States. Within the pediatric reports, 11 MDRs were associated with female patients, 10 MDRs were associated with male patients, and 2 MDRs did not report patient gender. Pediatric patient age ranged from 10 years of age to 21 years of age. The average age of the patients in the pediatric reports was 16 years of age. The percentages of pediatric reports within PAC data sets reviewed annually between the 2015 and 2024 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 the implant date and date of event provided for each report; and was calculable for 19 of the 23 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 2693 days with an average of 819 days and median of 673 days.

There were 5 reports in which the event occurred between zero- and 30-days post-implant procedure and 14 reports in which the event occurred greater than 30 days post-implant procedure (see Table 3 and Table 4).

Table 3. Reported problems and event types for pediatric MDRs* in the 2024 PAC data set with TTE ≤ 30 days (n= 5)

Reported Problem	Injury	Malfunction
Device explanted	2	0
Impedance issue	2	0
Battery charging issue	1	1
Infection	1	0
Discomfort	2	0
Lead break/fracture	1	0
Worsening symptoms	1	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 2024 PAC data set with TTE > 30 days (n=14)

Reported Problem	Injury	Malfunction
Impedance issue	2	2
Battery charging issue	2	6
Device explanted	5	0
Worsening symptoms	0	0
Discomfort	0	0
Infection	2	0
Lead break/fracture	2	0
Electromagnetic Interference	0	0

* 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 2024 PAC data set

Adverse Event	MDR Report Count	Number of Unique events
Battery/Charging issue	10	9
Device explanted	8	7
Device replaced	5	4
Infection	3	3
Lead break/fracture	3	2
Return or worsening of symptoms	1	1
Potential electromagnetic interference	0	0
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=10 MDRs, 9 unique events):* Reports of battery/charging issues described resolved, unresolved, and unknown outcomes:
  - Resolved (N= 3 unique events)
    - Overdischarge and device position issues resolved with a Physician Recharge Mode action (N= 1)
    - Device communication issue resolved with technical services troubleshooting (N= 1)
    - Implanted stimulator (battery) migration/flipped resolved with surgical intervention (N= 1)
  - Unresolved (N= 3 unique events)
    - Device communication issue/poor coupling. MDR noted that a new recharger was being sent (N= 2)
    - Rapid battery drain and low impedance on 2 electrodes (N= 1)
    - Lost charging unit and device unresponsive (N= 1)
  - Unknown (N= 3 unique events)
    - Overdischarged stimulator (N= 1)
    - Premature battery discharge (less than 1 year) no anomalies found during device evaluation (N= 1)
    - Device position issue; implanted under the muscle (N= 1)

- *Device Explant (N= 8 MDRs, 7 unique events) and Device Replacement (N= 5 MDRs, 4 unique events):*
  - 3 unique events were associated with explant without replacement described as impedance issue and discomfort (N= 1) and infection (N= 2)
  - 4 unique events note explant and replacement and were associated with
    - Impedance issue and infection (N= 1)
    - Impedance issue and broken lead (N= 1)
    - Battery/charging issue (N=1)
    - Foreign body reaction (N= 1)

- *Infection (N= 3 MDRs, 3 unique events):*
  - Stimulator/battery implant site infection with battery and leads removed without reported replacement. TTE of 88 days (N= 1)
  - Incision site infection twice, impedance issues, and device replacement. TTE 22 days (N= 1)
  - Infection at extension wire towards base of skull. Entire system removed without replacement due to it being the patient's second infection. TTE 76 days (N =1)

- *Return or Worsening of Dystonia Symptoms (N= 1 MDRs, 1 unique events):* Reports of worsening of dystonia symptoms described as unresolved:
  - One (1) contact (electrode) broken on implant date and patient discomfort

- *Lead break/fracture (N= 3 MDRs, 2 unique events):*
  - Unresolved worsening dystonia symptoms and 1 contact broken on implant date. Also described in above bullet (N= 1 unique event)
  - One unique event described impedance issues and kinked lead resolved with replacing all four leads (N= 1 unique event)

MDR Conclusions

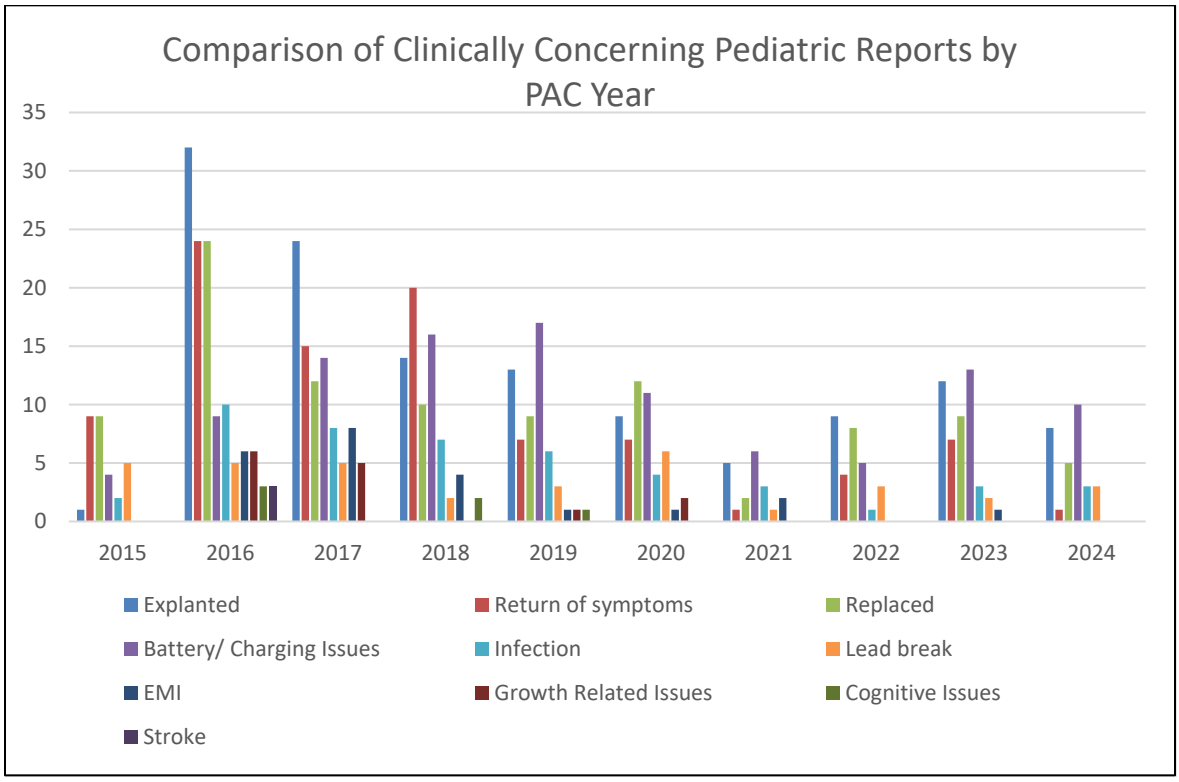
A total of 23 MDRs, reporting 21 unique events, were associated with use of the Dystonia indication of the Medtronic Activa® Dystonia Therapy system in pediatric patients. Device explant/replacement was the most frequently reported pediatric patient problem. The labeling does address the issue and these 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 were overdischarge and communication issues. 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 2024 PAC data.

No new patient or device problems were identified in the 2024 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 – 2024 PAC data sets



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

IV. POST-MARKET 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 2023 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 similar 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 (soletra) OR (percept) OR (dbs) AND (pediatric) AND (Dystonia).

The search was conducted on November 6, 2023 using two electronic biomedical databases (PubMed and Embase) for the period between November 6, 2021 and November 6, 2022 (dates included). Although the publication period of interest for this review is between 2022 and 2023, the searches were expanded to 2021 to guarantee that no relevant studies were missed. 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, hemidystonia, and cervical dystonia (torticollis)	Non-pediatric or combined (pediatric and adult) populations where pediatric and adult populations are not analyzed separately Not a primary dystonia (secondary or acquired)
Intervention	Medtronic Activa® Dystonia Therapy system Medtronic Percept™ PC (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,	No exclusion

PICOTS	Inclusion Criteria	Exclusion Criteria
	occupational/physical therapy, speech therapy, surgery) • No comparison group	
Outcomes	Safety 1. New safety concerns not listed at the time of HDE approval 2. Known/anticipated safety concerns a. Hemiplegia/Hemiparesis b. Worsening of Motor Impairment c. Dysphagia d. Sensory Impairment e. Speech/Language f. Subcutaneous Hemorrhage/Seroma g. Cerebral Spinal Fluid Abnormality h. General* i. Infection ii. Erosion iii. Lead fractures iv. Hardware Breakage v. Implanted Pulse Generator (IPG) Failure i. Déjà vu corrected by surgically revised lead placement j. Irritating cough with stimulation ON 3. Other AEs e.g., those similar to AEs recorded with Activa systems approved for Parkinson's disease and Essential Tremor * Includes adverse events related to the system components	Studies were excluded if they did not report safety outcomes.
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 • SLRs, meta-analyses	Laboratory studies, animal studies, economic and cost-effectiveness analyses

PICOTS	Inclusion Criteria	Exclusion Criteria
		SLRs and meta-analyses for which all included references were published prior to November 6, 2022
Language	Articles published in English	Non-English language articles
Publication Dates	November 7, 2022 to November 6, 2023	Published outside of date range

Abbreviations: AE: Adverse Event; HDE: Humanitarian Device Exemption; IPG: Implanted Pulse Generator; OUS: Outside the US; SLR: Systematic Literature Review; US: United States

Results

In total, 102 unique records were identified from the database searches and screened at the title/abstract level. After excluding 58 records that were not relevant to the review at the title/abstract level, there were 44 full-text records assessed for eligibility. Of the 44 records retrieved and screened at the full-text level, no studies were relevant to this review update. A list of excluded full texts and their reasons for exclusion is available in Table 7. Figure 1 illustrates the PRISMA diagram of the literature flow.

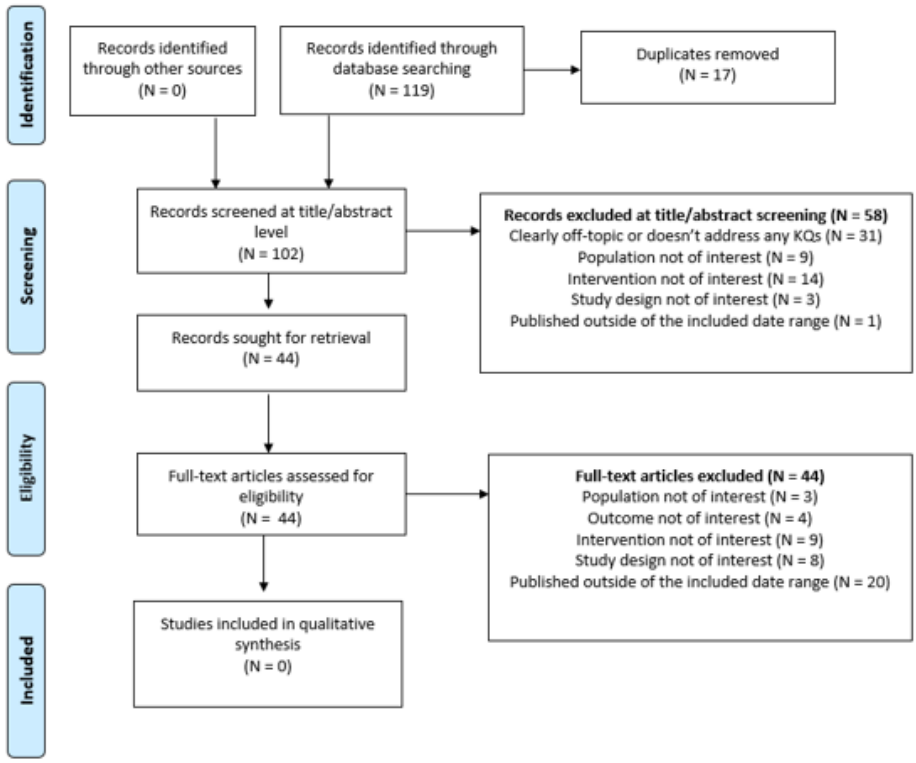
Three studies of relevant Medtronic devices appeared in the search. These were excluded due to population not of interest (adults with drug-resistant epilepsy)[7] or the outcomes of interest were not reported[8,9].

Table 7. Excluded Studies

Reference	Reason for Exclusion
Cif et al. 2023[10]	Intervention not of interest
El et al. 2023[11]	Intervention not of interest
Garofalo et al. 2023[12]	Intervention not of interest
Grossen et al. 2023[13]	Intervention not of interest
Hernandez-Martin et al. 2023[14]	Intervention not of interest
Koy et al. 2023[15]	Population not of interest
Lumsden et al. 2023A[16]	Outcomes not of interest
Lumsden et al 2023B[17]	Study design not of interest
MacLean et al. 2023[7]	Outcomes not of interest
McEvoy et al. 2023[9]	Outcomes not of interest
Novelli et al. 2023[18]	Study design not of interest
Peltola et a. 2023[19]	Population not of interest
Singha et al. 2023[20]	Intervention not of interest
Tunyi et al. 2023[21]	Intervention not of interest
Vogt et al. 2023[22]	Intervention not of interest
Wang et al. 2023[23]	Intervention not of interest

Reference	Reason for Exclusion
Zaman et al. 2023[8]	Outcomes not of interest
Alkubaisi et al. 2022A[24]	Published outside of the included date range
Alkubaisi et al. 2022B[25]	Published outside of the included date range
Bozkaya et al. 2022[26]	Study design not of interest
Chaib et al. 2022[27]	Published outside of the included date range
Dhar et al. 2022[28]	Published outside of the included date range
Fasano et al. 2022[29]	Published outside of the included date range
Ferrero-Turrión et al. 2022[30]	Study design not of interest
Fung et al. 2022[31]	Published outside of the included date range
Koy et al. 2022[32]	Published outside of the included date range
Li et al. 2022[33]	Published outside of the included date range
Malatt et al. 2022[34]	Published outside of the included date range
Mandarano et al. 2022[35]	Published outside of the included date range
Munoz et al. 2022[36]	Published outside of the included date range
Okazaki et al. 2022[37]	Published outside of the included date range
Salamatova et al. 2022[38]	Population not of interest
Shalash et al. 2022[39]	Published outside of the included date range
Srinivasan et al. 2022[40]	Study design not of interest
Thomas et al. 2022[41]	Study design not of interest
Villessot et al. 2022[42]	Published outside of the included date range
D'Hardemare et al. 2021[43]	Study design not of interest
Gimeno et al. 2021[44]	Published outside of the included date range
Goswami et al. 2021[45]	Published outside of the included date range
Rajan et al. 2021[46]	Published outside of the included date range
Saryyeva et al. 2021[47]	Study design not of interest
Tai et al. 2021[48]	Published outside of the included date range
Eggink et al. 2020[49]	Published outside of the included date range
Skogseid et al. 2018[50]	Published outside of the included date range

Figure. 1. Article Retrieval and Selection



Literature Review Conclusions

No studies related to safety of the Medtronic Activa® Dystonia Therapy in pediatric patients were identified within the searches of published literature between November 7, 2022, and November 6, 2023. No new conclusions regarding the safety of the Medtronic Activa® Dystonia Therapy in pediatric populations can be drawn at this time based on the available literature.

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 2025.

FDA will continue surveillance and will report the following to the PAC in 2025:

- Annual distribution number

- MDR review
- Literature review

V. REFERENCES OF NOT INCLUDED PAPERS

1. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine*. 1997;126(5):376-380.
2. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019;10:ED000142.
3. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*. Mar 29 2021;372:n71. doi:10.1136/bmj.n71
4. Garritty C, Gartlehner G, Nussbaumer-Streit B, et al. Cochrane Rapid Reviews Methods Group offers evidence-informed guidance to conduct rapid reviews. *Journal of Clinical Epidemiology*. 2021/02/01/ 2021;130:13-22. doi:https://doi.org/10.1016/j.jclinepi.2020.10.007
5. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. Jul 21 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097
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