FDA Executive Summary

Prepared for the
Spring 2025 Review by the
FDA's Pediatric Advisory Committee

Medtronic Activa Neurostimulator for Dystonia Treatment (H020007)

Table of Contents

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 data relating to safety and probable benefit, 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 2024 (see below). The ADN of 8,000 has not been exceeded in 2024.

Please note: The DBS System for Dystonia utilizes devices approved under the Dystonia HDE (H020007) and approved and commercially released devices which are identical to devices approved under DBS PMA (P960009) for Movement Disorders, and Epilepsy. Patients

implanted with the PMA approved device for the HDE-approved dystonia use indication are provided with the device manual(s) and labeling information associated with the dystonia indication for device use. Therefore, the number of Medtronic Dystonia Kits sold may not reflect the number of implanted or active Medtronic Dystonia kit devices. The kits contain a neurostimulator, extension, lead, and controller except where indicated. (See below tables).

Medtronic Dystonia Kit Number	**Kit Neurostimulator Model Name**	**Number of Kits Sold**
3307*	*Soletra Model 7426***	0
3309*	*Soletra Model 7426***	0
3310**	*Activa PC Model 37601****	0
3317*	*Activa PC Model 37601****	0
3319*	*Activa PC Model 37601****	0
3320**	*Activa SC Model 37602*	0
3330**	Activa SC Model 37603	0
3337*	Activa SC Model 37603	0
3339*	Activa SC Model 37603	0
33TH17*	*Activa PC Model 37601****	0
33TH19*	*Activa PC Model 37601****	0
33TH37*	Activa SC Model 37603	0
33TH39*	Activa SC Model 37603	0
33TH40**	Percept PC Model B35200	0
33TH47*	Percept PC Model B35200	0
33TH49*	Percept PC Model B35200	0
33TH60**	Percept RC Model B35300	0
33TH57	Percept PC Model B35200	0
33TH59	Percept PC Model B35200	0
33TH67	Percept RC Model B35300	0
33TH69	Percept RC Model B35300	0
Total		**0**

Data timeframe: January 1, 2024 - December 31, 2024

*Kits discontinued

**Kits provided for replacement procedures when only the neurostimulator needs to be replaced (e.g., following normal device battery depletion).

*** *Medtronic no longer manufactures the Soletra Model 7426, Activa PC Model 37601, and Activa SC Model 37602*

Number of dystonia devices implanted and active implants (in use) in the calendar year 2024	
#devices implanted	1,670
#active implants	20,199
#implants in pediatric patients in the year	422
#active implants in pediatric patients in the year	4,733

Data timeframe: January 1, 2024 - December 31, 2024

*Implanted and active devices include the following device components: Neurostimulator(s), Leads, and Extensions

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 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, 2023 and September 27, 2024. The reports entered during this timeframe are related to devices implanted between April 20, 2010 and August 13, 2024. The search resulted in the identification of 512 MDRs which were all submitted by the manufacturer. For the purpose of this MDR analysis, these 512 MDRs will be referred to as the 2025 PAC data.

Please note: An FDA Inspection of an operating unit within Medtronic resulted in a change in the firm's Medical Device Report Decision Guidance for all operating units. A retrospective

review of Complaint Files received by the firm was conducted and resulted in the correction of some Complaint Files to MDR submissions. The 2025 PAC dataset includes an additional 261 Malfunction Report MDRs that resulted from the retrospective review. These additional MDRs have therefore increased the overall number of MDRs compared to previous PAC datasets. Of these 261 MDRs, 233 MDRs were associated with broken or damaged AC power supply and power cords used by patients to charge their device recharger/patient programmer. The remaining 28 MDRs were associated with recharger/patient programmer issues such as difficulty with recharging the implanted device (N= 25 MDRs) and lead impedance issues (N= 3 MDRs).

The number of MDRs in PAC data sets by PAC year are displayed graphically in Chart 1. The event types by age category are presented in Tables 1a,1b, and 1c. Of note, as stated in Table 1c, no MDRs associated with pediatric death were reported within the 2025 PAC data.

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

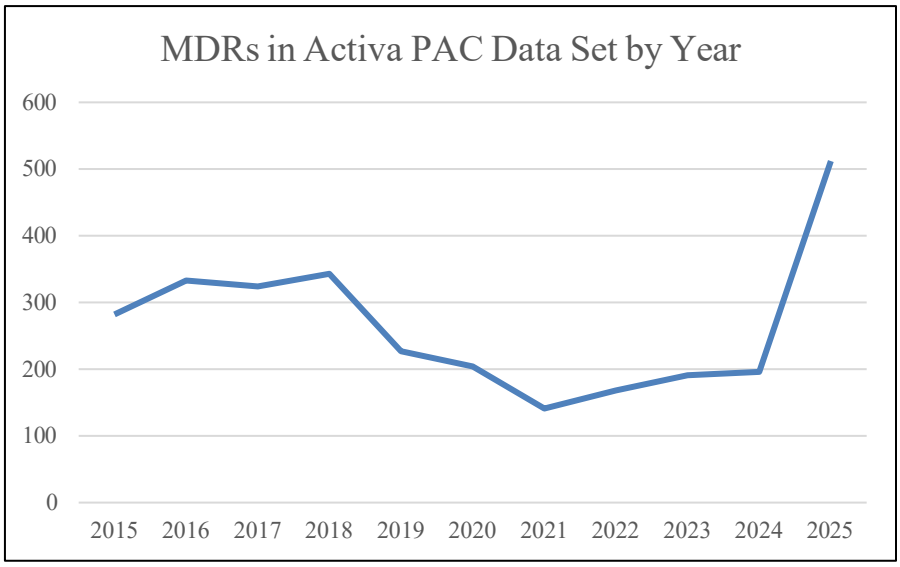


Table 1a. Event types by age category for MDRs included in the 2015, 2016, 2017, and 2018 PAC data sets.

	2015 PAC	2015 PAC	2015 PAC	2015 Total	2016 PAC	2016 PAC	2016 PAC	2016 Total	2017 PAC	2017 PAC	2017 PAC	2017 Total	2018 PAC	2018 PAC	2018 PAC	2018 Total
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	2019 PAC	2019 PAC	2019 Total	2020 PAC	2020 PAC	2020 PAC	2020 Total	2021 PAC	2021 PAC	2021 PAC	2021 Total	2022 PAC	2022 PAC	2022 PAC	2022 Total
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, 2024, and 2025 PAC data sets.

	2023 PAC	2023 PAC	2023 PAC	2023 PAC	2024 PAC	2024 PAC	2024 PAC	2024 PAC	2025 PAC	2025 PAC	2025 PAC	2025 PAC
Event Type	**PEDS (%)**	**ADULT (%)**	**UNK (%)**	**Total**	**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**	36 (8.4)	313 (72.8)	81 (18.8)	**430**
Injury	13 (14.6)	46 (51.7)	30 (33.7)	**89**	11 (15.2)	32 (44.4)	29 (40.2)	**72**	8 (9.8)	47 (57.3)	27 (32.9)	**82**
Death	0 (0)	0 (0)	0 (0)	**0**	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**	**44 (8.6)**	**360 (70.3)**	**108 (21.1)**	**512**

Patient sex information was reported in 483 of the MDRs, of which 286 were female and 197 were male patients. Patient age was available in 404 MDRs, which included 44 pediatric reports and 360 adult reports. The patient age was unknown in 108 reports. The number of MDRs that originated in the United Stated (US) and outside of the US (OUS) for the 2025 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 2025 PAC data set

Reporter Country	Pediatric	Adult	Unknown	Total
US	41	336	70	447
OUS	2	21	33	56
Unknown	1	3	5	9
Total	44	360	108	512

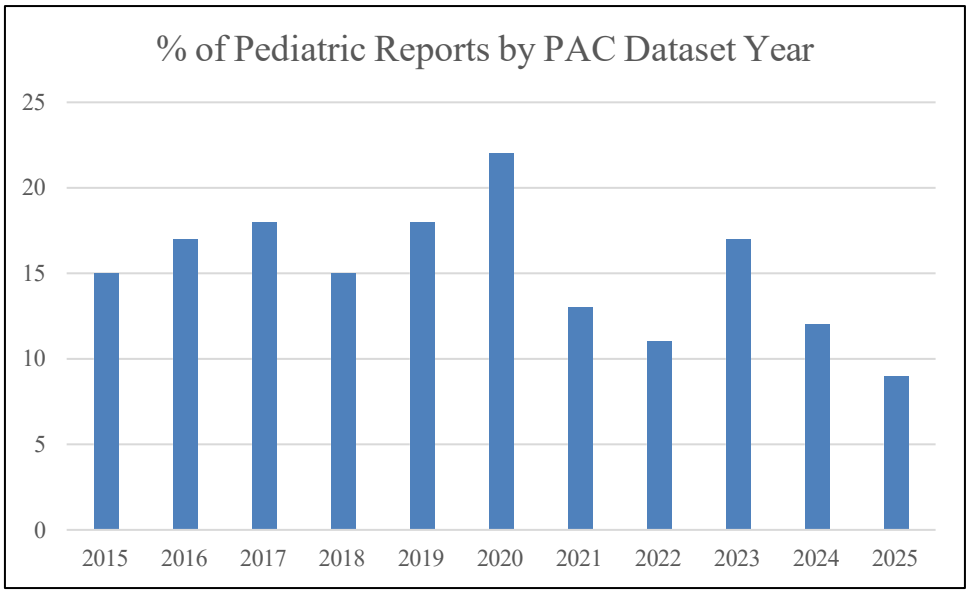
Pediatric MDR Review (N= 44)

The reporting country for the majority of pediatric MDRs was the United States (N= 41 MDRs); 2 MDRs were reported from outside the United States, and 1 MDR did not report a reporter country. Within the pediatric reports, 21 MDRs were associated with female patients and 23 MDRs were associated with male patients. Pediatric patient age ranged from 8.2 years of age to

21.7 years of age. The average age of the patients in the pediatric reports was 17 years of age. The percentages of pediatric reports within PAC data sets reviewed annually between the 2015

and 2025 datasets ranged from 9% and 22%. The 2025 dataset contains the smallest percentage of pediatric age reports (see Chart 2).

Chart 2. Percentage of Pediatric Reports by PAC Dataset Year



Time to Event (TTE) for Pediatric MDRs (N= 38 out of 44 MDRs)

The TTE was calculated based on the reported Implant Date and Date of Event provided for each MDR. TTE was calculable for 38 of the 44 pediatric reports received. The remaining 6 MDRs did not report an implant date, therefore TTE was not calculable. 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. 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 3992 days (11 years) with an average of 1391 days (3.8 years) and median of 1254 days (3.4 years).

There were 3 reports in which the event reportedly occurred between zero and 30 days post-implant procedure (on day 0/day of implant) and 35 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 2025 PAC data set with TTE ≤ 30 days; day of implant/day 0 (n= 3)

Reported Problem	Injury	Malfunction
Device explanted	0	1
Impedance issue	0	2
Battery/Charging issue	0	2
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 adverse event of clinical interest.

Table 4. Reported problems and event types for pediatric MDRs* in the 2025 PAC data set with TTE > 30 days (n= 35)

Reported Problem	Injury	Malfunction
Impedance issue	1	2
Battery/Charging issue	1	27
Device explanted	6	1
Worsening symptoms	1	1
Discomfort	0	1
Infection	2	0
Lead break/fracture	2	0
Electromagnetic Interference	0	0

* A single MDR may be associated with more than one adverse event 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 2025 PAC data set

Adverse Event	MDR Report Count	Number of Unique events
Battery/Charging issue	32	28
Device explanted	8	7
Device replaced	4	4
Infection	3	2
Lead break/fracture	2	2
Return or worsening of symptoms	2	2
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 of clinical interest.

- *Battery/Charging Issues (N=32 MDRs, 28 unique events):* Reports of battery/charging issues described resolved, unresolved, and unknown outcomes:
  - Resolved (N= 4 unique events)
    - Overdischarge due to losing recharger 2 years prior. Resolved with device replacement (N= 1)

        - Device would not charge due to the loose desktop charger connector pin. Troubleshooting found the battery was already at 100%. (N= 1)
        - Poor charge coupling/connection. Replaced patient programmer to resolve. (N= 1)
        - Recharge error code seen. Resolved with a charger reset (N= 1)
    - Unresolved (N= 4 unique events)
        - Patient programmer screen went black due to a broken telemetry board (N= 1)
        - Inside of the recharger port (where connector pin plugs in) was damaged. An e-mail sent to replace the charger (N= 1)
        - Desktop charger connector pin was bent. (N= 1)
        - Wireless recharger would not turn on. The MDR noted a replacement was sent (N= 1)
    - Unknown (N= 20 unique events)
        - Damaged or broken desktop charger connector pin (N= 16)
        - Bilateral devices battery malfunctions (N= 1)
        - Unable to turn on device (N= 1)
        - Difficulty charging one INS (two implanted) (N= 1)
        - Low impedance during charging (N= 1)

- *Device Explant (N= 8 MDRs, 7 unique events): 3 unique device explants without device replacements and 4 unique device explants with device replacements:*
    - 3 unique events were associated with explant without replacement described
        - Worsening dystonia (N= 1)
        - Infection (N= 1)
        - Broken desktop charger connector pin and no symptoms reported (N= 1)
    - 4 unique events note explant and replacement and were associated with
        - Lead break (N= 1)
        - Impedance issue (high impedance) (N= 1)
        - Battery/charging issue (overdischarge) (N=1)
        - Lead break and high impedance (N= 1)

- *Infection (N= 3MDRs, 2 unique events):*
    - Infection and impaired healing. Possible related to cobalt allergy. Time to event is unknown (N= 1).
    - Infection at implantable neurostimulator pocket found during healthcare provider follow-up appointment. Time to event was 1.5 years (N= 1)

- *Return or Worsening of Dystonia Symptoms (N= 2 MDRs, 2 unique events):*
    - Reports of loss efficacy and dystonic storms. Device was explanted (N= 1)
    - Left foot turning in and difficult to walk. Battery charge level could not be determined for an unknown reason. Outcome is unknown (N= 1).

- *Lead break/fracture (N= 2 MDRs, 2 unique events):*
    - Right extension removed and replaced due to damage (N= 1)
    - Fracture in one extension and described high impedance on left and right

sides. Explant and replacement of both extensions reported (N= 1)

MDR Conclusions

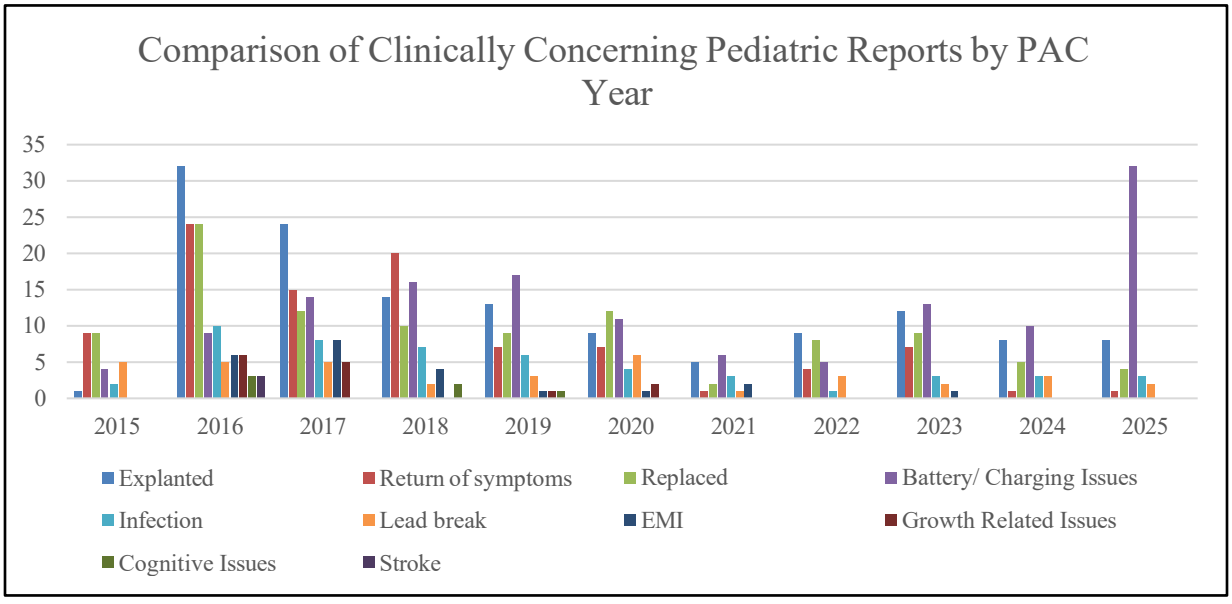
A total of 44 MDRs, reporting 39 unique events, were associated with use of the dystonia indication of the Medtronic Activa® Dystonia Therapy system in pediatric patients. No MDRs associated with pediatric death were reported within the 2025 PAC data.

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 rechargers that had broken desktop connector pins, overdischarge of the implanted stimulator, and implanted stimulator 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. Of the 44 MDRs associated with pediatric age patients, 18 were submitted due to the previously described retrospective review of complaint files following an FDA inspection of a Medtronic operating unit (see page 5). These additional MDRs have increased the overall number of MDRs compared to previous PAC datasets. These 18 MDRs were all associated with broken or damaged AC power supply and power cords used by patients to charge their device recharger/patient programmer and did not report any patient symptoms or injury.

No new patient or device problems were identified in the 2025 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 – 2025 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 2024 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 7, 2024 using two electronic biomedical databases (PubMed and Embase) for the period between November 7, 2023 and November 6, 2024 (dates included). The following inclusion and exclusion criteria were used (Table 6):

Table 6. Inclusion and exclusion criteria

PICOTS	Inclusion Criteria	Exclusion Criteria
Population	Children from birth to < 22 years of age with chronic, intractable primary dystonia, including focal (includes cervical dystonia and torticollis), segmental, generalized, or hemidystonia	Non-pediatric or combined (pediatric and adult) populations 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, with off-label use targeting other than STN and GPi)	No use of Medtronic device or unknown device
Comparison	• Other active treatments or standard of care (e.g., botulinum toxic injections, 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 a. Hemiplegia/Hemiparesis	Studies will be excluded if they do not report safety outcomes

PICOTS	**Inclusion Criteria**	**Exclusion Criteria**
	b. Worsening of Motor Impairment (e.g., gait impairment and falls) c. Dysphagia d. Sensory Impairment e. Speech/Language f. Subcutaneous Hemorrhage/Seroma g. Cerebral Spinal Fluid Abnormality h. Seizures i. General* i. Infection ii. Erosion iii. Lead fractures iv. Hardware Breakage v. IPG Failure j. Déjà vu corrected by surgically revised lead placement k. 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 (see appendix) * Includes adverse events related to the system components	
Timing	Any	No exclusion
Setting	US and OUS	No exclusion

Study Design	• RCTs • Cohort studies (prospective/retrospective) • Case-control studies • Cross-sectional studies • Case series • Case reports • SLRs • Meta-analyses	• Laboratory studies • Animal studies • Economic and cost-effectiveness analyses • Narrative review articles • Registries • Unavailable articles • Systematic reviews and meta-analyses for which all included references were published prior to November 6, 2023
Language	Articles published in English	Non-English language articles

PICOTS	**Inclusion Criteria**	**Exclusion Criteria**
Publication dates	November 7, 2023 to November 6, 2024	Published outside of date range

Abbreviations: AEs: adverse events; GPi: internal globus pallidus; HDE: humanitarian device exemption; OUS: outside the United States; PICOTS: patients, interventions, comparisons, outcomes, timing, and setting; RCT: randomized controlled trial; SLR: systematic literature review; STN: subthalamic nucleus US: United States

Results

In total, 83 records were identified from database searches, and after de-duplication, 66 unique records were screened at the title/abstract level. After excluding 43 records that were not relevant to the review, we assessed 23 records at the full-text level for eligibility. Of the 23 records retrieved and screened, no studies were relevant to this review update. A list of the excluded studies at the full-text level with their reasons for exclusions is available in Table 7. Figure 1 illustrates the PRISMA diagram of the literature flow.

Six studies of relevant Medtronic devices appeared in the search. They were excluded due to having a population not of interest (secondary dystonia)[5-8] and outcomes not of interest (no adverse events reported).[9,10.]

Table 7. Excluded Studies

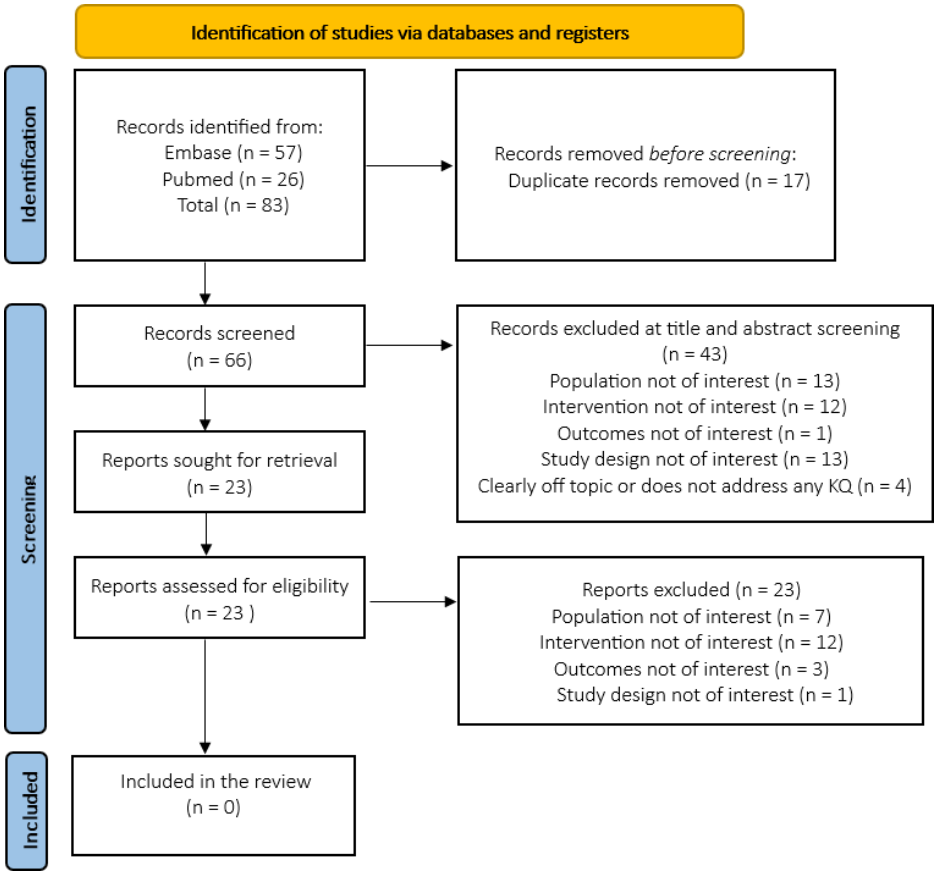
Reference	**Reason for Exclusion**
Alamri et al. 2024[5]	Population not of interest (secondary dystonia)
AlGethami et al. 2024[11]	Intervention not of interest (device NR)
David et al. 2024[12]	Intervention not of interest (device NR)

Duga et al. 2024[13]	Intervention not of interest (device NR)
Kaufmann et al. 2024[6]	Population not of interest
Larsh et al. 2024[9]	Outcomes not of interest (AEs NR)
Lunardini et al. 2024[10]	Outcomes not of interest (Medtronic Activa; AEs NR)
Mithani et al. 2024[14]	Intervention not of interest (device NR)
Monfrini et al. 2024[15]	Population not of interest
Romito et al. 2024[7]	Population not of interest
Singha et al. 202[16]	Intervention not of interest (device NR)

Reference	**Reason for Exclusion**
Vogt et al. 2024[17]	Intervention not of interest (device NR)
Zhai et al. 2024[18]	Intervention not of interest (device NR)
Zhao et al. 2024[19]	Intervention not of interest (device NR)
Cajigas et al. 2023[8]	Population not of interest (acquired dystonia)
El Otmani et al. 2023[20]	Intervention not of interest (device NR)
Garofalo et al. 2023[21]	Intervention not of interest (Boston Scientific)
Hasani et al. 2023[22]	Intervention not of interest (device NR)
Koy et al. 2023[23]	Population not of interest (acquired dystonia)
Lumsden et al. 2023[24]	Study design not of interest (Conference abstract; device NR)
McEvoy et al. 2023[25]	Population not of interest (patient 22 years old; no AEs reported)
Thiel et al. 2023[26]	Intervention not of interest (device NR)
Zaman et al. 2023[27]	Outcomes not of interest (Medtronic percept was used; no AEs reported)

* device NR (device Not Reported)

Figure 1. Literature Flow



Literature Review Conclusions

No studies related to the safety of Medtronic Activa® or Percept Dystonia Therapy in pediatric patients with primary dystonia were identified within the published literature between November 7, 2023, and November 6, 2024. No new conclusions regarding the safety of these devices in pediatric populations with primary dystonia can be drawn at this time based on the available literature.

V. 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 2026.

FDA will continue surveillance and will report the following to the PAC in 2026:

- Annual distribution number

- MDR review
- Literature review

VI. LITERATURE REVIEW REFERENCES

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. AHRQ Methods for Effective Health Care. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality (US); 2008.
4. Robinson KA, Chou R, Berkman ND, et al. Twelve recommendations for integrating existing systematic reviews into new reviews: EPC guidance. J Clin Epidemiol. Feb 2016;70:38-44. doi:10.1016/j.jclinepi.2015.05.035
5. Alamri A, Breitbart S, Warsi N, et al. Deep Brain Stimulation of the Globus Pallidus Internus in a Child with Refractory Dystonia due to L2-Hydroxyglutaric Aciduria. Stereotact Funct Neurosurg. 2024;102(4):209-216. doi:10.1159/000538418
6. Kaufmann E, Peltola J, Colon AJ, et al. Long-term evaluation of anterior thalamic deep brain stimulation for epilepsy in the European MORE registry. Epilepsia. Aug 2024;65(8):2438-2458. doi:10.1111/epi.18003
7. Romito LM, Colucci F, Zorzi G, et al. Illustration of the long-term efficacy of pallidal deep brain stimulation in a patient with PKAN dystonia. Letter. Parkinsonism and Related Disorders. 2024;123doi:10.1016/j.parkreldis.2024.106977
8. Cajigas I, Morrison MA, Luciano MS, Starr PA. Cerebellar deep brain stimulation for the treatment of movement disorders in cerebral palsy. Article. Journal of Neurosurgery. 2023;139(3):605-614. doi:10.3171/2023.1.JNS222289
9. Larsh TR, Gilbert DL, Vadivelu S, Binder DK, Pedapati EV, Wu SW. Post Deep Brain Stimulation Time Course of Aperiodic Activity in Childhood and Young Adult Dystonia. Letter. Movement Disorders Clinical Practice. 2024;11(10):1305-1307. doi:10.1002/mdc3.14159
10. Lunardini F, Satolli S, Levi V, Rossi Sebastiano D, Zorzi GS. The effect of GPi-DBS assessed by gait analysis in DYT11 dystonia: a case study. Letter. Neurological Sciences. 2024;45(1):335-340. doi:10.1007/s10072-023-07063-6
11. AlGethami HJ, Breitbart S, Warsi NM, Fasano A, Ibrahim GM, Gorodetsky C. Severe Pediatric Dystonia Responding to Deep Brain Stimulation in 22q11.2 Microduplication Syndrome: Rare Clinical Presentation. Mov Disord Clin Pract. Mar 2024;11(3):309-311. doi:10.1002/mdc3.13955
12. David R, Scala MR, Ellenbogen J. Review of the targeting accuracy of frameless and frame-based robot-assisted deep brain stimulation electrode implantation in pediatric patients using the Neurolocate module. J Neurosurg Pediatr. Mar 1 2024;33(3):207-213. doi:10.3171/2023.10.Peds23275
13. Duga V, Giossi R, Romito LM, et al. Long-Term Globus Pallidus Internus Deep Brain Stimulation in Pediatric Non-Degenerative Dystonia: A Cohort Study and a Meta-Analysis. Mov Disord. Jul 2024;39(7):1131-1144. doi:10.1002/mds.29815
14. Mithani K, Zhang K, Yan H, et al. Effect of Deep Brain Stimulation on Comorbid Self-injurious Behavior: A Systematic Review and Meta-analysis of Individual Patient Data. Article

in Press. Neuromodulation. 2024;doi:10.1016/j.neurom.2024.07.009
15. Monfrini E, Avanzino L, Palermo G, et al. Dominant VPS16 Pathogenic Variants: Not Only Isolated Dystonia. Article. Movement Disorders Clinical Practice. 2024;11(1):87-93. doi:10.1002/mdc3.13927
16. Singha S, Dwarakanath S, Yadav R, et al. Deep brain stimulation in pediatric dystonia: calls for therapeutic realism over nihilism. Childs Nerv Syst. Mar 2024;40(3):881-894. doi:10.1007/s00381-023-06182-x
17. Vogt LM, Yan H, Santyr B, et al. Deep Brain Stimulation for Refractory Status Dystonicus in Children: Multicenter Case Series and Systematic Review. Article. Annals of Neurology. 2024;95(1):156-173. doi:10.1002/ana.26799
18. Zhai Z, Sun K, Liu T, et al. Deep brain stimulation for pediatric pantothenate kinase-associated neurodegeneration with status dystonicus: A case report and literature review. Clin Neurol Neurosurg. Jun 2024;241:108306. doi:10.1016/j.clineuro.2024.108306
19. Zhao M, Yan X, Wang L, Yin F. Cervical Dystonia Caused by Variant of ATP13A2 Responsive to Subthalamic Deep Brain Stimulation. Letter. Movement Disorders. 2024;39(6):1074-1076. doi:10.1002/mds.29759
20. El Otmani H, El Moutawakil B, Daghi M, et al. Deep Brain Stimulation for Dystonia: Experience of a Moroccan University Hospital. Article. Pediatric Neurology. 2023;148:23-27. doi:10.1016/j.pediatrneurol.2023.08.002
21. Garofalo M, Beudel M, Dijk JM, et al. Elective and Emergency Deep Brain Stimulation in Refractory Pediatric Monogenetic Movement Disorders Presenting with Dystonia: Current Practice Illustrated by Two Cases. Article. Neuropediatrics. 2023;54(1):44-52. doi:10.1055/a-1959-9088
22. Hasani E, Schallner J, von der Hagen M, et al. Deep Brain Stimulation in a Patient with TSPOAP1-Biallelic Variant of Autosomal-Recessive Dystonia. Letter. Movement Disorders. 2023;38(11):2139-2140. doi:10.1002/mds.29618
23. Koy A, Kühn AA, Schiller P, et al. Long-Term Follow-Up of Pediatric Patients with Dyskinetic Cerebral Palsy and Deep Brain Stimulation. Article. Movement Disorders. 2023;38(9):1736-1742. doi:10.1002/mds.29516
24. Lumsden DE, Tsagkaris S, Perides S, et al. 10-Year Follow-Up of Deep Brain Stimulation in the Management of Childhood Dystonia. Conference Abstract. Developmental Medicine and Child Neurology. 2023;65:11. doi:10.1111/dmcn.15476
25. McEvoy SD, Limbrick DD, Raskin JS. Neurosurgical management of non-spastic movement disorders. Review. Child's Nervous System. 2023;39(10):2887-2898. doi:10.1007/s00381-023-06100-1
26. Thiel M, Bamborschke D, Janzarik WG, et al. Genotype-phenotype correlation and treatment effects in young patients with GNAO1 -associated disorders. Article. Journal of Neurology, Neurosurgery and Psychiatry. 2023;94(10):806-815. doi:10.1136/jnnp-2022-330261
27. Zaman Z, Straka N, Pinto AL, et al. Deep brain stimulation for medically refractory status dystonicus in UBA5-related disorder. Note. Movement Disorders. 2023;38(9):1757-1759. doi:10.1002/mds.29428