FDA Executive Summary

Prepared for the
Spring 2022 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.

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 2021 (see below). The ADN of 8,000 has not been exceeded in 2021.

Number of devices sold in the US in the year 2021	
Medtronic Dystonia Kit	**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, 2021

Number of dystonia devices implanted and active implants (in use) in the US in the year 2021	
# of devices implanted	553
# of active implants	3690
# of implants in pediatric patients in the year	79
# of active implants in pediatric patients in the year	477

*cut-off date: December 31, 2021

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 actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- 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, 2020 and September 27, 2021. The reports entered during this timeframe are related to devices implanted between July 8, 2001 through July 28, 2021. The searches resulted in the identification of 168 MDRs. For the purpose of this MDR analysis, these 168 MDRs will be referred to as the 2022 PAC data. The majority of the MDRs were submitted by the manufacturer (N= 167 MDRs) and one was submitted by voluntary reporter. Patient gender information was reported in 147 of the MDRs of which 73 were female and 74 were male patients. The event types by age category are presented in Table 1a and 1b. The number of MDRs reported annually have decreased overall overtime and is presented in Chart 1.

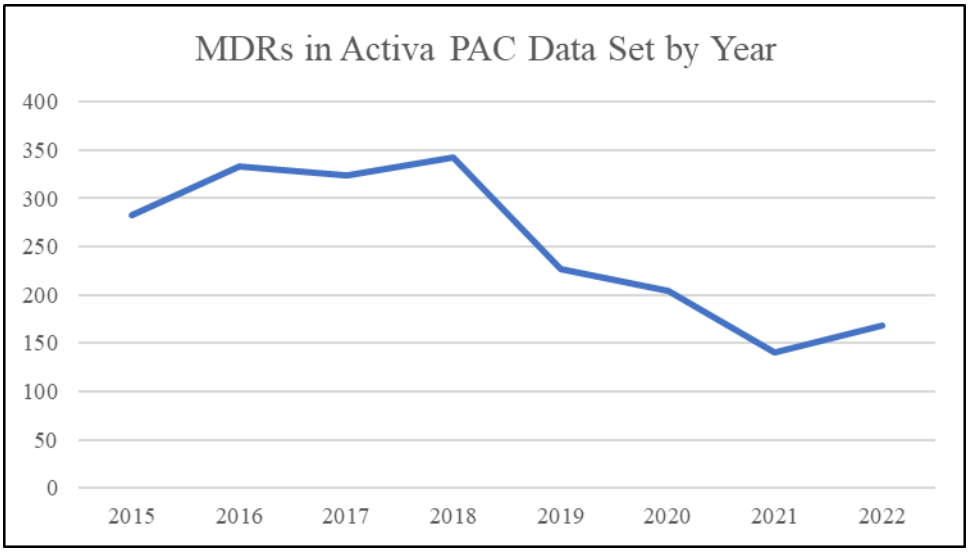
Table 1a. Event types by age category for MDRs included in the 2015, 2016, 2017, and 2018 PAC data sets.

	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**

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



The number of MDRs that originated in the United Stated (US) and outside of the US (OUS) for the 2022 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 2022 PAC data set

Reporter Country	Pediatric	Adult	Unknown	Total
US	18	80	34	132
OUS	0	10	21	31
Unknown	0	2	3	5
Total	18	92	58	168

Pediatric MDR Review

Patient age was available in 110 of the MDRs, which included 18 pediatric reports and 92 adult reports. The patient age was unknown in 58 reports. Pediatric patient age ranged from 3 to 21.7 years of age. The average age of the patients in the pediatric reports was 14.9 years. The percentages of pediatric reports within the 2015, 2016, 2017, 2018, 2019, 2020, 2021, and 2022 PAC data sets were similar (15%, 17%, 18%,15%, 18%, 22%, 13%, and 11% respectively).

The reporting country for all 18 Pediatric MDRs was the United States. Within the pediatric reports, 14 MDRs were associated with female patients, 3 MDRs were associated with male patients, and 2 MDRs did not report patient gender.

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, date of event provided, and the event text for each report. The TTE was only able to be conclusively calculated for 17 of the 18 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 2952 days with an average of 616 days and median of 310 days.

There were 6 reports in which the event occurred between zero and 30 days post-implant procedure and 11 reports in which the event occurred greater than 30 days post-implant procedure.

Table 3. Reported problems and event types for pediatric MDRs in the 2022 PAC data set
*** with TTE ≤ 30 days (n=6)**

Reported Problem	Injury	Malfunction
Device explanted	2	1
Impedance issue	2	2
Battery charging issue	1	0
Infection	1	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 2022 PAC data set with TTE > 30 days (n=11)

Reported Problem	Injury	Malfunction
Device explanted	4	1
Impedance issue	3	2
Battery charging issue	2	2
Worsening symptoms	2	2
Lead break/fracture	1	1
Discomfort	0	0
Electromagnetic Interference	0	0
Infection	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. 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 2022 PAC data set

Adverse Event	MDR Report Count	Number of Patients
Device explanted	9	7
Device replaced	8	6
Battery/Charging issue	5	5
Return or worsening of symptoms	4	3
Lead break/fracture	3	2
Infection	1	1
Potential electromagnetic interference	0	0
Growth related issues	0	0
Cognitive issue	0	0
Stroke	0	0

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

- *Device Explant (N=9 MDRs, 7 unique events) and Device Replacement (N=8 MDRs, 6 unique event):* Of the 9 reports of device explants:
  - 1 MDR was associated with explant without replacement and described lead break/fracture and impedance issues. The issues resulted in explant of the two broken leads and aborting a procedure to add two rescue leads. The final outcome was not reported.
  - 8 MDRs that note explant and replacement were associated with impedance issues (N= 5 MDRs), battery/charging issues (N= 3 MDRs), and return/worsening symptoms associated with lead breaks (N= 2).
- *Battery/Charging Issues (N=5 MDRs, 5 unique events):* Reports of battery/charging issues were associated with overdischarge due to patient not charging the device (N= 1) and device "turning itself off" (N= 1); the device was not explanted or replaced in either report. Battery

and charging issues that were associated with explant and replacement included a recharging issue (N=1), depletion of battery after 5 months (N= 1), reported normal battery depletion (N= 1), and intermittent charging battery issue (N=1). No patient symptoms were noted in reports of battery/charging issues.

- *Return or Worsening of Dystonia Symptoms (N= 4 MDRs, 3 unique events):* Two MDRs associated with one event reported worsening symptoms as well as lead break and impedance issues resulting in device explant and replacement as noted the first bullet (Device Explant and Device Replacement). The remaining reports were associated with:
    - A device settings issue (N= 1 MDR) noting: "Patient was no longer receiving therapeutic stimulation. The patient was seen in the emergency department and was reprogrammed to their previous settings which resolved their symptoms"
    - A lead placement issue (N= 1 MDR) of which the outcome was not reported, noting: "MRI results showed that the deep brain stimulation leads were in the wrong brain target due to poor placement. It is planned to remove the system and replace in correct location."
- *Lead break/fracture (N= 3 MDRs, 2 unique events):*
    - Two MDRs associated with one unique event of lead break/fracture were associated with return/worsening symptoms as described in the third bullet (Return or Worsening of Dystonia Symptoms).
    - One report noted the lead break was discovered in both leads during an attempt to add two rescue leads. The procedure was aborted after removing the 2 broken leads as described in the first bullet (Device Explant and Device Replacement).

- *Infection (N= 1 MDR, 1 unique event):* The report of infection did not result in device explant. Additional Information received from the firm noted "Both the parietal incision and chest incision were opened and washed out; cultures were also taken from both sites. The device remained implanted, and the patient was sent to the ICU for observation. The cultures showed staph infection. Four days after the surgery, it was reported that the patient's pre-op fever had come down and the patient was doing well after surgery and was discharged from the hospital."

MDR Conclusions

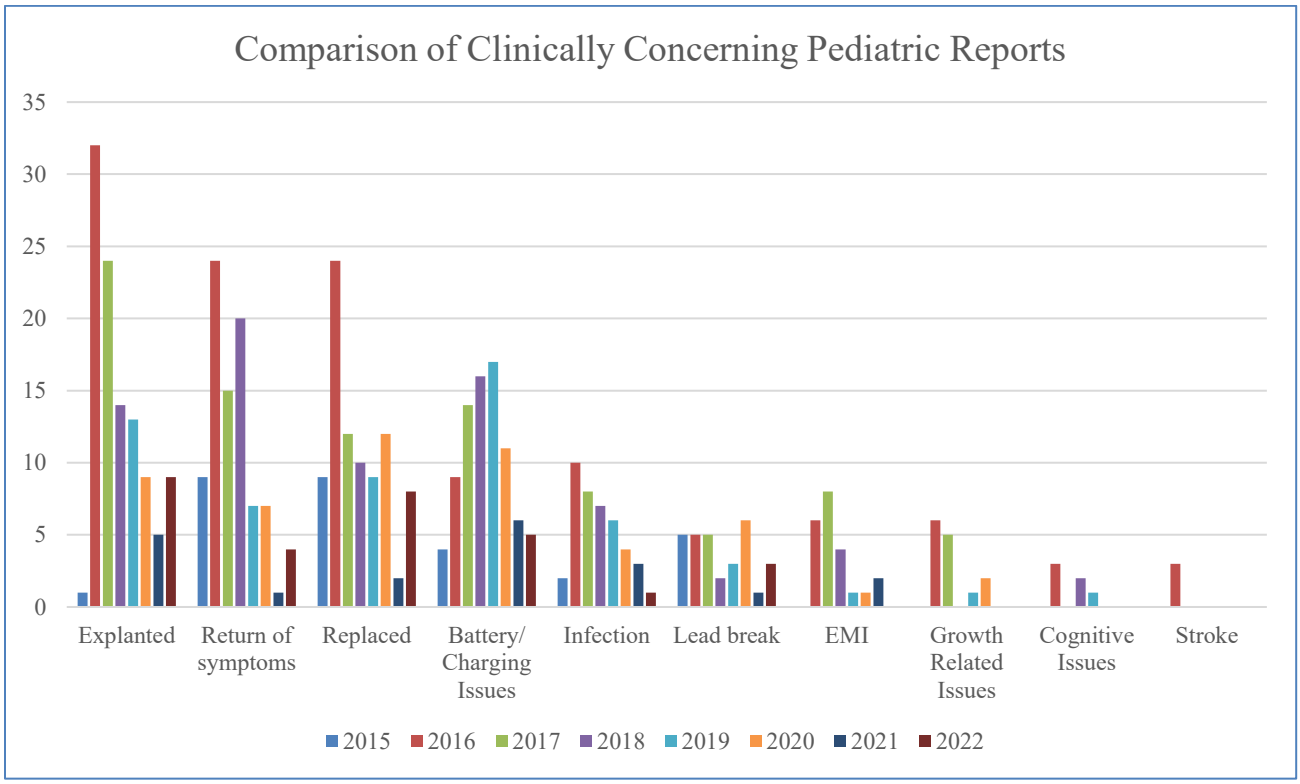
A total of 18 MDRs, reporting 15 unique events, were associated with use of the Dystonia indication of the Activa neurostimulator in pediatric patients. Device explant/replacement was the most frequently reported pediatric patient problem. The 9 MDRs reporting device explant had calculable time between implant and reported issues that ranged from 0 days (day of implant) to 833 days (2.3 years). Of these 9 reports of device explant, 8 also report device replacement. The labeling does address these issues 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. Device problems (such as battery/charging issues and lead fractures) 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 or cognitive issue were reported within the 2022 PAC data.

No new patient or device problems were identified in the 2022 PAC data when compared to PAC data from previous years. The most frequently reported clinically significant or concerning pediatric reports by year are presented in Chart 2. There were no growth related or cognitive issues reported in the 2021 or 2022 PAC datasets, and stroke has only been reported in the 2016 dataset thus far.

Chart 2. Comparison of the number of clinically concerning pediatric reports* for 2015 – 2022 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 2021 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

On, 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, 2020 and November 6, 2021 (dates included). The following inclusion and exclusion criteria were used (Table 6):

Table 6.

PICOTS	Inclusion Criteria	Exclusion Criteria
Population	Children aged 7 to 17 with chronic, intractable primary dystonia, including generalized and/or segmental dystonia, hemidystonia, 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	Studies will be excluded if they do not report safety outcomes

PICOTS	Inclusion Criteria	Exclusion Criteria

	• Speech/Language
	• Subcutaneous Hemorrhage/Seroma
	• Cerebral Spinal Fluid Abnormality
	• General*
	  ○ Infection
	  ○ Erosion
	  ○ Lead fractures
	  ○ Hardware Breakage
	  ○ IPG Failure
	• Déjà vu corrected by surgically revised lead placement
	• Irritating cough with stimulation ON
	
	* Includes adverse events related to the system components
	
	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, 2020
Language	Articles published in English	Non- English Language
Publication dates	Nov 7 2020 to Nov 6 2021	Published outside of date range

In total, 77 records were identified, and 68 screened at title/abstract level after removal of duplicates. After excluding 23 records that were not relevant to the review through manual review, there were 45 full-text articles to potentially assess eligibility. We retrieved and screened 45 records at the full text level, and excluded 41 of these references. Thus, 4 records published between November 7, 2020 and November 6, 2021 reported on safety or adverse events and were included in this review (See Figure 1 for more detail).

All studies used the case series or cohort study design. All 4 studies were published outside the U.S. One study each was conducted in Germany, Iran, Great Britain, and Canada. The included studies enrolled between 1 and 28 pediatric patients with primary or idiopathic dystonia. Duration of follow-up after direct brain stimulation (DBS) ranged from 3 months through 8.5 years. Patients ranged in age from 3 to 28 years of age, and between 36.36% and 100% were male. All patients were treated with the Medtronic Activa® Dystonia Therapy System. Below we narratively describe the findings of the individual studies. Evidence tables providing full study details are described in Appendix B.

The included reports evaluated the safety of Medtronic Activa® Dystonia Therapy including safety outcomes identified at the time of HDE approval and in the 2020 annual literature review: worsening of symptoms, migration of leads, lack of response to DBS, wound site infection, Median Euclidean Distance (mm) and Median Radial Error (mm), major perioperative and postoperative complications (i.e., status dystonicus), stimulation-induced adverse events, and declines in cognitive function.

Results

Coblentz et al. 2021 assessed 4 patients with primary dystonia. The authors report that one patient had no response to DBS, one patient experienced status dystonicus immediately postoperatively in the absence of electrical stimulation, and no patients experienced stimulation-induced adverse events.

Furlanetti et al. 2021 assessed robot-assisted DBS in 28 patients with primary/idiopathic dystonia. They found no major perioperative complications but 3 patients each experienced migration of the leads and worsening symptoms and 1 patient had a wound site infection requiring temporary removal of the leads. No major perioperative complications were noted.

One retrospective review of a prospectively conducted cohort study by *Ghamsari et al. 2021* of 11 TOR1A mutation positive dystonia patients reported that none of the patients experienced mechanical/infection-related complications or cognitive decline.

de Almeida Marcelino et al. 2020 reported on one male implanted at age 20 who experienced a total of 6 hospitalizations for worsening of dystonia symptoms. At 3 months, 6 yrs and, 6.5 yrs after surgery, a technical defect was observed and either both connecting cables or connecting cables and leads were replaced. The other three hospitalizations occurred at 4, 7, and 8 years post-implantation and were due to battery exemption and improved after replacement.

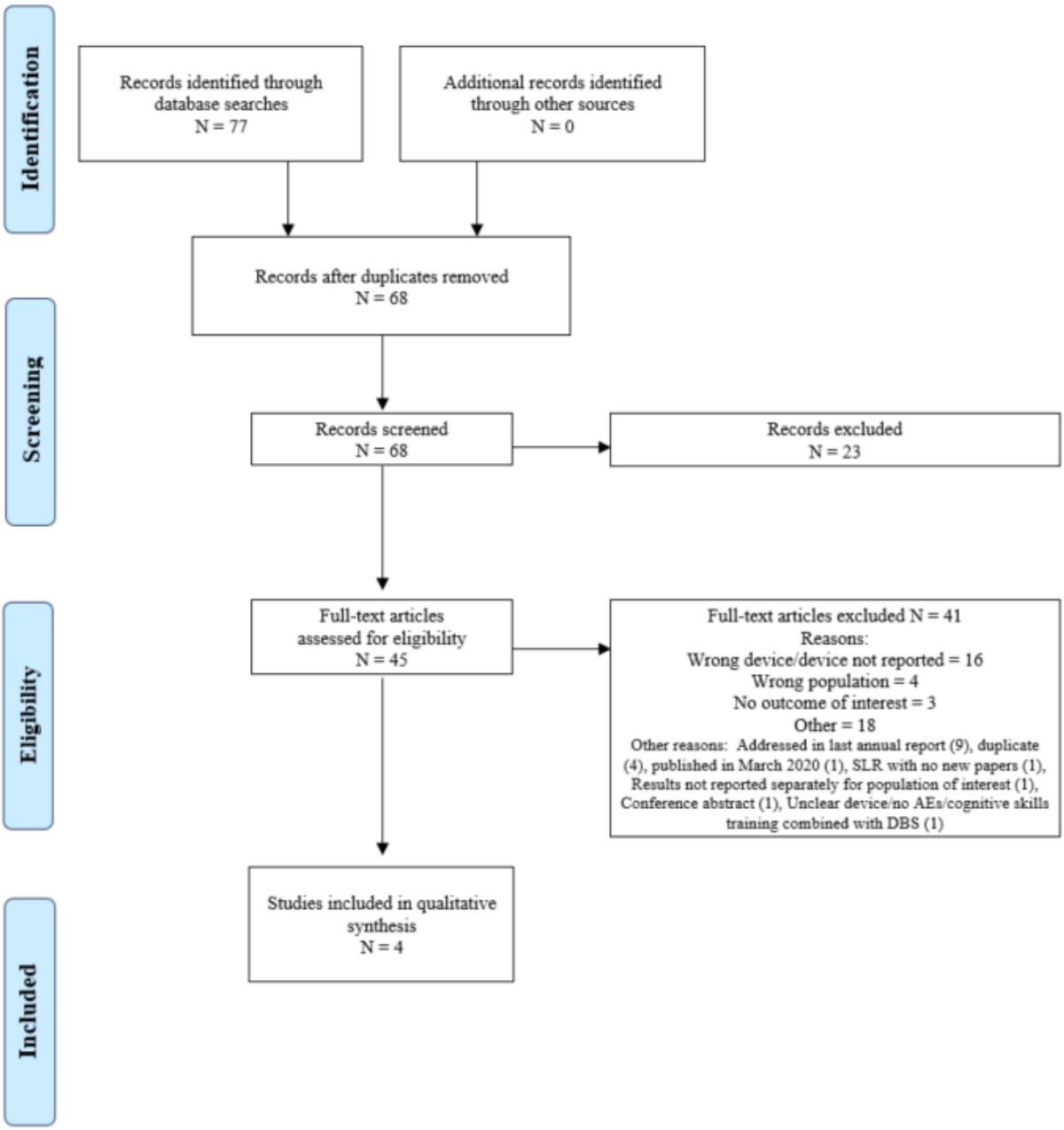
The published, peer-reviewed clinical evidence considering use of Medtronic Activa® Dystonia Therapy is limited to observational studies in very small numbers of patients. This SLR identified 2 case series

studies, 1 retrospective review of a small cohort study and 1 prospective cohort study with a subset of patients relevant to this SLR published between November 7, 2020 and November 6, 2021. We did not perform any Risk of Bias (RoB) assessment as the studies contributing data to the overall evidence base were limited to case series and cohort studies, which, as noted above, are generally considered to be at high risk of bias across most RoB domains. The quality of the body of evidence is universally poor due to the high potential for RoB of the studies, heterogeneity of patient populations, and to the very low numbers of studied patients (n=44).

Literature Review Conclusions

The current literature review for the period between 11/07/2020 and 11/06/2021 did not identify any new safety concerns or new adverse events compared to what was known/anticipated at the time of HDE approval or since the 2021 annual literature review. Worsening symptoms requiring hospitalization was the most serious adverse event reported. There were three reports of lead migration and one report of a patient with defects with connecting cables and leads requiring multiple hospitalizations.

Figure. 1. Article Retrieval and Selection



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 2023.

FDA will continue surveillance and will report the following to the PAC in 2023:

- Annual distribution number
- Literature review
- MDR review

V. References of Included Papers:

1. Coblentz, A., Elias, G. J. B., Boutet, A., Germann, J., Algarni, M., Oliveira, L. M., Neudorfer, C., Widjaja, E., Ibrahim, G. M., Kalia, S. K., Jain, M., Lozano, A. M., Fasano, A. Mapping efficacious deep brain stimulation for pediatric dystonia. Journal of Neurosurgery: Pediatrics. 2021. 27:346-356

2. de Almeida Marcelino, A. L., Mainka, T., Krause, P., Poewe, W., Ganos, C., Kühn, A. A. Deep brain stimulation reduces (nocturnal) dyskinetic exacerbations in patients with ADCY5 mutation: a case series. J Neurol. 2020. 267:3624-3631

3. Furlanetti, L., Ellenbogen, J., Gimeno, H., Ainaga, L., Narbad, V., Hasegawa, H., Lin, J. P., Ashkan, K., Selway, R. Targeting accuracy of robot-assisted deep brain stimulation surgery in childhood-onset dystonia: A single-center prospective cohort analysis of 45 consecutive cases. Journal of Neurosurgery: Pediatrics. 2021. 27:677-687

4. Ghamsari, M., Ghourchian, S., Emamikhah, M., Safdarian, M., Shahidi, G., Parvaresh, M., Moghaddasi, M., Habibi, S. A. H., Munhoz, R. P., Rohani, M. Long term follow-up results of deep brain stimulation of the Globus pallidus interna in pediatric patients with DYT1-positive dystonia. Clin Neurol Neurosurg. 2021. 201:106449

References of Not Included Papers:

1. Abel, M., Pfister, R., Hussein, I., Alsalloum, F., Onyinzo, C., Kappl, S., Zech, M., Demmel, W., Staudt, M., Kudernatsch, M., Berweck, S. 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. 12:662910

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4. Besa Lehmann, V., Rosenbaum, M., Bulman, D. E., Read, T., Verhagen Metman, L. A Case Report of Myoclonus-Dystonia with Isolated Myoclonus Phenotype and Novel Mutation Successfully Treated with Deep Brain Stimulation. Neurology and Therapy. 2020. 9:187-191

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