FDA Executive Summary

Prepared for the
April 21, 2021 meeting of 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 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 through the present day 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 Food, Drug, and Cosmetic Act (FD&C) 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. One (1) Medtronic Activa Dystonia Kit was sold in the US in the year 2020 (see below). The ADN of 8,000 has not been exceeded in 2020.

Number of devices sold in the US in the year 2020*	
Medtronic Dystonia Kit Model Numbers	**Number of Kits Sold**
3310	0
3317	0

3319	0
3320	0
3330	0
3337	0
3339	0
33TH37	0
33TH39	0
33TH40	1
33TH47	0
33TH49	0
Total	1

*cut-off date: 12/17/2020

Number of dystonia devices implanted and active implants (in use) in the US in the year 2020*	
# of devices implanted	454
# of active implants	3679
# of implants in pediatric patients in the year.	47
# of active implants in pediatric patients in the year.	483

*cut-off date: 12/17/2020

III. POSTMARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

Overview of the MDR Database

Each year, the FDA receives over 1.4 million medical device reports (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 subjected 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, 2019 and September 27, 2020. The reports entered during this timeframe are related to devices implanted between January 5, 2005 through August 31, 2020. The searches resulted in the identification of 141 MDRs. For the purpose of this MDR analysis, these 141 MDRs will be referred to as the 2021 Pediatric Advisory Committee (PAC) data. All of the 141 MDRs were submitted by the manufacturer. Patient gender information was reported

in 135 of the MDRs of which 81 were female and 54 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.

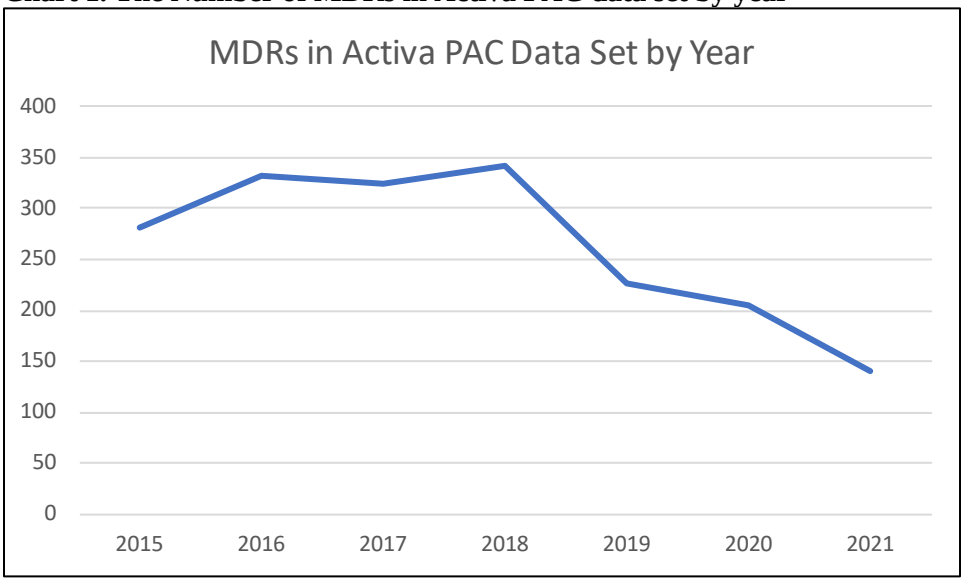
Table 1a. Event types by age category for MDRs included in the 2015, 2016, 2017, and 2018 PAC data sets.

	PAC 2015				PAC 2016				PAC 2017				PAC 2018			
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, and 2021 PAC data sets.

	PAC 2019				PAC 2020				PAC 2021			
Event Type	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
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
Death	0 (0)	3 (100)	0 (0)	3	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**

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 2021 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 2021 PAC data set

Reporter Country	Pediatric	Adult	Unknown	Total
US	18	77	24	119
OUS	1	10	11	22
Unknown	0	0	0	0
Total	19	87	35	141

Pediatric MDR Review

Patient age was available in 106 of the MDRs, which included 19 pediatric reports and 87 adult reports. The patient age was unknown in 35 reports. Pediatric patient age ranged from 8 to 21.8 years of age. The average age of the patients in the pediatric reports was 15 years. The percentages of pediatric reports within the 2015, 2016, 2017, 2018, 2019, 2020 and 2021 PAC data sets were similar (15%, 17%, 18%,15%, 18%, 22%, and 13% respectively).

The reporting country for 18 Pediatric MDRs was the United States. 1 Pediatric MDR was reported from outside the United States (Mexico). 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 from those that occurred greater than 30 days post-implant, an analysis of the time to event (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 18 of the 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 1789 days with an average of 477 days and median of 407 days.

There were 5 reports in which the event occurred between zero and 30 days post-implant procedure and 13 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 2021 PAC data set * with TTE ≤ 30 days (n=5)

Reported Problem	Injury	Malfunction
Battery charging issue	3	1
Impedance issue	0	3
Device explanted	2	0
Infection	2	0
Discomfort	0	0
Lead break/fracture	0	1
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 2021 PAC data set with TTE > 30 days (n=13)

Reported Problem	Injury	Malfunction
Device explanted	3	0
Impedance issue	2	1
Discomfort	0	3
Electromagnetic Interference	0	2
Battery charging issue	0	1
Worsening symptoms	0	1
Infection	1	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 2021 PAC data set

Adverse Event	MDR Report Count	Number of Patients
Battery/Charging issue	6	5
Device explanted	5	3
Infection	3	2
Device replaced	2	1
Potential electromagnetic interference	2	1
Return or worsening of symptoms	1	1
Lead break/fracture	1	1
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.

- *Battery/Charging Issues (N=6 MDRs, 5 unique events):* Reports of battery/charging issues were associated with impedance issues (N=3), recharging issue (N=1), unknown battery issue (N=1), and migration issue (N= 1). The reported battery/charging related issues also were associated with patient discomfort (N=1) and unexpected therapeutic results (N= 1).
- *Device Explant (N=5 MDRs, 3 unique events)and Device Replacement (N=2, 1 unique event):* Of the 5 reports of device explants, 3 were associated with infection and did not result note replacement of the device and 2 noted device replacements due to unexpected therapeutic results.
- *Infection (N= 3 MDRs, 2 unique events):* Two reports of infection (for 1 unique event) alledged nonstandard of care infection prevention procedures during surgical placement. One MDR did not note a possible cause of infection. None of the MDRs that noted infection reported device replacement.
- *Potential electromagnetic interference (EMI) (N=2 MDR, 1 unique event):* One patient implanted with two stimulators was reported to have issues with bladder, “tone” and with their movements possibly associated with frequent visits to a family member in the hospital. Associated device issues included the neurostimulators turning off and the settings cleared (patient and programming information was not available). Both neurostimulators were reprogrammed and the symptoms resolved and the root cause was not determined.
- *Return or Worsening of Dystonia Symptoms (N= 1 MDR,1 unique event):* One patient reported a shocking sensation and loss of therapeutic effect. The outcome was not reported.
- *Lead break/fracture (N= 1 MDR, 1 unique event):* One report noted a patient with high impedance associated with a fractured lead/ “contact 3 looked mangled” . Root cause and outcome were not reported.

MDR Conclusions

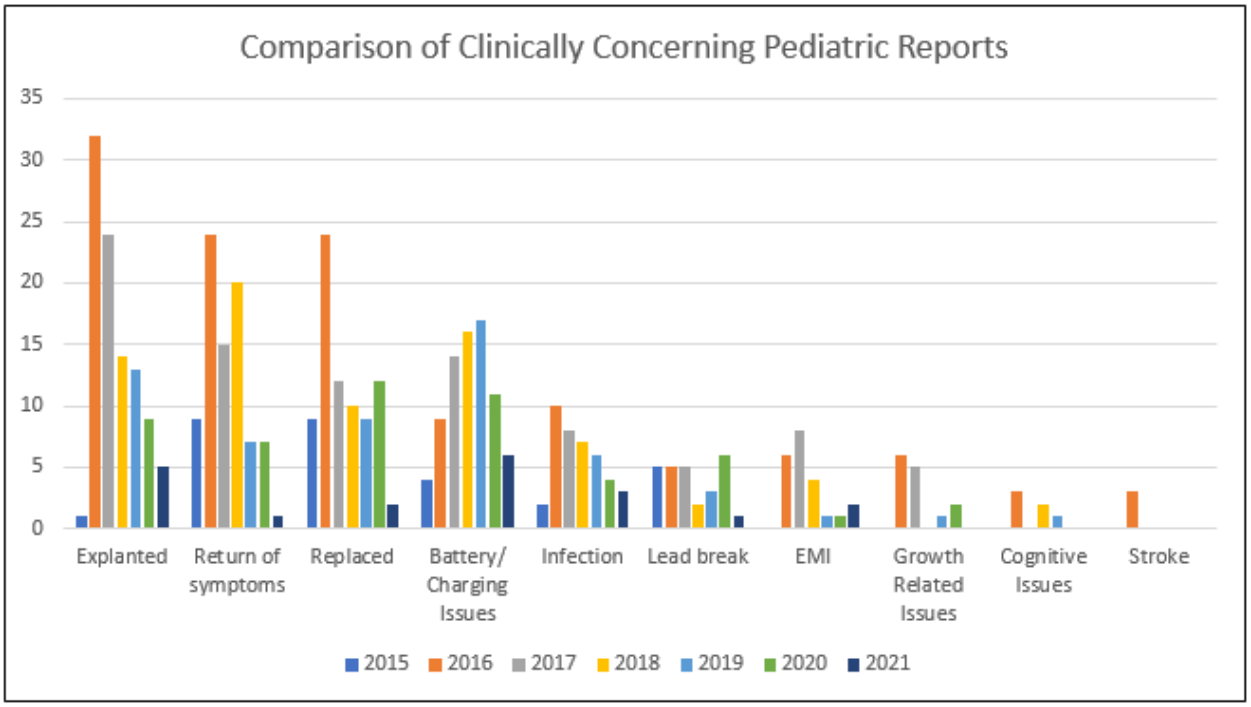
A total of 19 MDRs, reporting 15 unique events, were associated with use of the Dystonia indication of the Activa neurostimulator in pediatric patients. Device explant and infection was the most frequently reported pediatric patient problem. The labeling does address the issue of infection and these events are known to occur with use of other neurostimulators. Other reported patient problems are noted in either the device labeling or clinical summary.

The most frequently reported device problem was battery/charging issues. Device problems (such as battery/charging issues, lead fractures or electromagnetic interference) stated in the MDRs are noted in the device labeling or are known device issues with neurostimulator devices in general.

Two MDRs for one unique event note seizure following the total removal of the implanted neurostimulator system due to infection and subsequent sepsis. These reports also noted the patient had a history of intractable epilepsy, stroke, and lobectomies. No MDRs associated with pediatric death or cognitive issue were reported within the 2021 PAC data.

No new patient or device problems were identified in the 2021 PAC data when it was compared to previous years. The most frequently reported clinically significant or concerning pediatric reports have remained similar across PAC data sets and is presented in Chart 2.

Chart 2. Comparison of the number of clinically concerning pediatric reports* for 2015, 2016, 2017, 2018, 2019, 2020, and 2021 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 2020 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 December 12, 2020, 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 6, 2019 and November 6, 2020 (dates included). The following exclusion criteria were used:

- Duplicates and corrections/errata
- Conference abstracts/Oral presentations
- No primary dystonia
- Review articles
- Systematic reviews and meta-analyses for which all included references were published prior to November 6, 2019
- Registries
- Non-pediatric or combined (pediatric and adult) population where pediatric and adult subjects are not analyzed separately
- No humans in the study (e.g., animal study)
- Not written in English
- Unavailable article
- Unrelated topic, or no device intervention
- No Medtronic devices used, or no identification of the device manufacturer

Through this search, 41 records were initially identified (Fig 1): 12 titles from PubMed and 29 from EMBASE. After removal of duplicates (n=8), there were 33 articles identified for title and abstract review. Based on the predefined exclusion criteria, 11unique records were excluded for the following reasons: conference abstracts (n=8) [18, 27, 28,29, 30, 31, 32, 33], no pediatric stratified analysis (n=5) [2, 10, 16, 22, 24]), registry (n=1) [4], systematic reviews and meta-analyses with included references published prior to November 6, 2018 (n=1) [11], no Medtronic device used or device manufacturer not identified (n=5) [6, 13, 15, 16, 19, 20, 26], and unrelated topic or no device intervention (n=8) [1, 3, 7, 8, 14, 17, 21, 25].

Considering the limited number of eligible references for the reporting year, case reports and case series were included for completeness as long as the device was identified as being manufactured by Medtronic and the implant was placed in the on-label targets of STN or GPi. Thus, 4 articles were identified as *eligible and retained for final review*: articles by *Giordano F. et al, Tambirajoo K. et al, Xu W., et al, and Marotta R. et al.* See Flowchart, Fig.1 (Article retrieval and selection). All four describe case reports and small case series; there were no references describing controlled studies.

Results

Giordano F. el al presents a case of an 8-year-old male patient underwent bilateral DBS of GPI for status dystonicus. He died 2 months later due to multiorgan failure triggered by bacterial pneumonia. A post-mortem pathological study of the brain was done. At visual inspection, no grossly apparent softening,

hemorrhage, or necrosis of the brain adjacent to the DBS lead tracts was detected. High-power microscopic examination of the tissue surrounding the electrode trajectories showed lymphocyte infiltration, astrocytic gliosis, microglia, macrophages, and clusters of multinucleate giant cells. Significant astrocytosis was confirmed by GFAP staining in the electrode site. The T cell lymphocyte activity was overexpressed with activated macrophages detected with CD3, CD20, CD45, and CD68 stains respectively. There was no gliosis or leukocyte infiltration away from the surgical tracks of the electrodes. This is the first post-mortem examination of a child's brain after bilateral DBS of GPI. The authors concluded that comparison with adult post-mortem reports showed no significant differences and confirms the safety of DBS implantation in the pediatric population too.

Tambirajoo K. et al presents a case series of four male children (man age 13 ± 1.08 years) who underwent Medtronic DBS implantation between 2011 and 2018. Three out of the four patients had double bilateral electrodes implanted, targeting the anteromedial and the posteroventral GPi. The fourth patient was treated with single bilateral DBS electrodes within the sensorimotor GPi. For the three patients with double bilateral GPi electrode placement, Patient 1 presented with infection at 17 months follow-up, Patient 2 presented hardware issues at 4 and 8 years follow-up, but the article did not provide specifics about the hardware issues, and Patient 3 presented infection at 4 month follow-up. Patient 4 with single bilateral DBS electrodes presented migration of the left lead at the 4 months follow-up and infection at 19 months follow-up. The authors postulated that the higher rates of postoperative hardware-related complications and infections in their cohort were most likely related to a combination of factors such as the greater number of electrodes implanted, self-mutilating behavior (picking at surgical wounds, self-injury unknowingly or deliberately), severe physical impairment and low body weight/poor nutrition, and the nature of the hyperkinetic dystonic movements, leading to repeated mechanical skin irritation overlying the hardware and mechanical stress to the implants. This reference also includes a review of the literature on the adverse events associated with deep brain stimulation in patients with childhood-onset dystonia; however, the article was published prior to November 6, 2019 and are therefore not discussed here.

Xu, W. et al present a 10-year follow-up study on nine patients who underwent STN-DBS for treatment-refractory pediatric isolated dystonia one decade ago (mean age at surgery: 15.9 ± 4.5 years). The study concluded that, in general, STN-DBS treatment was reasonably well tolerated by the patients. They reported that none of the patients experienced surgery-related adverse effects. The main device-related adverse effect was replacement of the IPG after battery expiration (n = 8). One patient experienced a breakage of the right electrode, which was replaced at the same anatomical location. Various stimulation-related adverse effects also occurred during treatment, although some could be resolved by DBS parameter adjustments. Stimulation-related adverse effects reported by patients at 10-yr follow-up included swallowing difficulties/dysarthria (n = 1), gait disturbance (n = 4), dysarthria (n = 3), weakness (n = 2), vertigo (n = 1), anxiety (n = 1), depression (n = 2), and cognitive deficits (n = 2). One patient was reported to have gained weight at 10-year follow-up. The article further discussed that although some adverse side effects were transient, mild, or could be resolved by DBS parameters adjustment, other adverse effects were more serious and enduring. For example, two out of the nine patients were reported to have experienced cognitive deficits, in particular impairment of executive functions, at 10-yr follow-up. However, the main adverse event, occurring in eight patients was device-related, namely replacing the IPG after battery expiration, often resulting in full or partial symptom remission and subsequent recovery after IPG replacement This reference also includes a review of the literature on the adverse events associated with deep brain stimulation in patients with childhood-onset dystonia; however, the article was published prior to November 6, 2019 and are therefore not discussed here.

Marotta R. presented a study on 9 patients affected by drug-resistant generalized dystonia who underwent GPi-DBS treatment. Eighteen DBS-GPi electrodes were implanted in 9 patients, 12 electrodes were

circumferential and 6 directional. At surgery, mean age was 16 years and mean disease duration was 7,8 years. Mean postoperative follow-up was 13 months. The study reported transient side effects observed /were 1 case of dysartria, 1 case of weakness, 1 case of phosphenes: in all cases the implanted electrodes were circum ferential. The study had no hardware-related complications, while one patients had a small subarachnoid and cortical hemorrhage below the electrode entry point resolved after a few days without neurological deficits.

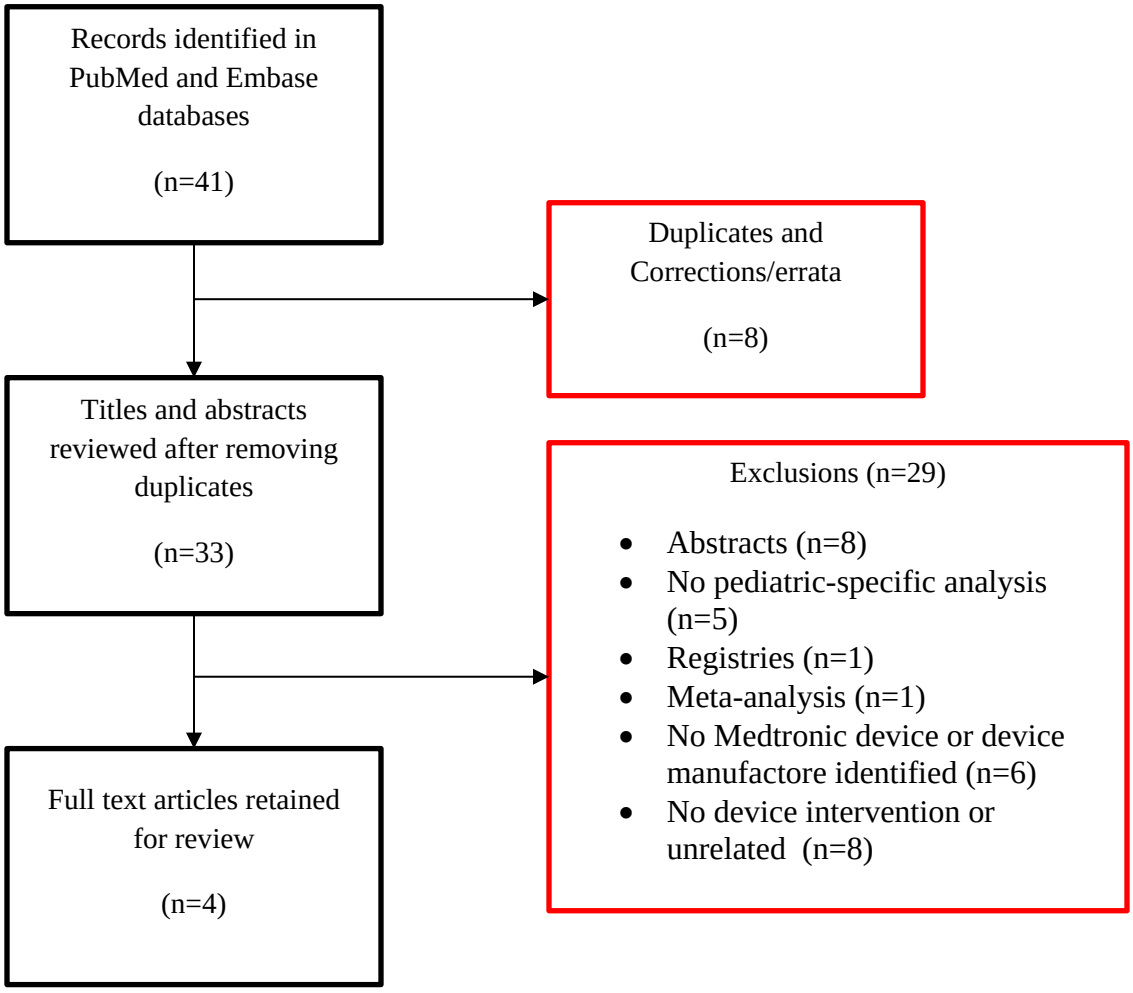
Evidence Assessment: The experiences reported from these cases do not raise new safety concerns in pediatric patients treated with DBS for primary dystonia. However, the body of evidence reported in the literature for this year is limited to a small number of publications comprising several case reports.

Literature Review Conclusions

The current literature review for the period between 11/06/2019 and 11/06/2020 did not identify new safety concerns compared to what was known/anticipated at the time of HDE approval in 2003, and the annual literature reviews previously conducted. However, as noted the report is based on a limited number of publications and a small cohort of patients.

It is important to note that the current labeling for the device highlights the severity of dystonic storm as an adverse event, and describes the potential for rebound effects should the battery not have an adequate charge to deliver therapy (which appears to have occurred in *Xu, W. et al*).

Fig. 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 2022.

FDA will continue surveillance and will report the following to the PAC in 2022:

- Annual distribution number
- Literature review
- MDR review

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