FDA Executive Summary

Prepared for the

Spring 2020, Meeting of the

FDA's Pediatric Advisory Committee

H020007

Medtronic Activa Neurostimulator for Dystonia Treatment

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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 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 provides a reasonable representation of the number of devices needed to treat an individual.Eighteen (18) Medtronic Activa Dystonia Kits were sold in the US in the year 2019 (see below). The ADN of 8,000 has not been exceeded.

Number of devices sold in the US in the year 2019*	
Medtronic Activa Dystonia Kits	**Number of Kits Sold**
3310	5
3317	0
3320	5
3330	5
3337	3
3339	0
Total	18

*cut-off date: 12/17/2019

Number of devices implanted and active implants (in use) in the US in the year 2019	
# of devices implanted	642
# of active implants	3793
# of implanted Peds	97
# of active implants Peds.	534

*cut-off date: 12/17/2019

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, 2018 and September 27, 2019. The reports entered during this timeframe are related to devices implanted between October 11, 2001 through September 17, 2019. The searches resulted in the identification of 204 MDRs. For the purpose of this MDR analysis, these 204 MDRs will be referred to as the 2020 Pediatric Advisory Committee (PAC) data. All of the 204 MDRs were submitted by the manufacturer. Patient gender information was reported in 192 of the MDRs of which 118 were female and 74 were male patients. The event types by age category are presented in Table 1a, 1b, and 1c.

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

	PAC 2015							PAC 2016						
Event Type	**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**
Injury	22	15.2%	84	58.3%	38	26.3%	**144**	34	18.3%	122	65.9%	29	15.6%	**185**
Death	1	50%	1	50%	0	0%	**2**	0	0%	0	0%	3	100%	**3**
Total	**42**	**14.8%**	**176**	**62.4%**	**64**	**22.6%**	**282**	**56**	**16.8%**	**223**	**66.9%**	**54**	**16.2%**	**333**

Table 1b. Event types by age category for MDRs included in the 2017 and 2018 PAC data sets.

	PAC 2017							PAC 2018						
Event Type	**PEDS**		**ADULT**		**UNK**		**Total**	**PEDS**		**ADULT**		**UNK**		**Total**
Malfunction	27	15.9%	107	63.3%	35	20.7%	**169**	29	15.5%	136	72.7%	22	11.7%	**187**
Injury	31	20.1%	90	58.4%	33	21.4%	**154**	18	12.1%	102	68.9%	28	18.9%	**148**
Death	0	0%	1	100%	0	0%	**1**	6	75%	2	25%	0	0%	**8**
Total	**58**	**17.9%**	**198**	**61.1%**	**68**	**20.9%**	**324**	**53**	**15.4%**	**240**	**69.9%**	**50**	**14.5%**	**343**

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

	PAC 2019							PAC 2020						
Event Type	**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**
Injury	19	21.3%	56	62.9%	14	15.7%	**89**	20	26.6%	47	62.6%	8	10.6%	**75**
Death	0	0%	3	100%	0	0%	**3**	0	0%	0	0%	0	0%	**0**
Total	**41**	**18.0%**	**161**	**70.9%**	**25**	**11%**	**227**	**44**	**21.5%**	**145**	**71%**	**15**	**7.3%**	**204**

The number of MDRs that originated in the United Stated (US) and outside of the US (OUS) for the 2020 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 2020 PAC data set

Reporter Country	Pediatric	Adult	Unknown	Total
US	41	138	2	181
OUS	3	7	12	22
Unknown	0	0	1	1
Total	44	145	15	204

Pediatric MDR Review

Patient age was available in 189 of the MDRs, which included 44 pediatric reports and 145 adult reports. The patient age was unknown in 15 reports. Pediatric patient age ranged from 7 to 21 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 and 2020 PAC data sets were similar (15%, 17%, 18%,15%, 18%, and 22% respectively).

The reporting country for 41 Pediatric MDRs was the United States. 3 Pediatric MDR did not include the reporting country. Within the pediatric reports, 19 MDRs were associated with female patients, 25 MDRs were associated with male patients.

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 25 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 2626 days with an average of 308 days and median of 26 days.

There were 13 reports in which the event occurred between zero and 30 days post-implant procedure and 12 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 2020 PAC data set * with TTE ≤ 30 days (n=13)

Reported Problem	Injury	Malfunction
Impedance issue	1	5
Battery charging issue	1	4
Discomfort	2	3
Worsening symptoms	2	2
Lead break/fracture	1	1
Device explanted	0	1
Infection	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 2020 PAC data set with TTE > 30 days (n=12)

Reported Problem	Injury	Malfunction
Battery charging issue	1	4
Impedance issue	0	4
Discomfort	1	2
Worsening symptoms	1	2
Infection	2	0
Device explanted	1	0
Lead break/fracture	0	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. 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 2020 PAC data set

Adverse Event	MDR Report Count	Number of Patients
Battery/Charging issue	11	10
Device replaced	12	8
Device explanted	9	7
Return or worsening of symptoms	7	5
Lead break/fracture	6	5
Infection	4	4
Growth related issues	2	1
Potential electromagnetic interference	1	1
Cognitive issue	0	0
Stroke	0	0

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

- *Battery/Charging Issues (N=11 MDRs, 10 unique events):* Reports of battery/charging issues were associated with recharging issues (N=9), unknown battery issues (N=1), and impedance issues (N=1). The reported battery/charging related issues also resulted in device replacement (N=4), return or worsening symptoms (N= 3), patient discomfort (N=3) and device explant (N= 1).

- *Device Replacement (N=12 MDRs, 8 unique events) Device Explant (N=9 MDRs, 7 unique events) and:* Of the 9 reports of device explants, 7 noted device replacements due to: patient discomfort (N=2), growth related issues (N=2), battery/charging issues (N=1), impedance issues (N=1), and infection (N= 1). Reports of device explants without reported replacements were due to infection (N=2).

- *Return or Worsening of Dystonia Symptoms (N=7 MDRs,5 unique events):* MDRs reporting return or worsening dystonia symptoms were associated with several different device problems including impedance issues (N=2), failure to communicate (N=2), unknown device problem (N= 2), and battery/charging issue (N=1).

- *Lead break/fracture (N= 6 MDRs, 5 unique events):* High impedance (N= 2) and growth-related issues (N= 2) associated with a fractured lead. Additionally, one MDRs noted lead fracture and one MDR noted lead damage during the implant procedure. The broken lead was replaced, and the damaged lead was not used for programming.

- *Infection (N= 4 MDRs, 4 unique events):* Reports of infection were from patient's inability to bathe regularly due to dystonic symptoms (N= 1), lack of access to post-operative care (N=1), a post-operative infection (N=1) and unknown causes (N=1). The reports did not include the types of infection or culture results. Due to infections, there were device explants (N=3) with one replacement (N=1), and one treatment with antibiotics without device explant (N=1).

- *Growth Related Issues (N=2 MDRs, 1 unique event):* Two MDRs noted a patient required replacement of their extension due to damage and "the cause of the damage to their extension was due to growth". The extension and battery were replaced.

- *Potential electromagnetic interference (EMI) (N=1 MDR, 1 unique event):* One patient received a 24-hour encephalogram with unclear results due to the DBS device being left on during testing. No device problem was reported.

MDR Conclusions

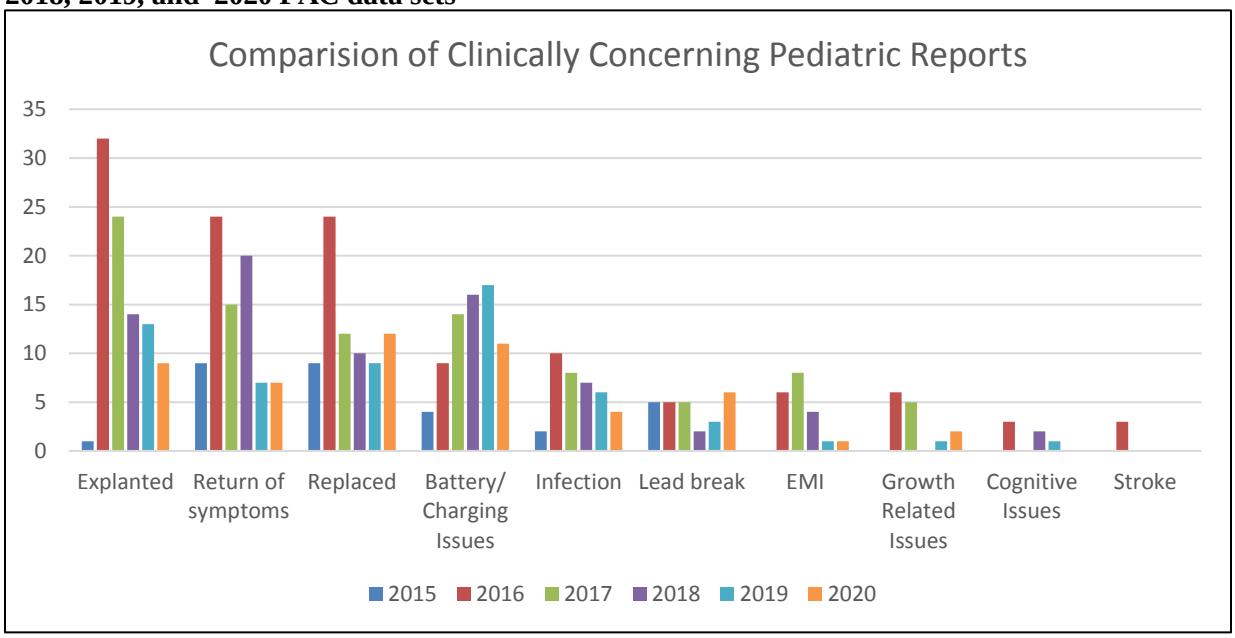
A total of 44 MDRs, reporting 35 unique events, were associated with use of the Dystonia indication of the Activa neurostimulator in pediatric patients. Battery/charging issues and return or worsening of symptoms were the most frequently reported pediatric patient problems. The labeling does address the issue of symptom return/worsening 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 charging issues, lead fractures or electromagnetic interference) stated in the MDRs are either noted in the device labeling or are known device issues with neurostimulator devices in general.

Two MDRs note seizure and the need for electroencephalogram and CT Scan but seizure is not noted as related to the DBS therapy. No MDRs associated with pediatric death, cognitive issue, or stroke were reported within the 2020 PAC data.

No new patient or device problems were identified in the 2020 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 1.

Chart 1. Comparison of the number of clinically concerning pediatric reports* for 2015, 2016, 2017, 2018, 2019, and 2020 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 2019 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, 2019, 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, 2018 and November 6, 2019 (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, 2018
- 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, 18 records were initially identified (Fig 1): 6 titles from PubMed and 12 from EMBASE. After removal of duplicates (n=5), there were 13 articles identified for title and abstract review. Based on the predefined exclusion criteria, 11unique records were excluded for the following reasons: conference abstracts (n=2) (3, 9), no pediatric stratified analysis (n=1) (12), registry (n=1) (7), systematic reviews and meta-analyses with included references published prior to November 6, 2018 (n=1) (6), no Medtronic device used or device manufacturer not identified (n=2) (2, 4), and unrelated topic or no device intervention (n=2) (5, 11).

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 *Benato et al*, *Li et al*, *Marcé-Grau et al*, and *Zhang 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

Benato et al (1) presents a case series of four patients in Italy, two of which were implanted with Medtronic devices and two who were implanted with devices from another manufacturer and are therefore not pertinent to this discussion. One patient with bilateral GPi placement presented with skin erosion three months after surgery "above the left electode skull borehole, which was successfully managed with a cutaneous flap." According to the authors, this event resulted in a dislocated left electrode to which two episodes of dystonic storm over the next five years were attributed. The left electrode was ultimately revised five years after the initial placement, which resolved hyperkinetic movements in the patient's right side. This appears to have occurred in close proximity to the publication date for the article. The second patient implanted with a Meedtronic system is not described as having experienced any complications related to the device. This reference also includes a review of the literature; however, all articles included were published prior to November 6, 2018 and are therefore not discussed here.

Li et al (8) describes the case of one patient in China implanted with leads bilaterally in the STN, with one IPG for each side. While the authors indicate that the patient's clinical status was stable for some time after surgery, roughly five years following the initial implant the patient's status "suddenly deteriorated" and "[w]within two months, she developed progressively severe episodes of generalized dystonia." The battery leading to the left STN lead was found to be "nearly depleted" and was replaced several days

later, though not before the patient developed a dystonic storm. The patient improved thereafter, though not fully to past levels.

Marcé-Grau et al (10) describes the case of one patient in Spain implanted with leads bilaterally in the GPi. The patient experienced "clear improvement," particularly in "the fluency and intelligibility of his speech, and in tongue and mandibular dystonia." The authors do not indicate whether the patient experienced any complications or adverse events relateds to the DBS treatment.

Finally, *Zhang et al*. (13) describes a series of five cases, only two of which are considered pediatric because the implants were placed prior to age 22. While one of the adult patients required an electrode replacement, the authors state that "[a]part from this, no hardware-related or long-term stimulation-related adverse events were observed. In fact, during the parameter tuning session (no more than 3 months after electrode implantation), stimulation-induced anesthesia, dysarthria, and contralateral muscular spasm were observed in cases of excessive current spreading beyond the anatomical border of the thalamus. Such adverse events can be resolved by limiting the parameters to underthreshold or changing the long-term stimulation mode (monopolar or bipolar)."

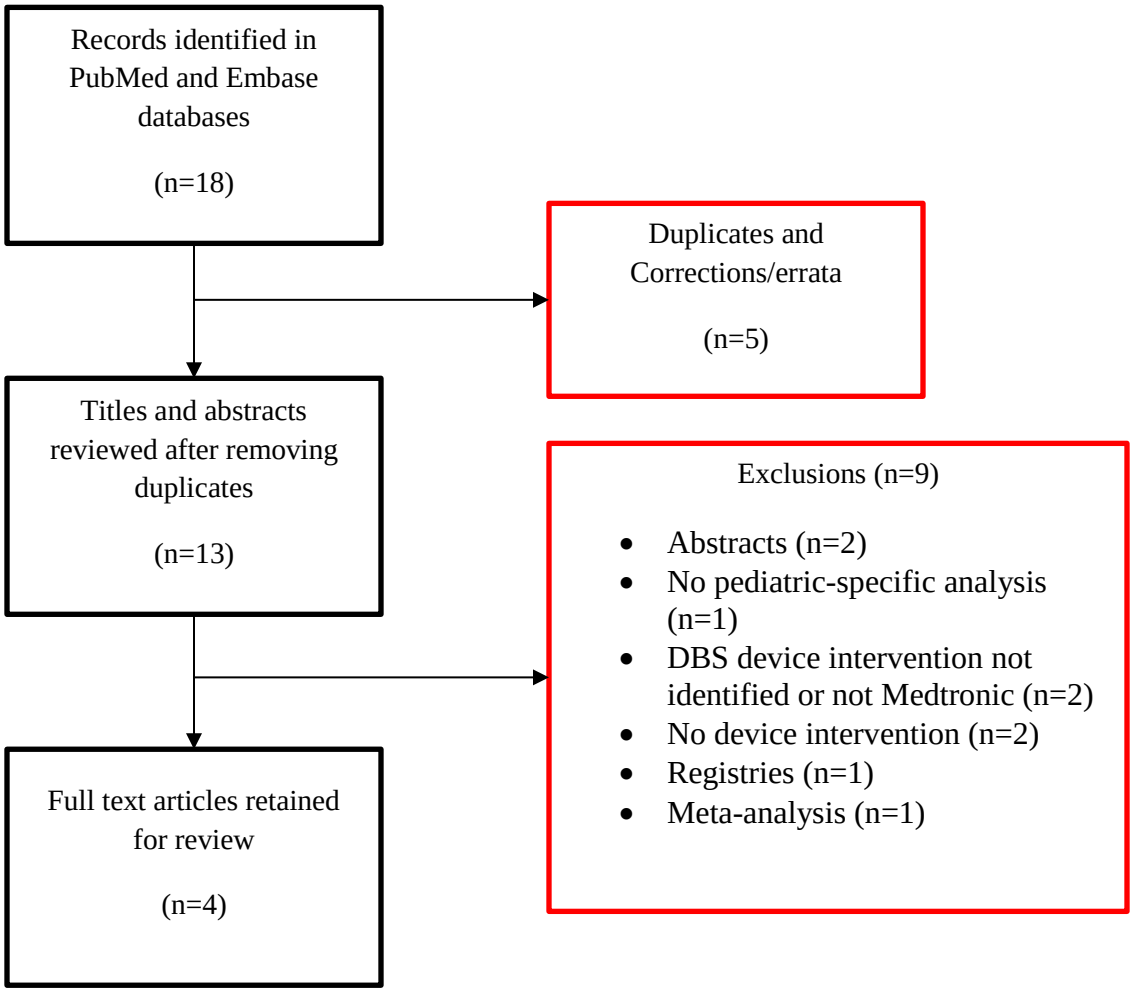
Evidence Assessment: The experiences reported from these cases do not raise new safety concerns in pediatric patients treated with DBS for primary dystonia. However, the body of evidence reported in the literature for this year is limited to a small number of publications comprising several case reports.

Literature Review Conclusions

The current literature review for the period between 11/06/2018 and 11/06/2019 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 *Li et al*).

Fig. 1. Article Retrieval and Selection



SUMMARY

Evalution of data available to CDRH, including MDRs and published scientific literature, has identified no new safety concerns compared to what was known and 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 2021.

Continued surveillance and will report the following to the PAC in 2020:

- Annual distribution number
- Literature review
- MDR review

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