FDA Executive Summary

Prepared for the
March 23, 2018 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.

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 number of devices implanted in the U.S. in 2017 was 710 implants. The number of devices implanted in pediatric patients (<22 years of age) in the U.S. in 2017 was 100 implants.

III. POST-MARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

Overview of the MDR Database

Each year, the FDA receives over several hundred thousand 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 post-market surveillance data sources.

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device 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, 2016 and September 27, 2017. The reports entered during this timeframe are related to devices implanted between August 29, 2003 through September 27, 2017. The searches resulted in the identification of 343 MDRs. For the purpose of this MDR analysis, these 343 MDRs will be referred to as the 2018 Pediatric Advisory Committee (PAC) data. Two of the MDRs were submitted by voluntary reporters and the remaining 341 MDRs were submitted by the manufacturer. Patient gender information was reported in 315 of the MDRs of which 174 were female and 141 were male patients. The event types by age category are presented in Table 1.

Table 1. 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	Pediatric	Adult	Unknown	Pediatric	Adult	Unknown	Pediatric	Adult	Unknown	Pediatric	Adult	Unknown
Malfunction	19	91	26	22	101	22	27	107	35	29	136	22
Injury	22	84	38	34	122	29	31	90	33	18	102	28
Death	1	1	0	0	0	3	0	1	0	6	2	0
Total	42	176	64	56	223	54	58	198	68	53	240	50

The number of MDRs that originated in the United Stated (US) and outside of the US (OUS) for the 2018 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 received in the 2018 PAC data set by Age Category

Reporter Country	Pediatric	Adult	Unknown	Total
US	43	200	9	252
OUS	2	16	38	56
Unknown	8	24	3	35
Total	53	240	50	343

Pediatric MDR Review

Patient age was available in 293 of the MDRs, which included 53 pediatric reports and 240 adult reports. The patient age was unknown in 50 reports. Pediatric patient age ranged from 5 to 21 years of age. The average age of the patients in the pediatric reports was 17 years. The percentages of pediatric reports within the 2015, 2016, 2017 and 2018 PAC data sets were similar (15%, 17%, 18%, and 15% respectively).

The reporting country was available in 45 of the 53 pediatric MDRs and included the United States (N=43), China (N=1), and France (N=1). Within the pediatric reports, 20 MDRs were associated with female patients, 31 MDRs were associated with male patients. There were 2 pediatric MDRs in which the patient gender was not reported.

The dystonia indication for the Activa Neurostimulator was approved under Humanitarian Device Exemption (HDE) H020007 in patients seven years of age and above. Although the majority of the MDRs reported on-label use of the device, it should be noted that, in the 2018 PAC data, off-label use of the device was reported in one MDR involving a five-year-old patient. The five-year-old patient experienced an infection four to six weeks post- implant, which required device and lead explant. No further information was reported on patient outcome or replacement of the device.

The three pediatric deaths (see Table 1), associated with six MDRs, originated in the United States:

- Three MDRs were associated with a 20-year-old patient with a complicated medical history including Wilson's Disease, Primary and Acquired Torsion Dystonia, Cerebral Palsy, chronic pain, disorders of the gastrointestinal tract, spastic paresis, seizures, and mitochondrial metabolism defect. Recent history included gastrointestinal issues, a positive culture for *Clostridium difficile* and pneumonia. The patient was hospitalized 3 times in the four months preceding death. The Deep Brain Stimulator (DBS) battery was scheduled to be replaced during the 2nd hospitalization due to it "alarming" but battery replacement remained on hold due to multiple medical complications. The patient was subsequently placed in hospice and died within one month. The cause of death was reported as related to a "progressive diagnosis and the multiple complications associated with it". The implant duration was reported to be 1.6 years.
- One MDR was associated with an 18-year-old patient who died at home due to respiratory failure; the patient hyperventilated, stopped breathing, then went into cardiac arrest and was unable to be revived by EMS. The cause of death was reported as "related to their underlying disease". The patient had "a history of progressive myoclonic epilepsy, primary torsion dystonia, developmental delay, non-verbal, J-tube for feeding, near constant blepharospasm, diffuse hypertonia, severe generalized dystonia, decrease ROM, contractures, Dentatorubral Pallido-Lenticulo Atrophy (DRPLA) encephalopathy". The implant duration was reported to be 1.5 years.
- Two MDRs were associated with an 18-year-old patient with chronic respiratory failure, which developed as a complication of the need for pain management and antispasmodics. "It was noted the patient had suicidal behavior with attempted self-injury and psychiatry intervention". The patient was hospitalized for ventilator weaning. The ventilator weaning was successful, but "the patient became increasingly combative and had repeated tracheostomy decannulation episodes". The decision was made to not replace the tracheostomy and a Do Not Resuscitate (DNR) order was instituted. The patient died due to "chronic respiratory failure" 2 days later. The implant duration was reported to be one (1) year and fifteen (15) days.

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 39 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 3405 days with an average of 669 days and median of 407 days.

There were four reports in which the event occurred between zero and 30 days post-implant procedure and 35 reports in which the event occurred greater than 30 days post-implant procedure.

Table 3. Reported problems and event types for pediatric MDRs* with TTE ≤ 30 days (n=4)

Reported Problem	Injury	Malfunction
Battery charging issue	0	1
Impedance issue	0	2
Return or worsening symptoms	0	1
Infection	1	0
Device explant due to infection	1	0
Patient discomfort	0	1

* A single MDR may be associated with more than one problem of clinical interest. Multiple MDRs may relate to the same event.

Table 4. Reported problems and event types for pediatric MDRs* with TTE > 30 days (n=35)

Reported Problem	Injury	Malfunction	Death
Cardiac Arrest	0	0	1
Cognitive Issues	0	0	1
Infection	1	0	3
Return or worsening symptoms	6	6	3
Lead break/fracture	2	0	0
Impedance Issues	4	4	0
Device explanted	10	1	0
Device explanted due to infection	1	0	0
Device replaced	9	0	0
Electromagnetic Interference	0	2	0
Battery charging issue	4	4	3
Normal battery depletion	0	1	0
Patient discomfort	2	1	0

* A single MDR may be associated with more than one problem of clinical interest. Multiple MDRs may relate to the same event.

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*

Adverse Event	MDR Report Count	Number of Patients
Return or worsening of symptoms	20	15
Battery/Charging issue	16	11
Device explanted	14	11
Device replaced	10	7
Infection	7	5
Potential electromagnetic interference	4	3
Lead break/fracture	2	1
Cognitive issues	2	1
Growth related issues	0	0
Stroke	0	0

* A single MDR may be associated with more than one problem of clinical interest. Multiple MDRs may relate to the same event.

- *Return or Worsening of Dystonia Symptoms (N=20 MDRs, 15 unique events):* MDRs reporting return or worsening dystonia symptoms were associated with several different device problems: Battery/charging issue (N=6), impedance issue (N=5), potential EMI (N=2), migration of device/device component (N=1), failure to communicate (N=1), and failure to deliver energy (N=1). Six MDRs reported unknown device problems contributing to return or worsening dystonia symptoms.
- *Battery/Charging Issues (N=16 MDRs, 11 unique events):* Reports of battery/charging issues were associated with recharging issues (N=9), unknown battery issues (N=4), premature battery depletion (N=2), and an over-discharged battery (N=1). The reported battery/charging related issues also resulted in device replacement (N=2) and patient discomfort (N=1). The remaining outcomes for battery/charging related issues were not clinically significant and included no known impact on patient (N=6), and results unexpected (N=2).
- *Device Explant (N=14 MDRs, 11 unique events) and Device Replacement (N=10 MDRs, 7 unique events):* Of the 14 reports of device explants, 10 mentioned device replacements due to: premature battery depletion (N=2), impedance issues (N=2), lead break or damage (N=2), patient discomfort of a zapping/shocking sensation near the implanted neurostimulator (N=1), migration of device component (N=1), unable to communicate/program (N=1) and "device failed" (N=1). Reports of device explants without reported replacements were due to infection (N=3), and normal end of battery life (N=1).
- *Infection (N= 7 MDRs, 5 unique events):* Limited information was provided on the potential causes of the reported infections. One patient death was reported in three MDRs which stated the presence of infection. These three MDRs reported a concomitant diagnosis of positive culture for *Clostridium difficile* six months prior to death. The patient also had a concomitant diagnosis of pneumonia two months prior to death. Three other MDRs reported the presence of infections and resulted in device explants. One MDR reported a foreign body reaction in addition to infection and did not report the patient outcome.
- *Potential electromagnetic interference (EMI) (N=4 MDRs, 3 unique events):* There were 4 pediatric MDRs associated with potential EMI. Sources of EMI included exposure to optometry equipment (N=2, 1 unique event), an unspecified medical procedure which also caused patient discomfort (N=1), and "walking through a mall and started walking bad" (N= 1). Based on the limited information provided in the MDRs, the cause-effect of EMI on the device is unclear, but it may be associated with EMI inadvertently changing device settings or turning off the device.
- *Lead break/fracture (N= 2 MDRs, 1 unique event):* There were 2 reported MDRs describing events associated with lead break/fracture in one patient, resultinging in device replacement. A one quarter of an inch break was discovered following low impedance and the return of symptoms. This was reported as the third revision of the right lead due to breaks. The timeframe between revisions was not reported.
- *Cognitive Issues (N=2 MDRs, 1 unique event):* Two death MDRs reported cognitive

issues in one patient. The patient displayed suicidal behavior with attempted self-injury and psychiatric intervention. (See the third bullet of the 'Pediatric MDR Review', section above for further details).

MDR Conclusions

A total of 53 MDRs, reporting 41 unique events, were associated with use of the Dystonia indication of the Activa neurostimulator in pediatric patients. Return or worsening of symptoms and battery/charging issues 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. Limited information on the battery/charging issues was provided within the MDRs. 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.

The pediatric deaths (N= 6 MDRs, 3 unique events) reported within the 2018 PAC data did not implicate the device as the cause of death, and each death report included information relating comorbid medical conditions that contributed to disease processes and subsequent death. Cognitive changes and suicidal behavior with attempted self-injury were associated with two MDRs (1 unique death event).

No MDRs associated with pediatric stroke or potential growth-related issues were reported within the 2018 PAC data.

No new patient or device problems were identified in the 2018 PAC data when it was compared to previous years.

IV. POST-MARKET LITERATURE REVIEW: SAFETY DATA

Purpose

The intent of this systematic literature review is to provide an update of adverse events (AEs) associated with the use of the Medtronic Activa neurostimulator since the previous literature review performed for the 2017 PAC meeting. Specifically, the systematic review was conducted to address the following question:

- *What is the safety of the Medtronic Activa neurostimulator device in the pediatric population treated for dystonia?*

Methods

This literature search was conducted using the same search criteria used for the systematic literature reviews performed for previous PAC meetings. The following search terms were used:

(medtronic dystonia) OR (medtronic activa deep brain stimulation) OR (medtronic dbs) OR (medtronic activa) OR (activa) OR (dbs) AND (pediatric) AND (Dystonia)

PubMed and EMBASE databases were systematically searched on November 6, 2017. Papers published since the last search, i.e. from November 6, 2016 to November 6, 2017 (dates included), were evaluated. We also cross-referenced citations provided by the MDR data search. Then the following exclusion criteria were applied, either from reading of the abstracts or the full articles:

- Duplicates
- Conference abstracts/Oral presentations
- No primary dystonia
- Registries and/or No device data
- 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
- No Medtronic software used in the device.

The search yielded a total of 42 articles: 12 from PubMed (1-10, 41, 42), and 30 (11-40) from EMBASE. Eight (8) citations from the MDR data search were cross-referenced. The combined search identified 6 duplicates that were removed (15-17, 20, 24-25), resulting in 36 unique articles. Based on the pre-specified exclusion criteria, 33 articles were excluded for various reasons, namely: unrelated topic (n=15)(3-7, 9-10, 12-13, 21, 26, 29, 40-42), no primary dystonia (n=4)(2, 14, 36, 37), non-pediatric population or mixed (pediatric and adult) populations where subcohorts are not analyzed separately (n=1)(19), registry projects and/or no device-associated data (n=4)(16, 18, 27, 38), conference abstracts (n=8)(11, 22-23, 28, 30-32, 34), and 1 DBS review article that involved neither the use of the device nor pediatric population (n=1)(1). After these exclusions, three articles were identified as eligible for full review. Among them, the article by *Krause P et al., (8*) had been electronically published in 2016 and presented in the 2016 PAC meeting, resulting in two articles for inclusion in this systematic review, one case report by *Lin, J-P et al* (35) and a report on results from a pediatric cohort of patients, by *Kaminska M et al* (39) (See Flowchart, Fig.1 -Article retrieval and selection).

Results

The case report by *Lin, J-P et al* (35) is based on ex-24-week gestation pre-term twins (a boy and a girl) from the UK, conceived by in-vitro-fertilization (IVF), who suffer from severe spasms and hypotonia. The boy is the subject of the case report and was described as the most severely affected (level 3 Manual Abilities Classification System, MACS); experiencing periods of severe dystonia, nocturnal dystonia that impaired sleep, and fluid intake problems. He also had suffered bilateral cerebellar hemorrhagic infarction with intact cerebellar vermis, auditory nerves, and basal ganglia. At the age of five, he was confirmed deaf. The neck and trunk dyskinetic movements (choreoathetosis) were a concern for the placement of a cochlear implant (CI), because the movements would interfere with the CI magnet that sits behind the ear. To reduce the dystonic choreoathetosis and minimize the risk of interferenace with the CI, a Medtronic Activa RC rechargeable 16-channel 3389 bilateral electrodes DBS system was implanted.

The authors report that the DBS bilateral stimulation consisted of standard monopolar settings. The post-operative course was uneventful. The goal of reducing the dystonic choreoathetosis was achieved three and half months after DBS implantation, and a CI was implanted five months later. During the first 3 years and 10 months post- DBS implantation, little change on the dystonia was observed, as measured by the Burke-Fahn-Marsden-Dystonia-Rating-Scale (BFMDRS). However, the authors also report that there were overall improvements, as measured by the Canadian Occupational Performance Measure (COPM) (sustained benefit from 1-year onward) and the Care Provider Child Health Index Living with Disability (CPCHILD) (12.5% improvement, mostly in the domains of positioning, mobility, communication, and/or social interaction). The observed improvements were maintained until the DBS implant had to be explanted (3 years and 10 months post-initial DBS implantation) due to a combination of neurostimulator battery erosion, failutre to settle after two DBS repositionings, and long-term use of antibiotics. Ten days after DBS removal, the patient developed status dytonicus associated with ileus and acute gastric bleeding. The DBS was re-implanted 3-weeks later, but required (along with medication) 230 days to restore sleeping and sitting. The patient continues the use of CI and he is almost back to the level of function before the episode of status dystonicus, except for bowel function (constipation) exacerbated by medication.

The article by *Kaminska M et al.(39),* presents results from a 10-year (2005 to 2015), one site, prospective study, with 129 patients who underwent DBS surgery and were followed for at least 6-months (mean 3.3-years) post-DBS implantation. These patients were prospectively monitored for treatment-related complications. Of the 129 patients, 32 were implanted with Kinetra/Soletra stimulators, 92 were implanted with Activa RC, 2 with Activa PC[1], and 3 patients were new

[1] Please note that Kinetra, Sonetra, and Activa RC/PC/SC systems are manufactured by Medtronic and considered similar/equivalent DBS systems.

implants from other centers (the DBS system is not specified in the publication). During the course of the study, 22 patients (of the 32 initial Kinetra/Soletra implants) had the DBS system replaced with an Activa RC; twenty nine (29) patients transitioned to adult services, 10 died, 1 was lost to follow-up, and 89 remained under follow-up. Authors report that most deaths were not related to the DBS systems, with the exception of 1 patient, with type 6 Aicardi-Goutieres Syndrome, who died 24 hours post-DBS electrode revision. The post-mortem examination failed to identify the cause of death.

Kaminska M et al.(39) report that a commonly observed complication in the study was surgical site infection. The table below presents the % distribution; surgical site infection is reported to be lower for patients receiving the Activa DBS system, especially for those who were younger than 7 at the time of implant. Authors also report that the surgical site infections occurred within six months of implantation, with prolonged use of antibiotics been unsuccessful in 85% of the patients with surgical site infections, and eventually resulting on complete removal of the DBS system.

	% Surgical Site Infection
All New Implants	10.3
All Implant Revisions	10.1
New Activa RC Implants	8.6
All Implants, in Patients under 7 years at the Time of Implant	7.6
New Activa RC Implants in Patients under 7 years old	4.7

Source: *Kaminska M et al*, page 170

The table below presents other complications as reported by *Kaminska M et al* (39). DBS hardware problems were the most common complication. Of note, 3.4% of Activa RC DBS systems experienced an unexpected battery switching off compared to 18.7% for the other DBS systems. Although, recharghing problems were reported, the authors state that 84% of the patients/care givers indicated the recharching was “not at all” or only a little” care burden.

Complication	**Overall %**
Unexpected Battery Switched-Off (Soletra/Kinetra)	18.7
Electrode/Extension Problems (All)	18.4
Transient Seroma at IPG Site in post-operative Period	8.0
Electrode/Extension Malfunction	7.7
Electrode/Extension Fracture	4.6
Status dystonicus following sudden DBS cessation	4.6
Short/Tight Extension	3.8
Unexpected Battery Switched-Off (Activa RC)	3.4
Electrode/Extension Migration	2.3
Skin Erosion, Requiring Explants	2.3
Intracraneal Bleeding (asymptomatic)	0.8
CSF Collection on a Scalp	0.8
Recharching of Stimulator (48 returned questionnaires)	
Shielded Battery Syndrome (Kinetra replaced with Activa RC)	14*
Battery Repositioned for diffulty Recharing in Overweigth Patients	2

Complication	Overall %
Significant Difficulty Mantaining Connection During Recharging	23
Recharger Replaced at Least Once	38
Battery Flat at Least Once	23

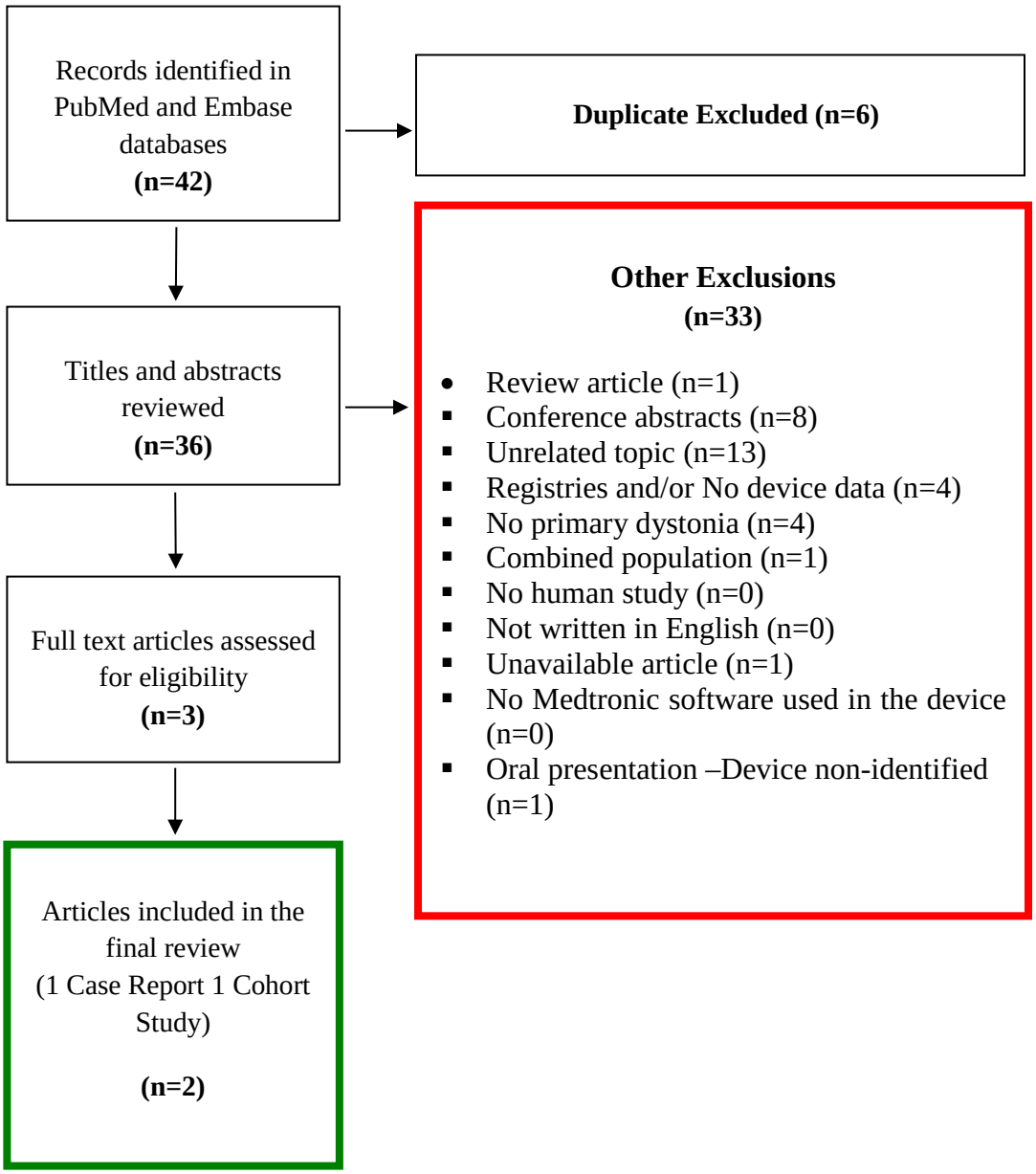
*Out of 14 patients
Source: *Kaminska M et al*, page 172

There were a total of 69 revisions reported due to reasons other than infection, but the "other" reasons are not specified in the publication.

FDA - Literature Review Conclusions

No new safety concerns were identified by the current literature review. However, this is based on a limited number of publications (1 case report, and 1 prospectice study) with important limitations such as small sample size, the use of different device models and/or device components or combination of them, insufficient/inadequate patient follow-up and patient information, undefined criteria to determine infections and/or adjudication of adverse events with respect to potential DBS device association.

Fig. 1. Article Retrieval and Selection



V. SUMMARY

Overall, FDA's Review Team has identified no new safety concerns compared to what was previously described and reported. Based on the available data, and taking into account the probable benefits and risks for the device, the safety profile of the device remains acceptable.

Therefore, FDA will continue routine surveillance including MDRs and literature reviews to provide focused updated device safety post-market data to the 2019 PAC.

VI. REFERENCES

(35). Jean-Pierre Lin, Margaret Kaminska, Sarah Perides, Hortensia Gimeno, Lesley Baker, Daniel E. Lumsden, Anzell Britz, Sandra Driver, Alec Fitzgerald-O'Connor, Richard Selway. "Bilateral globus pallidus internus deep brain stimulation for dyskinetic cerebral palsy supports success of cochlear implantation in a 5-year old ex-24 week preterm twin with absent cerebellar hemispheres" European J of Paediatric Neurology. 2017 Vol 21, Issue 1:202-213

(39). Kamiska M; Perides S; Lumsden E; Nakou V; Selway R; Ashkan K; Lin J-P. Complications of Deep Brain Stimulation (DBS) for Dystonia in children - The challenges and 10 year experience in a large paediatric cohort. Eur J Paediatr Neurology 2017 21 (1):168-175

(Remaining articles, available upon request)