Executive Summary

Enterra® Therapy System

H990014

Prepared by the Center for Devices and Radiological Health

for the September 26, 2019 Pediatric Advisory Committee meeting

TABLE OF CONTENTS

INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this document provides the Pediatric Advisory Committee (PAC) with postmarketing safety information to support its annual review of the Enterra® Therapy System ("Enterra"). The purpose of this annual review is to (1) ensure that the Humanitarian Device Exemption (HDE) for this device remains appropriate for the pediatric population for which it was granted, and (2) provide the PAC an opportunity to advise FDA about any new safety concerns it has about the use of this device in pediatric patients.

This document summarizes the safety data the FDA reviewed in the year following our 2015 report to the PAC. It includes data from the manufacturer's annual report, postmarket medical device reports (MDR) of adverse events, and peer-reviewed literature.

BRIEF DEVICE DESCRIPTION

Enterra is a surgically-implanted gastric electrical stimulator (GES). The mechanism(s) by which Enterra works is not well understood but may involve indirect neuromodulation of parasympathetic nerves and/or ganglia which regulate gastric function.

Enterra consists of the following:

1. A neurostimulator placed in a subcutaneous pocket in the abdomen, which functions like a pacemaker in delivering electrical pulses to the stimulation leads. The neurostimulator contains a sealed battery and electronic circuitry.
2. Two intramuscular leads that connect to the neurostimulator, implanted into the muscularis propria on the greater curvature at the limit of the corpus-antrum. The leads deliver electrical pulses to the stomach muscle.
3. An external clinician programmer.

Schematic diagrams of the implantable components and device placement are provided in Figure 1 and Figure 2, respectively.

FIGURE 1: Implantable components

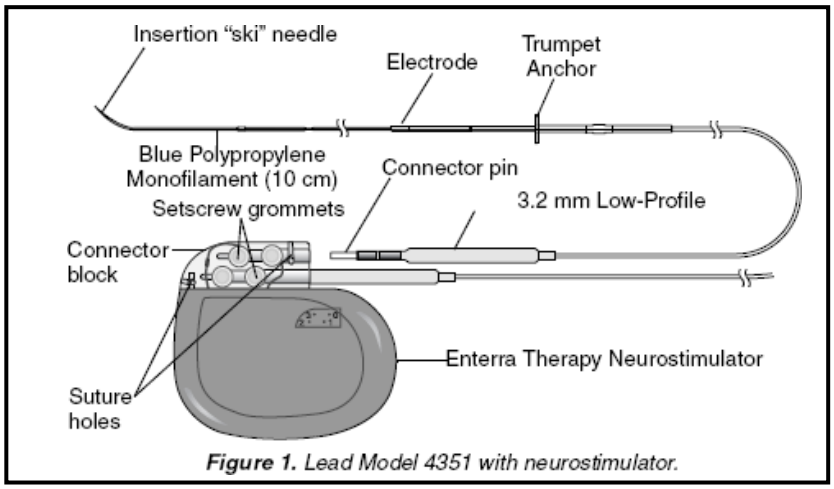
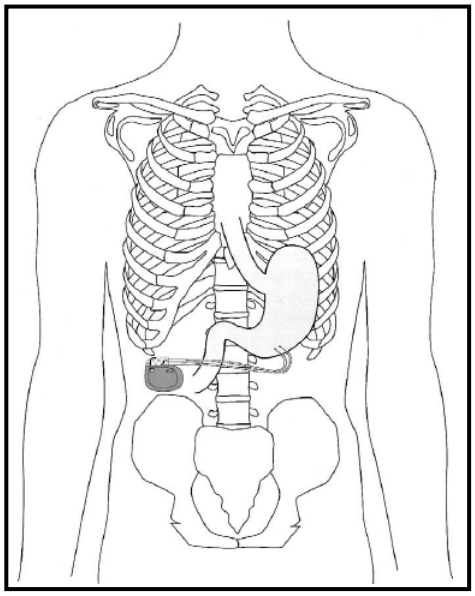


Figure 1. Lead Model 4351 with neurostimulator.

FIGURE 2: Device placement



INDICATIONS FOR USE

Medtronic Enterra Therapy is indicated for the treatment of chronic, intractable (drug-refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology in patients aged 18 to 70 years.

REGULATORY HISTORY

September 23, 1999: Granting of Humanitarian Use Device (HUD) designation for Enterra (HUD #990014)

March 30, 2000: Approval of Enterra HDE (H990014)
March 25, 2013: Approval to profit on the sale of Enterra

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. However, it is to be noted that unless the sponsor requests to update their ADN based on the 21st Century Cures Act, the ADN will still be based on the previously approved ADN of 4,000. The approved ADN for Enterra is 4,000 total per year.

The total number of Enterra devices *sold* in the U.S. for the current and previous reporting periods is detailed in Table 1; the number of devices *implanted* in pediatrics is detailed in Table 2.

TABLE 1: Distribution numbers

Model Number & Component Name	Devices Sold From 02/01/18 – 01/31/19	Devices Sold From 02/01/17 – 01/31/18	Devices Sold from 02/01/16 – 01/31/17	Devices Sold From 02/01/15 – 01/31/16	Devices Sold from 02/01/14 – 01/31/15
37800 Implantable Neurostimulator (INS)	1,951	2,017	1,865	1,611	1,391
3116 Implantable Neurostimulator	0	0	0	208	95
4351 Intramuscular Lead	2,106	2,535	2,462	2,151	2,151

TABLE 2: Number of devices implanted in pediatric patients

Reporting Period: 1-Feb-2018 to 31-Jan-2019	Total N (newly implanted this period)	Female			Male			Gender Unknown		
		<2	2<18	≥18<22	<2	2<18	≥18<22	<2	2<18	≥18<22
Newly implanted Pediatric patients implanted during this reporting period	47	0	12	24	0	8	1	0	1	1
Total Pediatric implant base this period	287	0	53	154	0	41	28	0	4	7

MEDICAL DEVICE REPORT REVIEW

Overview of MDR database

The MDR database is one of several important postmarket surveillance data sources used by the FDA. Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MDR 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 in a "real world" setting/environment, including:
  - rare, serious, or unexpected adverse events
  - adverse events that occur during long-term device use
  - adverse events associated with vulnerable populations
  - off-label use
  - 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. Other limitations of MDRs include, but are not necessarily limited to:

- 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 Enterra Therapy System

MDR Search Methodology

The database was searched using the following search criteria:

A. Search 1
   - **Product Code:** LNQ
   - **Report Entered:** between May 1, 2018 and April 30, 2019

B. Search 2
   - **Brand name:** Enterra%
   - **Report Entered**: between May 1, 2018 and April 30, 2019

C. Search 3
   - **Premarket submission number**: H990014
   - **Report Entered**: between May 1, 2018 and April 30, 2019

The searches resulted in identifying 325 MDRs: all the 325 reports were submitted by the manufacturer during this timeframe.

Seven (7) MDRs were excluded since these MDRs described “Interstim” device. Thirteen (13) MDRs were excluded from further analysis since these MDRs described events reported in twelve (12) journal articles. Eight (8) of these article reports were excluded from the MDR analysis and the Literature Review as they are articles discussing off-label indications (i.e. sacral neuromodulation for fecal/urinary incontinence), five (5) article reports were excluded because they were outside the defined search parameters (i.e. did not include pediatric patients or outside the search period) for this analysis.

The remaining 305 MDRs involved MDRs received between May 1, 2018 and April 30, 2019. They included 1 death, 184 injury, and 120 device malfunction reports. These 305 MDRs are discussed below.

Event Type by Patient Age

Table 3 below provides the distribution of the MDRs by reported event type and age grouping. Nine (9) reports identified a pediatric patient from 3.4 to 21.5 years old. These have been placed into two age categories of < 18 and 18-21 years old and included 6 injury MDRs and 3 malfunction MDRs.

TABLE 3: Overall event type distribution by patient age

Event Type	Total MDR Count 5/1/2018 – 4/30/2019	MDR Count by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18-21)	Adult (≥ 22)	Indeterminate (Age blank)
Death*	1	0	0	1	0
Injury	184	3	3	119	59
Malfunction	120	0	3	77	40
Total MDR Count	305	9		197	99

Comparison of Current Patient Event Type Information with 2017 and 2018 Data

Table 4 below compares the Event Type distribution for this analysis to that of prior years 2017 and 2018. The current period appears to reflect about an 30% decrease of MDR submissions compared with the 2018 PAC presentation period (May 1,2017 to April 30, 2018), in the numbers of serious injury and malfunction reports. Similarly, pediatric MDR submissions decreased from 12 in the previous analysis period to 9 in this current analysis period.

TABLE 4: Overall event type distribution by year

	Total MDR Count		
Event Type	PAC Meeting 2017 5/2016 - 4/2017	PAC Meeting 2018 5/2017 - 4/2018	PAC Meeting 2019 5/2018 - 4/2019
Death	2	0	1
Injury	255	285	184
Malfunction	144	150	120
Total MDR Count	401	435	305

Patient Gender and Age Information

In the 305 MDRs received from May 2018 to April 2019, 197 patients were noted as adult (≥22 years old) and 99 MDRs did not provide a patient age (indeterminate age reports). Nine (9) MDRs contained pediatric patients' ages that ranged from 3.4 to 21.5 years, with a mean age of 17.7 years (SD ± 5.7 years). There were also 263 MDRs which noted the gender of the patient: 229 MDRs as female (including 6 pediatric), and 34 MDRs as male (including 2 pediatric). The remaining 42 MDRs did not include the patient's gender (including 1 pediatric).
Individual review of the 42 reports narrative sections to determine gender identifiers (male or female, she or her, he or him, etc.), did not result in identifying additional female or male noted events, instead these reports identified the individual involved in the event only as "the patient".

Time to Event Occurrence

An analysis of the Time to Event Occurrence (TTEO) was performed. The TTEO is based on the implant duration and was calculated as the time between the Date of Implant and the Date of Event. For those reports without a date of event, the TTEO was calculated using the reported date of implant removal. There are total 211 MDRs (out of 305 MDRs) provided event date or explant date, including 6 of the 9 pediatric reports.

Table 5 below provides the MDR count for the TTEO for the pediatric, adult, and indeterminate age patient populations.

TABLE 5: MDR count for the TTEO by patient age

Time to Event Occurrence (TTEO)	MDR Count by Patient Age (years)			
	Pediatric (<18)	Pediatric (18-21)	Adult (≥22)	Indeterminate (Age blank)
≤ 30 days (n=50)	1	1	45	3
31 days - ≤ 1 year (n=45)	1	0	35	9
> 1 year – ≤ 5 years (n=95)	0	3	77	15
> 5 years (n=21)	0	0	19	2
Totals (N=211)	2	4	176	29

Characterizations of the 9 MDR Narratives of Pediatric Events from May 1, 2018 – April 30, 2019 as it relates to TTEO:

A. TTEO within the first 30 days of implant. (N= 2)

- A 3-year-old female reported by a healthcare professional regarding a removal of an implanted neurostimulator (INS) in the patient due to an infection. It was noted that the patient still had her leads implanted. There were no further complications reported or anticipated. The infection was first noticed in February 2018 and the INS was removed in March 2018. The leads were deliberately left in the patient to allow for an implant later. The device was not returned to the manufacturer.

- A 19-year old patient reported by a healthcare professional with symptoms of persistent nausea, vomiting, and poor intake since device implant. The patient's vomiting had slowed down at one point, about two weeks after implant. The device stimulation voltage was increased a couple of times but was not able to effectively manage the patient's gastroparesis. The patient also has increased frequency of bowel movement. The device stimulator was turned off for an upcoming placement of a decompression gastrostomy and feeding jejunostomy. The device remains implanted at the time of report.

B. TTEO between 31 days and ≤ 1 year of implant. (N=1)

- A 17-year-old male reported by a healthcare professional with symptoms of vomiting and was admitted in a hospital. It was noted that the patient was in the hospital due to an episode of gastroparesis. The healthcare professional reported that the patient was vomiting blood during the current hospitalization. No further complications were reported/anticipated.

C. TTEO between >1 year and < 5 years of implant. (N=3)

- A 20-year-old female reported by a consumer that the patient's battery only lasted a year and a half. The battery was replaced. There were no further complications that have been reported as a result of this event.

- A 21-year-old female reported by a healthcare professional regarding sudden severe shocking/jolting/burning in the location of the patient' stomach. It was noted that the issue started about 3 weeks ago and the doctor adjusted the INS and the patient had some relief, but the issue had worsened on the day of the report. The patient was redirected by the doctor to go to the emergency room for pain relief. Additional information was received that the device was interrogated, the parameters were changed to a rate of 28hz, 1s on and 4s off. However, it didn't help, the patient decided to turn off the device until she could see her doctor for an abdominal x-ray and possible pocket revision. The issue was not resolved at the time of the report. No further complications were reported/anticipated.

- A 21-year-old female reported by a healthcare professional regarding a device explant due to pain. The patient turned off her device for a month and felt better without the device, and her nausea and vomiting were manageable, so the device was explanted.

Additionally, there are three pediatric reports that the TTEO date was unknown. (N=3)

- A 13-year-old female reported by a consumer that the patient had an infection due to an injury to her stomach. It was reported that the patient was hit in her stomach, right in the gastrostomy tube, which caused the device leads to penetrate her stomach. The patient received intravenous antibiotic for her infection. The patient's gastroparesis was also getting worse. The reporter commented the device was a great device, but it was too fragile to run or play with. No further complications were reported or anticipated.

- A 20-year-old female reported by a consumer that a patient experienced shocking sensation from her device. Her doctor adjusted the device setting with no relieve of her symptom. The doctor then performed an omental coverage of the leads, but the

patient was still experiencing shocking sensation. There was no information provided regarding the next step of treatment.

- A 21-year-old female reported by a healthcare professional that the patient experienced nausea and shocking sensation with her device. The device was examined, and the battery was found dead. It was unknow if the battery discharge was due to a normal battery depletion. A device replacement is planned.

Characterizations of the Time to Event Occurrences (TTEO) in the adult and indeterminate age populations from May 1, 2018 – April 30, 2019

For the adult (N=176) and indeterminate age (N=29) populations with TTEO data, issues with the use of this device continue to occur most frequently after > 1 year up to < 5 years from the date of implant, followed by issues occurring ≤ 30 days in adult group, and between 31 days up to ≤ 1 year in the indeterminate group. In comparison to last year's analysis of reports for these TTEO groups, the same types of issues continue:

- Return of symptoms of nausea and vomiting and/or loss of therapeutic effect secondary to impedance issues or battery issues
- Pain and inappropriate simulation/shocking secondary to impedance or lead issues
- Infection, migration and erosion issues
- Electromagnetic compatibility/interference problem

In this current analysis, the common complaint of pain continues to occur because of inappropriate simulation/shocking as well as positioning/migration of the device or its components. The inappropriate stimulation/shocking, most often caused by device/lead positions, or setting of the devices; revision or coverage of leads or turn down the setting relieve the problems. Electromagnetic compatibility interference from medical testing (CT, Fiber Scanner) or medical procedures (kidney transplant, colon surgery) as well as patients encountering metal detection devices also caused abnormal shocking and unexpected decrease of therapeutical effects with the device.

Infection, migration and erosion issues also continued to occur as in the previous years' analyses. Infection was specifically mentioned in 20 MDRs, and typically occurred within the first three years of device placement with half of them occurred in the first year after device placement. Infection associated with the device or component (i.e. "pocket", "lead", "INS" and "battery") was found in 14 reports, while two (2) reports mentioned a urinary tract infection, one (1) report mentioned an infection with peritoneal dialysis, and the remaining three (3) reports did not mention site or cause of the infection.

Eight (8) reports noted lead erosion into stomach or through the skin, and one (1) report noted pocket erosion through the skin. The erosion occurred between two months and six years of implant. Two lead erosion MDRs also revealed intraabdominal abscess in connection with the leads by CT scan. Emergent explorations in both cases found leads eroded into stomach, and small bowel

severely thickened due to adjacent to intraabdominal abscess and required bowel resections. The entire device was completely removed in both cases.

Migration or expulsion of device were reported in 37 MDRs. Three (3) reports noted leads wrapped around patients' stomach; one (1) report noted leads wrapped around a patient's intestines and one of the leads had grown into the intestines, which led to bowel obstruction, a bowel resection was done, and the device was removed and replaced. Additionally, there is one (1) report stated a patient had small bowel obstruction from the leads, a surgical intervention was given to the patient, no further information was provided. The migration of device occurred between one month and five years of implant. Pain/shocking, nausea, and decreased therapeutic effects were reported symptoms of migration, and interventions involved remove and replacement of device to address these symptoms.

As noted in previous year, adult and indeterminate age patients continue to predominantly experience nausea and vomiting with decrease in therapeutic effectiveness. Thirty-three (33) MDRs discussed battery depletion (2 reports cited normal battery depletion) which lead to patient complaints of "therapy effectiveness, decreased". These continue to occur from four months after placement to six years, average 2.7 years with typical resolution noted as reprogramming or replacement of the battery and/or leads. There was one (1) report noted a patient had nausea, abdominal pain and distension after reprogramming, later the patient was found to have bowel volvulus and ischemic bowel, a right-side hemicolectomy was done. The physician of the patient did not feel that the volvulus was connected to the device programming.

Review of Death Report (N=1)

There is one (1) report of patient death in this year's analysis. One (1) report involved a 68-year-old patient originally submitted from a legal representative of the patient, who was implanted with an implantable neurostimulator for gastric stimulation. After the patient was implanted with a stimulator on October 31, 2016, the patient developed complications related to the device. The representative stated the "stimulator was in a defective condition and unreasonably dangerous for its intended or expected use and posed a risk of serious harm to the patient and others," to which the patient was never warned about. The representative stated, "the patient sustained injuries resulting in multiple harms (including physical pain, mental suffering, mental anguish, permanent injury, and permanent impairment of the power to labor and earn money), losses, and death due to complications related to the stimulator (on or about May 4, 2017)." There was no information to confirmatively conclude the cause of death. The device was not returned to the manufacturer for evaluation.

Most Commonly Reported Patient Problem Codes (PPC)[1]

Table 6 below provides the most prevalent reported patient problem codes found in the MDRs reviewed during this year's analysis, differentiated by patient age. The top reported patient

[1] The total PPC does not equal the total MDR count since one MDR might have multiple patient problems. Patient problem codes indicate the effects that an event may have had on the patient, including signs, symptoms, syndromes, or diagnosis.

problem code continues to be Vomiting and Nausea, as seen in previous analyses and is still often characterized as related to changes in device impedance or battery problem. In the current analysis period, there was no change in the use of the code “No known impact or consequence to patient” (n=81) and “Therapeutic Response, Decreased/Paresis (n=57), as compared to prior analysis period. Complaints of pain and the more general “Malaise”/ “Complaint, Ill-defined, remain unchanged in relative ranking from last year’s analysis. Overall, the top patient problems present nothing significantly new as compared to prior analysis period, and 253/305 reports continue to state the device was not returned for evaluation. However, there are 2 MDRs in the current analysis period in which the leads become entangled in the bowel of the patients that caused bowel obstruction. Each of these events involved migration of the device components. Additionally, one report noted a bowel volvulus and ischemic bowel after device reprogramming. However, the physician of the patient did not feel that the volvulus was connected to the device reprogramming.

TABLE 6: Most commonly reported patient problem codes received by patient age

Patient Problem	Total Patient Problem Code in MDR	Total Patient Problem Code in MDR by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to 21)	Adults (≥ 22)	Indeterminate (Age blank)
Vomiting/ Nausea	105	1	3	83	18
No known impact or consequence to patient***	81	0	1	33	47
Pain/ Discomfort/ Pain, Abdominal	80	0	3	57	20
Complaint, Ill-Defined*/Malaise	80	1	2	63	14
Therapeutic Response, Decreased/Paresis	57	1	1	45	10
Electric Shock/Nerve Stimulation, Undesired	56	0	3	46	7
Therapeutic Effects, Unexpected**	43	0	2	29	12
Infection/ Wound Dehiscence	27	2	0	19	6
Erosion	9	0	0	6	3
Weight Fluctuations	8	0	0	7	1
Total Patient Problem Code Count	546	5	15	388	138

Note: The total MDR Occurrences does not equal the total MDR count since one MDR might have multiple patient problems.

**MDRs coded with "Complaint, Ill-Defined" often included reports of nausea and/or vomiting.*

***MDRs coded with "Therapeutic Effects, Unexpected" typically involved issues of the device not operating as the patient anticipated.*

****A code of "No Known Impact or Consequence to Patient" indicates that while a device behavior may have been identified in the*

report, the manufacturer or reporter did not report any patient impact or consequence because of the reported device behavior.

Most Commonly Reported Device Problem Codes (DPC)[2]

Table 7 below provides the most commonly reported Device Problems for all MDRs differentiated by patient age. The top 2 reported device problem codes used in this analysis period are new device codes, “Insufficient information” (n=70) and “Adverse event without identified device or use problem” (n=65). The change to new device codes is associated with discontinuance of some previous device codes, such as “Device operates differently than expected”, which was the top reported device problem code in the last three years. There was an increase in the use of the code “Inappropriate shock” to rank the third (n=50), as compared to prior analysis period (ranked the fifth). “High”/ “Low impedance"/ “Impedance issues”/ “Unstable” continues as in the prior analysis period to rank the fourth (n=42). There was a decrease in the use of code “Energy output problem”/ “Failure to deliver energy” (n=39), and “Battery problem”/ “Premature Discharge of battery”/ “Low battery issue” (n=37) compared to prior analysis period. Additionally, there is another new device code of “Patient device interaction problem” (n=17).

A review of reports found that the device problem code “Insufficient information” was commonly associated with a device not properly functioning but did not provide a detailed information of the malfunction, most of the corresponding patient problem code is “No known impact or consequence to patient”. Adjustments to the device, its placement, and replacement of the leads or battery were the interventions used for the patients. The reports with “Adverse event without identified device or use problem” related to patient issues in which the device is functioning as expected but the patient has an infection, pain, complain ill-defined, or device intolerance issues.

The device problem codes “Energy output problem”/ “Failure to deliver energy are related to nausea, vomiting, shocking, and decreased therapeutic effect issue; “Battery problem”/ “Premature Discharge of battery”/ “Low battery issue”, “High”/ “Low impedance"/ “Impedance issues”/ and “Unstable” are associated with reports of low impedance or battery issues. The reports of “Inappropriate Shock” typically involved the position of device, battery depletion or electromagnetic compatibility/interference. The reports of “Patient device interaction problem” are related to positional shocking, patient falls and/or trauma to the device site. Reprogramming, replace or revision of device are interventions for the patients. As noted previously in the patient problem section, 253/305 reports state the device was not returned for evaluation.

[2]The total DPC does not equal the total MDR count since one MDR might have multiple patient problems. Device problem codes describe device failures or issues related to the device that are encountered during the event.

TABLE 7: Most commonly reported device problem codes received by patient age

Device Problem	Total Device Problem Code in MDR	Total Device Problem Code in MDR by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to 21)	Adults (≥ 22)	Indeterminate (Age blank)
Insufficient information	70	0	2	37	31
Adverse event without identified device or use problem	65	2	1	40	22
Inappropriate shock	50	0	3	40	7
High/Low impedance/ Impedance issues/Unstable	42	0	0	24	18
Energy output problem/failure to deliver energy	39	0	0	35	4
Migration or expulsion of device	38	1	0	24	13
Battery problem/ Premature Discharge of battery /Low/Battery issue	37	0	2	21	14
Electromagnetic compatibility issue/ Electromagnetic interference (EMI)	20	0	0	18	2
Patient device interaction problem	17	1	0	15	1
Break/Device or Device Fragments Location Unknown/	14	0	1	9	4
Total Device Problem Code Count	378	4	8	254	112

Note: The total MDR Occurrences does not equal the total MDR count since one MDR might have multiple device problems.

Discussion of Pediatric Patient Problem as it relates to Device Problem Information

Table 8 identifies the MDR occurrences of the top patient problems and issues in pediatric patients only, in comparison to the prior analysis period's findings.

TABLE 8: Clinical events identified with pediatric patients - year-to-year comparison*

Clinical Events	Occurrences in MDRs** 5/1/2018 – 4/30/2019	Occurrences in MDRs** 5/1/2017 – 4/30/2018	Occurrences in MDRs** 5/1/2016 – 4/30/2017
Nausea/Vomiting [Complaint ill- defined]	6	15	9
Therapeutic Response, unexpected/Paresis	4	3	5
Pain/Discomfort/ Abdominal pain/ Burning sensation	3	6	6
Electric Shock/Nerve Stimulation, Undesired/ [Inappropriate Electric Shock]	3	3	0
Infection	2	0	3

*Only the most observed patient problems and issues in pediatric MDR narratives are included.

**The total MDR Occurrences does not equal the total pediatric MDR count (n= 9) since one MDR might have multiple clinical events.

As in the prior analysis period, the clinical events for the nine (9) pediatric MDRs found in this analysis also involve complaints of nausea, vomiting, pain, and shock, corresponding to the device issue of "Therapeutic Response, unexpected"/ "Paresis", and high impedance. There is a clinical event of infection that was not listed in the prior year analysis. These complaints and device problems are most often due to battery and lead issues. Adjustments of the device settings, battery replacement, hospitalization, reposition and revision of device, and explant of stimulators were the noted interventions.

Re-Interventions in Pediatric Patients from 5/2018 through 4/2019

Re-interventions addressing types of clinical events reported above are listed below in Table 9. This table summarizes the re-interventions identified in the narratives and the causal events leading to these re-interventions.

TABLE 9: Re-interventions in pediatric patients* (5/2018 -4/2019)

Re-Interventions	Number of Re-Interventions	Causal Event
Replacement/Repositioning • Device or Battery	3	• Shocking/burning • Battery depletion
Explant • Device or INS	2	• Infection • Pain
Reprogramming/ Calibration	4	• Loss of therapeutic effect • Shocking/jolting/burning
Hospitalization/Emergency room	3	• Infection • Loss of therapeutic effect • Pain/discomfort • Vomiting/hematemesis
Surgery (gastrostomy) /Feeding tube	1	• Loss of therapeutic effect • Nausea/vomiting/poor intake
Office follow-up treatment	3	• Impedance issues • Discomfort/poor intake

*Note that the total counts do not equal the number of MDRs since one MDR might have multiple noted re-interventions.

** Temporary involves the mention of temporary removal of the device and has no comment of actual replacement in the report.

Conclusions Based on MDR Review

- There have been 9 pediatric (out of 305) MDRs submitted for the Enterra Therapy System between May 1, 2018 and April 30, 2019. Of these, 6 were injury events, and 3 were device malfunction events.
- The Time to Event Occurrence (TTEO) was calculated for 211(out of 305) MDRs based on the available information contained in the reports, including 6 out of 9 pediatric reports. Review of the pediatric reports with TTEO showed:

- Two (2) pediatric patients (ages 3&19), had a TTEO of less than 30 days of implant.
    - One (1) had removal of an INS due to an infection. The leads were still implanted.
    - One (1) had persistent nausea/vomiting and poor intake. The device stimulation voltage was increased but was not able to effectively manage the patient's gastroparesis. The patient also has increased frequency of bowel movement. The device stimulator was turned off for an upcoming placement of a decompression gastrostomy and feeding jejunostomy.

- One (1) pediatric patient (age 17), had TTEO occurrence of 31 days to 1 year of implant.
    - One (1) was admitted in a hospital due to an episode of gastroparesis. The healthcare professional reported that the patient was vomiting blood during the current hospitalization.

- Three (3) pediatric patients (ages 20 & 21), had TTEO of 1 to 5 years of implant.
    - One (1) had a premature depleted battery. The battery was replaced.
    - One (1) had sudden severe shocking/jolting/burning in the location of the patient' stomach. The doctor adjusted the INS and the patient had some relief, but the issue became worse again. The doctor redirected the patient to go to the emergency room for pain relief. The patient decided to turn off the device until she could see her doctor for an abdominal x-ray and possible pocket revision.
    - One (1) had a device explant due to pain.

Additionally, there are three (3) pediatric reports (ages 13, 20 &21) that the TTEO date unknown. (N=3)

- One (1) had an infection due to an injury to her stomach. The patient was hit in her stomach, right in the gastrostomy tube, which caused the device leads to penetrate her stomach. The patient received intravenous antibiotic for her infection. The reporter commented that the device was a great device, but it is too fragile to run or play with.
- One (1) experienced shocking sensation from her device. The device setting was adjusted but no relieve of symptom. The patient then had an omental coverage of the leads but was still experiencing shocking sensation.
- One (1) experienced nausea and shocking sensation from her device. The device was found to have a depleted battery. It is unknow if the battery

depletion was due to a normal battery depletion. A device replacement was planned.

- The most common reported pediatric patient problems share similar complaints as identified in previous year's analyses:
    - "Nausea"/ "Vomiting", and two patients required hospitalization, and one of them required gastrostomy and jejunostomy feeding to solve the problem.
    - "Unexpected"/ "Decreased Therapeutic Response"/ "Paresis".
    - "Pain"/ "Discomfort" associated with shocking, return of symptoms and impedance changes.
    - "Infection"
- Device Problems in pediatric patients are slightly different from the previous two (2) analysis periods, with the most frequently reported device problem being: "Inappropriate Shock", that was associated with complaints of "pain", "shocking sensation", and "low therapeutic effect". Adjustments to the device impedance settings, repositioning of device or replacement of the battery resulted in relief of some complaints.
- Reports continue to identify other underlying device functionality issues with the device lead (i.e. misconnection, break, migration or malfunction) in addition to battery depletion issues.
- The manufacturer's evaluations of the various device issues were hindered due to devices not being returned in most cases (253 of 305 MDRs).

As in prior analysis period, complaints of return of symptoms (nausea, vomiting), decreased therapeutic effect, as well as incidences of shocking, appear to center around malfunctions with leads and/or connection issues involving the leads.

- Overall, the Patient Problems and Device Problems observed among pediatric patients were similar to those observed in adult patients.
- The types of adverse events being seen in the current analysis period are consistent with what has been observed in prior analysis periods, with some exceptions. There was one (1) report describing volvulus, ischemic bowel and a right-side hemicolectomy in an adult patient after a recent device reprogramming. Additionally, three (3) reports noted leads wrapped around patients' stomach; one (1) report noted leads wrapped around a patient's intestine, one of the leads had grown into the patient's intestines and led to a bowel obstruction; and one (1) report noted a small bowel obstruction from the leads. A bowel resection was performed in two reports, four reports stated the device was removed and replaced. These problems were not reported in any of the pediatric reports.

LITERATURE REVIEW
LITERATURE REVIEW

Purpose

A systematic literature review was conducted to evaluate the safety and probable benefit of Enterra gastric electrical stimulator (GES) for any indication in the pediatric population (<22 years old). This is an update from the literature reviews presented at the Pediatric Advisory Committee (PAC) meetings on September 23, 2014, September 16, 2015, September 14, 2016, and September 12, 2017, and September 23, 2018. Specifically, the literature review was conducted to address the following questions:

1. What is the probable benefit of Enterra for the following clinical endpoints: improvement in upper GI symptoms; reduction in need for nutritional support; and improved gastric emptying time (GET)?
2. What adverse events are reported in the literature after treatment with Enterra?

Methods

On June 10, 2019, a search in PubMed and Embase was performed using the following search terms:

- PubMed
  “Enterra” OR "gastric electric stimulation" OR "gastric electrical stimulation" OR "gastric electrostimulation" OR "gastric pacemaker" OR "gastric pacing" OR (stimulation AND gastroparesis) OR “gastrointestinal neuromodulation”
  Filters: Publication date from 2018/05/01 to 2019/04/30; Humans; English

- Embase
  (enterra OR 'gastric pacemaker'/exp OR 'gastric electrical stimulation'/exp OR 'gastric electric stimulation' OR 'gastric electrostimulation' OR 'gastric pacing'/exp OR '(stimulation and gastroparesis)' OR 'gastrointestinal neuromodulation') AND [humans]/lim AND [english]/lim AND [2018-2019]/py

The search was limited to studies published from the last PAC meeting update (May 1, 2018 and April 30, 2019), in human subjects, and in the English language. This search yielded a total of 85 citations (22 in PubMed and 63 in Embase). After a review of titles, abstracts, and full text, 2 articles were selected for full epidemiological review and assessment. (see Figure 1. Article Retrieval and Selection).

Results

In the two articles selected in this review, the studies may have included pediatric or adolescent patients. These papers were included in this review to be as inclusive as possible, given the limited literature on Enterra. Because these studies included adult subjects along with possible pediatric subjects, it is not clear if safety and probable benefits derived by the mixed cohort were experienced specifically by pediatric subjects. However, these papers were included in this review to be as inclusive as possible, given the limited literature on Enterra.

Probable Benefit Results

The study by Shada et al. [1] is a retrospective analysis of data collected prospectively from patients with medically refractory gastroparesis of idiopathic or diabetic origin undergoing implantation of the Enterra gastric electrical stimulation (GES) to initiate gastric electrical stimulation therapy at two Wisconsin institutions from October 2005 to June 2017. The objective of the study was to assess improvement in the Gastroparesis Cardinal Symptom Index (GCSI) scores following GES treatment. The study population consisted of 64 diabetic patients (23 males, 41 females) with a mean age 46 ± 12 years and 55 idiopathic patients (6 males, 49 females) with a mean age 44 ± 14 years. Based on how age was reported in the paper (as mean ± SD), it is unclear how many pediatric subjects were included if any, or what the characteristics or outcomes of the pediatric patients were. Patients with postsurgical gastroparesis attributable to presumed vagal nerve injury were excluded. All patient had been diagnosed clinically with idiopathic or diabetic gastroparesis with documented delayed gastric emptying on a nuclear medicine gastric emptying study, and all had persistent symptoms despite medical therapy with prokinetic medications. Delayed gastric emptying was defined by a half time of gastric emptying that exceeded 120 minutes, percent of radionuclide tracer retained at 2-hours of >60%, or percent retained at 4 hours of >10%. Gastric emptying studies were repeated 6 months postoperatively in all patients during the early portion of this clinical series; and discontinued later in the series due to poor correlation with the results gastric emptying studies and symptomatic outcomes. These data were collected retrospectively at the time of this study via chart review of the medication list (reconciled at the time of the clinical encounter) and by telephone follow-up. A total of 119 patients received gastric electrical stimulation therapy. Patient demographics and details about previous treatments for gastroparesis were recorded prospectively in the GES study files of each institution. All devices were placed laparoscopically. Mean follow-up time was 34.1 ± 27.2 months in diabetic and 44.7 ± 26.2 months in idiopathic patients.

For the Shada et al. [1] study, gastroparesis-related symptom severity and quality of life were assessed with the validated GCSI, which consists of 9 variables and 3 subscales: nausea/vomiting, fullness/early satiety, and bloating/distention. A score of 0 for an individual variable is consistent with no symptoms, and a score of 5 is consistent with very severe symptoms. The scores for the 9 questions in the GCSI are added to create an instrument with a scoring range of 0 to 45, with a lesser score indicating a more favorable response. Satisfaction with the outcomes of GES treatment was assessed on a 5-point Likert scale, with a score of 1 consistent with “extremely dissatisfied” and 5 consistent with “extremely satisfied”. Surveys were administered at the preoperative visit and gathered post-implantation at 6 weeks, 6 months, 1 year, and annually thereafter, up to 5 years. If a patient was lost to clinical follow-up for greater than 1 year, surveys were conducted via telephone interview. During the initial 5–6 years of this clinical series, a non-validated symptom survey was administered to assess 6 symptoms on a 4-point Likert scale before implantation of the GES. The GCSI survey was administered to 24% of patients before implantation. One year after implantation, 24.3% of patients completed this assessment; at 2 or more years postoperatively, 28.6% of patients completed the survey. GCSI scores did not differ for diabetic or idiopathic patients at any interval. Patients with gastroparesis related to both indications experienced significant improvements in GCSI scores

compared with preoperatively at both 1 and 2 or more years after implantation. Overall satisfaction with the GES was determined to be 4.1 on a 5-point Likert scale. Satisfaction was reported as 3.9 out of 5 in diabetic patients (assessed at a mean of 32 ± 26 months postimplant) and 4.4 out of 5 in idiopathic patients (67 ± 49 months postimplant). From the entire cohort, 23.5% provided satisfaction ratings (22% of diabetic patients and 26% of idiopathic patients). Before GES placement, operatively placed feeding tubes were present in 22% of diabetics and 17% of idiopathic patients ($P = .37$). After GES placement, 67% of feeding tubes were removed. In diabetic patients, gastric emptying half time T½ was reduced (297 ± 127 minutes vs 119 ± 35 minutes; $P = .03$); in contrast, gastric emptying T½ was unchanged in patients with idiopathic gastroparesis (232 ± 111 minutes vs 183 ± 187 minutes, $P = .24$). Gastric emptying times normalized with GES in 36% of diabetic and 15.3% of idiopathic patients.

The objective of the prospective study by Abell et al. [2] was to assess the effects of both temporary and permanent gastric electrical stimulation on inflammatory, autonomic, entric, electrophysiologic, and hormonal entities in diabetic and idiopathic patients. Patients above 18 years of age with persistent symptoms of gastroparesis for at least 6 months, and refractory to anti-emetic and prokinetic therapies, were selected consecutively; however, it is unclear how many adolescent subjects were included, or what the characteristics or outcomes of the adolescent patients were. The 41 gastroparetic subjects receiving temporary GES for 5-7 days consisted of 13 males and 28 females, mean age 45.7 years; 21 diabetic, 20 idiopathic. Thirty-six of those patients (9 males, 21 females; mean age 43.1 years; 14 diabetic, 16 idiopathic) were implanted and 30 were followed up at 6 months after permanent GES. The 43 patients who underwent permanent GES placement consisted of 15 males and 28 females, mean age 46.3 years; 23 diabetic, 20 idiopathic. Temporary stimulation patients who were then implanted and returned for six-month follow-up were included in the permanent phase of the study. Permanent gastric electrical stimulation was performed by mini-laparotomy. Patient symptoms were measured by two methods: a traditional patient-reported outcome (PRO) and the gastroparesis cardinal symptom index (GCSI) and were repeated after temporary and permanent GES. A daily traditional PRO-based GI symptoms diary was used for 5-7 days at which time, repeat gastric emptying tests, electrophysiology, and patient symptoms diaries were reviewed.

For the Abell et al. [2] study, results for the temporary and permanent gastric electrical stimulation (GES) are reported first in sequence and then by improvement status. In this group of patients, GES both early and late effects were evaluated. Early changes are those that occur by the measures taken during the temporary GES implantation and persist and are durable and sustained at the permanent GES follow-up visit. Late changes are those changes that occur only at the six-month perm GES follow-up visit. Other changes include rebounding effects where measures significantly change at temporary GES but return to baseline levels by permanent GES six-month follow-up. Overall, patient symptoms improved with both temporary and permanent GES by both symptom scoring measures. The effects occurred early, during temporary GES, and continued through permanent GES. Importantly, nausea and vomiting were significantly improved from baseline. When measured by the GCSI scale, nausea reduced from a baseline level of 3.5 to 1.7 and 2.6 at temporary GES and permanent GES, respectively. Similarly, GCSI vomiting scores reduced from the baseline level of 2.4 to 0.6 and 1.8 at temporary GES and permanent GES, respectively. The direction and magnitude of the changes were also reflected in the traditional PRO scale with similar findings. Symptom responses did not differ by diabetes status at any time point for either scale. However, idiopathic patients experienced a significant, non-persistent drop in GCSI bloating scores at temporary GES (baseline: 3.9, temporary GES: 1.7, permanent GES: 3.3) which was not as pronounced in diabetic patients (baseline: 3.4, temporary GES: 1.9, permanent GES: 2.6). Similarly, the reduction in GCSI score for appetite loss was greater in diabetic patients, while the reduction in GCSI scores of total satiety, nausea, anorexia, and total symptoms was greater in idiopathic patients. The prokinetic effect, as measured by gastric emptying, was found for patients that had any delayed emptying and started early and continued. In patients with any delay, total liquid emptying significantly decreased from 94% at baseline to 52% and 58% for temporary GES and permanent GES, respectively; baseline total solid emptying decreased from 152% to 105% and 100% for temporary GES and permanent GES, respectively.

Safety Results

In the Shada et al. [1] study, a total of 8 patients opted to have their GES device removed because of a perceived lack of benefit at a mean time interval of 36 ± 29 months after implantation. Of these 8 patients who had the device removed, 3 underwent total gastrectomy at the same time. Additional operative procedures related to gastroparesis after the initiation of GES in the cohort included 4 patients who had a new feeding jejunostomy tube replace, and 2 patients who underwent a pyloroplasty. A total of 18 patients were known to have died during the study interval (15.1%). Mortality rates were greater in patients with diabetes (25% diabetic vs 3.6% idiopathic) at a mean interval of 17 ± 3 months (OR = 9.6; 95% CI 2.1–44.2; $P = .001$). No mortalities were device related. The causes of death in the patients with diabetic gastroparesis were listed as cardiac arrest/myocardial infarction in 5, hypoglycemia in 1, cerebrovascular accident in 1, and unknown causes in the remaining 9 patients. The 2 patients with idiopathic gastroparesis who died during the study interval died from unknown causes.

The Abell et al. [2] study did not report on device related adverse events.

CRITICAL ASSESSMENT OF THE LITERATURE

The current systematic literature review includes 2 articles, both studies reported an improvement in GI symptoms and reduced gastric emptying times. Regarding the need for nutritional support, Shada et al. [1] reported that before GES placement, operatively placed feeding tubes were present in 22% of diabetics and 17% of idiopathic patients ($P = .37$). After GES placement, 67% of feeding tubes were removed. Abell et al. [2] reported a reduction in GCSI scores for appetite loss and anorexia following GES treatment by Enterra. The mortality rate reported in the Shada et al. [1] study is higher (18 patients, 15.1%) than the studies included in previous years' results; however, deaths in this study were attributed to diabetic complications and were not device related. The Abell et al. [2] study did not report on adverse events or mortality rates following GES. Overall, the probable benefit of the Enterra device as reported in these articles are consistent with what has been reported previously.

The results of this systematic literature review should be interpreted considering key limitations. First, our review only included two papers for which it could not be confirmed or excluded that these studies included pediatric patients because of the way patient age was reported. However, these papers were included in this review to be as inclusive as possible, given the limited literature on Enterra. Secondly, common study limitations, including retrospective study design, small sample sizes, and short follow-up duration are present in these studies. The Shada et al. [1] study was limited in that not all patients were administered the GCSI before GES, and a number of patients at both institutions were lost to follow-up. In addition, the Shada et al. [1] study is a retrospective review of a multi-institutional case series, which has its own limitations, such as different referral patterns, selection criteria, and perioperative protocols. The Abell et al. [2] study was limited by sample size, lack of a controlled arm, and a short follow-up duration. In addition, Dr. Abell's disclosure indicates that he has been an investigator for Medtronic which may introduce conflict of interest.

Because these studies included adult subjects along with possible pediatric subjects, it is not clear if safety and probable benefits derived by the mixed cohort were experienced specifically by pediatric subjects. Despite the favorable results demonstrating probable benefits of Enterra therapy, these study design factors limit the generalizability of the results to the pediatric patients at large for treatment of gastroparesis.

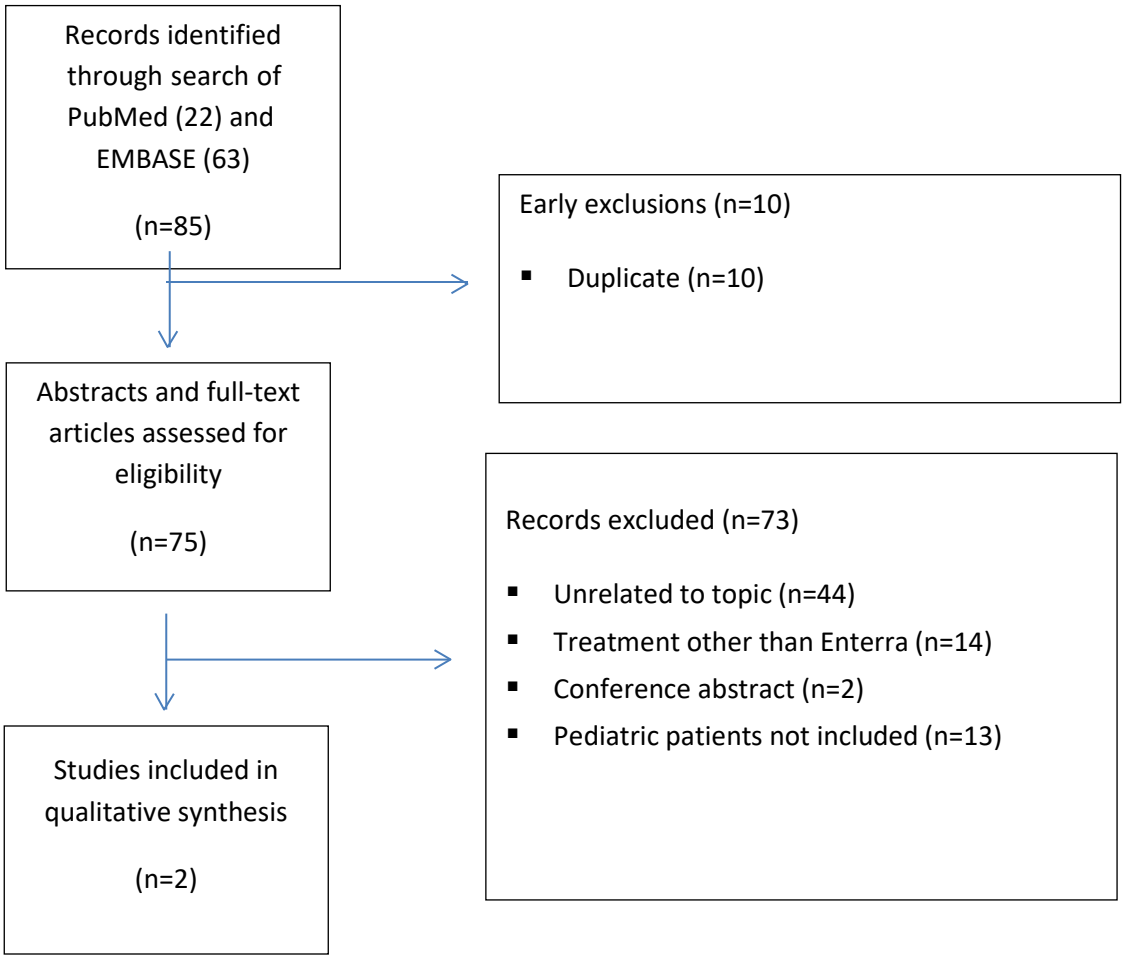
CONCLUSION

Our systematic literature review revealed limited data with regards to the safety profile of the Enterra device. Only one of the included articles, Shada et al. [1] reported limited adverse events. Therefore, we are unable to determine if safety concerns are comparable to previous years' systematic review results**.** Additionally, based on how patient age was reported in these studies, it was not clear if pediatric patients were included.

The studies suggest probable benefits of Enterra with respect to improvement in long-term gastroparesis symptoms and quality of life. In the Shada et al. [1] study, patients reported high degree of satisfaction with the symptomatic outcomes of treatment. When in place, feeding tubes could often be removed with successful treatment. The Abell et al. [2] study suggests that both temporary and permanent gastric electrical stimulation may improve symptoms and physiology of GP by several possible mechanisms. Despite possible reduction of symptoms, some patients with GP who are implanted with Enterra may experience device-related adverse events that require additional surgery. The findings of this systematic literature review should be interpreted considering the insufficient evidence reported in terms of inadequate number and quality of papers with adequate sample size of pediatric patients and long-term follow-up. These factors limit our ability to make any firm conclusions about the probable benefits and safety of Enterra in the pediatric population.

These findings are consistent with results of the Enterra systematic literature reviews that were presented at the PAC meetings on September 23, 2014, September 16, 2015, September 14, 2016, September 12, 2017, and September 23, 2018.

Figure 1. Article Retrieval and Selection



REFERENCES

1. Shada, et al. Wisconsin's Enterra Therapy Experience: A multi-institutional review of gastric electrical stimulation for medically refractory gastroparesis. Surgery, October 2018; Volume 164, Issue 4, pages:760-765.

2. Abell, et al. Gastroparesis syndromes: Response to electrical stimulation. Neurogastroenterology & Motility, 2019 31:3 Article Number e13534

OVERALL SUMMARY

The FDA did not identify any new safety signals during this review of the Enterra annual report received, the MDRs received, and the peer-reviewed literature published since our last report to the PAC.

The FDA believes that the HDE for this device remains appropriate for the pediatric population for which it was granted. The FDA will continue to implement the PAC's recommendations in addition to our routine monitoring of the safety and distribution information for this device.