FDA Executive Summary

Prepared for the
September 23, 2014 meeting of the
FDA's Pediatric Advisory Committee

H990014

Enterra® Therapy System

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I. INTRODUCTION

In accordance with the Pediatric Research Equity Act (PREA), this review provides a safety update based on the post-marketing experience with the use of the Enterra® Therapy System in pediatric patients since approval in 2000. The purpose of this review is to provide the Pediatric Advisory Committee with post-marketing safety data so the committee can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This memorandum will include summaries of the pre-market clinical study, post-market medical device reporting (MDR) for adverse events, and the peer-reviewed literature regarding safety data associated with the device.

The Enterra gastric electrical stimulator (GES) is a first-of a-kind surgically implanted device used to treat gastroparesis. Gastroparesis ("stomach paralysis") is a chronic neuromuscular motility disorder which is characterized by delayed gastric emptying in the absence of mechanical obstruction, abdominal pain, bloating, severe nausea, vomiting, malnutrition, and fluctuations in serum glucose levels in patients with diabetes. In addition to gastroparesis of diabetic or idiopathic origin, there can be several other causes for gastroparesis, including complications from surgery (postsurgical gastroparesis), pancreatic carcinoma and other types of malignancies, gastrointestinal dysmotility syndromes with autoimmune bias, and autonomic neuropathies and other neurologic disease conditions that impact gastric function (e.g., Parkinson's disease). In the case of idiopathic or diabetic etiologies, there is usually abnormal peristaltic contractile activity. Medical interventions include pharmacotherapy to enhance gastric emptying and reduce nausea and vomiting, dietary modifications, and enteral or parenteral nutrition. Only one drug, metoclopramide, is currently approved for prokinetic treatment of gastroparesis. There is evidence in the medical literature that patients with chronic, symptomatic gastroparesis have clinically significant symptoms that can impact survival. There are currently no other devices available that are indicated for the management or treatment of gastroparesis refractory to standard medical interventions. Benefits cited for Enterra therapy include reductions in nausea and vomiting, and improvements in quality of life. The mechanisms by which the gastric electrical stimulator works are not well understood, but may involve indirect neuromodulation of parasympathetic nerves and/or ganglia which regulate gastric function.

This memorandum summarizes the safety data regarding H990014 through the present day. These topics will include the pre-market clinical study history, post-market medical device reporting (MDR) for adverse events, and peer-reviewed literature regarding safety data associated with the device.

II. BRIEF DEVICE DESCRIPTION

The Medtronic Enterra Therapy System for gastric electrical stimulation (GES) is indicated for use in the treatment of chronic, intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology. The device consists of the following:

1. Model 3116 Neurostimulator (Model 7425G Neurostimulator was obsoleted). The original neurostimulator was the Itrel III Model 7425G pacemaker that was previously approved for an indication to treat intractable pain of the trunk or limbs (approved under P840001). The Model 3116 Neurostimulator is placed in a subcutaneous pocket in the abdomen, and has pacemaker functions in delivering electrical pulses to the stimulation leads. The Neurostimulator contains a sealed battery and electronic circuitry.

2. Implantable, unipolar intramuscular leads. Two leads are implanted via laparotomy or laparoscopy into the muscularis propria, approximately 1-2 cm apart, on the greater curvature at the limit of the corpus-antrum. The initial lead originally used with the Enterra GES was a Medtronic Model 4300 lead with polyurethane insulation and sliding sheath. This lead has been replaced with the Medtronic unipolar Model 4351 lead, which has a polyurethane insulation and flexible platinum:iridium electrode coil, and a 10-mm electrode that is mechanically connected to the coil. When connected to the Neurostimulator, the lead delivers electrical pulses to the stomach muscle, and can be configured in the either unipolar mode (neurostimulator case with positive charge, leads with negative charge) or bipolar mode (neurostimulator case off, one or more lead electrodes positive). The leads connect to the sockets in the connector block of the Neurostimulator.

   In 2009, there was a Class I recall of the Model 4351 lead, notifying healthcare professionals of the risks of bowel obstruction and/or perforation of the bowel (worldwide incidence, 0.4%), that could lead to necrosis and infection in some cases.

3. External clinician programmer. The programmer originally employed the Model 8840 N'Vision Programmer and Model 8870 Software Application Card (Model 7432 programmer and Model 7547 Memory Module Software Cartridge are now obsolete). The software has been modified to incorporate the Model 8840 N'Vision Programming System. The Clinician Programmer includes "nominal" parameter programming to automatically set the stimulation parameters to standard settings that were utilized during clinical trial.

Standard stimulation parameters are the following:

1. Amplitude, voltage was adjusted to maintain 5 mA stimulus intensity
2. Pulse width, 330 μS
3. Frequency, 14 pulses/S

4. Cycle ON, 0.1 S
5. Cycle OFF, 5

Schematics of the implantable components and placement are provided in the following figures:

Figure 1. Labeled schematics of the Enterra Therapy System neurostimulator and lead

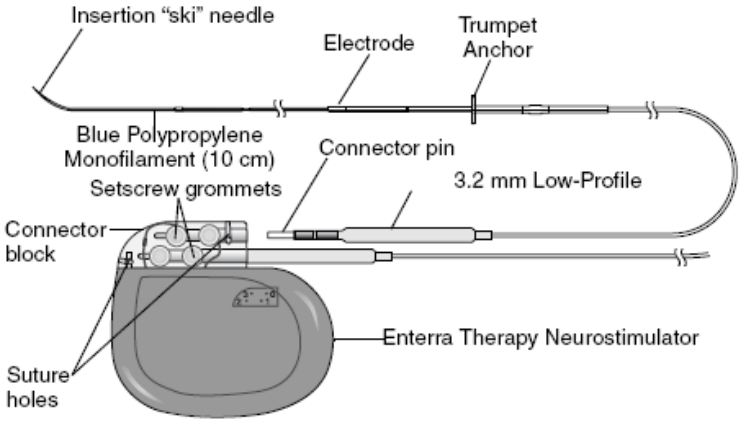
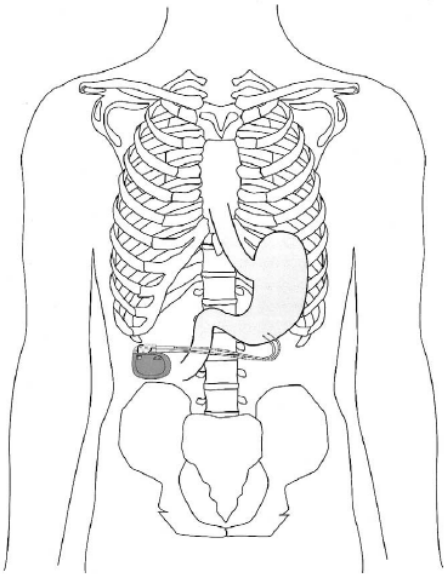


Figure 1. Lead Model 4351 with neurostimulator.

(reference, http://professional.medtronic.com/devices/enterra/leads-and-extensions/index.htm)

Figure 2. Schematic diagram showing placement of the implantable Enterra device components



Theory of operation

The Enterra GES was initially thought to improve symptoms of gastroparesis through delivery of electrical pulses to the stomach, which entrain and regularize gastric slow wave activity. However, it has been found that the low-energy, high frequency stimulation programs that are used do not directly lead to contraction of the smooth muscle (Islam et al, 2008). GES does not cause a predictable change in gastric myoelectric activity as measured by electogastrography (EGG) or demonstrable improvement in gastric emptying (Teich et al, 2013). It has been hypothesized that the mechanism of Enterra therapy may stem from neural communication along a vagal- cerebral pathway (Islam et al, 2008). Other theories include a role of GES in fundic relaxation, modulation of the autonomic nervous system, and/or affecting the release of gastrointestinal hormones, but these mechanisms remain unproven (Islam et al, 2008, Teich et al, 2013).

III. HUD DESIGNATION AND HDE APPROVED INDICATIONS FOR USE

1. HUD Designation

Gastric Electrical Stimulator

2. HDE Approved Indications for Use

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

IV. REGULATORY HISTORY

The regulatory history of the Enterra Therapy device spans the time period from 1994 to 2013 and includes feasibility and multicenter investigational device exemption (IDE) clinical trials, and a humanitarian device exemption (HDE). The clinical data used to support the HDE for the Enterra GES was compiled from clinical trials that were conducted under the IDE. An additional data set was collected under the HDE.

Investigational Device Exemption (IDE) Clinical Trials

G940061

The aim of this study was to evaluate whether gastric stimulation using the Model Itrel Model II improved gastric emptying of mixed solid-liquid or semi-solid meal. Efficacy in decreasing subjective symptoms of gastroparesis (nausea, vomiting, bloating, anorexia, early satiety and abdominal pain) while resulting in reduced patient medication was also examined.

17 patients, who failed less invasive procedures and all available medications whose only available alternative was parenteral nutrition, were enrolled.

Evaluated measures included gastric emptying test, gastric electrical activity, electrocardiogram, quality of life. Information concerning medication, nausea, and vomiting was collected.

Adverse events included, but were not limited to: high impedance, vomiting, nausea, lead dislodgement, abdominal pain, weight loss, infection, bloating, abdominal distention, deep vein thrombosis, sinus tachycardia, IPG inadvertently reprogrammed, broken leads, and chest pain.

Patients were followed monthly for the first year following implantation of the device. It was concluded that although GES at 4 times the basal rate improved symptoms and gastric emptying, further studies would be needed to identify the optimum frequency range and to identify which patients would benefit from gastric stimulation.

G960167

This Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS), was originally intended for a full PMA submission. However, the WAVESS study did not provide an adequate demonstration of efficacy. Rather than investing in an additional Phase II study, the Sponsor petitioned the FDA for HDE approval for the device. The primary endpoint of significantly reduction in weekly vomiting frequency was not met.

Humanitarian Device Exemption (HDE)

Medtronic, Inc. submitted a Humanitarian Use Device (HUD) application to the Office of Orphan Products. The HUD designation was given on September 23, 1999 (HUD #990014).

a) Compassionate Use Electrical Stimulation Study (CUESS, see H990014/R16) was approved in a letter dated August 11, 1999. This was an unblinded, open-label study of 49 gastroparesis patients, and was designed to provide gastric stimulation safety information. In a table of patient demographics, the sponsor notes that, of the 50 subjects enrolled in CUESS, 9 were described as "postsurgical (i.e., not an indicated use)." The sponsor reported improvements in device placement, and a reduction in adverse events.

b) Enterra Therapy Clinical Study
The study design entailed within patient analyses to determine the following:

i. primary endpoint, reduction in weekly vomiting frequency;
ii. secondary endpoint 1, reduction in symptoms of gastroparesis, including:

- Vomiting
- Nausea
- Early satiety
- Bloating
- Postprandial fullness
- Epigastric pain
- Epigastric burning

iii. secondary endpoint 2, long term (12 month) reduction in weekly vomiting frequency

Vomiting frequency was determined using patient diaries of vomiting episodes. The weekly average was normalized to the number of days recorded in the diaries. The sponsor reported that the secondary endpoint of long term (12 month) reduction in weekly vomiting frequency was statistically significant; and that the data from this study are consistent with safety and probable benefit of Enterra Therapy. Results of the study indicate that the primary endpoint was not attained.

On March 30, 2000, this humanitarian use device (HUD) was approved by the Division of Reproductive, Gastroenterology and Urology Devices within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration under Humanitarian Device Exemption (HDE) application H990014, which was the subject of this advisory panel meeting. Post-approval studies were not a requirement associated with approval of H990014.

The Indications for Use statement was the following:
Medtronic Enterra Therapy is indicated for the treatment of patients with chronic, intractable (drug-refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology.

Subsequently Medtronic requested a determination under 520(m)(6)(A)(i)(I) of the Federal Food, Drug and Cosmetic Act, as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA). FDASIA waives the profit restrictions on HDE devices, provided that the device is intended for treatment of pediatric patients or a pediatric subpopulation.

The Sponsor claimed that the subject device had an intended subpopulation of pediatric patients, and supported this claim by showing that the device labeling stated that the safety and effectiveness of the device had not been established in patients < 18 years of age. The FDA-approved Indications for Use of the Enterra did not identify a target population based on age. The Sponsor suggested that the age-related warnings implied that the device was intended to treat a subpopulation of pediatric patients (i.e., patients aged 18 – 21 years old). FDA agreed with the determinationan approvable letter was issued on January 18, 2013, informing the Sponsor that a revised Indications for Use of the subject device would be needed, in order to reflect the intended patient population by age. Full approval was issued for Amendment 1, in which the IFU was modified. .

The revised Indications for Use statement was the following:
Enterra Therapy is a gastric electrical stimulation system for the treatment of chronic intractable nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology in patients aged 18 to 70 years.

In March, 2013, Medtronic received full approval to begin selling the device for a profit, since the intended patient population includes a sub-population of patients aged 18 through 21 years of age.

V. BACKGROUND – GASTROPARESIS

Definition and Criteria

Alternative Treatments

Gastroparesis is a disorder defined by symptoms of and evidence for gastric retention or disordered gastric emptying in the absence of mechanical obstruction. The most common etiologies are diabetes mellitus, postviral illness, idiopathic, and postsurgical. Gastroparesis can also be secondary to systemic diseases such as amyloidosis, collagen tissue disorders such as scleroderma, neurological disorders such as Parkinson's disease, and myotonic dystrophy. Symptoms include nausea, vomiting, post-prandial fullness, early satiety, abdominal discomfort, bloating, anorexia, pain, and weight loss. (Gonzalez et al, Islam et al, 2008). Gastroparesis is stratified into 3 groups by severity of symptoms (mild, compensated, or gastric failure; Islam et al, 2008). Measuring the gastric emptying of solids is the mainstay for diagnosing gastroparesis. Scintiscanning carried out at baseline, 1, 2, and 4 hours after radiolabeled meal ingestion is considered the gold standard for measurement. Retention of over 10% of the meal after 4 hours is considered abnormal. (Gonzalez et al).

Mainstay therapies include dietary modification, prokinetic and antiemetic medications. Dietary

modifications usually include small, frequent, low-fiber and low fat meals. Prokinetics include metoclopramide, domperidone, and erythromycin. Antiemetics include phenothiazines, antihistamines, and serotonin antagonists. Patients with more severe and uncontrolled symptoms may require long-term or permanent enteral or parental support. Other alternatives have included endoscopic injection of botulinum toxin in the pylorus as well as surgical options such as pyloromyotomy, pyloroplasty, gastrostomy tubes for decompression, jejunal feeding tubes, and in extreme cases, partial or total gastric resection. (Islam et al 2008, Gonzalez et al).

VI. CLINICAL DATA USED TO SUPPORT HDE APPROVAL WITH A FOCUS ON SAFETY ISSUES

A. Background Regarding Clinical Studies

1. Worldwide AntiVomiting Electrical Stimulation Study (WAVESS, reported in G960167).

For this study, clinical data were obtained from 27 patients enrolled at 11 centers. Eligible patients who were enrolled:

- Had symptomatic gastroparesis ≥ 1 year, as documented by a specialized Gastric Emptying Test (GET)
- Were refractory or intolerant to at least two anti-emetic, and two prokinetic drugs;
- Had > seven vomiting episodes /per week.

The primary effectiveness objective of the study was to determine if there was a reduction in weekly vomiting frequency (WVF) with the device ON. The secondary objective of reduction in symptom frequency scores assessed vomiting, nausea, early satiety, bloating, postprandial fullness, epigastric pain, and epigastric burning. There were 2 phases to this study:

Phase I was designed as a 2-month, randomized (1:1), placebo controlled, double blind on-off cross-over study to evaluate the safety of the device, and the effectiveness of the Enterra therapy in significantly reducing vomiting in patients who have been diagnosed with gastroparesis of diabetic or idiopathic etiology. Patients with drug-refractory gastroparesis were eligible if they were responsive to temporary percutaneous stimulation system (temporary pacing leads connected to and external pulse generator) as determined by gastric emptying test results. A positive response was classified as a 50% improvement in half gastric emptying time, or a reduction in nausea and vomiting of at least 80%. Thirty-three patients, including 17 with diabetic and 16 with idiopathic forms of gastroparesis, were enrolled, including 27 at centers within the US, and 6 at centers located in Canada and Europe. The subjects ranged in age from 19 to 65 years old, and had a mean vomiting frequency of 47.6 episodes per week (median 26.5). After baseline assessments and

device implantation, eligible study participants were randomized to 1 of 2 groups. The first group had the device programmed to therapy ON for 1 month post-implant, followed by 1 month of therapy OFF. The second group had device therapy programmed to therapy OFF for the first month, followed by therapy ON for the second month. Each subject served as his/her own control, and completed a vomiting diary. Success was defined as a ≥80% reduction in vomiting frequency, based on data obtained from patients' diaries. At the end of the 2 month period, and before the blind was broken, the patients were asked which month they preferred (month 1 versus month 2). Out of the 33 subjects, (10 diabetic and 11 idiopathic) 21 subjects preferred therapy ON, 7 preferred therapy OFF, and 5 had no preference. These results did not reach statistical significance for the combined group ($P > .05$). Subgroup analysis showed that preference for therapy ON was significant ($P < .05$) for the idiopathic subgroup, but not the diabetic group ($P = .08$). There was no significant difference in vomiting frequency between therapy ON mode (mean 23.0 ± 35.5) versus device OFF mode (29.0 ± 38.2). The failure to demonstrate device-dependent improvements in vomiting frequency have been attributed by some to a placebo effect (Bartolloti, 2011).

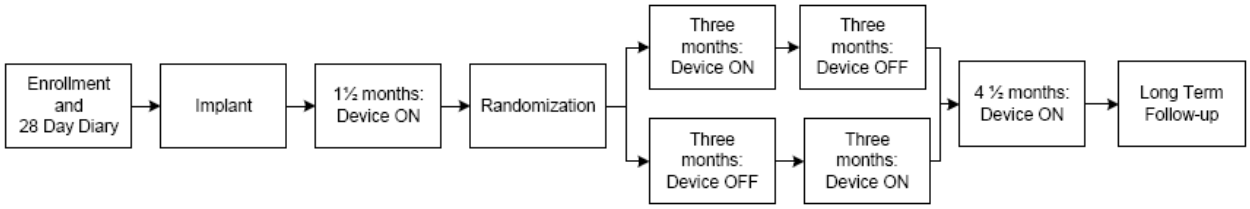
Phase II was a longitudinal monitoring study of Phase I enrolled subjects. After the blind was broken, all Phase I subjects had the option of choosing Enterra therapy programmed to ON, or therapy programmed to OFF. The subjects were followed through 12 months. Weekly vomiting frequency, symptom severity scores, gastric emptying, and QOL were evaluated (Medical Outcomes Short-Form 36 Health Survey) using the Wilcoxin signed rank test for improvements from baseline to the 6- and 12-month time points. Reduction in weekly vomiting frequency (WVF) was calculated as a percentage: ((WVF during OFF - WVF during ON)/ (WVF during OFF))*100%. With the Enterra Therapy System programmed to deliver therapy ON, results demonstrated significant reductions in vomiting frequency, with idiopathic subjects experiencing a mean reduction in weekly vomiting frequency of 23.1%, and diabetic subjects experiencing a the mean weekly reduction of 26.1%. However, , vomiting frequency was also observed to decrease with the Enterra Therapy System programmed to the therapy OFF mode: the mean decrease in weekly vomiting frequency of device On versus device OFF was 9.8 ± 18.6 in the idiopathic group, and 2.5 ± 25.5 in the diabetic group. Modest improvements in gastric retention were observed in both diabetic and idiopathic groups at the 6- and 12-month time points. At 6 months, the median 2-hour and four-hour gastric retention was decreased by 18% and 26%, respectively. At 12 months, the median 2-hour and four-hour gastric retention was decreased by 27%, and 55%, respectively. Improvements were also seen in 73% of study participants in both the ability to tolerate solid meals, and Quality of Life scores. The most frequently observed adverse events included device infections (N=10), lead penetration (N=4), irritation/inflammation over the neurostimulator site (N=5), and pain at the neurostimulator site (N=5). Adverse events requiring surgical interventions included infection of the neurostimulator pocket (N = 2 events), perforation of the lead and migration of the pulse generator (N = 1), and repositioning of a migrated pulse generator (N = 1). There was one patient death, which was caused by cardiopulmonary arrest, and was found to be unrelated to Enterra therapy.

2. WAVESS Compassionate Use Study. This was an open-label, non-randomized study of 18 patients who did not meet the entry criteria for patients enrolled in the WAVESS study. The patients had drug-refractory gastroparesis, and were "likely to die within the next few weeks if they did not receive this therapy".

3. Compassionate Use Electrical Stimulation Study (CUESS, see H990014/R16). Under the auspices of the HDE, an unblinded, open-label study of 49 gastroparesis patients (51 patients were enrolled), was designed to provide gastric stimulation safety information.

4. Enterra Therapy Clinical Study. The study was initiated in July, 2002, terminated January, 2009, and enrolled 87 patients. Of these patients, 55 had diabetic gastroparesis, and 32 had idiopathic gastroparesis. The study was a prospective, double-blind, cross-over study to evaluate the safety (adverse events), efficacy (symptom reduction) and clinical utility (health status) of Enterra GES therapy.

Figure 3. Schematic of the design of the Enterra Clinical Study.



The study design entailed within patient analyses to determine the following:

The primary effectiveness endpoint was reduction in weekly vomiting frequency. This objective was not met, since the median difference in WVF of therapy ON versus therapy OFF was 0% ($p = .215$) in subjects with diabetic etiology, and 17.3% ($p = 1.0$) in subjects with idiopathic etiology.

The secondary effectiveness endpoint for Objective 1 was reduction in symptoms of gastroparesis, including:

- Vomiting
- Nausea
- Early satiety
- Bloating
- Postprandial fullness
- Epigastric pain
- Epigastric burning

The 7 symptom frequency scores were summed, and composite scores were derived by comparing scores that collected during the therapy ON period relative to scores collected during therapy OFF.

This endpoint was also not achieved, since the median reduction in symptom scores for therapy ON versus therapy OFF was 0% ($p = .903$) in the diabetic arm, and 0% ($p = .932$) in the idiopathic arm.

The secondary effectiveness endpoint, Objective 2, was long-term (12 month) reduction in weekly vomiting frequency. This endpoint was found to be statistically significant. The median percent reduction in WVF from baseline to 12 months was 67.8% ($p < .001$) for thee diabetic arm, and 87.1% ($p < .001$) in the idiopathic arm.

The safety endpoint was to characterize the adverse events (AEs) experienced with the use of Enterra Therapy.

Patient Deaths

There were 12 deaths in the diabetic arm and 2 deaths in the idiopathic arm, and 1 additional death that occurred after enrollment, but before device implantation. The probable causes of death include wounds not healing after a fall; coagulopathy of uncertain etiology; brainstem hemorrhage; cardiopulmonary arrest; myocardial infarct; complications including pneumonia, respiratory failure, cardiac arrhythmia, and renal failure; septicemia; and complications of diabetes and heart disease. These deaths were reviewed by a medical advisor or Adverse Event Committee, and found to be patient-related.

Device-Specific Adverse Events

At the time of database closure, the most frequently reported device- and therapy-related adverse events included pain and paresthesia, and migration of the implantable components (Table 1)

Table 1. Most frequently (>5%) reported device- and therapy-related adverse events

Adverse Event Type	**Diabetic Arm (N = 55 Subjects)**	**Iodiopathic Arm (N = 32 Subjects)**
Device infections	2 (7 events)	
Implant site pain 1	1 (N=2 events)	5
Abdominal pain	(N=4 events)	4 (N=4 events)
Paresthesia		4 (N=4 events)
Lead migration/dislodgement	1 (N=2 events)	2 (N=2 events)
Neurostimulator migration	1 (N=2 events)	2 (N=2 events)

Serious Adverse Events

Serious adverse events included those that were patient-related and device- or therapy-related (Table 2)

Table 2. Serious adverse events

Serious Adverse Event Type	Diabetic Arm: Event Description	Iodiopathic Arm: Event Description
Exacerbation of gastroparesis	The lead became detached from neuroregulator during pregnancy	
Neurostimulator pocket infection	This event resulted in device removal	
Leads became twisted and dislodged	This patient required surgical replacement of the leads, and pocket revision	The lead migration required dual lead replacement surgery
Chest pain and pneumonia	This event was patient-related	
Gastrointestinal hemorrhage	This patient required replacement of a gastric tube, and increased dosage of a proton pump inhibitor	
Sinus tachycardia with apneic episode	This patient required defibrillation, telemetry and administration of Narcan (patient later died)	
Jolting/shocking sensations at the stimulator site		The symptoms were resolved by re-programming of the device.
Diabetic ketoacidosis	This patient was re-hydrated	
Implant site hematoma at the neurostimulator pocket	This subject experienced exacerbation of gastroparesis symptoms including nausea, vomiting, and dehydration	

The data from this study are consistent with safety and probable benefit of Enterra Therapy in adults aged 18 – 65. Results of the study indicate that the primary endpoint was not attained.

Study Results – Data Regarding Probable Benefit

The finding that the benefits associated with GES outweighed the risks of use were based on the WAVESS and WAVESS Compassionate Use trials. Enterra Therapy was shown to decrease the frequency of vomiting episodes and symptom scores among subjects with diabetic and idiopathic gastroparesis at the 6- and 12-month time points. Subjects receiving Enterra Therapy also reported improvements in the Quality of Life (QOL), as determined by assessments with the Mental Component Summary and Physical Component Summary scores. Enterra Therapy enables patients

with intractable gastroparesis to seek an additional therapeutic option for this medical condition, when more conventional interventions are not effective.

Benefit-Risk Analysis (Basis for Approval)

Based on the results of clinical trial, it was concluded that clinical results from the performed studies indicated that GES therapy resulted in reduced nausea and vomiting, and improved solid food intake and health related quality of life for diabetic and idiopathic patients with drug refractory gastroparesis. The data demonstrated that the types of adverse events observed with use of the Enterra Therapy System were similar to those reported for other implantable electrical stimulation devices. These adverse events were treatable and did not cause significant morbidity and mortality. Overall, it was determined that the Enterra system would not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighed the risk of illness or injury. These results supported the humanitarian use of the GES system.

Gastroparesis is a serious medical condition that affects a small population of children (less than 4,000 cases per year in the United States). Based on experience with use of the system in pediatric patients (2-21 years), adverse events of particular concern include cyanosis, sepsis, electric shock, abnormal loss of weight, malnutrition, and surgery, because immaturity could adversely impact the patient response to these adverse events, or the risks could be elevated. Issues such as battery depletion, erosion of the implantable components, ineffectiveness, and lead damage are concerning, since they may necessitate surgical revision to fix the issue, adding additional exposure to general anesthetics, and surgery risks.

VII. ANNUAL DISTRIBUTION NUMBER (ADN) AND UNITED STATES DEVICE DISTRIBUTION DATA

The Pediatric Medical Device Safety and Improvement Act of 2007 amended section 520(m) of the Food and Drug Administration Amendments Act and now allows HDEs indicated for pediatric use and approved on or after September 27, 2007, 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). The ADN is the number of individuals affected by the disease or condition per year (i.e., annual incidence) multiplied by the number of devices reasonably necessary to treat an individual. According to statute, the ADN cannot exceed 3,999. If the calculated ADN exceeds 3,999, FDA must restrict to the ADN to 3,999 based upon FDAAA legislation.

An individual ENTERRA device implanted in a specific patient consists of multiple modular components (leads and neuroregulator). The following Table lists the number of devices shipped and sold within the United States.

Table 3: Annual Distribution Number (ADN) of device components shipped within the United States.

Reporting Period	Estimated Number of Neurostimulators Sold	Estimated Number of Leads Sold
March, 2001 – March, 2002	169	383
March, 2002 – March, 2003	311	596
March, 2003 – March, 2004	245	457
March, 2004 – March, 2005	438	791
March, 2005 – March, 2006	576	1,093
March, 2006 – March, 2007	781	1,370
March, 2007 – January, 2008	569	1,045
January, 2008 – December, 2008	1,062	1,876
January, 2009 – January, 2010	781	1,370
February, 2010 – January 2011	1,065	1,745
February, 2011 – January, 2012	1,165	1,820
February, 2012 – January, 2013	1,300	1, 961
February, 2013 – January, 2014	1,318	1,928
TOTAL	**9,780**	**16,435**

As stated in section 520(m)(8) of the Act, the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after March 25, 2013, to ensure that the HDE remains appropriate for the pediatric populations for which it is granted.

The sponsor's estimate is reasonable and consistent with FDAAA legislation requirements. The tracking data clearly demonstrates that the number of patients implanted with the ENTERRA device does not exceed 4,000 per year has been provided.

Medtronic, Inc. reviewed the device registry database to estimate the number of pediatric patients with an active neurostimulator. Note that patients are removed from the database the year they turn 22. The data were broken down by gender, and by those patients above and below 18 years of age, and provided to FDA.

Table 4: Estimated number of pediatric patients receiving Enterra Therapy in each reporting period by gender and age (data provided by Medtronic, Inc.)

Reporting Period 2/1 to 1/31 for year ending	Total N (newly implanted this period)	Female		Male		Gender Unknown	
		<18	**≥18≤22**	**<18**	**≥18≤22**	**<18**	**≥18≤22**
2000	1(1)	1	0	0	0	0	0
2001	1(0)	0	1	0	0	0	0
2002	6(5)	2	4	0	0	0	0
2003	17(11)	3	11	0	3	0	0
2004	31(14)	5	18	2	6	0	0
2005	41(16)	6	23	3	7	0	2
2006	48(14)	11	24	3	6	0	4
2007	58(21)	12	31	5	6	0	4
2008	66(21)	13	36	6	8	0	3
2009	75(27)	16	41	9	7	0	2
2010	105(48)	26	52	11	11	1	4
2011	139(51)	38	64	20	11	1	5
2012	165(50)	55	65	21	17	3	4
2013	200(61)	59	91	27	18	2	3
2014	206(35)	60	93	29	20	2	2

Based on the information provided by, there are approximately 3 times more female pediatric patients who are implanted with the device, when compared to males. Note that females compared with males.

In terms of adverse events observed in the pediatric patient population, there have been overall, 176 adverse events reported in 50 Medical Device Reports (MDRs). Of these, the most common adverse events were upper abdominal pain (N=7), vomiting (N=10), device dislocation (e.g., device flipping around, device dislocation and neurostimulator migration, N=7), device ineffective (N=9), electromagnetic interference (e.g., device turning off while walking through a security gate, and reset following surgery with electrocautery, N=6), implant site pain (N=6) and paresthesia (N=6).

Two patients required device removal, including one patient who had erosion of the neurostimulator implant site, and one patient who reported shocking sensations, which were later attributed to possible symptoms of gastroparesis.

Sixteen patients received device replacements due to lead fracture (N=2), lead erosion through the stomach (N=1), neurostimulator malfunction (N=1), pain at the neurostimulator implant site (N=2), shocking sensations after walking into a strong magnetic field (N=1), decreased therapeutic response or uncomfortable stimulation (N=3), replacement of temporary leads with permanent leads (N=1), battery depletion (N=2), lack of effect (N=1), and reasons unknown (N=2).

Table 5 was provided by Medtronic, and summarizes the device-related failures or issues that were observed in pediatric patients.

Table 5. Categorization of the most frequent device-related failures or issues observed in pediatric patients.

Device failures or issues related to the device that are encountered or alleged during the event (FDD)	No. of times the FDD is found in the MDRs
BREAK	1
COMPONENT(S), DETACHMENT OF	1
CONTINUITY, INTERMITTENT	1
DEVICE OPERATES DIFFERENTLY THAN EXPECTED	13
DEVICE REMAINS IMPLANTED	2
DISLODGED OR DISLOCATED	2
ELECTROMAGNETIC COMPATIBILITY ISSUE	2
ELECTRO-MAGNETIC INTERFERENCE (EMI)	4
ELECTRONIC PROPERTY ISSUE	2
ENERGY OUTPUT TO PATIENT TISSUE INCORRECT	1
FAILURE TO DELIVER ENERGY	1
HIGH IMPEDANCE	1
IMPEDANCE, HIGH	1
IMPLANT, REPOSITIONING OF	3
INAPPROPRIATE SHOCK	4
LEAD(S), FRACTURE OF	1
LOW BATTERY	1
MAINTAIN, FAILURE TO	1
MALPOSITION	1

MIGRATION OF DEVICE OR DEVICE COMPONENT	3
NO INFORMATION	4
NO KNOWN DEVICE PROBLEM	6
POCKET STIMULATION	1
POSITIONING ISSUE	1
PREMATURE DISCHARGE OF BATTERY	1
REPLACE	1
SHOCK, ELECTRICAL	1
SHOCK, INAPPROPRIATE	5
UNINTENDED COLLISION	2
UNSTABLE	1
Grand Total	69

VIII. POSTMARKET DATA: POST-APPROVAL STUDIES

None. Post-approval studies were not a requirement associated with approval of H030009.

IX. POSTMARKET DATA: LITERATURE REVIEW WITH FOCUS ON SAFETY DATA

Systematic Literature Review on the Safety and Probable Benefit of Enterra in the Pediatric Population

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 (≤21 years old). More 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 May 14, 2014, a search in PubMed and EMBASE was performed using the following search terms:

> 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."

The search was limited to studies published between March 31, 2000 (approval date) and April 1, 2014 (cutoff date for executive summary preparation), human studies, and English. This search yielded a total of 1,187 citations (465 in PubMed and 722 in Embase).

A first pass of the articles was conducted by reviewing the title and abstract of each returned hit and making exclusions. Of the 1,187 identified articles, 963 were excluded during the first pass for the following reasons: duplicates (n=382), conference abstracts (n=192), non-human (n=143), non-study (n=106), unrelated to the topic (n=97), and non-English (n=43). These exclusions left 224 articles for review during the second pass (Figure 1. Article Retrieval and Selection).

The second pass was conducted by review of abstracts and full-text. Additional exclusions were made for the following reasons: not pediatric population (n=63), non-systematic/clinical reviews (n=56), unrelated to the topic (n=54), other gastric stimulation treatments (n=10), non-study (n=5), duplicates (n=2), non-English (n=2), non-human (n=2), and non-clinical study (n=1).

The second pass exclusions left 29 papers for full epidemiological review and assessment as part of qualitative synthesis.

Results

Of the 29 papers included in this systematic review, 7 papers included pediatric patients only and the remaining 22 papers included both, pediatric and adult patients. Probable benefit and safety results are presented first for the pediatric-only papers, followed by results for the papers on pediatric and adult subjects.

Studies of Pediatric Patients Only

There were 7 papers that included pediatric patients only. Age of the study subjects ranged from 2 to 19 years. Two papers included children only (defined as age 2 to 12 years) [1, 2]; both were case reports with a sample size of 3 and 1, respectively. Two papers included adolescents only (defined as age 12 to 21 years) [3, 4]; both were case reports with a sample size of one. The remaining 3 papers included both children and

adolescents [5-7]; these were case series with sample size of 9, 24, and 16, respectively. Descriptions and results of the papers that included children only are presented in Table 1 and papers that included adolescents only are presented in Table 2.

Five of the of the 7 papers that included pediatric patients only were in the US, one in Sweden, and the country was not reported in one publication. All 7 were case reports or case series, with sample size ranging from 1 to 24. Duration of follow-up ranged from 0.5 months to 37 months after Enterra implantation. Indications for use included the following: intractable gastroparesis (GP) of unspecified etiology; GP of idiopathic, post-surgical, and post-infectious etiology; drug-refractory severe nausea and vomiting; and functional dyspepsia. For the four case series that included data on both temporary and permanent GES, we limited our review to outcomes after permanent device placement.

Probable Benefit Results

Most papers reported decreased severity and frequency of GI symptoms in the pediatric population, including improvements in vomiting [5-7], nausea [5-7], postprandial fullness [6, 7], early satiety [6, 7], bloating [6, 7], epigastric pain [6, 7], and burning [6, 7]. Two papers also reported improvements in total symptom score, which incorporates multiple GI symptoms [5, 7]. One case report stated that the patient had general improvement in symptoms, without stating the specific symptoms [4]. Another case report reported that the patient continues to have weekly episodes of pain and retching lasting 12 to 24 hours at 37 months after Enterra implantation [2].

Four papers described the effect of Enterra on the need for nutritional support. Two papers described a decreased need for feeding tubes and parenteral nutrition after treatment with Enterra. Among 22 children with functional dyspepsia, Lu et al. reported that the number of patients requiring gastric or jejunal feeding decreased from 11 to 3 and the number requiring parenteral nutrition decreased from 6 to 3 [6]. Similar results were reported in a retrospective review of the first 16 pediatric patients implanted with Enterra at a hospital in Ohio. At baseline, the main route of nutrition was oral feeds in 10 patients, jejunal feeds in 3 patients, and total parenteral nutrition (TPN) in 3 patients. At 0.5 to 23 months follow-up, the feeding patterns improved with an increase in the number of patients tolerating oral feeds and a decrease in the number of patients receiving enteral and parenteral nutrition. More specifically, 13 patients were on oral feeds exclusively, 2 patients were on oral plus G-tube feedings, and 1 patient received oral and G-tube feeding plus intermittent TPN [7]. The other two papers were case reports. Hyman et al. reported that a 7.5 year old boy with intractable gastroparesis continues to receive J-tube feedings at 37 months post Enterra implantation [2]. In another case report, Yeh et al. reported that a 15 year old girl with postinfectious gastroparesis was able to tolerate some oral nutrition, but was still reliant on overnight gastrojejunal feeding tube [4].

There were two pediatric studies that evaluated the effect of Enterra on gastric emptying. In a case study of a 7.5 year old boy with intractable gastroparesis and visceral pain, gastric emptying was reported to be normal at 12 months; however, he could not be weaned from J-tube to oral feedings [2]. In contrast, Islam et al. reported that gastric emptying values did not improve in a small case series of 9 boys and girls aged 8 to 17 years with chronic nausea and vomiting who were treated with Enterra [5].

Safety Results

A number of adverse events were reported in the 7 papers that included pediatric patients only.

A study by Islam et al. was the only paper to report device explants. Islam et al. reported that one patient was explanted due to recurrent symptoms, one patient was explanted due to skin erosion over the pocket caused by trauma to the area, and one patient was explanted due to infection [5]. The timing of device removal was provided only for the patient who was explanted due to skin erosion that occurred 2 years after device implantation.

There were two cases of infections not resulting in an explant. One patient had a cutaneous fungal infection under the bandage 10 days post-implant, which was treated with antifungal agents [1]. Another patient reported having superficial incisional erythema, which was treated and resolved with oral antibiotics [7].

There were multiple reports of pain and tenderness at the implantation site with no mention of device explantation. Lu et al. reported that four patients had mild abdominal discomfort/tenderness at the implantation site [6] and Teich et al. reported that two patients had tenderness of the stimulator within the superficial pocket [7]. Neither paper reported on the timing of these events.

Lastly, one patient underwent a revision procedure to replace a failed battery less than 1 year after initial device placement [6].

No deaths were reported in the 7 papers that included pediatric patients only.

One case-report reported that no Enterra-related AEs had occurred up to 37 months after implantation [2] and two papers did not report whether or not any AEs occurred [3, 4].

Studies of Pediatric and Adult Patients

Our systematic literature review includes 22 papers evaluating the use of Enterra in a mix of pediatric and adult patients. Because the results in these studies were not stratified by age group, these papers are presented together. Age of study participants ranged from 2 to 87 years. Of the 20 studies with primary data collection, the age of subjects in 17 of these studies was ≥ 18 years old. There were 3 exceptions; the study by Lahr et al. included 95 subjects aged 11 to 71 years old [8] and the study by Brody et al. included 50 subjects aged 16 to 59 years [9]. Lastly, the study by Andersson et al. included 27 patients who received temporary GES and then a subset of 20 'responders' who received permanent device placement [10]. Age range of the 27 patients who received the temporary device is reported as 2 to 81 years. Although the age range was not given for the subset of 20 patients who received the permanent device, it was noted that this subgroup includes a 2 year-old girl.

Indications for use included drug-refractory gastroparesis of diabetic, postsurgical, and idiopathic etiology and also functional dyspepsia. Sample size in these studies ranged from 10 to 233 subjects. The largest case series, with 233 evaluable subjects, was a retrospective review by Keller et al. of all patients with refractory GP who were implanted with Enterra between October 2000 and July 2011 at Temple University Hospital in Philadelphia [11]. There were nineteen case reports/series, one prospective cross-over study, and two systematic literature reviews and meta-analyses. Six of the 19 case series were based on retrospective chart review. Of the 20 primary research papers included in this review, 18 were conducted in the U.S. and 2 were conducted in Sweden. Notably, 12 of the 18 U.S. studies were conducted at the University of Kansas.

The systematic literature review and meta-analyses included in our review were conducted by Chu et al. [12] and by O'Grady et al. [13] The study by Chu et al. included 10 Enterra studies published between 1995 and 2011; 4 of the 10 studies are included in our review. The study by O'Grady et al included 13 studies

published between 1992 and 2008; 7 of 13 papers were included in our review. Both systematic reviews did not provide an age range of participants in the included studies. However, based on individual studies that were included in this systematic review by FDA, we know that pediatric patients were included in some of the papers that were captured in the systematic reviews by Chu et al. and O'Grady et a. The probable benefit and safety results for the two systematic reviews will be presented separately in the next section.

Probable Benefit Results

There were 19 case reports and case series with age of subjects ranging from 2 to 87 years. All 19 studies examined change in upper GI symptoms after treatment with Enterra. The majority of studies reported improvements in the total symptom score based on the frequency and/or severity of upper GI symptoms associated with gastroparesis including vomiting, nausea, early satiety, bloating, postprandial fullness, epigastric pain, and epigastric burning [8, 9, 14-25]. In a case series of 19 patients, Andersson et al. reported that 13 patients were responders with at least 50% decrease in GI symptoms [26]. Most of these results are based on symptoms at 6- and 12-months after Enterra implantation. The study by Lin et al. reported that improvements in GI symptoms based on the total symptom score was sustained beyond 3 years [17].

In addition to the global symptom score, individual gastrointestinal symptoms at follow-up were compared to baseline values. The severity and/or frequency was also reduced for the following GI symptoms: nausea [8-11, 16, 18-23, 25, 27], vomiting [8-10, 12, 16, 18-23, 25, 27], bloating [9, 11, 16, 18-20, 22, 25], early satiety [8, 16, 18-20, 22, 25], abdominal/epigastric pain [8, 11, 16, 18-20, 25], abdominal/postprandial fullness [9, 16, 18, 19, 22, 23, 25], epigastric burning [9, 19, 20, 22, 25], and distension [8]. Some studies, however, reported no improvement in a number of GI symptoms including: early satiety [9], bloating [23], fullness [20], abdominal pain [23], epigastric and chest pain [9], and chest burning [9].
Nine papers presented data on the need for nutritional support after treatment with Enterra. The majority of patients receiving nutritional support at baseline (via enteral feeding tubes or total parenteral nutrition) had enteral access withdrawn after device placement [16-18, 20, 21, 24, 25, 27, 28]. These studies were largely based on 6 to 12 months of follow-up. Consistent longer-term results were presented in the study by Lin et al. which reported that, of the 15 patients requiring nutritional support at baseline, only 5 continued nutritional support beyond 3 years [17].

Results on the effect of Enterra treatment on gastric emptying time was reported in 12 papers. Some of the papers reported that GET was not improved after treatment with Enterra [15, 16, 18, 19, 21] while other papers reported improvements in gastric emptying and retention [8, 9, 25, 28]. Two papers reported faster GET during earlier, but not later follow-up periods. Forster et al. reported improved GET at 3 months after device placement but not at 6- and 12 months follow-up [27]. In a different paper, Forster et al. reported improvement in gastric emptying at 6 months but not at 12 months post implant [14]. Reddymasu et al. reported that, of the 7 out of 18 patients with available GET follow-up data, gastric emptying time became slower in 29% of subjects at 1 year [20].

A prospective cross-over study by McCallum et al., which included 55 subjects ranging in age from 20 to 63 years, reported improvements in upper GI symptoms at 1 year post implant, including reductions in the total symptom score and weekly vomiting frequency. Improved 4-hour gastric retention was also reported at 1 year compared to baseline. [29]

The probable benefits of Enterra treatment were also reported in the two systematic literature reviews. Chu et al. [12] and O'Grady et al. [13] both reported significant improvements in the total symptom score, vomiting severity, and nausea severity. O'Grady et al. also reported decreased need for total or

supplemental nutritional support in 8 of the 13 studies with data on nutritional status [13]. Chu et al. did not report on need for nutritional support outcomes. GET results varied in the two systematic reviews. O'Grady et al. reported improvements in 4-hour gastric emptying in 5 of 13 studies ($P<0.001$) [13]. However, Chu et al. reported differences in gastric retention by GP etiology. Improved 2- and 4-hour gastric retention was reported in patients with diabetic GP (both $P<0.01$) but, there was no improvement in gastric retention at 2-hour in idiopathic GP patients and 4-hour in postsurgical GP patients (both $P>0.05$) [12].

Safety Results

It is important to note that for all adverse events reported in the 22 papers including both pediatric and adult patients, none of the papers specified the age of the subject experiencing the adverse event. Therefore, we do not know if the adverse event occurred in a pediatric patient or an adult patient.

A total of 77 deaths were reported in papers describing pediatric and adult patient populations. The vast majority of these deaths were identified as being not related to the Enterra device. Most deaths were attributed to cardiovascular causes including the following: myocardial infarction (MI) (n=6) [14, 16, 17, 28]; coronary artery disease (n=1) [17]; cardiomyopathy (n=1) [17]; cardiopulmonary complications (n=2) [9]; cardiopulmonary arrest (n=1) [27]; pulmonary embolus (n=6) [14, 16, 17, 24, 25]; aspiration pneumonia (n=3) [14, 16, 17]; complications of diabetes (n=4) [14, 16, 17, 25]; cardiovascular or renal complications of diabetes (n=20) [25]; refusing hemodialysis (n=3) [14, 16, 17]; complications of renal failure (n=2) [28]; and complications of nephrotic syndrome (n=1) [11]. Deaths were also attributed to GI causes including: failure to thrive from continued gastroparesis symptoms (n=1) [11]; malnutrition/anorexia (n=1) [25]; and malnutrition due to nausea, vomiting, and unwillingness to receive enteral or parenteral nutrition (n=1) [20]. Other causes of death included the following: sepsis related to MI (n=1) [16]; sepsis related to ESRD (n=2) [16, 17]; septic osteomyelitis (n=1) [9]; unspecified sepsis (n=1) [23]; brain stem hemorrhage (n=1) [16]; uncontrollable hemorrhage from profound coagulopathy during a pancreas transplant (n=1) [24]; pancreatic cancer (n=1) [23]; liver cirrhosis (n=1) [25]; and suicide (n=4) [14, 17, 25]. Lastly, 13 deaths were reported in the study by Hou et al; however, circumstances surrounding the deaths were not provided [15].

There were a total of 124 device explants reported. The most common reasons for explantation were infection at the pulse generator or electrode site (n=39) [11, 14, 16-18, 25, 27, 29] and total or sub-total gastrectomy due to persisting upper GI symptoms (n=17) [9, 17, 23-25, 28]. Studies also reported explants resulting from problems with the leads. Three studies conducted at the University of Kansas each reported that one patient who developed small bowel volvulus around the wires underwent surgery to resect part of small bowel and remove the device [14, 16, 17]. Explants were also reported as result of lead dislodgement [25]. Other reasons for device explantation are as follows: lack of symptom improvement (n=18) [11, 23, 25]; pain at the neuroregulator site (n=6) [24, 28]; and mechanical issues (n=9) [11]. Less frequent reasons for device explant included the following: feeding tube placement (n=1) [24]; need for MRI (n=1) [24]; injury involving fractured sternum and ribs (n=1) [17]; electrodes detached from gastric muscle as a result of trauma (n=1) [18]; and one patient with a connective tissue disorder wanted device removal for unknown reason [9]. Lastly, Hou et al. reported that 7 subjects underwent device removal but did not provide the reasons for explant [15].

Forty-two patients underwent revision surgery. The most frequently reported reason for revisions was to address subcutaneous pocket issues (n=21) [11]. Other reasons necessitating device revision are as follows: incisional hernia (n=4) [11]; battery depletion (n=3) [11]; device erosion through the incision (n=3) [24]; lead erosion (n=3) [11, 28]; pain at the implantation site (n=3) [9]; "flipping" of the device (n=2) [9]; repositioning of the device to the right of the umbilicus (n=2) [14]; and replacement of detached lead

resulting from an auto accident in which the patient's sternum and ribs were fractured (n=1) [14].

Subsequent hospitalizations were reported for the following conditions and procedures: gastroparetic flares (n=90) [11]; gastroparesis-related symptoms (n=9) [23]; J-tube placement (n=4) [23]; bowel obstruction due to J-tube placement (n=1) [23]; deep vein thrombosis due to central line placement (n=1) [23]; central line infection (n=1) [23]; gram-negative rod bacteremia (n=1) [23]; syncopal episodes (n=2) [23]; psychotic episode (n=1) [23]; and seizure (n=1) [23].

The following postoperative adverse events were reported that did not result in device explant or revision: hematoma in the device pocket (n=1) [24]; aspiration pneumonia requiring intubation and ventilatory support (n=1) [28]; atrial fibrillation (n=1) [28]; subcutaneous abscess around a feeding jejunostomy tube site requiring removal of the tube (n=1) [28]; and hypoglycemia (n=1) [28].

In a prospective cross-over study, McCallum et al. reported that a total of 732 adverse events had occurred, of which 687 were patient-related and 45 were therapy- or device-related. Fifteen of the 45 therapy/device-related events were serious (3 lead migration/dislodgements, 2 device migration, 1 implant site hematoma, 1 implant site infection; the remaining 8 SAEs were not directly related to the device but were coded as therapy-related because they occurred within 2 weeks of device implantation) and 3 of the events required surgical intervention [29].

Lastly, four studies did not report whether or not any adverse events had occurred [8, 19, 21, 26].

The safety of Enterra treatment was also described in the two systematic literature reviews. Chu et al. reported that the most common complications were infection (3.87%), lead or device migration (2.69%), peptic ulcer disease (1.18%), penetration of the electrode into the stomach lumen (1.18%), skin erosion after abdominal wall trauma (1.18%), and small bowel obstruction caused by the wires (1.18%) [12]. Safety results in the study by O'Grady et al. were limited to device explants or reimplantations, which occurred at a rate of 8.3% [13]. The reasons for device removal included: infection (n=8); erosion through the skin (n=6); pain at implantation site (n=4); perforation of the stomach by leads (n=2); device migration (n=1); and small bowel infarction related to volvulus around the wires (n=1) [13].

Discussion of the Literature

The seven studies in pediatric patients only reported probable benefits of Enterra in improved upper GI symptoms (particularly nausea and vomiting) and reduced need for enteral and total parenteral nutritional support. Results on gastric emptying and retention were less consistent, with some papers reporting an improvement and other papers reporting no change from baseline values. The 22 studies of pediatric and adult patients reported similar findings regarding the probable benefits of Enterra treatment.

The results of this systematic literature review should be interpreted in light of key limitations. First, our results are limited by the small number and sub-optimal design of the included studies. In our search of the literature spanning 14 years, there were only 7 papers reporting on the use of Enterra in the pediatric population. Furthermore, the quality of the evidence was generally low, as all 7 papers were case reports and case series with small sample size describing a single-site experience. The 20 studies that included mixed pediatric and adult populations also had limitations of mostly case report/series design with small sample sizes and conducted at single study centers. It is notable that in total, 13 of the 29 papers included in this qualitative synthesis were of studies conducted at the University of Kansas and there is indication of data repetition in at least some of these studies. For example, 3 separate papers from the Kansas group each describe one patient who developed small bowel volvulus around the wires and required surgical repair and device explant [14, 16, 17]. All of the aforementioned factors limit the generalizability of the results from these studies to the pediatric gastroparesis population at large. Furthermore, the 20 studies of mixed age

populations and the 2 systematic reviews were not specific to the pediatric population. Because these studies did not present the results separately for pediatric patients, it is not clear if benefits derived by the mixed group were experienced specifically by pediatric patients. Similarly, it is not clear if any of the reported adverse events occurred in pediatric patients. Lastly, none of the included papers were well-controlled studies. Although there was one cross-over study in which the patients served as his/her own control [29], there were no double-blinded randomized placebo-controlled studies to evaluate treatment probable benefit.

There were sources of bias that may contribute to overestimation of device probable benefit. The 20 primary studies of pediatric and adult patients reported high attrition rates. Non-responders may have been explanted or declined to participate in follow-up evaluations, leading to greater representation of responders in study results. A similar type of patient selection bias was essentially built into studies that employed temporary GES and selected only the responders (based on study-specific definitions) to undergo permanent Enterra placement.

Literature Conclusion

In general, the results of our systematic literature review suggest probable benefits of Enterra in the pediatric population with respect to improved upper GI symptoms and reduced need for nutritional support. Although, the evidence for improved gastric emptying time is less clear. The most commonly reported adverse events following device placement are infection, lead or device migration, pain at the implantation site, and recurrent symptoms. In some cases, these events led to explantation of the device. The literature raised no new safety concerns. However, the results of this systematic review should be interpreted carefully in light of key limitations in the included studies. In our search of the literature spanning over 14 years, there were only 7 studies specifically in pediatric patients, all of which were case reports/series in design, which are considered the lowest level of evidence. Furthermore, the remaining 22 papers in our review included mixed populations of pediatric and adult patients, with the majority of papers including subjects 18 years and older. None of these publications presented results stratified by pediatric versus adult population, limiting the ability to assess device performance in the pediatric population.

In conclusion, although there is some published literature describing device performance, the small number of publications that included only pediatrics and the low quality of the evidence (case reports and case series), limit the ability to make conclusions about the probable benefits and safety of Enterra in the pediatric population.

Figure 1. Article Retrieval and Selection

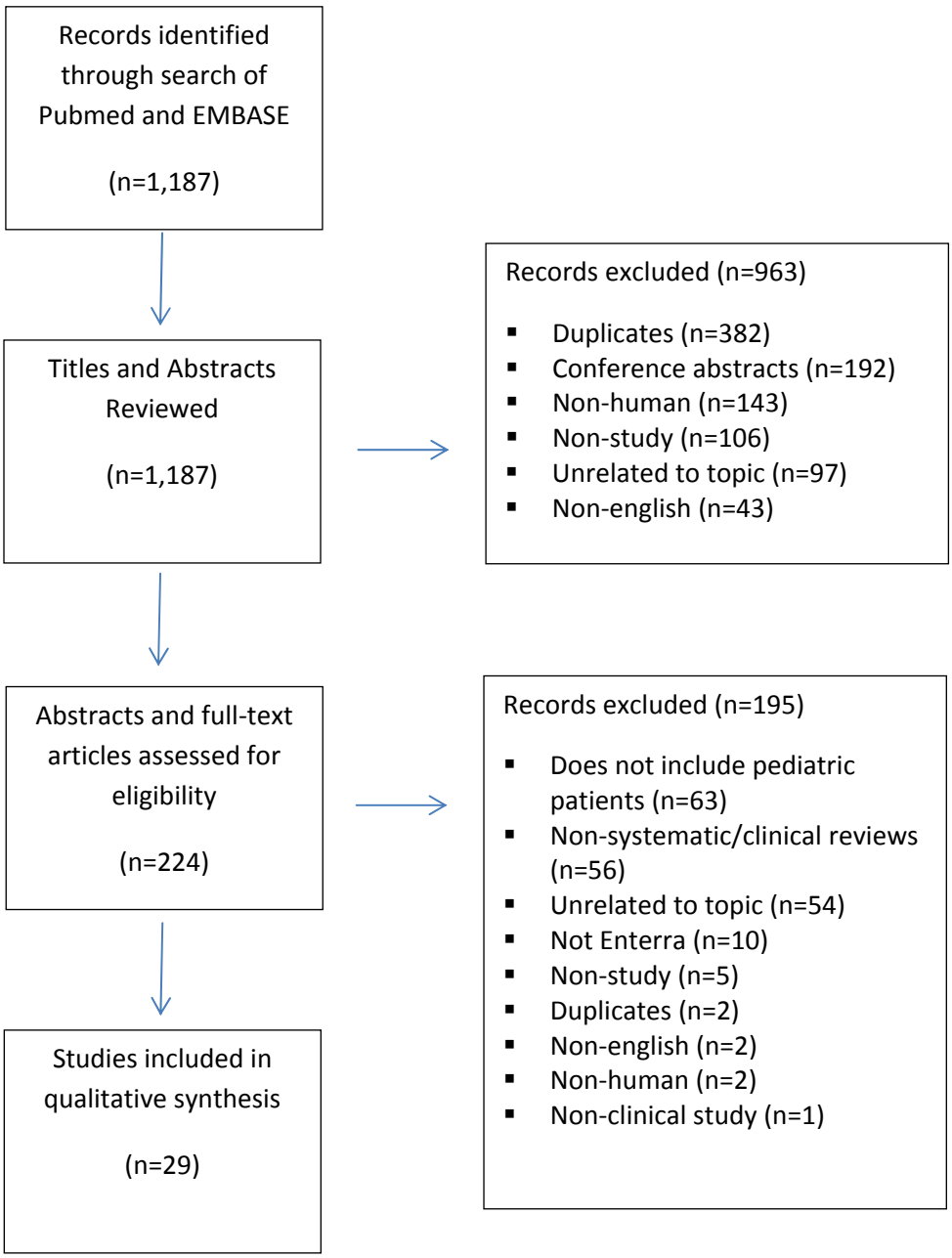


Table 6. Studies that included children only (defined as age between 2 and 12 years)

Source (Author, Year)	Study Population	Age (Years)	Sample Size	Follow-Up Duration	Probable Benefit Results	Safety Results
Elfvin 2011	3 children (1F, 2M) with drug-refractory nausea and vomiting	2, 2 4/12, 2 11/12	N=3	12 Months	All 3 patients had decreased weekly vomiting frequency (WVF) of more than 50% at 6 months. Further decrease in WVF observed at 12 months (12-month data available for only 2 of 3 patients).	No children experienced any complications related to the implantation procedure. No discomfort or other complications related to Enterra noted. One patient had a cutaneous fungal infection under the bandage after 10 days; infection was treated with antifungal agents.
Hyman 2009	1 boy with intractable visceral pain and GP	7.5	N=1	Outcomes reported at 12 and 37 months	Normal gastric emptying at 1 year; Patient could not be weaned from J-tube to oral feedings; At 37 mos, patient experiencing weekly episodes of pain and retching lasting 12-24hrs and continues J-tube feedings.	No immediate or long-term complications noted.

Table 7. Studies that included adolescents only (defined as age between 12 and 21 years)

Source (Author, Year)	Study Population	Age (Years)	Sample Size	Follow-Up Duration	Probable Benefit Results	Safety Results
Ong 2012	Caucasian female with life-long severe idiopathic GP	13	N=1	3 years	Patient showed gradual reduction in vomiting frequency and was able to gradually increase oral intake. Anti-emetic medications were stopped at 12 months. At 3 years, patient was able to tolerate solid and liquid meals with complete resolution of vomiting.	None reported
Yeh 2012	Female with severe post-infectious GP	15	N=1	3 months	GI symptoms improved and patient was able to tolerate some oral nutrition. However, patient was still reliant on overnight gastrojejunal feeding tube for 70% of her calories.	None reported

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

Overview of Manufacturer and User Facility Device Experience Database (MAUDE)

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MAUDE 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/ 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.
- MAUDE data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MAUDE 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.

In this analysis, a sampling of the adult and unidentified patient age reports was performed due to total number of reports received, and the timeframe required for completion of this analysis, in order to provide a relative comparator of reported device adverse event experience between the adult/unknown and pediatric patient populations.

MDRs Associated with the Enterra Therapy System

The MAUDE database was searched to identify all relevant MDRs related to the Enterra Therapy System from March 30, 2000 to April 1, 2014. The MAUDE search resulted in 1,162 MDRs; 1,151 MDRs were submitted by the Manufacturer, one MDR was submitted by a User Facility, and ten MDRs were Voluntary Reports. No MDRs were submitted by Distributors. Additionally, 32 of the 1,162 MDRs were identified as pediatric (patients < 22 years of age) reports.

Patient Event Type Information

The Event Types reported within the 1,162 total MDRs included 44 deaths, 697 injuries, and 382 malfunctions. Of the 32 MDRs identified as pediatric reports, 20 (62.50%) MDRs were injury reports and 12 (37.50%) MDRs were malfunction reports. No death reports were identified for the pediatric patient reports. Table 8 below provides the Event Type distribution for pediatric patients (ages less than 22), adult patients, and patients with indeterminate age (BLANK).

Table 8. Overall Event Type distribution by Patient Age.

Event Type	**Total MDR Count**	**Patient Age (years)**			
		<18	**18 through 21**	**≥ 22**	**BLANK**
DEATH	44 (3.78%)	**0**	**0**	21	23
INJURY	697 (59.98%)	**9**	**11**	338	339
MALFUNCTION	392 (33.73%)	**5**	**7**	189	191
OTHER	27 (2.32%)	**0**	**0**	25	2
BLANK	2 (0.17%)	**0**	**0**	2	0
Total MDR Count	1,162 (100.00%)	**14 (1.2%)**	**18 (1.55%)**	575 (49.48%)	555 (47.76%)

Patient Age and Gender Information

The pediatric patients' age ranged from 2 years to 22 years old with a mean patient age of 17 years old. Patient gender information was provided in 978 of the 1,162 MDRs; 786 were female patients and 192 were male patients. Of the 32 pediatric MDRs, patient gender information was provided in 30 MDRs; 26 female patients and four male patients. In an effort to understand the large discrepancy between female and male patients, the issue of gender bias was addressed with the Office of Device Evaluation (ODE) and Division of Epidemiology (DEPI) as well as with the Manufacturer directly. All entities provided information based on literature reviews[i] that suggested the following:

- Gastroparesis is more commonly diagnosed in females than males, in all age categories
- Idiopathic gastroparesis affects women at a much higher frequency than men
- Gender-specific (female: male) incidence of definite gastroparesis was found to be at a rate of 4:1 however, through all studies and MDR reviews there is no information to substantiate concrete reasons for the increased incidence of gastroparesis in females over males.
- The most common symptoms of gastroparesis in children appear to have a male predominance in infancy and a female predominance in adolescence.

Patient Problem and Device Problem Information

Table 9 below shows the top Patient Problems and Device Problems reported in MDRs identified with the Enterra Therapy System in pediatric patients. (Note: A code of "No known Impact or Consequence to Patient" indicates that while a device behavior was identified in the report, the manufacturer or reporter did not report any patient impact or consequence as a result of the reported device behavior).

Table 9. Top Patient Problems and Device Problems reported in MDRs for pediatric patients (n = 32).

Patient Problem	Number of MDRs*	Device Problem	Number of MDRs*
Therapeutic Response, Decreased	9	Device Operates Differently than Expected	6
Electric Shock	9	No Known Device Problem	5
Pain	8	Inappropriate Shock	6

Infection	2	Migration of Device or Device Component	2
Surgical Procedure	1	Explanted	1
Nausea	1	High Impedance	2
Vomiting	2	Electro-Magnetic Interference (EMI)	2
No Known Impact or Consequence to Patient	3	No Information	1
Therapeutic Effects, Unexpected	2	Unintended Collision	1

***Please note that a single MDR may have multiple Patient Problems and/or Device Problems**

Top Patient Problem Codes by Age

In comparison to Table 9 which provides a listing of pediatric problem codes , Table 10 below provides the top Patient Problems for all MDRs and differentiated by patients younger than 22 years of age, patients 22 years of age and older, and patients of indeterminate age (BLANK).

Table 10. Top Patient Problems by Patient Age.

Patient Problem	**Total MDR Count**	**Patient Age (years)**		
		< 22	**≥ 22**	**BLANK**
Therapeutic Response, Decreased	**359**	**9**	171	179
Electric Shock	**165**	**9**	89	67
Pain	**153**	**8**	90	55
Infection	**100**	**2**	55	43
Surgical Procedure	**95**	**0**	79	16
Nausea	**87**	**1**	59	27
Vomiting	**87**	**2**	55	30
No Known Impact or	**66**	**3**	20	43

Consequence to Patient				
Therapeutic Effects, Unexpected	**64**	**2**	38	24
Total Patient Problem Count	**1263***	**36**	**691**	**536**

*Please note that the total MDR Count does not equal the number of MDRs since one MDR might have multiple patient problems. A code of "No known Impact or Consequence to Patient" indicates that while a device behavior was identified in the report, the manufacturer or reporter did not report any patient impact or consequence as a result of the reported device behavior.

Table 11 below provides the Patient Problem distribution for patients younger than 18 years of age and patients 18 years of age through 21 years of age. (Note: The code of "No Information" (n=0) did not provide any insight as to a pediatric problem and was therefore omitted from the table identifying the top pediatric patient problems. A code of "No known Impact or Consequence to Patient" indicates that while a device behavior was identified in the report, the manufacturer or reporter did not report any patient impact or consequence as a result of the reported device behavior)

Table 11. Top Pediatric Patient Problems by Patient Age.

Patient Problem	Total MDR Count of Pediatric Patients	Patient Age (years)	
		< 18	18 through 21
Therapeutic Response, Decreased	**9**	6	3
Electric Shock	**9**	0	9
Pain	**8**	1	7
Infection	**2**	2	0
Surgical Procedure	**0**	0	0
Nausea	**1**	1	0
Vomiting	**2**	2	0
No Known Impact or Consequence to Patient	**3**	1	2
Therapeutic Effects, Unexpected	**2**	1	1

Top Device Problem Codes by Age

In comparison to Table 9 which provides a listing of pediatric problem codes , Table 12 below provides the top Device Problems for all MDRs and differentiated by patients younger than 22 years of age, patients 22 years of age and older, and patients of indeterminate age (BLANK).

Table 12. Top Device Problems by Patient Age.

Device Problem	**Total MDR Count**	**Patient Age (years)**		
		< 22	**≥ 22**	**BLANK**
Device Operates Differently than Expected	**192**	6	76	110
No Known Device Problem	**160**	5	81	74
Inappropriate Shock	**159**	6	85	68
Migration of Device or Device Component	**77**	2	43	32
Explanted	**74**	1	55	18
High Impedance	**62**	2	30	30
Electro-Magnetic Interference (EMI)	**55**	2	28	25
No Information	**54**	1	29	25
Unintended Collision	**32**	1	18	14
Total Device Problem Count	**957***	**25**	**499**	**433**

*Please note that the total MDR Count does not equal the number of MDRs since one MDR might have multiple device problems.

Death Reports

As indicated in Table 8, overall there were 44 identified MDRs with event type noted as death. There were no identified pediatric deaths; however, 23 MDRs were reports of indeterminate patient age, and therefore can't be ruled out as being potentially involving pediatric patients. Through

individual review of each death report along with the information provided through the event descriptions and manufacturer narratives, there was no clear stated causality between the use of the device and the reported patient deaths.

The causes of death included cardiac failure, respiratory failure, pulmonary embolus, pneumonia, sepsis, and renal failure. Patient comorbidities were also reported as a possible cause of death in a number of reports. The majority of reports stated that the cause of death was not device related or believed not to be device related, while the remaining reports did not offer any further information.

Review of MDR narratives of Pediatric Events

The 32 pediatric MDR narratives were individually reviewed to identify noted patient problems and issues related to each MDR adverse event. Table 13 below identifies the MDR count of the top noted patient problems and issues observed in the narrative of these pediatric MDRs.

Table 13. Clinical events identified with pediatric patients.

Event	**MDR Count***
Inappropriate Electrical Shock	9
Return of Symptoms [Therapeutic Response, Decreased]	7
Movement/Flipping of Device	4
Electromagnetic Interference (EMI)	3
Impedance Issues	3

*Only the most observed patient problems and issues in pediatric MDRs narratives are included and therefore, does not equal the total pediatric MDR count (n= 32).

Inappropriate Electrical Shock (n = 9)

The nine MDRs that identified electric shock in pediatric patients were reviewed to determine the reported cause of shock. Review of the MDRs determined shock was primarily due to a patient fall/trauma or Accidents (falling, car accident, extreme movements, etc.) – accidents or major weight loss can lead to the migration of the device resulting in inappropriate shock or lack of therapeutic effect; major accidents can result in a malfunctioning pulse generator and/or a break in

the electrical leads.

Electromagnetic Interference (EMI) – walking through security gate, metal detectors.

Additionally, Medtronic has mentioned shock as a potential side effect in the device labeling under Warnings:

"The voltage induced through the lead and Neurostimulator may cause uncomfortable jolting or shocking levels of stimulation."

The Enterra Therapy System uses electrical stimulation to treat the secondary symptoms of gastroparesis and thus, patients may experience shocking sensations at times even when the device is operating as intended.

Return of Symptoms [Therapeutic Response, Decreased] (n = 7)

The seven MDRs that identified pediatric patients with a return of symptoms were reviewed. Reoccurring symptoms included nausea, vomiting, and pain. The most common causes for patients to exhibit the return of symptoms were EMI and patient accidents/extreme body movements. Extreme body movements and patient accidents can cause device leads to snap and/or dislodge from the anchored stimulator resulting in a nonfunctioning device. EMI can occur from various non-medical and other medical product sources that the patients may be exposed to during any of their post-implantation care and living environments.

Movement/Flipping of Device (n = 4)

The four MDRs that identified device movement/flipping in pediatric patients were reviewed to determine the reported cause of device or component movement. Upon reviewing the MDRs, none of the reports provided adequate information to determine the cause of device or component migration. Pediatric patients with movement/flipping of the device did experience high levels of pain and the return of symptoms including nausea and vomiting. (Note: Device movement /flipping was noted in reports coded with migration of device or device component, pain, explanted, and/or therapeutic effects- unexpected)

Electromagnetic Interference (EMI) (n =3)

The three MDRs that identified EMI in pediatric patients were reviewed. One report stated that the patient had walked through a security gate. One report stated that the patient experienced a loss of therapeutic effect after a nerve conductivity test. One report stated that EMI contributed to lead

issues with the device without citing a specific source.

Impedance Issues (n =3)

Three MDRs were identified with impedance issues in pediatric patients. None of the reports stated the cause of the high impedance readings. Usually, high impedance is the result of an unsecure lead connection to the IPG. This prevents the IPG from providing therapeutic stimulation to the patient.

Re-interventions

Re-interventions addressing types of clinical incidences reported above are listed below in Table 14. This table identifies the re-interventions identified in the MDR narratives to treat the types of issues noted above.

Table 14: Incidences of Re-Interventions in Pediatric patients

Re-Interventions	**Number of Incidences (N=36)**
Revision	6
Replacement • Device • Battery • Lead	 6 1 4
Explant • Permanent • Temporary	 2 1
Reprogramming/ Calibration	7
Hospitalization for follow-up	4
Office follow-up treatment	2
No Information	3

*Please note that the total Number of Incidences Count does not equal the number of MDRs since one MDR might have multiple noted re-interventions.

Re-interventions, as listed in the table 14 above, were as a result of multiple issues. Revision procedures were noted for complaints of shocking/jolting sensation and pain, movement of the device in the pocket, or following trauma/injury to the implant site. Replacement might involve the entire system, leads, or battery. Replacement procedures were completed for complaints of shocking sensations, lead replacement to address the return of symptoms, or lead dislodgement or cracking. Explant procedure was noted for complaint of erosion and infection over the skin of the device pocket or for complaints of shocking sensation. Reprogramming/calibration was performed for complaints of shocking sensation, reported high impedances with return of symptoms, and following exposure to a security gate system. Hospitalization was noted for patients with complaints of shocking/jolting sensations, device moving and flipping in pocket and causing pain, trauma/injury to implant site with return of symptoms, infection at implant site, reported pain at incision site, and reports of return of symptoms including violent vomiting requiring medication.

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 Date of Implant and Date of Event. Of the 1,162 total MDRs, the TTEO was available/determined for 442 MDRs, including 13 of the 32 pediatric reports.

Table 15 below provides the MDR count for the TTEO for the pediatric and adult patient population.

Table 15. MDR count for the TTEO for the pediatric and adult patient population.

Time to Event Occurrence (TTEO)	**MDR Count**			
	Pediatric (< 18 years of age)	**Pediatric (18 to 21 year of age)**	**Adults (≥ 22 years of age)**	**Blank**
Perioperative	0	0	25	16
≤ 30 days	2	1	33	3
31 days - 1 yr	2	4	134	9
1-5yrs	3	1	178	6

>5yrs	0	0	25	0

The 2 MDRs listed for pediatric patients less than 18 years old and occurring less than 30 days post implant involved:

- One patient who reported return of symptoms following the dislodgement of temporary leads. Surgical intervention was performed with replacement of device and leads completed.
- The second patient reported a device pocket infection that was drained and Intra-venous antibiotics administered.

The 2 reported events with a TTEO of 31 days to less than one year in the patients less than 18 years old involved:

- One patient who experienced loss of therapeutic effect and return of symptoms following a MVA. The device was initially turned off and then turned back on, reprogrammed with no further problems noted.
- The second patient reported to have touched a voltage meter leading to complaints of "stomach hurting" which resulted in follow with the healthcare provider in the office.

The reported events with TTEO of one to five years in patients less than 18 year old involved:

- one patient had high impedance readings noted during routine office follow-up. There was no change in therapy response noted, and the device was reprogrammed.
- The second patient had a return of symptoms through possible trauma, which was not confirmed. No further information was provided in the report.
- The third patient had a reported loss of efficacy following a nerve conductivity test with return of symptoms, and no further information provided.

For patients ages 18 to 21 years old, with a TTEO ≤ 30 days, one patient experienced a shocking sensation nine days post-implant, and the patient was hospitalized and device turned off. The device was later explanted.

For patients, ages 18 to 21 with TTEO of 31 days to less than 1 year, the 4 MDRs are characterized as follows:

- One patient experienced a shocking/jolting sensation with pain. The patient was hospitalized and a lead revision was performed.

- The second patient experienced shocking and burning sensation following an injury. Patient hospitalized with severe nausea and vomiting. The device was initially reprogrammed and device and leads were later replaced.

- The third patient reported movement of the device. The wound was explored with leads noted to be twisted and sutures broken. The leads were untwisted and new sutures placed to secure the device. Another surgery was performed when the device was noted to be moving again, with the position revised. Device eventually replaced when complaints of increase of symptoms was reported.

- The fourth patient reported shocking/jolting sensation and no further information was provided.

Finally, for patients 18 to 21 years of age with a TTEO or over one year from date of implant, there was one report of a patient complaining of shocking sensations. The device was initially reprogrammed with revision surgery performed to replace the device and leads.

MDR Summary

There have been 32 MDRs which identified pediatric patient use submitted for the Enterra Therapy System between March 30, 2000 and April 1, 2014. No deaths were reported among the 32 MDRs involving pediatric patients. Pediatric patient issues primarily included shock, a return of symptoms (pain, nausea, and vomiting), device movement/flipping, EMI, and impedance issues. The TTEO occurs earlier for pediatric patients than adult patients and appears likely due to increased activity and movement in the pediatric population. Consultation with ODE, DEPI and the manufacturer identified some literature that documents the increased presentation of gastroparesis in female versus males in the pediatric and adult populations, but the underlying reasons for this are not well understood. Overall, Patient Problems and Device Problems observed among pediatric patients were similar to the issues observed in adult patients. These issues are known inherent risks for the device and do not represent any new or previously unknown concerns regarding patient safety.

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[i] Literature references noted as reviewed in the Age and Gender portion of POST-MARKET DATA: MEDICAL DEVICE REPORTS (MDRs) can be found in the Enterra Level II Analysis (CON146327).