CITIZENS' PETITION SEEKING IMMEDIATE ACTION BY THE

FEDERAL FOOD & DRUG ADMINISTRATION (FDA)

REQESTING A REVIEW OF THIS DOCUMENT BY THE:
Gastroenterology and Urology Devices Panel

FOR

GASTRIC ELECTRICAL STIMULATION (GES), LEVEL III DEVICE,

March 16, 2004

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1. Introduction

This citizen's petition is brought forth by the Gastroparesis and Dysmotilities Association (GPDA) on behalf of patients living with Gastroparesis who desire to have effective treatment options available in order to help improve their quality of life.

Medtronic Inc has an implantable device, called Enterra Therapy™ classified as a HUD (Humanitarian Use Device) since 2000, for treating patients with intractable nausea and vomiting of gastric dysmotility origin (Severe Gastroparesis) which is refractory to medical management.

In order for this device to have qualified for the HUD designation, it was subjected to the requirements establishing safety. A Humanitarian Device Exemption (HDE) application is similar in both form and content to a premarket approval (PMA) application, but exempt from the documentation of effectiveness required of a PMA.

A Humanitarian Device Exemption (HDE) is intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect, or are manifested in fewer than 4,000 individuals in the United States per year (see 21 CFR 814.102(a)).

Therefore, a Humanitarian Use Device is for a condition manifested in a small number of cases, and for which the device does not pose an unreasonable or significant risk of illness or injury; its effectiveness does not have to be demonstrated; and yet, it holds a probable benefit to the patient's health care management.

In the time that has passed since the Enterra Therapy™ received HUD designation in 2000, a number of research papers, published in peer review journals, have now clearly established the efficacy of this device.

Medtronic Inc is a responsible and reputable company presently taking all the correct steps in accordance with industry practices to bring the Enterra Therapy device to a PMA (premarket approval) status. Patients clearly want this.

However, this industry sponsored multi-center clinical trial is progressing very slowly, since the patient group that the treatment is targeted for are terribly ill and present a medically complex and challenging clinical picture.

When the obvious emerges, it is important for the obvious to be stated in order to speed along full FDA approval for this safe, reversible, and efficacious therapeutic device; thus unburdening patients from the arduous insurance appeal processes they currently have to navigate in order to access this treatment; and for which some patients (our estimation is about 20%) exhaust all appeals and lose their fight.

This petition will provide 1) an outline to the present barriers and burdens in accessing this HUD; 2) a patient profile; 3) an outline of the recent evidence of efficacy with Enterra Therapy; and 4) the petition will urge the FDA Gastroenterology and Urology Device Panel to review the current efficacy data and make recommendations.

Other devices, like spinal cord stimulation, have come to PMA approvals on less scientific evidence for efficacy. This petition has pooled the scientific evidence for efficacy of Gastric Electrical Stimulation.

Definitions: unless otherwise stated, GES (Gastric Electrical Stimulation) and Enterra Therapy will be used interchangeably.

A. What barriers exist under the current HUD (Humanitarian Use Device) designation?

Most state Medicare providers recognize the HUD status for Gastric Electrical Stimulation (GES) and easily grant approval for Enterra Therapy. However, Gastroparesis like all the digestive motility diseases is poorly recognized and misunderstood. The '**average**' patient with Gastroparesis must go through 2 to 3 appeals that can take over 2 years for Social Security to approve their disability claim; then begins the wait for Medicare status. Therefore, some of these very ill patients may have to wait 3 to 4 years to finally get Medicare status. This statement can be verified by gastroenterologists who see a large number of Gastroparesis patients in their clinical practice. The prolonged wait for Medicare status compromises patient care.

Private insurance providers view the Enterra Therapy as "investigational" and clearly stipulate in their policies that Gastric Electrical Stimulation is not covered. Patients who are prescribed the Enterra Therapy by their doctors must prepare for an immediate denial from their insurance providers, and then begins the appeal process. Families need to be organized and show fortitude to present their case. On average, patients go through 2 to 3 appeals before they finally obtain insurance approval, if they get approval at all. Those who are overwhelmed with their illness and without good emotional support may find these barriers insurmountable.

One tragic example was brought to our attention; a young 32 year old, male, Type I diabetic; in one year, had been in the hospital more than at home due to uncontrolled episodes of vomiting from his Gastroparesis. His GI specialist recommended Enterra Therapy. Three insurance appeals later the young man's surgery was scheduled for Enterra Therapy. In the time that these lengthy appeals took place, his kidneys failed and he was placed on renal dialysis in the same week that his GES surgery was scheduled. The GI specialist cancelled the surgery due to dialysis and informed the family that if GES had been implanted before his kidneys failed the patient could have had the device. Now because of dialysis, the family has been informed he cannot obtain the device. Weeks later, this has been clarified and now the family awaits the IRB (Institutional Review Board) review for approving Enterra Therapy. This may take up to 3 months, all the while this young man's health continues to deteriorate as his family watches helplessly. A year has transpired in their pursuit to get this treatment for their son.

Severe Gastroparetic patients are very ill, with their lives tied to frequent hospitalizations; and feeding formulas. Enteral or parenteral nutrition takes many hours to infuse-- some must run 24 hours a day. These housebound / hospitalized patients are usually young women, in the prime of their lives with small children. They are suffering from an overwhelming, life threatening illness. Many are vomiting numerous times a day. Their sleep pattern is disrupted due to nocturnal symptoms. This coupled with constant nausea and sleep deprivation robs them of their ability to concentrate and makes them emotionally fragile. Somehow, they have to find the emotional reserves and physical energy to fight insurance appeals for a reversible, safe and efficacious treatment that holds hope of decreasing their crippling upper digestive symptoms.

2. Petitioners

This petition is submitted on behalf of the following petitioners.

Mr. and Mrs. LaCasper, 9150 Elizabeth Lake Road, White Lake, MI, 48286. Their son, Type I Diabetic, is still waiting for his GES. It has been an agonizing year long wait due to red tape, insurance appeals and misunderstandings. The family feels helpless as they witness their young adult son's repeated hospitalizations due to uncontrolled vomiting and blood sugar levels. His Gastroparesis began to intensify

over the last 4 years. The family feels strongly that their son's erratic blood sugar levels and constant vomiting helped to accelerate his kidney failure. He recently became a dialysis patient.

Dottie Plosgrove, 3109 Lacross, Bryant, AR**.** 72022. Dottie is an idiopathic Gastroparetic patient who was advised by her specialist to get the GES back in 1996. The device was still categorized by the FDA at this time as an experimental device so her insurance provider refused to cover the surgery. Several years later, they still refused to pay for it. Dottie fought for years with her insurance provider; then she fought for years to gain disability status and Medicare. Finally, through Medicare, she received her GES and is very happy with the results.

Debbie Ritter, 5227 Quail Ave. North, Crystal, MN, 55429. Deb has been a Type I Diabetic for 37 years. As a young girl she suffered with nausea and vomiting due to erratic blood sugar levels. Over the past 10 years her nausea and vomiting intensified. By 1996 she was diagnosis with Gastroparesis. Nothing helped to manage her symptoms and many hospitalizations ensued. Her weight fell from 137lbs to 89lbs. GES was advised. Two insurance appeals failed. Deb was admitted into the hospital for end stage digestive failure from Gastroparesis and was told she was dying. A final call from her hospital bed to her insurance provider succeeded in convincing them. Rushed into surgery, she awoke free of nausea; the first time in over a decade. Deb now has a renewed life. She can eat and has gained weight. Her blood glucose levels are significantly more stable than they have ever been in 37 years.

Jennifer Sivils, 1026 Phelps Circle, Arkadelphia, Arkansas, 71923. Jennifer is a young mother of 3 children. She suddenly fell ill with idiopathic Gastroparesis in 1998. Her weight fell from 157lbs to 98lbs. Her family witnessed her constant vomiting, hospitalizations and rapid decline. Jennifer's life was being sustained with parenteral nutrition since any food or liquids consumed would be vomited back-up. Medications did nothing to help her. Jennifer was enrolled in the WAVESS study group for GES. Jennifer and the other patients in this study group were a catalyst for bringing Enterra Therapy from an experimental designation to a Humanitarian Use Device designation by the FDA. Once Jennifer received her Enterra Therapy, she still needed to be maintained on parenteral nutrition. But once Enterra was implanted, slowly she began to gain weight, and for the first time, she was able to keep down broths and soups without vomiting them back-up. After 4 years, Jennifer is now off parenteral nutrition. She can now maintain her weight by eating and no longer must endure hospitalizations. She still gets tired and has infrequent bouts of nausea and vomiting, but she is thankful to be alive and to be able to eat again.

Beth Nelson, 16226 Beechwood Road, Findlay, OH, 45840. Beth has idiopathic Gastroparesis which developed suddenly post-operatively from a surgery unrelated to her digestive system. She was 38 years old at the time and is a mother of 2 children. Beth never vomited from her Gastroparesis. Instead she developed extraordinarily intense nausea. The nausea was 24/7 and would wake her at night or prevent her from falling asleep. Beth could no-longer eat; and even the sight, smell or sound of food would intensify her nausea. Her weight fell from 140 to 107 and weakness ensued. Beth was placed on Propulsid (Cisapride) in June of 2000, which worked very well. She was able to gain 20 lbs. Propulsid was soon after pulled from the market and was no longer available. Her doctor's institution chose not to back the compassionate access program for re-accessing Propulsid. So when her supply ran out, she again started to lose weight due to unrelenting, intractable nausea. In June 2001, Beth had her GES placed. She awoke from surgery and was nausea free. Months later, she had reoccurrence of nausea, but as time goes on she now has very little to no nausea and merely has to be cautions not to eat too much just before bedtime. She reports that GES has worked better for her than did the Propulsid for overall control of her symptoms. She has gained back her weight, is eating again and enjoys being a mother.

Barbara King, 3000 Moss Creek Drive, Johnson City, TN, 37604. In 1997, Barbara is a grandmother with 3 grown children. She started to have problems with slow transit constipation thought to result from autonomic nerve dysfunction. The constipation was refractory to all treatments. In 1999 her colon was removed. The year following, she began to develop small bowel and gastric dysmotilities. Taking IV medications through her central catheter line, nothing helped to halt the downward spiral wrought from constant nausea and vomiting. Barbara was no longer able to travel or visit her grandchildren. She was in and out of the hospital and in jeopardy of losing her job. Three insurance appeals had to be fought for the right to access Enterra Therapy. The insurance fights left her life in limbo. Her family had to financially

come up with the money while still waiting for a decision by their insurance provider. Barbara recently received her implant and has had a significant reduction in her nausea and vomiting and now feels her life is no longer tied to a hospital.

3. Statement of facts

A. Patient profile

Gastroparesis is a neuro-muscular disorder of the stomach and shows a spectrum of severity from mild, through severe. On the mild end of this continuum, various medical labels exist to describe this group of 'dyspeptic patients.' This confusion is related to the paucity of scientific knowledge surrounding these disorders of the upper digestive tract. Mild Gastroparesis may be called: "non-ulcer dyspepsia," 'motility-like dyspepsia,' "Functional dyspepsia" or post enteric infection "dysmotility." Diagnosis therefore rests upon the findings of **symptoms**, since other standard 'tests,' are normal**.** Dyspeptic symptoms are: nausea, abdominal bloating, early satiety, a persistent feeling of fullness, mid epigastric discomfort or pain developing soon after a meal. **Signs** may consist of vomiting, abdominal distention and weight loss. No two experts will agree upon where the milder forms of digestive 'functional' disorders end and more severe forms of 'motility' diseases begin.

However, in its severe classical form, Gastroparesis is easily recognizable by most gastroenterologists. It includes the finding of delay in gastric emptying along with severe dyspeptic symptoms. In some cases, patients may experience weight loss and /or become malnourished, requiring supplemental support in the form of jejunostomy tube feedings or total parenteral nutrition in order to meet their nutritional needs. Often, diagnosis rests upon the experience of the clinician since there is not a great deal of research or consensus to guide the definition or diagnosis of this disease.

Eighty percent of Gastroparetic patients are females and the mean age of onset is 35 years.1 For Gastroparetic patients followed **over a 6 year period,** McCallum et al found 15% remained dependent upon Enteral/parenteral nutrition. For all the Gastroparetic patients that were followed during this 6 year period: 35% were Idiopathic, 29% Diabetic, 13% post surgical, 8% Parkinson's disease, 5% Collagen vascular disease, 4% CIP and the remainder misc.1

Patients with Gastroparesis are mostly young and middle aged women in the prime of life. They have frequent hospital admissions, loss of work time, and a dismal future.2

The most troubling signs and symptoms of severe Gastroparesis are unrelenting nausea and vomiting. This frequently occurs with abdominal pain due to the distended, poorly functioning stomach, and also pain from chronic acid reflux resulting from gastric stasis.

This constant nausea and vomiting leads to dehydration and electrolyte imbalances usually necessitating emergency room visits with concomitant spiraling malnourishment.

In severe Gastroparesis, nutritional compromise is the hallmark of these unrelenting symptoms for which there are no effective treatments. These patients show a slow, insidious progression of malnourishment and many will require jejunostomy tubes or total parentral nutrition to stabilize their weight. Even with the placement of 'tubes' to rehydrate and provide nutrition---this does not alleviate symptoms.3 Patients will still 'pool' secretions in their stomachs and vomit this up. Venting gastrectomy tubes allow for the drainage of stomach secretions and gastric decompression, but this further jeopardizes hydration and electrolyte balance—and again, this does not alleviate the confounding and enormously difficult to manage symptom of nausea.

Total Parenteral Nutrition carries its own risks of Small Bowel Bacterial Overgrowth, liver failure, and life threatening sepsis.

Patients with Gastroparesis, even of **moderate** severity, are often disabled with nausea even with combined anti-emetic and prokinetic drugs. Though their weight may not be dangerously compromised, they are disabled due to upper digestive symptoms—**nausea presenting as the most common debilitating symptom for all Gastroparetic patients—be they: mild, moderate or severe. In moderate to severe Gastroparesis the nausea is so intense as to disrupt sleep patterns.**
Understandably **medical** management of symptomatic Gastroparesis does not provide robust symptom control for many, because no medical therapies are currently 'on the market' for these patients that have been developed for their disease. All current medications have been borrowed from other medical uses.

B. Current treatment options.

Current treatment options (medical and surgical) have really not changed for decades (excluding Enterra Therapy and Botox trials).

The diabetic Gastroparetic patients are a readily identifiable group of Gastroparetic patients that have been studied the most. Gastroparesis diabeticorum has been recognized as a serious complication of diabetes since the early 1940/s.4

A paper published in 1986 exploring the use of jejunostomy feedings in the management of Gastroparesis Diabeticorum outlined the limited treatment options for these patients. It discussed recent drug trials with metoclopramide and Domperidone and noted that clinical efficacy may diminish with time and patients become refractory to the drugs. 5

McCallum published a paper in 1985 titled "Review of the Current Status of Prokinetic Agents in Gastroenterology."6 In 2003, the drugs outlined in this paper are still the same; except for Propulsid (Cisapride), which is no longer available except through a compassionate use protocol.

Current medical management has less to offer now than it did back in the 1980's.

In the United States, only two drugs are FDA approved for treating Gastroparesis:

Metoclopramide (Reglan) initially approved in the 1960's in Europe for use as an antiemetic in pregnancy. Since then it has been used extensively as a prokinetic and antiemetic for treating Gastroparesis. This drug has a high rate of side-effects such as: restlessness, anxiety, drowsiness, depression, tremor, and muscle rigidity. Acute dystonic reactions are more common in younger patients, while tardive dyskinesia can occur in older patients. Overall, about 30% of patients have one or more adverse side effects and cannot continue using metoclopramide.1

Erythromycin was first developed in the 1950's but was not used in Gastroenterology until some decades later. Numerous studies have proven that this antibiotic is highly effective in producing peristaltic contractions in the stomach antrum. This effect is gained at very low doses. In effect, it produces a 'dumping syndrome' in the stomach (emptying too rapidly). This might explain why individuals that need to use this drug for its 'antibiotic effect' have a good number of side effects, like nausea and abdominal cramping. Many patients using erythromycin for its prokinetic effect may also run into problems of increased nausea and abdominal cramping. As well, its prokinetic effects tend to wane after 6 months to one year.

Other common medical treatments:

Cisapride (Propulsid) was originally developed to treat severe nocturnal Gastro Esophageal Reflux Disease (GERD). When it was released in the 1980's, it was quickly recognized to have a broad range of pro-motility effects on various segments of the GI tract. It became widely studied for treatment of Gastroparesis, but was voluntarily pulled from the market in 2000 due to safety concerns. *Propulsid is still available under a restricted release, yet the restrictions are so great, most Gastroenterologists cannot take the time to fill out the enormous amount of paper work required to access this drug for their patients.* The

FDA has never eased this access with a supplemental New Drug Application (sNDA) which would allow restricted marketing. The American Society of Consultant Pharmacists submitted a paper to the Food and Drug Administration (May 22, 2002, FDA Docket number: 02N-0115) recommending that Propulsid be brought back with appropriate safeguards. This has not occurred.

Domperidone (Motilium) is a dopamine receptor antagonist drug. It has been marketed world wide since 1978. It is in a broad pharmacological class of medications called the: 'Substitute Benzamides' which hail from the Phenothiazine psychotropic drug family. This broad category of drugs has been around for a long time. The Phenothiazine drugs were brought into use for psychiatry in the late 1940s and early 1950s. Metoclopramide and **Levosulpiride (Levobren, Levopraid)** all belong to this same pharmacological family. Levosulpiride is used widely in Europe as a prokinetic drug. Of this pharmacological class of drugs, Domperidone has the least central nervous system side effects; therefore it is well tolerated and now considered the first line drug choice for treating Gastroparetic patients. Domperidone is used worldwide. It has been extensively studied as a treatment for Gastroparetic patients and found to be safe and effective in controlling symptoms of nausea and vomiting. Despite this, it has never received FDA approval—though application has been brought to the FDA and was denied even against the panel's recommendation for approval.

Zelnorm (Tegaserod) has recently come onto the market. It is used to treat constipation predominate Irritable Bowel Syndrome—it is currently being investigated as a treatment for Gastroparesis, but still too early to say if it is showing effectiveness as a treatment option.

Note: patients with Gastroparesis must take promotility and anti-nauseant drugs for decades. There is a paucity of long term studies demonstrating safety and efficacy of these drugs and no longitudinal studies in pediatrics.

Sturm et al did a systematic analysis of available prokinetics for treating patients with Gastroparesis. His conclusion: response to medical treatment is suboptimal at best. 7

Lack of favorable medical response for those with more severe Gastroparesis has lead to investigation of surgical and other novel approaches. Surgical options too (other than Botox) have remained the same for more than 15 years.

Botox. injections into the pylorus have been studied in Diabetic Gastroparesis patients. It has about a 50% chance of producing a response of decreasing symptoms like vomiting and lasts for about 6 to 9 months. Long term use and complications have not been studied. Concerns regarding fibrosis developing in the pylorus due to long term Botox use have not been ruled out.

Surgical interventions for palliative treatments of severe diabetic and idiopathic Gastroparesis such as pyloroplasty, or elimination of the stomach through near total Gastrectomy (Billroth I, Antrectomy, Roux-En-Y) or addition of a venting gastrostomy; show little improvement in symptom management. A review of the literature by Reardon et al, of these surgical palliative procedures showed, that of 12 patients, only 3 had resolution of their symptoms, with the majority having no improvement or only temporary improvements, or a worsening of symptoms to include bilious vomiting.8

Experts agree that the entire stomach is affected in Gastroparesis; therefore, treatment by partial gastrectomy is unsatisfactory as a method to attempt to ameliorate symptoms. Treatment by total gastrectomy is used as a palliative measure; however, it is a major surgical procedure which carries risks of its own. This procedure has significant morbidity, and a mortality rate of 3..5%.9. Also, once the stomach is removed, the option no longer exists to take advantage of any new pharmacological therapies that may come along; and dependency on enteral / parenteral nutrition is permanent.

Of all the treatments outlined above, it must be pointed out that to date, Enterra Therapy is the only reversible treatment on the market that has been specifically developed and researched for Gastroparesis patients.

Sadly, one can list all the FDA approved treatment options for severe Gastroparesis in the above few paragraphs.

C. Morbidity and Mortality

Morbidity related to the symptoms of nausea and vomiting has been documented. Nausea and vomiting of any origin be it post operative, medication induced, enteric infection, motion sickness, or induced by pregnancy; are debilitating and very upsetting for family members to witness. A recent review by Hasler et al 10 examining the impact of nausea and vomiting cites these statistics:

- Gastroenteritis, food borne and non-food borne and other intestinal infections cost 3.4 billion dollars in the US.11
- In a 1980 study, acute enteric infections increased medical expenses by 1.25 billion and the lost productivity cost 21.8 billion.12
- In British studies looking at pregnancy-related nausea and vomiting, these researchers estimated the impact at a loss of 8.5 million working days per year. The severely affected women missed, on average, 62 hours of work during their pregnancy.13,14
- Employee productivity declined and resulted in increased health care costs for employees tracked during their course of chemo-therapy (the main symptoms interfering with productivity was nausea and vomiting).15
- A group of out patient surgical centers wanted to find out the impact of post-operative nausea and vomiting on recovery times. These symptoms created increased costs on average of $415 / patient. The increased time of recovery also was found to prevent the performance of 96 – 576 additional surgical procedures.16

Whatever the cause for nausea and vomiting, relief is basically sought from the same pharmacological armamentarium for symptom control; and results are mixed.

The episodes of nausea and vomiting cited above are transient yet this helps to provide an appreciation of the cost and degree of debilitation from these upper digestive symptoms.

Morbidity and Mortality of Gastroparesis

One published epidemiological study reflects **morbidity in Diabetic Gastroparesis patients by tracking rates of hospitalization.** Bell et al 17 investigated the number of hospitalizations and discharges in one year (1998) for patients with Diabetic Gastroparesis in the State of North Carolina. The results based on the North Carolina Hospital Discharge database showed there were 1,476 discharges with total charges of $11,378,466 over 7850 total hospital days.

This is only one state and one year. This data does not reflect the largest group of those suffering with Gastroparesis, namely the "idiopathic" group. This published scientific paper also does not take into account the number of patients who may be on enteral or parenteral nutritional support due to their Gastroparesis. These costs and morbidity can be extrapolated to the US population.

Patients tracked by Abell et al (Gastroenterology, 112(4): A2, 1997) showed the average yearly costs of hospitalization for Gastroparetic patients were $80,000 dollars per year. This is just the hospitalization costs alone.

There is a paucity of scientific literature to paint the full picture of the impact of Gastorparesis on people's lives. Few studies have looked at the symptom impact on patient's quality of life. This is evidenced by a "Pub Med" search using the search parameters: <quality of life survey,>. When IBS (Irritable Bowel Syndrome) is plugged into this parameter it yields 68 published papers; Crohn's diseases yields 103; colitis, 136; GERD (Gastro esophageal Reflux Disease), 130; Functional dyspepsia, 21; Functional

abdominal pain, 20; Gastroparesis—6, even though Gastroparesis has the highest degree of morbidity and mortality within this list.

In Severe Gastroparesis, nausea and vomiting are intractable and can persist for years. It is these symptoms that make the patients miserable, keeps them housebound, sends them to hospital, causes weight loss, devastates their quality of life / psychological status, causes them to be fatigued and unable to sleep.

For Gastroparetic patients, Nausea is debilitating. Vomiting can be life threatening. These two signs and symptoms along with other dyspeptic symptoms take away their desire and ability to eat thus intensifying the problem of malnourishment.

Mortality statistics exist for Gastroparesis. Overall mortality rates are 5% 18 and closer to 10% for specialists who see a preponderance of GP patients. Mortality rates for the diabetic Gastroparetic patients are much higher. Symptomatic Gastroparesis diabeticorum is associated with a grave prognosis. Approximately 30% die within 3 years; 56% may die within 5 years.19 A more recent, but small study by Abell et al shows similar comparisons. In a small group of 33 Gastroparetic patients using prokinetics and antiemetic therapy, (5 males and 28 females with a mean age of 42 years) followed for 10 years; mortality was 43% for the Diabetics and 13% for the Idiopathic patients. 20

D. The approach to symptom control in other disciplines

In the Cancer scientific literature, much is written about nausea and vomiting and its impact on cancer patients.

i. Some excerpts from the Cancer literature:

> Nausea and vomiting may be among the most discomforting, distressing side effects of cancer therapies. Despite advances in the pharmacologic and non pharmacologic management, nausea and vomiting remain two of the most dreaded side effects by cancer patients and their families.21-23

> Ballatori et al reports 24: "About 20 years ago vomiting and nausea ranked as the most distressing side effects of cancer chemotherapy from the patients' point of view. 25 Unfortunately, despite progress achieved with the $5HT_3$ receptor antagonists chemotherapy-induced nausea and vomiting remains a distressing adverse event. In fact, in two studies carried out after their introduction in clinical practice, nausea still ranks number 1 as the adverse event of chemotherapy of most "concern to patients, with vomiting ranking as the 3rd and the 5th most distressing symptom."26, 27

> "According to cancer experts, about 75 percent of people treated for cancer experience nausea and vomiting. These side effects of cancer treatment can drastically affect a person's quality of life."28

In cancer care, the signs and symptoms of nausea and vomiting warrant special registries and validated research tools:

> The Anti Nausea CHemOtherapy Registry (ANCHOR) study brought to light that Chemotherapy-Induced Nausea and Vomiting (CINV) remains a significant, under recognized problem for many patients undergoing chemotherapy for cancer, even with the use of standard anti-emetic treatments (agents used to manage CINV). The study also showed that healthcare providers underestimate the prevalence and burden of CINV on patients' daily lives. 29

> A quote from Steven Grunberg, M.D., professor of Medicine and Pharmacology, at the University of Vermont and lead study author of ANCHOR: "Preliminary results from the

> ANCHOR study brought to light what many cancer patients have long known - but have been reluctant to voice - that nausea and vomiting disrupt daily functioning." 29

The Cancer literature illustrates that standardized tools, many subjective, can be developed for looking at signs and symptoms of nausea and vomiting. This can guide the research into effective treatments. These tools also can be used in different institutions.

> Vomiting and retching are **objective** and definitive *signs*, obvious to the observer and patient and not dependent on the patient's impressions. 30

> *Symptoms*, such as nausea, arise from **subjective** components and dimensions unique to the individual—despite their subjective qualities— nausea affects a patients' self-care, coping abilities, and quality of life. 31

Standardized tools, some validated and others not, have been used in CINV research. Tools such as: patient self assessment surveys; self-recorded daily emesis episodes; ranking of nausea severity on a visual analogue scale (similar to the pain "visual analogue scale). Also, instruments such as the "Functional Living Index—Emesis (FLIE)," this tool addresses the impact of CINV on physical activities, social and emotional function and ability to enjoy a meal. 32

Finally, one of the best known tools is the "Nausea and Vomiting Symptom Distress Adaptation Scale" that was originally developed by Rhodes, Watson and Johnson. 33

Patients with Gastroparesis can suffer for decades with nausea and vomiting and often required two different classes of pharmacological anti-nauseant medication which are taken for years with mixed results. There are no registries or disease specific quality of life surveys to track the impact that nausea and vomiting have on patients with Gastroparesis.

ii. From Chronic Pain research

Chronic pain is analogous to chronic nausea. Both are subjective, both can be exceptionally difficult to control and both can be very debilitating.

Both too can result from a multiplicity of physiological phenomena originating either centrally (Central Nervous System) or peripherally to the CNS. Therefore the research approach into these two symptom entities can follow a similar path in the search for **effective therapeutic symptom management.**

Chronic pain research rests upon **subjective tools**, statistically valid and reliable, which are accepted by the research community to help measure the **efficacy** of new treatment measures. Though these tools may not be perfect, this approach has yielded a good many effective treatments which help relieve patient suffering. Not all tools have been validated. Nevertheless, they are used in research studies.

In pain research, **subjective** tools measuring primary outcomes such as the "Visual Analog Scale," "The McGill Pain Questionnaire," and the four-graded scale "4GS" are widely used in pain research; while secondary outcome measures such as: cost effectiveness, "health-related quality of life" (HRQOL) questionnaires, improvement in sleep, improvement in psychometric measures, and return to work, are frequently utilized. 34

In Pain research, the evidence gathered from these research designs (primarily hinged on subjective tools) is acceptable to the FDA for demonstration of efficacy. Devices such as the Spinal Cord Stimulation have come to PMA's based primarily upon ***empirical evidence.***

Grabow et al undertook a comprehensive review of the scientific papers published, examining the evidence for efficacy of Spinal Cord Stimulation (SCS) devices. He looked at randomized controlled trials, cohort studies, case-control studies, case series, and case reports which described SCS as the primary treatment modality for patients with Complex Regional Pain Syndrome. Fifteen papers were included for analysis. He concluded that **overwhelmingly the evidence for efficacy was empirical-- there were few randomized prospective studies on efficacy**. But, these devices ***suggested a significant therapeutic effect***.34

North et al also conducted a literature review regarding SCS focusing on recent studies investigating the efficacy of spinal cord stimulation for low back pain. In 2002, only two randomized prospective studies considering the efficacy of SCS as compared with other treatment methods had been published. North concluded: Most studies were limited by the same flaws, mainly retrospective. The ultimate efficacy of spinal cord stimulation remains to be determined. However, based upon current evidence, it may represent a valuable treatment option, particularly for patients with chronic pain of predominately neuropathic origin. 35

These SCS devices clearly represent a valuable treatment option for chronic pain, and patients are thankful to have access through a PMA status for these reversible devices that are safe, ***suggest efficacy***, and have an acceptable rate of complications.

Subjective tools can drive the search for new treatments in symptom management like pain, all the while helping researchers better understand the underlying bio-therapeutic underpinnings. This approach can also be applied to nausea and vomiting.

iii. Gastroenterology research into nausea and vomiting of Gastroparesis

Gastric Emptying VS measures of symptom reduction: Which one should be the primary outcome measure for determining efficacy of therapeutic treatments?

Historically, it was thought that symptoms of Gastroparesis were due to delayed gastric emptying, and therefore much of the focus in therapeutic trials for Gastroparesis was based on the effect of an intervention on gastric emptying.

This conventional wisdom needs to be scrutinized. Studies cited below, Forster, Lin, Abell, show gastric emptying, as measured by scintigraphy, is only loosely associated with symptoms, if at all.

As well, the same theme runs throughout the literature looking at prokinetics. Again, research authors studying prokinetics which improve gastric emptying find that this may only modestly improve symptoms. They often conclude that gastric emptying and symptoms are unrelated to one another.36-38

Finally, a basic research study cited below by Chen et al also found no correlation between gastric emptying in canine models and the ability of GES to halt vomiting in vasopressin induce vomiting in these animal models.39

Gastric emptying as the primary outcome for determining effectiveness of pharmacological treatment has traditionally been used as the measure for effectiveness instead of looking at symptom measure outcomes. ***Dr E. Soffer,*** from the Cleveland Clinic Foundation, in Ohio alluded to this at the First International Task Force Meeting on Gastroparesis (Orlando, FL, 2003). He raised some basic issues with the designs of drug trails looking into effective treatments for nausea and vomiting of Gastroparesis. In general, he noted that pharmacological trials are well designed for testing postoperative nausea/vomiting or post chemo-therapy nausea/vomiting; however, he further pointed out that this is not the case with the study of drugs and reduction of symptoms in Gastroparesis.

Excerpt from Dr. Soffer's presentation at the Task Force meeting:

> It is not infrequent with the design of pro-kinetic drug trials, that the end point for determining drug trial success is the improvement of neurological functioning of the stomach (improved GE) rather than the outcome of improved symptom control in the patient.

Because of the recognized inconsistencies between gastric emptying and correlation to symptoms, Dr. Soffer is suggesting that perhaps GE is not a good measure for efficacy when searching for therapeutic interventions into symptoms like nausea and vomiting of Gastroparesis.

a. Gastric emptying studies by scintigraphy:

In 2000 international protocols were developed for a 4 hour gastric emptying (GE) study in order to **standardized** control values for interpreting results.40. This standardization for interpreting GE values was an important step forward. However, this approach is still considered a **screening tool** since it lacks sensitivity in tracking the early phases of GE. Also, most centers still employ the 2 hour GE study. This traditional approach to GE studies means each institution establishes its own protocols, thus lacking any uniformity across various institutions. Each center will vary in test meals, volumes, fat and caloric content; and varying protocols including duration of examination, timing of sampling of ga mma counts after ingesting the meal, and the parameters used to analyze the data. 1

Facts about gastric emptying studies:

- **They are not universally standardized between institutions—therefore serve as a poor tool for comparing results between institutions.**
- **Really serves as a screening tool.**
- **Experts agree, evidence to date shows there is a poor correlation between GE and symptoms.**

The science around Motility is probably one of the least understood areas of gastroenterology. The physiological measure of gastric emptying and how it correlates to symptoms remains enormously controversial.

Further evidence of the shortcomings of GE studies and the correlation to symptoms: A clear phenomenon has been described by clinicians regarding some of their diabetic Gastroparetic patients who can present with profound delayed gastric emptying but who are free of dyspeptic symptoms. These patients are considered to have asymptomatic Gastroparesis. Evidence of the reverse can also be found by clinicians. Idiopathic Gastroparetic patients can initially be diagnosed with delayed gastric emptying only to have GE improve over time, yet they remain debilitated with nausea.

Gastric emptying may be valuable to know as sciences delves into the underlying mechanism of the disease process; and gastric emptying is important for over all gut function; but, as outlined here, it is not needed as a marker of efficacy for Enterra Therapy.

Gastric emptying is not an 'either/or;' or 'all or nothing,' direct measure of efficacy. All experts agree, there is not a consistent relationship between gastric emptying and symptoms. The understanding of the neuro/electrical activity of the stomach is still in its infancy. Many patients can have "disordered" emptying that is not necessarily delayed. Much is yet to be understood, but does not need to be fully comprehended in order to find therapeutic options to reduce symptoms in suffering patients.

b. Measure of symptom reduction

The measure of efficacy for the Enterra Therapy device is currently clouded by the concept regarding Gastric Emptying. **The Enterra device is a palliative treatment for intractable nausea and vomiting in patients with Gastroparesis; and is marketed as such**. This device does not need to show improvement in Gastric emptying before it passes muster on efficacy.

Palliative in the Oxford dictionary means: 'to alleviate suffering.'

The mandate for determining efficacy for anti-emetic, anti-nauseant interventions should follow the examples as described above which are applied by other medical disciplines.

As noted in the cancer and pain literature, **subjective tools** are developed for use to determine efficacy of new treatment approaches. This has been acceptable to the FDA and has resulted in finding new effective symptomatic treatments for patients.

Our current poor understanding surrounding motility diseases like severe Gastroparesis creates enormous difficulties in advancing effective symptom control measures for patients. It is the symptoms for which Gastroparetic patients seek relief. Even without full understanding of the dynamics of the disease, symptom relief can be a primary objective and will be a major benefit for Gastroparetic patients. This primary endeavor will drive the comprehension of underlying mechanisms.

Enterra Therapy has never purported to enhance GE, though the phenomenon has been observed; so even though this area remains controversial, it is not necessary to consider it as a device for palliative treatment for symptoms of nausea and vomiting.

The arguments below will be set out to demonstrate that Enterra Therapy has the ability to significantly reduce nausea and vomiting in the target population and this effect reverses the disastrous impact of these symptoms on patients' lives through: reduced: hospitalization, reduced health care costs, and improvement in quality of life scores. These primary and secondary measures are acceptable in other fields of medicine as measures of efficacy for symptom management.

4. Arguments:

A. Efficacy

Enterra Therapy must be judge by its ability to **reduce the symptoms of nausea and vomiting**.
As well, **control of nausea and vomiting caused by severe Gastroparesis has the added dimension for which to measure efficacy.**

The intense nausea and vomiting that the Gastroparetic patients suffer from, results in the loss of their desire to eat, or fear of eating, since food intake can trigger unrelenting symptoms. Therefore, the use of **secondary measures** of BMI (Body Mass Index), or the patient's ability to return to more normal eating patterns (from dependency on 'feeding tubes' to eating), and cost effectiveness by hospitalization reduction can all provide objective evidence of efficacy.

Some research papers examining the use of GES (Enterra Therapy) have utilized these primary and secondary measures to determine efficacy.[56-59]

That said, many of the studies on GES do show modest improvement in gastric emptying around the 6 month mark. This has been correlated to improved glycemic control in the diabetic Gastroparetic patients. Glycemic measures then could also provide a secondary measure of effectiveness.

(Improved measures in gastric emptying seem to correlate with the amount of energy used with implantable devices. These devices (as mentioned below: known as "gastric pacing") are still experimental and not covered in this petition. Little is known about these experimental devices' and their ability to provide symptom control, though they demonstrate a powerful ability to empty the stomach).

We wish to establish that the Enterra Therapy passes the test for efficacy. This test is the last test needed in order to graduate from an HUD to a PMA category. A PMA category relieves patients of the burden of having to fight their case with insurance providers (which some lose) and permits much more rapid access to this safe, effective and reversible treatment option. This helps to save lives.

> In the regulations: *21 CFR 860.7(a)* the FDA specifically outlines the determination of safety and effectiveness of a device.

The Enterra medical device has already satisfied the sections of this regulation pertaining to safety. This is the requirement of an HUD status as mentioned in the Petition introduction.

Regarding establishment of **effectiveness** this petition will outline the published papers that fulfill the requirements of these regulations:

> 21 CFR 860.7 (a)(c)(2):
>
> > Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and reasonably be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use….
>
> 21 CFR 860.7 (a)(e)(1):
>
> > There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a **significant portion of the target population,** the use of the device for its intended uses and conditions of use, when accompanied by adequate direction for use and warning against unsafe use, will provide **clinically significant results.**

Some facts on Stimulation via implantable devices:

i. Equipment:

Enterra Therapy is: Gastric Electrical Stimulation using **high frequency and low energy stimulation** via two unipolar electrodes implanted in the circular muscle layer on the serosal side of the stomach either laproscopically or by laporotomy, with the transcutaneous leads and tissue pocket implanted neurostimulator which has a battery life of up to 5 to 10 years.

Other devices that also are called Gastric Electrical Stimulation (GES) require ***low frequency and high energy***. This approach **necessitates an external energy source** – also know as "Gastric pacing" (because it actually 'induces' gastric contractions at a rate similar to the normal native rhythm) are not discussed in this petition. These devices are still considered experimental.

With the exception of the leads, the Enterra implantable neurostimulator is a derivative of an implantable neurostimulator used to treat chronic neuropathic pain which was first marketed in the United States in 1984.

The pioneering device for Gastric Electrical Stimulation, then the genesis of an Enterra prototype and Enterra device, have been implanted in humans for the treatment of severe Gastroparesis for over 10 years now. The first implant patient was in January of 1992. These original patients have been followed and the data appears below. A very recent abstract on 10 years of experience with Gastric Electrical Stimulation is also cited. The majority of the target population has demonstrated persistent long term effectiveness of this potent anti-emetic, anti-nauseant device.

ii. What evidence presently exists in the published, peer reviewed journals which establishes efficacy of Enterra Therapy?

Papers are cited here, discussed and collated in tables to help compare the data. This does not represent the entirety of all the published and abstracted research on the Enterra Therapy, but represents the significant papers pertaining to Enterra Therapy.

Of interest, several of the papers in their opening comments don't even question the efficacy of the Enterra Device, since the data reviewed by these investigators state the device's effectiveness is unequivocal, and instead the investigators set out to try and discover by what means (the underlying bio-physiology) the device renders such a potent anti-emetic effect.

iii. Documentation of Expert Opinion

Two papers already provide a summary of key clinical studies done to date and a review of the literature. The expert analysis of this data will be quoted here. <u>This documents expert opinion.</u>

<u>Key summary of WAVESS study (International randomized double blinded cross over study of Enterra Therapy):</u>

From McCallum RW, and Sabu GJ: "Gastric Dysmotility and Gastroparesis," **Current Treatment Options in Gastroenterology 2001**; 4: 179-191:
Excerpts form the paper*: The device, manufactured by Medtronic…was recently shown by the multicenter WAVESS (World Wide Anti-Vomiting Electrical Stimulation Study) trial to significantly reduce vomiting and improve quality of life in patients with Gastroparesis. The WAVESS study group reported a more than a 50% decline in vomiting frequency in 93% of patients at 12 months and significant improvement in quality of life at 12 months. In a double-blind, crossover study, the WAVESS study group also demonstrated a clear patient preference of having the device turned on. In the majority of these patients, gastric emptying is improved significantly, but still has not returned to a normal state at 1 year.

*(Please refer to published paper for references refered to in the text).

<u>Review of GES (Enterra Therapy):</u>

From: Lin Z, McCallum RW: "Treatment of Gastroparesis with electrical stimulation," **Endoscopia 2002**; 14(2)April/June: 45-58:
Excerpts from the paper*: The efficacy of chronic GES with this implantable device (Enterra Therapy) in the treatment of symptomatic Gastroparesis was investigated in a multi-center World wide Anti-Vomiting Electrical Stimulation Study *WAVESS) trial, with promising results. Thirty-three patients with long-term Gastroparesis (17 diabetics, 9 men and 8 women, and 16 women Idiopathic Gastroparesis, mean age: 40 years) were studied for up to 12 months using the

implantable device. During the abdominal surgery, one pair of unipolar electrodes, 10 mm apart, was placed into the muscularis propria of the stomach at about 10 cm proximal to the pylorus for electrical stimulation. The electrodes were secured to the serosa of the stomach using 5-0 silk sutures. The other ends of the electrodes were connected to the pulse generator which was positioned in a subcutaneous pocket above the abdominal wall fascia to the right of the umbilicus using standard techniques.

The initial design of the WAVESS study was a double-blinded crossover (one month of either ON or OFF) followed by 12-month open label. In the double –blinded section of the study, there was a clear preference (3 to 1) for having the device turned on. In general, the main symptom of vomiting and quality of life were significantly improved at 6 and 12 months of GES. In the majority of these patients, gastric emptying of solids was improved but still not returned to the normal by 1 year. Additional analysis of long-term GES indicated a 30% reduction in hospital use in the first year after implantation for these patients. Analysis of nutritional outcome has shown a significant increase in BMI. In addition, 75% of patients who were requiring jejunal feeding tubes had the tubes removed within 6 months and were eating .

Researchers' personal clinical experience with Enterra Therapy published in this same review article:

Since 1998, 55 Gastroparetic patients (39 diabetic, 9 post-surgical and 7 Idiopathic) with documented delayed GE have received high frequency GES by a permanently implanted gastric neurostimulator made by Medtronic (Minneapolis, MN) at the University of Kansas Medical Center. To date, 26 patients (21F, 5M, mean age: 40 years; 19 diabetic, 3 Idiopathic and 4 post surgical Gastroparesis) have completed evaluation of GES for 6 months and 18 for one year. Severity and frequency of nausea and vomiting, 4-hour GE of a solid meal, electrogastrogram (EGG) and status of nutritional status were evaluated at baseline (before implant), 6 and 12 months of GES. In comparison to baseline, nausea and vomiting were significantly reduced after 6 and 12 months of GES. (fig.9). The mean percent of gastric retention at 4 hours was 45$\pm$ 27% at baseline, 31$\pm$27% at 6 months and 44$\pm$34% at one year of GES. On average, the patients had gained 4 kg. after 6 months to one year of GES ($P<0.05$). Of 22 patients, 15 initially required jejunostomy tube feeding. 12 of these 15 patients had jejunostomy tubes removed within 6months of GES while only 2 patients were still requiring enteral nutrition by a jejunostomy tube at one year of GES. EGG was performed on each patient for 30 minutes in the fasting state and for 120 minutes after the meal simultaneously with gastric emptying monitoring as previously described. The postprandial EGG power (amplitude) was increased from -0.1$\pm$1.1dB at baseline to 2.6$\pm$1.2dB at 6 months($P<0.05$) to 1.6$\pm$1.9dB at one year of GES. The mean frequency of the gastric slow wave before GES was similar to those after 6 months of GES. The primary dysrhythmia was tachygastria at baseline and at 6 month of GES was not corrected. Three of the implanted devices have been removed due to infectious complications. In one patient with a history of non-compliance and a colostomy, a superficial skin infection was not cared with in time the device became irreversibly infected. In another patient, a percutaneous G-tube was unfortunately placed through the device pocket, causing the device was infected. In the third case, a superficial wound infection progressed to include the device. All these patients were diabetic. One patient with long-standing diabetes and renal failure died due to a cardio-pulmonary arrest unrelated to the device 10 months after implantation.

*(Please refer to the published paper for references referred to in the text)

2nd Review article from: Abell TL and Minocha A: "Gastroparesis and the Gastric Pacemaker: A revolutionary treatment for an old disease," Journal **MSMA, Dec. 2002**; 43(12): 369-374

"The current GES device (Medtronic, Enterra Therapy) is used for the treatment of the symptoms of Gastroparesis, especially nausea and vomiting. GES can be placed both temporarily, via endoscope and /or gastrostomy tube, to see if a given patient will respond to GES."

"**Evidence for efficacy of GES (Enterra Therapy):**

The use of GES results in not only improvement of symptoms but also **enhances quality of life**. In addition, its use results in overall reduction of health care costs over the long run.

i. **Improvement of symptoms***:
The most impressive, and often dramatic effect of GES is a marked reduction in the symptoms particularly nausea and vomiting. Studies have consistently shown that over eighty percent of patients have at least a 50% reduction in nausea and vomiting.41-45 About fifty percent have at least an 80% reduction in these two symptoms, with some patients having an almost total elimination of vomiting. This has been demonstrated in short-term, as well as long-term studies which included a double-blind randomized phase of GES in patients with gastorparesis.44

ii. **Improvement in Gastric Emptying:**
A majority of studies have shown a consistent improvement in solid gastric emptying at one year as measured by radionucleotides using a standardized low fat meal. 40,44

iii. **Improved pancreatic function:**
Chronic pancreatitis has been associated with Gastroparesis. GES has been demonstrated to be associated with a significant improvement in pancreatic output, as measured by stool elastase. This improvement appears to be mediated, in part by pancreatic polypeptide. This may indicate a role for GES in the treatment of chronic pancreatitis but has not yet been studied.46

iv. **Improvement in autonomic function:**
Abnormalities of the autonomic nervous system are frequently associated with Gastroparesis and other GI motility disorders and may account for many of the associated symptoms. GES has been associated with an improvement in autonomic function over one year. The primary changes have been an increase in cholinergic function and a decrease in adrenergic function. These changes have been apparent in both traditional autonomic function testing such as EKG R to R interval testing and capillary photo-phlethysmorgraphy as well as by newer methods such as heart rate variability on the Holter Monitor using power spectrum analysis.48

v. **Improvement in measures of enteric nervous system:**
GES has been associated with improvements in the gastric electrical rhythm. EGG is a measure of the enteric nervous system. Studies show an overall normalization of the EGG.47,48

vi. **Improvement in nutritional status*:**
Use of GES results in clinical and statistically significant improvement of nutritional status of Gastroparesis patients as measured by body weight and serum albumin at one year. Much of that improvement is in the first 3 months of therapy. In one study, serum albumin went from 3.4 to 3.7 whereas mean weight increased from 149.9 pounds to 162 pounds at three months.49 A recent report demonstrated a significant reduction in HgA1c in patients with Diabetes Mellitus after GES.50

vii. **Reduced hospitalization*:**
Several studies, including data from a randomized study, have shown a reduction in hospital days in patients post GES implantation. In one recent study, the mean number of hospital days/year went from 48.8 to 27.8 days/year over one year.43

viii **Reduced use of health resources*:**
Another recent study has demonstrated a reduction in utilization of health care resources in patients with GES. Health care costs decreased from $6,972/month to $1,878/month

over a three year period.51 An investigator Derived Independent Outcome Measurement Scale (or IDIOMS) which measures severity of illness, intensity of medical services as well as underlying chronic illnesses, correlated well with improvements in symptoms, costs and other health related quality of life measures.

ix. Improvement in quality of life*:

GES results in significant improvements in quality of life as measured by the SF-36, when studied for one year.46 Six of the eight SF-36 sub scores named (Physical

functioning, Psychological, Bodily Pain, General Health, Vitality, and Social Functioning) were significantly improved at 6 and 12 months compared to baseline levels. At 12 months, the Physical Composite Summary (PCS) score and the Mental Composite Summary (MCS) score increased to 32.4 and 45.1 from baseline levels of 25.8 and 36.1 respectively. In fact, the 12 month PCS score was within one standard deviation of the normal range (50±10)."

*These measures have been recognized by other medical disciplines as demonstration of efficacy for symptomatic control.

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iv. Enterra Therapy and impact on Mortality

Another small study has recently presented as a poster: "Effects of Gastric Electrical Stimulation on Outcome and Mortality of Diabetic Gastroparesis." Abel et al presented this as a poster at the American Diabetes Association's 63 Scientific Sessions on June 15th 2003 in New Orleans, LA.

Summary: a quote from Kevin Blanchard, MD, one of the lead investigators: "Patients we see with Gastroparesis have symptoms that are often quite severe. GES actually improves all the parameters that we could measure. Patients tend to feel better. We also note decreased mortality among these patients."52

In this study, 41 patients were grouped as follows: 5 men and 4 women with Diabetes (DM) and gastroparesis with a mean age of 48.4 years, and 6 men and 26 women with idiopathic gastroparesis with a mean age of 37.9 years. These patients had received up to 8 years of GES with follow-up ranging from 2 to 8 years.

Researchers then compared the patients' baseline weekly vomiting frequency score (WVFS, 0-4), Gastrointestinal Total Symptom score (TSS: 0-50) and solid gastric emptying to the latest follow-up data. They compared patient mortality data with a group of medical controls consisting of 5 men and 28 women with gastorparesis, representing a mean age of 42 years, who were treated with antiemetic and prokinetic drugs and followed for up to 10 years (range 7 to 10 years).

In the GES group, WVFS and TTS improved for all by a mean of 53.3% ($P<0.01$). The DM subgroup improved significantly by a mean of 73.9% ($P<0.01$). Solid gastric emptying also improved for the entire GES group by a mean of 56.3% ($P<0.01$), but was less in the DM sub group (mean 49.8%).

Mortality in the GES group was 22% for the DM and 6% for the idiopathic group. In the medical controls, mortality was 43% for the DM group and 13% for the idiopathic medical controls.20

v. Enterra Therapy: Impact on reduction in health care costs through reduction in hospitalization and reduced need for enteral/parenteral nutrition.

An abstract by: Luo J, Abell TL, Nash K, Cutts T: "Gastric Electrical Stimulation is Associated with Reduced Health Care Costs, Compared with Baseline Costs and Medical Controls" (also presented as a poster at: the American Diabetes Association's 63 Scientific Sessions on June 15th 2003 in New Orleans, LA).

This abstract followed five patients (a subset of the GEMS study group) were tracked and compared medical controls. These medical controls have had their data published (GE 112(4): A2, 1997). The 'medical controls' represented a group of Gastroparesis patients who had been enrolled in an out-patient program designed to help reduce their hospital admissions by use of various techniques and combined anti-nauseant therapies; but not GES.

Baseline health care costs were considerable for both groups. Post GES, health care costs decreased significantly for GES patients. GES was associated with significant and sustained reduction in health care costs, compared to their baseline values as well as against the 'medical controls.' Please see Table I and II below:

Table I

The Medical Cost ($/mo) of the GES Group Versus the MED Group at Baseline and Different Follow-up Times

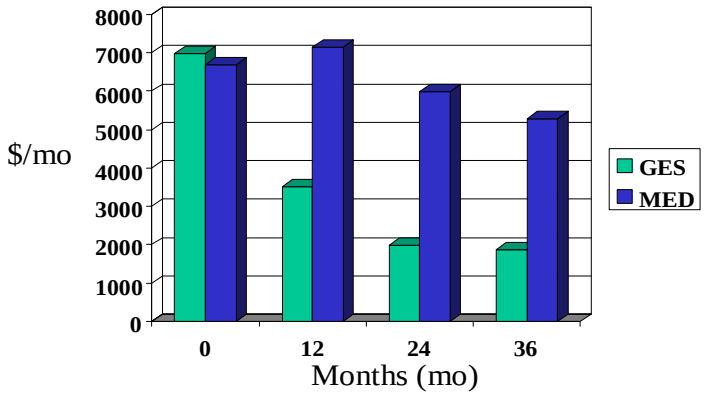
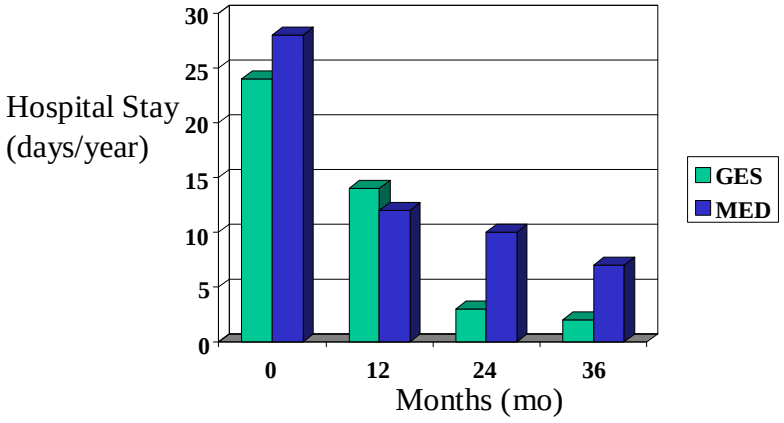


Table II

Length of Hospital Stay for the GES Group Versus the MED Group at Baseline and different Follow-up Times



In the: **Lin Z, McCallum RW: "Treatment of Gastroparesis with electrical stimulation," Endoscopia 2002; 14(2)April/June: 45-58**, publication, these authors reviewed literature on GES, they too concluded that:

GES indicated a 30% reduction in hospital use in the first year after implantation for these patients. Further, the WAVESS study showed a 75% reduction in the need for parenteral/enteral nutrition.

All the published papers that have been cited below, all show reductions in hospitalization and reduction in need for enteral/parenteral nutrition; **this clearly demonstrates significant cost savings.**

vi. Published Papers

Below is the collated information from 7 published research papers, and one abstract (Curuchi). Two of these papers were multicenter trials one of which was a double blinded cross over study. The abstract paper shows 10 years of experience, from three centers, on 133 patients with GES.
These research data are primarily derived from the most clinically challenging patients.

TABLE III. Methodology

Study Citation Year published	Study design	Number of Pts.	Description of severity documented	Primary Outcome(s)	Secondary Outcome(s)
Familoni 41 1997	Case study	One	Yes	Sx measures, VF: vomiting frequency and GE	
Foster 53 2001	Large single center study	25	Yes	Sx measures, VF and GE	
Lin 54 2002	Prospective study	15	Yes	Myoelectrical activity GE correlation to symptom measures	
Abell 55 2002	Prospective multicentered unblinded study	38	Yes	Sx measures, VF and GE	BMI Changes to nutrition patterns and Prokinetics and/or anti-emetics use
Abell 56 2003	Study group a subset of GEMS* Longitudinal study ST, Intermediate and long term follow-up of 5yrs.	12	Yes	VF TSS: Total Symptoms Scores	Quality of Life Measures BMI and wt. stabilization Blood Albumin Route of nutrition
Abell 57 2003	Multicentered, Randomized Double Blinded Cross over study	33	Yes	VF: vomiting frequency, TSS GE	Quality of Life measures
Forster 58 2003	Large single centered study	55	Yes	TSS VF GE	Quality of Life measures: SF-36 BMI and Wt. Reduction in Hospitalizations Diabetic Hemoglobin A1C
Curuchi 59	Ten year experience from 3 centers	133	Not available **	Mortality TSS VF GE	Quality of Life measures not reported in Abstract

(Patient – Pt., Vomiting Frequency – VF, Gastric emptying – GE, Treatment –Tx, Symptoms – Sx, History – Hx, Gastroparesis – GP, Jejunostomy tube – J-tube, WAVESS: World Wide Anti-Vomiting Electrical Stimulation Study, Body Mass Index -- BMI).

* GEMS Study Group. Electrical stimulation for the treatment of Gastroparesis: preliminary report of a multicenter international trial (abstr). Gastroenterology 1996;110:A668

** Abstract just accepted (February 22, 2004) for publication in Gastroenterology and will be presented as a poster at Digestive Disease Week, New Orleans, LA, May 16 – 19, 2004.

Four other recent abstracted papers are not included in the above table but have been mentioned in the review summary by Abell et al.

TABLE IV. Patient Characteristics.

Study Citation	Age Mean(range)	Sex F/M	Duration of symptoms Mean(range)	Idiopathic	Post-surgical	Diabetic	Documentation of Severity
Familoni 41	29, single Pt.	F				X	Refractory to all medications as evidenced by continued hospitalizations and no change in GE
Forster 53	41(21-66)	19/6		3	3	19	14 with J-tubes All, repeat hospitalizations in previous yr. All documented wt loss.
Lin 54	41(27-66)	11/4		4		11	Refractory to standard medical therapies
Abell 55	37. 5(18-49)	29/9	All Pts highly symptomatic >1 yr prior to study	24	5	9	Refractory as evidenced by significant wt. loss even with standard prokinetic/antiemetic drugs.
Abell 56	35. 7(19-48)	8/4	Mean : 7. 3 yrs	9		3	All with a Hx of hospitalizations, Refractory to 2 classes of Prokinetics and 2 classes of anti-emetic medications
Abell 57	38. 9(19-65)	24/9	Mean: 6. 3yrs Range: 1 – 28 yrs.	16		17	Study criteria of severity defined as: VF: >7/week GE: >60% @ 2hrs >10% @ 4hrs. GP Sx > 1 yr Refractory to 2 of 3 classes of Prokinetic And 2 of 3 classes of antiemetics.
Forster 58	40.5 (21-66)	41/14	Mean: 9.9 yrs.	7	9	39	All Patients were part of previous study groups: WAVES, or CUESS, or HUD protocol 25 Pts. On J-tube feedings at baseline
Curuchi 59				109***		24	

(Patient – Pt., Vomiting Frequency – VF, Gastric emptying – GE, Treatment –Tx, Symptoms – Sx, History – Hx, Gastroparesis – GP, Jejunostomy tube – J-tube, WAVESS: World Wide Anti-Vomiting Electrical Stimulation Study, CUESS: Compassionate Use of Electrical Stimulation Study, Body Mass Index -- BMI). ***This number represents idiopathic and post-surgical patients.

Outcomes of cited papers,
Summaries are provided below.

Familoni et al is an earlier case study looking into the emerging evidence of efficacy with use of higher frequencies of gastric electrical stimulation in controlling symptoms, nausea and vomiting and improving gastric emptying (GE). This patient with long standing diabetes mellitus (DM) could only tolerate liquids and was refractory to all available prokinetics. As well, she had been participating in a drug trial of Cisapride for 24 months without relief of symptoms. The only change in her treatment plan was the application of GES. Upon application of GES, she showed reduction in vomiting from an average of 3 times/day to 3 times/week. Nausea and abdominal pain were also reported as greatly decreased. Incremental improvements of liquid GE were also demonstrated to be well above baseline on weeks 1, 4, 15, and 52.

Excerpts from research paper: of note, on week 40 the patient made an unexpected visit to the emergency department due to greatly increased symptoms of nausea, vomiting and pain occurring for about 2 weeks. This unexpected visit provided a control for the efficacy of GES in alleviating symptoms. In the ER it was discovered that the stimulating electrode was no longer working. Upon stimulation at the second electrode site her symptoms resolved. It was not known for how long her electrode had malfunctioned, but return of stimulation resolved her complaints. Also, at 56 weeks, she again complained of increased symptoms. It was established that the electrodes were no longer viable. Symptoms increased around events of disrupted stimulation.

Forster et al, this large single centered prospective study wanted to explore GES impact on symptoms of nausea and vomiting and GE. Included in the study were patient representatives of the 3 largest groups which make up Gastroparetic sufferers; namely, the diabetic; idiopathic; and post-surgical sub groups. A patient profile of severe Gastroparesis is also provided in the paper's introduction. Of the 25 patients studied, 14 were dependent upon j-tube feedings; the entire study group had an average of 6 hospitalizations and 25 lb weight loss prior to enrolling in the GES study.

Methods: During follow-up appointments, symptom severity was assessed at baseline, 3 months, 6 months and 12 months utilizing a self-administered questionnaire. Patients were able to rate a variety of subjective symptoms and frequency of vomiting. Development of this questionnaire and the statistical tools used to analyze this data are documented in the paper.

Results: Symptom severity and frequency—on average—showed a remarkable and statistically significant decrease in both nausea and vomiting by 3 months and this was sustained throughout the study period of 12 months. Three patients did not appear to benefit from the GES. These 3 patients were diabetics, and two of them had had diabetes for the second and third longest of any of the diabetics enrolled in this study (26 and 30 years).

Improvement in GE showed a numerical improvement of statistical significance only at the 3 month interval. As expected, there was individual variation in GE.

The authors pointed out that improvement in symptoms of nausea and vomiting did not parallel improvement in gastric emptying times.

The authors noted two other secondary measures observed to illustrate the effective anti-emetic action of GES: by 3 months, 7 patients were able to have their jejunostomy tubes removed and by 6 months, 4 more j-tubes were removed. These patients were sufficiently comfortable with eating again that they no longer required enteral nutrition.

As well, the patients experienced a significant gain in body weight. The average weight of 60.1 ± 2.2 kg at baseline rose to 62.6 ± 2.7 kg (P= 0.003 by paired t tests) at 6 months.

Complications such as device pocket infection were found to be at an acceptable level.

In this paper, a panel discussion is documented with panelists providing critique. Of note, one of the investigators describes the phenomenon observed but unable to capture in the data. To quote Dr. Forster: "The data do not show how miserable a lot of these patients are, and when they come back , (for follow-up post GES implantation) a lot of them have gone out to eat, which they haven't been able to do for a while. A lot of them have been in the hospital for extensive periods of time prior to this procedure and once it has been put in and they get used to it, after a couple of weeks, they're not only out of the hospital, but they're able to get out and eat in restaurants."

Lin et al study sets out to investigate **by what means** the Enterra device renders such dramatic improvements (as published by other researchers) in reducing the degree of nausea and vomiting in drug refractory Gastroparetic patients.

They utilized two-channel serosal recording leads to directly measure gastric myo-electrical activity before and during GES in 15 patients for 3 months. Even though this paper's primary aim was to observe myo-electrical activity and analyze changes in wave patterns during fasting and meals—**these investigators also acknowledged that their patients had significant reduction in nausea and vomiting but little improvement in gastric emptying.**

Results of symptom scores Before GES, and at 3 month follow-up:
Nausea score (0-4) 3.3 ± 0.3 @ 3 months: 1.3 ± 0.6 (<0.01 P value (t test))
Vomiting Frequency (0-4) 2.3 ± 0.5 @ 3 months: 1.1 ± 0.5 (<0.01 P value (t test)).

Abell et al this was a non-placebo controlled, multi centered, international, feasibility study looking at 38 highly symptomatic Gastroparetic patients. This study is very detailed and thorough looking at a variety of measurable variables and observations. Even though this study was non-placebo, mid way through the study period, 10 patients inadvertently had had their GES turned off. This resulted in a dramatic increase in their symptoms.

Documentation of severity is outlined in the study. All patients had intractable symptoms of at least one year duration. All had had trials of prokinetics and antiemetics and despite these interventions 14 patients required enteral nutrition and a further 5 were on parenteral nutritional support and all patients had experienced significant weight loss prior to entering the study. Each patient had been carefully screened to exclude eating disorders such as anorexia nervosa. The vast majority of these patients were diagnosed as idiopathic Gastroparesis patients and the remaining patients were diabetic and post-surgical.

This Study also provided for an unblinded period at 6 months where patients voluntarily had their devices turned off for one week in order to compare symptoms in the previous week.

Baseline screening included assessments of gastrointestinal symptoms, GE, body weight, and use of anti-emetics, prokinetics and nutritional support status. Assessments were done at each follow-up visit of: 3, 6, and 12 months and during the unblinded one week off period at 6 months.

This study also included a phase I and phase II step, utilizing temporary GES in the phase I portion of the study. This temporary GES phase was used as a screening period to help identify patients who are 'responders' to GES and therefore will derive benefit from therapy. Parameters for 'responder' are clearly defined in the paper.

The breakdown of measured parameters for each assessment period is detailed in the paper. The results as summarized by the authors: "(GES) overall showed 35/38 patients (97%) experienced > 80% reduction in

vomiting and nausea. This effect persisted throughout the observation period (2.9 – 15.6 months, 341 patient-months). GE did not initially change, but improved in most patients at 12 months. At 1 year, the average weight gain was 5.5% and 9/14 patients initially receiving enteral or parenteral nutrition were able to discontinue."

This improvement was seen in these previously intractable symptomatic patients who had tried all available prokinetics. Most experienced a rapid and sustained symptomatic improvement. GE, if it did improve, was not seen until late into the observational period.

Complications: no cardiac arrhythmias were observed during the study. The infection rate observed was within the range of recent reports on cardiac pacemaker implants.

Two patients did not show improvement with GES. Their cases resulted in total gastrectomy as an attempt for palliation of their symptoms.

"A subset of 27 patients who were available and willing to be re-examined more than 12 months after implantation were subsequently reevaluated after the end of the study. Three had died (1 from lung cancer, 1 from heart failure, and 1 related to organ transplantation). Three patients had the device removed due to infections or erosions, and 2 of these patients (both diabetic) remained symptom free after removal of the pulse generator. In the remaining 18 patients, with a mean follow-up time of 30 months, the pulse generator was functioning well. In these patients, median vomiting frequency was 0 episodes per week versus 28 weekly episodes at baseline."

Writer's note: for these 18 patients, their sustained response to GES is dramatic.

Writer's note, these international participating study centers were in: USA, Canada, France, Belgium, Sweden, Germany and the Netherlands providing a nice cultural mix. Since nausea -- like pain, is a subjective symptom which can be modulated by cultural and social background—the fact that all of these patients experienced a parallel reduction in symptoms speaks to the potent, yet to be understood effectiveness of GES.

Abell et al This was a double blind, placebo controlled, international investigation with the primary aim to examine the efficacy of Enterra Therapy; also known as the 'WAVESS' (World Wide Anti-Vomiting Electrical Stimulation Study) study has recently been published in Gastroenterology, 2003.

Documentation of severity showed that patients had a mean duration of symptoms for 6.2 years and the majority were idiopathic. Fourteen of these patients required either enteral or parenteral nutrition; all were documented as refractory to two of three classes of prokinetic and two of three classes of anti-emetic medications; and all demonstrated delayed GE on scintigraphy at 2 and 4 hours.

Many parameters were measured at baseline and through the 4 follow-up visits at 1, 2, 6 and 12 months. The measured parameters included:

- WVF (Weekly Vomiting Frequency) and symptom severity
- Nausea, early satiety, Bloating, Postprandial fullness, Epigastric Pain, Total Symptom Scores
- SF-36 (a well recognized, universally utilized and validated general quality of life questionnaire)
- Two sub measures derived from the SF-36: Physical Composite Score and the Mental Composite Score.
- Adverse events
- Hospitalizations
- Route of supplemental nutrition
- Glycosalated hemoglobin in the diabetic patients and,
- GE times at 2 and 4 hours.

Summary of results: At the end of the blinded phase, vomiting frequency decreased by 50% in the total patient group for those whose device was turned 'on' compared to those with the device in the 'off' setting (p=0.05). Also, a 3 to 1 patient preference for the 'on' setting was expressed before unblinding. During Phase I (blinded double cross over), Total Symptom Scores (TSS), started to show improvement, in the 'on' vs. 'off' setting, but did not reach statistical significance till phase II.

In Phase II (unblinded) all the patients were switched to the 'on' position and followed up at 6 and 12 months. Results showed a significant drop in WVF. Compared to baseline the vomiting frequency dropped by 72% for the combined group of patients; 83% for the Idiopathic sub-group and 63% for the diabetic sub-group. As well, Physical and mental quality of life scores improved significantly compared to baseline (p=less than 0.05); TSS improved significantly from baseline (p=less than 0.05). Finally, GE showed statistically significant improvement for the combined groups at the 12 month follow-up; but (the authors noted) improvement varied widely and there was no association between changes in symptoms and gastric emptying. This is consistent with findings in other studies in Gastroparesis. These authors went on to state that the effect of GES is due to factors beyond gastric motility and dysrhythmias.

Of the 14 patients on enteral or parenteral nutrition, half no longer needed this route of nutrition at 12 months and were able to keep their food down—thus eating more normally. This had been something unachievable with medication.

All measurable parameters, for the patients who completed the 12 month study, showed improvements; many statistically significant as with: weekly vomiting frequency, total abdominal symptom score, GE tests and quality of life measures and as mentioned—some returned to eating once again.

Abell et al, this cited paper provides for a long term follow-up of a sub-set of patients from the original GEMS study group. 12 patients continued on with long-range follow-up after the initial 12 month study with the GEMS group. These 12 patients had additional follow-up sessions between 1 to 2 years and at 5 years. All patients at baseline (before GES) had symptoms of long duration—mean 7.3 years. Their Gastroparesis was associated with Diabetes in 3 patients and Idiopathic in 9 patients; consisting of 4 men and 8 women and a mean age of 35.7 years.

Measured parameters; from baseline and at 3, 6, and 12 months, then again between 1 – 2 years and at 5 years with GES; consisted of: TSS, laboratory blood work including albumin (a protein marker of nutritional status), weight, BMI (Body Mass Index), method of nutrition, (either oral, enteral or parenteral nutrition), WVF, and overall health-related quality of life measures.

Summary of findings: In the short-term follow-up period (0 – 12 months), gastrointestinal symptoms improved in all patients with a significant improvement in nutritional status. Patients' average weight increased as well as BMI from baseline. Blood work also showed improvement in mean serum cholesterol levels (180.6 $\pm$ 13.2 at baseline to 216.8 $\pm$ 19.7 at 3 months. This trend peaked at 6 months); and serum albumin levels changed from 3.5 $\pm$ 0.2 at baseline and peaked at 3 months; increased lymphocyte count from 30 $\pm$ 3.1% at baseline to 32.6 $\pm$ 5.9% at 12 months (p>0.30 by ANOVA). One patient had a low baseline lymphocyte count of 7.4 % at baseline that improved to 18.5% by the third month after GES.

Finally, patient route of nutrition changed from baseline. Eight patients had been on oral only nutrition with 2 on enteral and 2 on parenteral nutrition. At the one year follow-up one enteral patient was able to convert to oral only nutrition and one parenteral dependent patient was also able to convert to oral only nutrition. At the 5 year follow-up period, only one patient was requiring enteral and oral nutrition. An over all change of 30% compared to baseline.

All measured parameters showed improvement from 3 months and persisting through to 5 years showing enduring, statistically significant changes to: TSS, WVF, weight, and BMI measures. As well, 2 health-related quality of life measures showed improvement from baseline.

Forster et al, in this cited paper, Forster et al studied 55 patients from April 1998 till November 2001: 9 were from the original WAVESS study group, 32 from the CUESS study group (this was a prospective trial for determining compassionate use of the device (pre-HUD designation)) and 14 patients post HUD designation. This collection of patients represented a very ill population—many steadily losing weight and on enteral or parenteral nutrition at baseline. Average duration of symptoms was 9.9 years.

Measured parameters were taken at baseline then 6 and 12 months. These parameters consisted of: gastric emptying; total symptoms score; severity and frequency of nausea/vomiting; quality of life measures utilizing the SF-36 questionnaire; body weight and body mass index; and finally—Hemoglobin A1C in the diabetic patients.

Outcomes post GES:

- Six patients died, all diabetic and none related to the GES.
- GES had to be removed from 4 patients, all diabetic; three due to infections and one due to a small bowel volvulus. All patients recovered.
- In 3 other patients, the device needed to be moved or replaced. One was relocated due to migration of the device (patient was feeling so much better he had returned to golfing—this activity is felt to have caused the device migration) because the leads had lost contact with the stomach. The above mentioned patient with volvulus had GES replaced 9 months after surgical correction of the volvulus. The final patient was in a car accident, fracturing her sternum. Seven days after the accident her Gastroparetic symptoms dramatically increased—examination revealed that one of the leads had become detached from the force of the accident. The lead was replaced and her symptoms improved very soon after the surgery to correct the displaced lead.

Summary of results: of the compliment of patients followed for 12 months, gastric emptying was significantly improved at 6 months, but the numerical difference was small. This improvement was not sustained at 12 months. However, a third of these patients did achieve normal gastric emptying (<10% remaining at 4 hours on scintigraphy). Of this third, 58% were diabetic patients, 25% idiopathic, and 17% post surgical.

Gastrointestinal total symptom scores for both severity and frequency were significantly improved at 6 months ($P<0.05$). Total symptom scores remained significantly reduced at 12 months, this despite the lack of overall continued improvement in gastric emptying.

Quality of life parameters improved dramatically with mental composite scores approaching normal, rising from 37 to 48. Most of this improvement occurred in the first 6 months.

Patients demonstrated a marked decrease in the need for hospitalization. In the year prior to GES placement, the average days spent in the hospital was: 57 ± 9 (range: 0 to 252). The year following GES, this fell to 17 ± 3 days (range 0 to 69; $P<0.05$). This dramatic reduction in hospitalization could explain the improved quality of life scores.

Nutritional parameters also showed improvement, with the average patient showing a body weight increase by almost one kilogram and the body mass index increasing by 0.4 units. This improved body weight translated to the majority of patients having their jejunal feeding tubes removed and no one remained on parenteral nutrition. At baseline, 25 patients were on J-tube feedings (1 had a gastrojejunostomy); after GES, only 8 remained on j-tube feedings by 12 months.

The authors went on to conclude that GES is a potent anti-emetic despite not consistently showing improvements to gastric emptying times at 12 months. Yet, one third of the patients did achieve normal emptying at 4 hours after 12 months of therapy and they did not come exclusively from one etiologic sub group.

Improvements in weight, eating, quality of life measures, and reduction in nausea and vomiting clearly makes life more tolerable for the majority of these patients. These improvements need to be viewed from

the perspective that these patients are young (average age 40.5 years) women (76%) and men in the prime years of their life and they can be returned to families and employment activities resulting from GES therapy. It must be kept in mind that these patients were terribly ill at time of GES implant and losing ground with continued weight loss or persistence with nutritional support, all previously unresponsive to standard medical interventions.

For the diabetics, improvements in symptoms also allowed for better eating habits and improvement in glucose control. GES is able to markedly decrease or halt nausea and vomiting. This then translates to a number of advantages for diabetic patients:

- GES demonstrated reduced HbA1C and sustained improved glucose control. This could help reduce the occurrence of future diabetic complications because of improved blood glucose control.
- Also, reduction in vomiting makes the patients better candidates for pancreas transplantation, since immunosuppressant can be taken orally and predictably absorbed without vomiting.

Curuchi et al is a very recent abstract which has been accepted for publication and will appear in Gastroenterology this spring as well as being presented as a poster at the Digestive Disease Week (DDW) in New Orleans, LA, May, 2004. This abstract report provides data on 10 years of experience with GES from three centers. The published paper will also feature health related quality of life measures. This data is not available at this time for inclusion in this petition.

Evaluation of both safety and efficacy was the primary focus of this research project. Mortality rates were also tracked and compared to medical controls who had received traditional care and management for their Gastroparesis. The medical controls had also been followed for ten years. The controls have had their data published and represented 33 patients, 26 non diabetics and 7 Diabetic patients. (see *Diabetes* 52: A191, 2003).

Methods: All patients had consented for GES. Their presenting diagnosis, type of implant, survival, most recent gastric emptying (compared to baseline symptoms) was documented.

Ten years of experience at 3 centers tracked the results of patients coming in to receive their GES. One hundred and thirty three patients participated. Of these, 122 were permanent implants, and 11 temporary. Eight patients had their devices removed, most commonly due to infections. Eleven patients underwent replacement of their devices for battery change or other technical problems.

The results from 3,622 patient months (equating to 301.8 patient years of experience with GES) showed that of the 109 non diabetic Gastroparetic patients (post surgical and Idiopathic), 9 of the 109 had died (most from their primary disease) compared to 2 of the 26 non-diabetic controls. This represents a mortality rate of 12% VS 13% for controls.

More dramatic was the mortality rate for the diabetic patients who had GES VS controls. The Diabetic patients with GES (n=24) showed a mortality rate of 6% compared to the Diabetic controls who had a mortality rate of 43% (3 deaths out of 7).*

Data on the total GES patient group showed a persistent and enduring ability to decrease total symptom scores and vomiting frequency compared to baseline in these patients; as well as showing improvement in gastric emptying at 2 hours and 4 hours.

Baseline values for total group of GES patients VS follow-up:

Total Symptom Scores (0 to 50) =…….38.4 VS 18.2 at follow-up
Vomiting Frequency (0 to 4) =..……....3.57 VS 1.44 at follow-up
Gastric Emptying time @ 2 hours =..……..…...59.6 retention VS 39.3 at follow-up
Gastric Emptying time @ 4 hours =….……..…29.16 retention VS 14.9 at follow-up

No deaths were attributed to the devices.

The authors conclude that: GES has proven to be safe and effective for the last decade. Efforts need to continue to help identify which patients will benefit most from GES and under what conditions.

* Writer's note: Mortality numbers reported in this abstract on diabetic controls are from a small data set, yet this percentage closely parallels mortality numbers reported in the literature. Therefore, the drop in morality for Diabetics with GES as reported in this abstract suggests that GES is a life saving device. Patients' experiences also attest to this fact.

vii. Evidence to dispel 'placebo effect': Enteric cellular abnormalities, sustaining symptom reduction, improved bio-parameters and an Animal model

Gastroparesis is a severe neuro-muscular disorder affecting the entire stomach and often extending into the upper portions of the small bowel. Researchers who have looked at full thickness biopsy have found cellular abnormalities both in the Idiopathic and Diabetic patients. The degree of digestive failure that severe Gastroparetic patients face often warrants enteral / parenteral nutrition.

One consistent objective marker that comes through all of these cited papers is the fact that some of these terribly ill patients come off of enteral / parenteral nutrition around the 3 to 6 month mark or later with GES. For such a dramatic effect to occur in patients who were previously non-responsive to numerous medication trials (all of which have been extensively studied in Gastroparesis) provides powerful evidence against a placebo effect. As well, Abell et al cites data on patients followed for 5 years and cites 10 years of experience on patients. This data all shows a sustained potent anti-emetic, anti-nauseant effect with GES. Presumably a placebo would not be able to provided long-term sustained and measurable outcomes.

Also other 'bio-makers' cited in the literature such as improved pancreatic function and improved autonomic nervous system function and decrease in serum HbA1C in the Diabetic patients and sustained improved glucose control all provide evidence against a placebo effect.

An elegant study by Chen et al 39 further dispels the placebo effect. The aim of the study was to investigate 2 methods of electrical stimulation with parallel parameters as documented in human clinical trials (one of which being GES) and a third novel electro-acupuncture stimulation technique. Efficacy was to be determined on the ability of these methods to control vomiting and nausea behaviors in a canine model of gastric dysrhythmias. Controls were used and vasopressin was the emetic provoking agent.

(Comments and findings will only be provided for the stimulation parameters that were similar to Enterra therapy).

The investigator attempted to duplicate the same methods and stimulation parameters as used in the Forster et al and GEMS abstract (cited above in the tables) to see if the anti-emetic effect reported in humans could be replicated in the canine models. A further step was taken to provide for controls.

In the Chen et al study, their findings with the canine models (with placebo controls), showed the same reduction in the objective measures of vomiting and reduction in the observed behaviors that suggest nausea in the animals challenged with vasopressin who had GES (on). These investigators reported that gastric electrical stimulation with short pulses had no effect on gastric slow waves but completely prevented liquid vomiting and substantially reduced symptoms in their canine models leading them to hypothesize that the anti-emetic effect of GES is vagally medicated. This led them to state that the previous clinical trials (GEMS study group and Forster) were not attributed to a placebo effect in humans.

viii. Summary:

Effectiveness is satisfied by the fact that patients enrolled in these key trials / investigations and longitudinal studies, and who represent the most intractable and clinically challenging population,

consistently showed improvement in a ***significant portion of the study population*** as measured by various subjective and objective tools, and demonstrated in both primary and secondary outcomes which were (overall) statistically significant improvements sustained over time compared to baseline measures.

The fact that GES has been repeatedly replicated-- showing over all: significant reduction in nausea and vomiting and improvement in secondary measures, by different investigators in different institutions, and for years post implantation, resoundingly shows efficacy.

As well, GES demonstrates persistent, enduring and potent reduction of symptoms, primarily of nausea and or vomiting, as well as secondary gains in stabilization of weight and for some, more normalization of eating patterns. This results in improved quality of life and mental health, based upon standardized, recognized, validated measures.

The phenomena experienced by patients and observed by experts cannot be ignored. The bulk of evidence presented, including one double blind cross over study, makes a powerful case for efficacy—as powerful as for those devices already on the market with PMA status.

Medicine is not an exact science. The tenants of medicine are to provide compassionate care and alleviate suffering. Patients need to fully access a revolutionary treatment that can bring hope, and for many, relief from their chronic, debilitating illness.

5. Conclusions:

The literature demonstrates that GES effectiveness has an overall rate for palliative control of nausea and vomiting as high as 70 to 80% with enduring results. This potent anti-emetic, anti-nauseant effect, allows patients to feel better, eat better, gain weight and stay out of the hospital. One small study has demonstrated a decrease in mortality rates for GES patients.

Gastroenterologists who are beginning to use GES are finding these results extrapolated to their own client base.

It must be recognized that for these severely ill patients, GES is not a magic wand. Patients cannot expect a complete return to health and well-being post GES. Compared to where they were -- the depth of their suffering and despair -- they are thankful to gain some, or a large measure of relief. Even more profound is the ten years of experience with GES showing a decrease in mortality rates for diabetic patients with GES vs. those without. Some patients are also able to return to a more active lifestyle post GES. These all suggest a very potent anti-emetic effect with the ability to diminish the continuing eroding effects of intractable nausea and vomiting.

Not all will respond, but **all must have a right to access,** without hindrances, something that is safe, reversible and has now been proven effective; especially when taking into consideration how precious few treatment options for symptom relief are available for this patient group.

Of interest, some of the literature demonstrates the technique of temporarily placing electrodes via the endoscope, as a means of patient selection for which the device has a greater probability of long term success. This is a very responsible and logical approach. As well, investigators are scrutinizing the stimulus parameters in an attempt to continually improve the clinical management of symptoms. This work undoubtedly would speed up once PMA status is granted.

6. Environmental impact / Certification

Medtronic Inc, in following "Good Manufacturing Practices" has already satisfied the requirement of environmental documentation under 21 CFR 25.33(g). This would have been required for the HUD status.

The undersigned certifies, that, to the best of knowledge and belief of the undersigned, this petition includes all information and views upon which the petition relies, and includes representative data and information known to the petitioners' which are unfavorable to the petition. To the petitioners' knowledge, no other similar issue, act or transaction to this petition is under consideration.

7. Agency action requested:

The FDA immediately:

- **Refers this petition to their Gastroenterology and Urology Devices Advisory Panel for review and comments.**
- **The Commissionaire reviews this pertinent literature with Medtronic Inc and immediately invites Medtronic Inc to begin the process to transfer the Enterra Therapy Device from a HUD status to PMA status.**

The Petitioners are looking for a favorable ruling by the FDA Devices Advisory Panel determining efficacy of GES. This favorable ruling, even if it does not result in an immediate application by Medtronic for PMA status, will undoubtedly ease access for insurance approvals that patients currently have to fight and in some cases lose.

Petitioners' are requesting a response to this Petition within 180 days.

Dated the 16th day of March, 2004.

On behalf of all petitioners,
Jeanne Keith-Ferris, RN, BScN

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GPDA:

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