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Horizon Scanning Report

Enterra® Therapy Gastric Electrical Stimulation (GES) System for the treatment of the symptoms of medically refractory gastroparesis

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and Efficacy
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of New
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Surgical**



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College of Surgeons**

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Executive Summary

In the United States there are approximately 3 million and in Australia approximately 120,000 gastroparesis sufferers that could potentially benefit from the use of this therapy. Widespread use of Enterra Therapy could bring much needed symptom relief, improved nutritional status and, most importantly, improved quality of life to many of these patients.

Most of the included studies demonstrated a significant improvement in at least one of the outcome measures and attributed these positive effects to Enterra Therapy. The results also suggested that this improvement in symptoms is not related to any specific aetiology of gastroparesis. Just as important, where investigated, these studies showed that the associated risks of implanting and using Enterra Therapy were comparable to similar therapies/procedures (e.g. cardiac pacemaker implantation). While the use of Enterra Therapy has its risks, it is important to remember that alternative gastroparesis treatments also carry risks. In addition to the numerous side effects and decreasing effectiveness over time, use of the drugs cisapride and metaclopramide carry the risk of cardiac toxicity and other side effects serious enough to force some patients to stop their use (Keith-Ferris 2004). It is estimated that in approximately 30% of patients using metaclopramide, adverse side effects may force patients to stop taking the drug (Keith-Ferris 2004). Total parenteral feeding in nutritional modification also carries risks of bacterial overgrowth, liver failure and even life threatening sepsis (Keith-Ferris 2004).

The majority of data on Enterra Therapy have arisen mostly from case series studies, which are considered to provide a lower level of evidence compared to comparative studies. The case series studies were plagued by a range of methodological flaws, including low participant numbers and high levels of attrition, so the possibility of a placebo effect impacting on the data obtained cannot be dismissed. The substantial overlap of patients in some studies also gave a false appearance of abundant clinical data. In addition, the majority of the studies presented were in one way or another linked to the manufacturer, either through contributions by Medtronic or because the study was conducted by a clinician/investigator supported by Medtronic. Therefore, data from studies yielding higher quality evidence is required in order to eliminate the possibility of the placebo effect and to gain a more accurate indication of the true safety and efficacy of Enterra Therapy.

Although the exact financial impact of this new therapy has not been documented yet, a comparative study of Enterra Therapy versus an alternative intensive medical treatment showed not only the clinical but also the financial advantages of Enterra Therapy (Cutts *et al.* 2005). Reduced costs to individuals and health systems as a result of improved symptoms and fewer hospital visits will free up hospital resources (human, financial and material) in an environment where the health system is already under intense pressure.



Background

Background to the Condition

The stomach is the principal organ of digestion. When food is ingested a series of muscular contractions, known as peristaltic waves, spread across the stomach to churn and liquefy the food and promote mixing with digestive juices. Once this process is complete, the pyloric sphincter at the distal end of the stomach relaxes and peristaltic waves pump the liquefied food in a controlled manner into the small intestine for further digestion and absorption (GI Health 2005).

Stomach peristalsis originates from the interstitial cells of the Cajal in a small zone of the proximal gastric corpus near the greater curvature (the pacemaker area) of the stomach (Bortolotti 2002; Lin and McCallum 2003). From this area of the proximal stomach, a slow wave initiates and travels circumferentially and distally toward the pylorus at a frequency of three cycles per minute with increasing amplitude and velocity (Lin *et al.* 2004a). The resulting peristalsis and gastric contraction are thus regulated by the gastric pacemaker (GI Health 2005). Any disruption to the frequency or strength of the gastric slow waves can lead to gastric motility disorders.

Gastroparesis

Delayed gastric emptying, or gastroparesis, is a gastric motility disorder in which gastric muscle contraction is impaired. The symptoms associated with gastroparesis are very debilitating, and patients with severe gastroparesis must live with chronic nausea and vomiting, heartburn, early satiety, bloating, unpredictable glucose levels and epigastric pain (Abell *et al.* 2002; GI Health 2005). These symptoms often lead to reduced appetite, subsequent weight loss and, in severe cases, dehydration, electrolyte imbalances and malnourishment (Keith-Ferris 2004).

Although gastroparesis often results from impaired motor activity, impaired myoelectrical activity, or a combination of the two, in many cases it is idiopathic (Lin and McCallum 2003). Motor activity can be disrupted when the nerves controlling the movement of food through the digestive tract, in particular the vagus nerve, become damaged. This causes the movement of food along the digestive tract to slow or even stop, preventing the stomach from emptying fully between meals (Abell *et al.* 2002; GI Health 2005). Nerve damage can occur as a consequence of surgery, and in such cases is usually caused by inadvertent or unavoidable damage of the vagal nerve during vagotomy or gastric surgery (Lin and McCallum 2003). Vagal nerve dysfunction can also be a product of poor blood glucose control, which can lead to gastroparesis in diabetics (Abell *et al.* 2002). In these patients, gastroparesis symptoms tend to be worse and harder to manage than in non-diabetics because delayed gastric emptying, in combination with nausea and vomiting, makes glycaemic control extra challenging (Medtronic 2003).

When impaired myoelectrical activity is the cause of gastroparesis, the stomach pacemaker does not work correctly. In this case, abnormalities in the gastric slow waves cause deleterious changes in the timing and/or strength of gastric contractility, which



subsequently slows the movement of food through the gastrointestinal tract (Keith-Ferris 2004; Medtronic 2003).

Women account for approximately 80% of all gastroparesis sufferers, with the majority being young to middle aged and in the prime of their lives (mean age of onset is 34 years) (Keith-Ferris 2004). This may be a result of the naturally higher levels of progesterone in women, which when disturbed can significantly affect gastric smooth muscle motility (Buckles *et al.* 2003). Gastroparesis patients can be classed into three main groups according to disease causality: diabetic, surgical or idiopathic. Analysis of hospital data on patients with gastroparesis collected over six years showed that 35.6% of cases were idiopathic, 29% were diabetic and 13% were post-gastric surgery (Soykan *et al.* 1998). The remaining cases were Parkinson's disease (7.5%), collagen vascular disorders (4.8%), intestinal pseudo-obstruction (4.1%) and miscellaneous causes (6%) (Soykan *et al.* 1998).

Unfortunately, current knowledge regarding the pathophysiology of gastroparesis is scant (Fercozo *et al.* 2003). There is also a poor correlation between the severity of gastroparesis and the symptoms presented, which suggests the involvement of factors other than impaired gastric emptying (Abell *et al.* 2002). As a result, therapies aimed at the underlying causes of the disease have not yet been developed.

Description of the Technology

The Procedure

It has been hypothesised that an artificial pacemaker, in a similar fashion to the cardiac pacemaker, could promote gastric motility and alleviate the symptoms of gastroparesis by entraining gastric slow waves (Fercozo *et al.* 2003). With this concept in mind, Medtronic, Inc. (Minneapolis, MN, USA) developed Enterra™ Therapy, a gastric electrical stimulation system aimed at treating the chronic nausea and vomiting associated with gastroparesis (Medtronic 2004).

The Enterra Therapy Gastric Electrical Stimulation System is composed of an implanted neurostimulator, which sends electrical pulses to the stomach, two intramuscular leads with electrodes for attachment to the stomach wall, and a programmer for the physician to adjust the settings of the neurostimulator (Medtronic 2004). The system itself is similar in size to a cardiac pacemaker.

A one to three hour surgical procedure performed through an upper midline incision under general anaesthesia is required for implantation of the Enterra system (Medtronic 2004). The two electrodes are placed within the muscle layer of the greater curvature of the stomach at 9.5 cm and 10.5 cm proximal to the pylorus (Forster *et al.* 2003). Implantation of the electrodes can be performed either via laparotomy or laparoscopy (Lin *et al.* 2005). The other ends of the electrodes are connected to the neurostimulator, which is placed in the subcutaneous pocket above the abdominal wall fascia to the right of the umbilicus (Forster *et al.* 2003; Lin *et al.* 2005; Medtronic 2004).

Once implanted and activated, Enterra Therapy delivers high frequency/low energy electric stimuli to the stomach. Frequencies of 12 cycles per minute (four times the



natural frequency) with a 300 μ sec pulse width and an amplitude of 4 to 5 mA are typically used (Medtronic 2004). High frequency/low energy parameters are employed by Enterra Therapy because studies show that these parameters can significantly improve the symptoms associated with gastroparesis (Bortolotti 2002).

Other forms of gastric electrical stimulation, known as gastric electrical pacing, use low frequency/high energy parameters. These entrain gastric slow waves, induce gastric contractions and improve gastric emptying, but unlike Enterra Therapy gastric electrical pacing is unable to provide significant relief from gastroparesis symptoms (Fercozo *et al.* 2003; Keith-Ferris 2004).

Intended Purpose

Currently, Enterra Therapy is intended for sufferers of gastroparesis who are refractory to conventional medical treatment. Enterra Therapy is indicated solely for treating the symptoms of gastroparesis, i.e. chronic nausea and vomiting (Medtronic 2004). It is not a cure for gastroparesis, and does not entrain gastric slow waves, or improve gastric motility or gastric emptying (Keith-Ferris 2004; Medtronic 2004).

Given that there is a poor correlation between the severity of gastroparesis and its symptoms, it is likely that factors other than delayed gastric emptying are involved (Abell *et al.* 2002). Therefore, Enterra Therapy could potentially be extended to post-vagotomy or post-gastric surgery patients who experience nausea and vomiting but without delayed gastric emptying (Lin and McCallum 2003). There is also the possibility that this technology could help those experiencing chronic nausea and vomiting, small bowel dysmotility, recurrent small bowel bacterial overgrowth, intestinal pseudo obstruction or chronic constipation with an atonic colon (Lin and McCallum 2003).

Clinical Need and Burden of Disease

Although there are no specific statistics on gastroparesis, reports suggest that between 20% and 50% of diabetic patients, mostly type 1 diabetics, suffer from gastroparesis (Buckles *et al.* 2003). In an attempt to compensate for the lack of data, diabetes statistics have been used to extrapolate approximate numbers of gastroparesis sufferers in the United States (Keith-Ferris 2004). Approximately 5.8% of the American population (15.7 million people) are diabetic. Of these, approximately 10% (1.6 million) suffer severe gastroparesis. Given that a similar ratio of diabetic gastroparesis patients and idiopathic patients is observed in the literature, one can derive a conservative estimate of 3 million severe gastroparesis sufferers in the United States. This estimate does not take into account the number of post-surgical patients who also suffer from gastroparesis.

Applying the same logic to Australian population statistics for 2001 leads to a conservative figure of 120,000 Australians suffering from severe gastroparesis (Australian Bureau of Statistics 2005a). Again, this estimate is conservative so the true extent of the problem remains unknown (Australian Broadcasting Corporation 2004).



The consequences of gastroparesis can be very serious. In addition to learning to live with the symptoms, patients also endure physical, emotional and financial hardship and experience a significant reduction in their quality of life. There is also the risk of death from the disease, with mortality ranging from 5% to 10% (Keith-Ferris 2004). For diabetics the outlook is much worse, with approximately 30% of patients dying after three years and 56% dying within five years (Keith-Ferris 2004).

Stage of Development

In the United States, the Food and Drug Administration (FDA) designated Enterra Therapy as a humanitarian use device (HUD) in September 1999 by (US Food and Drug Administration 2000). This classifies Enterra Therapy as a device for use in the treatment of rare medical conditions (less than 4000 cases a year) (Medtronic 2004). The FDA also issued a humanitarian device exemption (HDE), which allows the manufacture and distribution of Enterra Therapy (Keith-Ferris 2004). The HDE classification, like a pre-market approval (PMA), requires that the device meets requirements for safety but, unlike a PMA, does not require documentation of effectiveness (Keith-Ferris 2004).

As a result of the HUD and HDE classification, Enterra Therapy is not commercially available in the United States (Medtronic 2004). This is somewhat controversial given that most of its components have been previously approved by the FDA for use in spinal cord and sacral nerve stimulation (Keith-Ferris 2004). The only component of the device not approved is the leads, even though they are similar to previously approved leads (US Food and Drug Administration 2000). A possible reason for this may be the lack of published controlled trials and data submitted to the FDA (Jones *et al.* 2003).

In Europe the situation is different. In March 2002, Enterra Therapy received the CE (Conformité Européene) mark making the device commercially available in Europe (Medtronic 2003).

In Australia, Enterra Therapy currently does not have approval from the Medical Services Advisory Committee (MSAC) and does not have a Medicare item number. While not commercially available in Australia, the device is available through a Special Access Scheme (M Kennedy, Medtronic Australasia, personal communication, January 13, 2006). No clinical trials have been conducted in Australia at the time of writing.

International Utilisation

COUNTRY	LEVEL OF USE		
	Trials underway	Limited use	Widely diffused
United States		✓	
Europe		✓	



Treatment Alternatives

Existing Comparators

Since there is currently no cure for gastroparesis, conventional therapy is centred on symptom management and relief. Conventional medical and surgical options for the treatment of gastroparesis have remained largely unchanged for decades (Keith-Ferris 2004). These include nutritional modification, pharmacological therapy and, in severe cases, surgery to bypass the stomach (Buckles *et al.* 2003; Lin *et al.* 2005).

Nutritional Modification

Nutritional modification is composed of two different approaches. The first approach requires a change in the eating habits of the patient. In order to compensate for delayed gastric emptying and reduce symptoms, patients are encouraged to eat six small meals a day rather than three large ones (GI Health 2005). Patients are also advised to consume liquid dietary supplements, which pass more easily through the stomach, and to avoid foods high in fat or fibre as these slow gastric emptying (GI Health 2005).

The second approach applies to patients who suffer constant nausea and vomiting so extreme that dehydration and malnourishment become a real danger. In these cases enteral or parenteral nutritional modification is employed. Enteral nutrition requires the insertion of a plastic tube through the skin into the small intestine in order to provide nutrients, hydration and, if required, medication (Parkman *et al.* 2004). The tube is placed surgically or radiologically and allows for nocturnal feeding so that the recipient can work and function during the day (Buckles *et al.* 2003). Parenteral nutrition involves the delivery of nutrients directly to the bloodstream with an intravenous solution (GI Health 2005). This method bypasses the digestive system altogether and is achieved by a catheter placed in the chest vein (GI Health 2005). Unfortunately, neither enteral nor parenteral nutrition is able to alleviate symptoms or increase gastric motility (Lin *et al.* 2004a). Moreover, parenteral nutrition carries the risk of small bowel bacterial overgrowth, liver failure and life threatening sepsis (Keith-Ferris 2004).

Pharmacological Therapy

Two classes of drugs are commonly used in the treatment of gastroparesis, prokinetics and antiemetics. Prokinetic agents promote motility in the gastrointestinal tract while antiemetic agents treat nausea and vomiting (Buckles *et al.* 2003; Parkman *et al.* 2004). In Australia, currently available drugs include metaclopramide (antiemetic and prokinetic), erythromycin (prokinetic), cisapride (prokinetic) and domperidone (prokinetic) (Australian Bureau of Statistics 2005b; Buckles *et al.* 2003). Unfortunately, use of these drugs is usually accompanied by unfavourable side effects such as restlessness, depression, anxiety, abdominal cramping and increased nausea (Keith-Ferris 2004). In addition, the effectiveness of some of these agents diminishes after prolonged use (Keith-Ferris 2004).



Surgical Intervention

As a last resort, when nutritional modification and pharmacological treatment are no longer effective, removal of the stomach (gastrectomy) is required as a palliative measure. This major surgical procedure carries the risk of morbidity and mortality, and relegates the patients to complete dependence on enteral/parenteral feeding for the remainder of their lives (GI Health 2005).

Role of Enterra Therapy

Enterra Therapy offers a fully reversible alternative to the treatment of symptoms associated with gastroparesis that is potentially free of the unfavourable side effects or dependency on supplemental nutrition required by other therapies. It is also more attractive than surgery for severe cases of gastroparesis since gastrectomy is not required, leaving the patient with the option to take advantage of future therapies/cures.

Clinical Outcomes

Due to a lack of published controlled trials, case series studies made up a large proportion of the available literature on the effectiveness of Enterra Therapy. Within these case series studies, substantial patient overlap meant that the clinical data appear to be more abundant than they really are. These patient overlaps have been noted within the text and in the tables of efficacy and safety findings (Appendix A).

Safety

Safety issues regarding Enterra Therapy can be categorised into either surgery related or device related events.

Surgery related

In discussing the surgery related risks of Enterra Therapy one must take into consideration that the recipients of this therapy are often at a higher risk of adverse events as a consequence of the malnutrition, skin contamination (due to enteral nutritional support), ostomies and compromised immune system often associated with gastroparesis.

The most common adverse event associated with the implantation of Enterra Therapy was infection at the generator site pocket, which in most cases necessitated the removal of the device (Abell *et al.* 2002; Abell *et al.* 2003a; Forster *et al.* 2003; Lin *et al.* 2004b; Lin *et al.* 2005; Mason *et al.* 2005). Despite this, one study claimed that the infection rate observed (4/33) was within the range observed for cardiac pacemaker implants (Abell *et*



al. 2002). Furthermore, the rate of morbidity observed in patients was similar to what could be expected of other laparotomy or laparoscopy procedures (Abell *et al.* 2002).

No 30-day mortality was reported as a result of the implantation procedure (Mason *et al.* 2005). In studies where mortality was reported, the deaths were attributed to unrelated causes rather than to implantation of the device.

Device related

In terms of device related safety issues, with the exception of discomfort, there were no major commonly reported safety issues identified in the papers retrieved. However, infrequent reports of incidents, including perforation of the stomach by the leads, pulse generator erosion through the skin, small bowel volvulus about the wires, fistula, erosion of the leads through the gastric mucosa and infection have been reported (Forster *et al.* 2003; Lin *et al.* 2004b; Mason *et al.* 2005; Oubre *et al.* 2005). Although infrequent in their occurrence, these events have all required surgical intervention (usually the removal of Enterra Therapy) for correction of the problem, and in doing so exposed the patient to further risks.

Only one study reported issues regarding the functioning of the implanted device (Abell *et al.* 2002). In this report, inadvertent deactivation of the device occurred as a result of interference by stray magnetic waves. This led to an increase in gastroparesis symptoms. However, deactivation is no longer an issue as it was only observed in the previous model of Enterra Therapy.

Discomfort and pain as a result of device implantation were reported in several instances. Causes identified included lead perforation of the stomach and migration of the device (Abell *et al.* 2003b; Forster *et al.* 2003). Other infrequent, mostly isolated incidents that could be attributed to the device included electrode dislodgement, insomnia, atrial fibrillation, hypoglycaemia, rib fracture and volvulus of the small bowel (Abell *et al.* 2002; Abell *et al.* 2003b; Forster *et al.* 2003; Lin *et al.* 2004b; Mason *et al.* 2005).

Though perhaps not an obvious safety issue at first, finite battery life is potentially problematic as the only way to replace the battery is via surgery, which exposes the patient to further risk (Medtronic 2004).

Effectiveness

Symptom relief

In many of the studies, the patient groups were composed of patients with different aetiologies (i.e. a mixture of diabetic, post-surgical and idiopathic gastroparesis). Two main outcome measures were used to measure symptom relief: frequency and severity of nausea and vomiting and the Total Symptom Score (TSS), a five or ten point severity and/or frequency score of symptoms including nausea, vomiting, early satiety, bloating, postprandial fullness and epigastric pain. The TSS gives a better indication of the effects of Enterra Therapy because it evaluates several symptoms in the one score.



In the only non-randomised comparative study retrieved, the effect of Enterra Therapy versus an intensive medical therapy outpatient program was compared (Cutts *et al.* 2005). The outpatient program included treatment with antiemetics, prokinetics and other medication. Nine patients (one diabetic and eight idiopathic) were included in each group (18 total). While the TSS for both groups was similar at baseline, Enterra Therapy performed significantly better overall than the intensive therapy option. Both groups experienced significant improvement after one year, compared to baseline, but the patients who received Enterra Therapy had a significantly greater reduction in TSS than the medical therapy group at both the one and two year follow up.

The Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS), a multi-centre 12 month study of patients with different aetiologies conducted in the US, Canada and Europe was conducted in two phases to evaluate the long and short term effects of Enterra Therapy (Abell *et al.* 2003b). Phase I, a 2 month placebo-controlled, double-blind, crossover trial, randomised patients to stimulation either ON or OFF for the first month after recovery from surgery and then programmed stimulation to the opposite setting for the second month. Data obtained through patient monitoring over the two months revealed a 50% decrease in the median weekly vomiting frequency in patients with stimulation ON ($P < 0.05$) versus OFF. Although TSS scores did not significantly differ between stimulation ON or OFF, at the end of the two months, prior to breaking the blind, patients expressed a statistically significant ($P < 0.05$) preference for stimulation ON over stimulation OFF. Phase II results of the study found that in this group of patients Enterra Therapy led to significant ($P < 0.05$) improvements in TSS at the 6 and 12 month follow up (Abell *et al.* 2003b). Similarly, another study of patients with different aetiologies found significant ($P < 0.05$) improvements in the TSS of patients 12 months after Enterra Therapy (Forster *et al.* 2003). Only one study investigated the effectiveness of Enterra Therapy on diabetic gastroparesis patients alone (Lin *et al.* 2004b). This study included a subset of 39 diabetic patients from Forster *et al.* (2003) plus an additional nine diabetic patients, and noted a significant improvement in the TSS at 6 and 12 months post-Enterra Therapy implantation ($P < 0.05$).

One study demonstrated a significant improvement in symptom severity (i.e. the clinical impact of nausea, vomiting and epigastric pain) in 70% (19/27) of patients (24 diabetic and 5 idiopathic) over a median follow-up period of 20 months after Enterra Therapy (Mason *et al.* 2005). However, the results of a small preliminary observation of 13 patients (12 diabetic and 1 idiopathic) suggested that this may not always be the case. Nausea and vomiting scores from this cohort showed that Enterra Therapy did not have any significant impact on these two parameters of symptom relief (Jones *et al.* 2003).

The long-term effects of Enterra Therapy (one to two years and up to five years) were documented by Abell *et al.* (2003a) in a report which included a subset of 12 patients (three diabetic and nine idiopathic) from a previous study (Abell *et al.* 2002). In this report the TSS decreased significantly ($P < 0.005$) between one and five years, indicating an improvement in symptoms. In terms of weekly vomiting episodes, there was a significant ($P < 0.05$) decrease in the mean vomiting frequency from 3.9 at baseline to 1.4 and 1.7 episodes per week at one to two years and five years, respectively (Abell *et al.* 2003a).

Not all reports presented as great a positive effect of Enterra Therapy as the studies mentioned so far. Clinical data obtained from studies using the TSS in post-surgical



gastroparesis patients have reported widely varying degrees of effectiveness of Enterra Therapy. This is illustrated by two studies which, despite being similar in design, reported dissimilar results. Oubre *et al.* (2005) assessed a subset of five post-surgical patients from Abell *et al.* (2002) and observed no significant improvement in the TSS at 3, 6 or 12 months after implantation and activation of Enterra Therapy. However, data extracted from an abstract by McCallum *et al.* (2005) (the full-text study was unavailable at the time of writing) reported significant ($P < 0.05$) improvements at 6 and 12 months post-implantation in the TSS of 16 post-surgical patients. These results potentially indicate that, in the post-surgical gastroparesis patients at least, the effectiveness of Enterra Therapy may also depend on individual patient factors (e.g. severity of symptoms).

The flow on effects of improved symptom control as a result of Enterra Therapy treatment have been briefly presented in the literature. In a cohort of patients with different aetiologies, which included a subset (29 patients) from Forster *et al.* (2003), it was observed that as a result of improved symptoms the majority of patients were able to significantly ($P < 0.05$) reduce their daily intake of one or both classes of drugs (prokinetics and antiemetics) (Lin *et al.* 2005).

Quality of life

While improvements (especially statistically significant improvements) in symptoms associated with gastroparesis are important, any improvement is meaningless without an accompanying increase in the patient's quality of life.

The most common tool used to assess quality of life was the SF-36 health status survey questionnaire. This tool has two summary scores, the Physical Composite Score (PCS) and the Mental Composite Score (MCS), both derived from the eight subscores of the SF-36. These are two norm-based measures for which the mean \pm standard deviation for the general population of the United States is 50 ± 10 .

Patients with different aetiologies from two studies demonstrated significant improvements in both the MCS and PCS 6 and 12 months after Enterra Therapy (Abell *et al.* (2003a) $P < 0.025$; Forster *et al.* (2003) $P < 0.05$). Lin *et al.* (2005) further supported the long-term durability of the effect of Enterra Therapy in a subset of 29 mixed aetiology patients from Forster *et al.* (2003). One-year follow-up results showed a significant ($P < 0.05$) improvement in MCS and PCS, compared to pre-implantation scores.

A retrospective review of 48 diabetic gastroparesis patients (39 of whom participated in Forster *et al.* (2003)) who received Enterra Therapy supported the positive impact of Enterra Therapy on quality of life in a diabetic patient population (Lin *et al.* 2004b). In this study, both the mean PCS and MCS improved significantly ($P < 0.05$) at six months, and significant ($P < 0.05$) improvement was maintained after 12 months' follow up, with both scores approaching the normal level.

Rather than use the SF-36 and the MCS and PCS, Oubre *et al.* (2005) used an investigator-derived independent outcome score (IDIOMS) to measure health-related quality of life. In this approach a decrease in the IDIOMS indicated an improvement in health-related quality of life (Oubre *et al.* 2005). Although this study used a subset of



patients from an earlier study (Abell *et al.* (2002)), data on quality of life had not been previously reported for these patients. In their results, Oubre *et al.* (2005) supported those of other studies that used the PCS and MCS by demonstrating a significant ($P < 0.05$) decrease in the IDIOMS score at 3, 6 and 12 months post-Enterra Therapy implantation, compared to pre-implantation. The results of Abell *et al.* (2003a) on the long-term effects of Enterra Therapy implantation on the quality of life of diabetic and idiopathic gastroparesis patients were similar. Using patient self report measures for nutrition quality of life and overall quality of life, the investigators showed a significant ($P < 0.05$) improvement in both aspects of quality of life for up to five years after Enterra Therapy implantation.

Nutritional status

Gastroparesis patients can sometimes lose weight and become dehydrated and malnourished as a result of their illness, so an important indicator of the effectiveness of any treatment is nutritional status. Primary route of nutrition (i.e. requirement for parenteral or enteral nutrition) and weight gain were the main outcome measures used to assess nutritional status.

Abell *et al.* (2002) found that implantation of Enterra Therapy was associated with a significant (mean 8.4%, $P = 0.007$) weight gain over 12 months, with the median weight of patients rising from 59 kg to 64 kg. The following year another study by Abell was reported (Abell *et al.* 2003a). While a significant ($P < 0.05$) increase in average weight was observed at up to 12 months post-implantation (68.1 kg at baseline to 74.1 kg at twelve months), the long-term effect of Enterra Therapy on weight gain at five years was not statistically significant.

The extent of the effectiveness of Enterra Therapy on weight gain was put into question in 2003. Forster *et al.* 2003 demonstrated that after 12 months of Enterra Therapy the average weight gain for participants was 0.9 kg, a result that while statistically significant ($P < 0.05$) had questionable clinical significance.

In a subset of 39 diabetic patients from Forster *et al.* (2003) plus another nine patients, Lin *et al.* (2004b) monitored routes of nutrition and found that of 22 patients requiring nutritional support (13 enteral and 9 parenteral) before Enterra Therapy implantation, none required parenteral nutrition at 12 months post-implantation and 5 required supplemental feeding; a significant ($P < 0.05$) reduction.

An even better impact on route of nutrition in gastroparesis patients was observed by Mason *et al.* (2005) where the number of patients requiring either parenteral or enteral nutrition dropped from 19 of 29 patients at baseline to none at a median follow up of 20 months post-implantation.

Taking into consideration that gastroparesis sufferers are vulnerable to weight loss, dehydration, malnutrition and the need for nutritional support, any positive change leading to improved nutritional status is welcome. However, it must be noted that in some parameters (e.g. weight gain) statistical significance does not always indicate clinical significance. Although on paper some results look promising they must be put into the



correct context. For example, although it's statistically significant, is an average weight gain of 0.9 kg over 12 months clinically meaningful? (Forster *et al.* 2003).

In reference to route of nutrition, there is the possibility that as a consequence of improvement in symptoms, such as nausea and vomiting, patients are more willing and able to return to oral nutrition. Hence, these two effectiveness indicators may be interrelated.

Gastric emptying

Though gastric emptying should not be used as an indicator of the effectiveness of Enterra Therapy, since it is not indicated for this purpose, many studies have nonetheless included gastric emptying as an outcome measure. Therefore, the information below is provided for reference purposes only.

Although some reports have shown a significant improvement in gastric emptying in some patients, most of the time a statistically significant improvement does not indicate a return to normal activity (Abell *et al.* 2003b; Lin *et al.* 2004b; McCallum *et al.* 2005; Oubre *et al.* 2005). In contrast, Mason *et al.* (2005) demonstrated that 46% (7/15) of patients who received Enterra Therapy achieved a return to normal gastric emptying after 20 months (median follow up), while Abell *et al.* (2002) achieved the same results over 12 months. However these results were atypical of the literature retrieved.

In many studies, although a return to normal gastric emptying time was achieved, there were many patients who either remained the same or experienced a worsening of gastric emptying times after Enterra Therapy implantation. In one example Lin *et al.* (2005) found that 8 out of 37 patients (which included a subset of 29 patients from Forster *et al.* (2003)) returned to normal gastric emptying one year post-implantation, while 13 had in fact experienced worsening of their delayed gastric emptying.

Thus, the evidence overwhelmingly suggests that Enterra Therapy is unable to improve gastric emptying. Taking into consideration that over time some gastroparesis patients recover, albeit a small percentage, it appears that a return of normal gastric emptying is unlikely to be due to Enterra Therapy implantation. The results also suggest that improvements in symptoms are not a result of (or related to) a return to normal gastric emptying. Furthermore, akin to other indicators of effectiveness, it appears that improvement in gastric emptying is not related to any specific aetiology of gastroparesis.

Potential Cost Impact

Cost Analysis

Unfortunately, due to the HUD classification of Enterra Therapy, information regarding the costs of Enterra Therapy and the associated hospitalisation is sparse. Per patient



estimates of the cost of Enterra Therapy implantation have been reported at US\$20,000 (Australian Broadcasting Corporation 2004; Jones *et al.* 2003).

Although classified as an HUD in the United States and not commercially available, the manufacturers claim that many insurance companies will pay for Enterra Therapy (Medtronic 2004). In Australia, approval for Enterra Therapy is pending (M Kennedy, Medtronic Australasia, personal communication, January 13, 2006). As a result, health funds tend to be reluctant to pay for the device or the hospital stay. However, the therapy is available through the Special Access Scheme. Costs for Enterra Therapy can be divided up as follows (in AUD): pulse generator \$9216, lead \$6986 (two required) and patient activator \$1352. No information was available on hospital costs.

Whilst the cost of such a therapy may at first seem high, the benefits and subsequent savings over time far outweigh the initial outlay. In a non-randomised comparative study of gastroparesis patients treated with an intensive outpatient medical therapy program versus Enterra Therapy over three years, the financial advantages of Enterra Therapy were demonstrated (Cutts *et al.* 2005). Prior to the commencement of either program, treatment costs for both groups were not significantly different. For both groups, hospitalisation days per year improved significantly over the three years, compared to baseline. However, after the first year, medical costs from the medical therapy group rose slightly and then decreased during the second and third years (not statistically significant). Similarly, the patient group receiving Enterra Therapy did not experience a drop in costs in the first year. However, a significant drop of over 70% was achieved during the second and third years ($P = 0.0022$ and $P = 0.0018$, respectively). This drop equated to a saving of over US\$41,000 per patient.

This example shows not only the ability of Enterra Therapy to reduce costs associated with gastroparesis, but also to reduce the number of hospital days required by the patient. Other than occasional visits to a doctor every six months to check the battery of the device and to monitor the stimulation parameters, no additional ongoing or maintenance costs were identified.

Ethical Considerations

Informed Consent

No information regarding the level of informed consent given by study participants was obtained.

Access Issues

Currently physicians cannot freely prescribe Enterra Therapy (Abell *et al.* 2002). Access to the therapy is restricted because physicians must first obtain approval from their hospital internal review boards before using it (Medtronic 2004).



In the United States most Medicare providers recognise HUD status for Enterra and grant approval for the therapy. However, because gastroparesis is a poorly recognised and understood disease, the average patient must go through two or three appeals that can take more than two years for Social Security to approve the disability claim. Only then can patients claim Medicare status, which may take 3 to 4 years. Many private insurance companies see Enterra as investigational and clearly state in their policies that it is not covered. If prescribed, patients will be initially denied coverage and must go through an appeal process two or three times, which is very draining and not always successful (Keith-Ferris 2004).

In Australia, despite the Special Access Scheme, funding for the device and the procedure remains a problem. Without a Medicare item number health funds tend to not pay for the device or procedure (M Kennedy, Medtronic Australasia, personal communication, January 13, 2006).

Training and Accreditation

Training

There is currently a lack of knowledge of Enterra Therapy even within the medical profession (Australian Broadcasting Corporation 2004). Physicians wishing to prescribe Enterra Therapy are encouraged to contact the manufacturer and request referral to a physician already experienced with the device prior to prescribing Enterra Therapy for the first time (Medtronic 2004). Once implanted, all device programming should be done by or under the supervision of a physician or other experienced medical professional who is familiar with using the software (Medtronic 2004).

Clinical Guidelines

Currently there are no clinical guidelines available for the use of Enterra Therapy. If consistent beneficial results are obtained, clinical guidelines will need to be developed.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.



A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, a Horizon Scanning Report is a ‘state of play’ assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

Search Strategy Used for Report

A search of MEDLINE, PubMed, *The Cochrane Library*, the Current Controlled Trials metaRegister, the International Network of Agencies for Health Technology Assessment, relevant online journals and the Internet was conducted up to December 2005. The search terms were: Enterra, gastric electrical stimulation, gastroparesis, gastric pacing, gastric pacemaker and gastroparesis treatment.

Availability and Level of Evidence

Twelve studies, comprising one non-randomised comparative study and 11 case series studies were retrieved that specifically reported on the safety and efficacy of Enterra Therapy in humans. Patient overlap was noted in some of the studies retrieved and was documented in the safety and efficacy data tables (Appendix A).

List of Studies Found:

Total number of studies included:	11
Non-randomised comparative studies	1
Case series studies	10 (9 published, 1 editorial, 1 abstract of a published study)

Sources of Further Information

At the time of writing there was only one clinical trial evaluating the safety and effectiveness of Enterra Therapy being undertaken (Current Controlled Trials 2005). The trial is currently in the recruitment phase and is being headed by T.L. Abell who has a record in Enterra Therapy research. The trial’s primary outcome is the reduction in frequency of weekly vomiting episodes, while the secondary outcomes are the reduction in gastroparesis symptoms and the long-term reduction in the frequency of weekly vomiting episodes.



Conclusions

Enterra Therapy is a gastric electrical stimulation system for the relief of symptoms associated with gastroparesis. While not a cure, Enterra Therapy offers many potential benefits to both the patient and the health system in terms of improved treatment outcomes and costs in treating the disease.

Despite the lack of studies on the economic impact of Enterra Therapy, the improvement in patient symptoms and reduction in need for medication and nutritional support mechanisms indicate that, over the long term, use of this technology (if approved) may provide significant reductions in costs and health system resource usage to treat gastroparesis patients.

However, currently available data must first be backed up by reliable, high quality results from large, randomised controlled clinical trials before Enterra Therapy can be widely distributed and used.

HealthPACT Advisory

Notwithstanding the lack of randomised controlled trials, in the context of a common condition associated with considerable morbidity where current therapies have significant limitations and side effects, the available evidence regarding the Enterra® system provides sufficient encouragement and the potential to improve the symptoms and overall quality of life of patients with gastroparesis to warrant the conduct of more robust randomised multi-centre research, including an economic evaluation. It is not recommended that this procedure be used outside the context of a clinical trial protocol.



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Appendix A: Table of Key Efficacy and Safety Findings

Study Details	Key Efficacy Findings								Key Safety Findings	Appraisal/Comments	
Prospective Non-Randomised Comparative Study with Concurrent Controls											
Cutts <i>et al.</i> 2005											
<p><i>Comparison:</i> Intensive medical therapy versus Enterra Therapy.</p> <p><i>Patients:</i> (n = 18) MED (medical therapy group) 9 (1 diabetic, 8 idiopathic); GES (Enterra Therapy group) 9 (1 diabetic, 8 idiopathic).</p> <p><i>Follow up:</i> 1, 2 and 3 years.</p> <p><i>Selection criteria:</i> Gastroparesis symptoms at least 1 year. Weight loss and/or nutritional support need and refractory to minimum 2 classes of prokinetic and antiemetic drugs.</p>		Baseline		Year 1		Year 2		Year 3		Overall ANOVA result	
		GES	MED	GES	MED	GES	MED	GES	MED	Between group	Within group
	TSS*	37.9±2.73	39.3±2.8	24.1±4.8	31.7±3.1	21.3±5.1	36.9±0.33	23.4±5.4	34.8±3.45	P<0.017	GES, P=0.001
	Between group comparison	Not significant		P < 0.05		P < 0.05		P < 0.05			MED, Not significant
	IDIOMS†	12.6±1.6	11±0.71	8.3±1.4	11.9±0.73	7.0±1.13	13.3±0.62	6.4±1.03	13.8±0.45	P<0.017	GES, P<0.001
	Between group comparison	Not significant		P < 0.05		P < 0.05		P < 0.05			MED, P<0.001
	Cost/year (\$000's)	83.7±27.9	80.2±26.7	79.2±26.4	85.7±28.6	23.7±7.9	71.9±24.0	22.1±7.8	63.4±22.4		GES, P<0.001
	Between group comparison	Not significant		Not significant		P < 0.05		P < 0.05			MED, P<0.19
Annual hospital days	24.8±13.7	26.8±8.4	14.1±9.0	13.3±5.8	3.2±1.5	11.6±5.4	2.8±1.8	6.4±5.5	Not significant	GES, P<0.002	
Between group comparison	Not significant		Not significant		Not significant		Not significant			MED, P<0.001	
<p>Data reported as mean ± standard error of the mean</p> <p>*TSS: Total Symptom Score</p> <p>†IDIOMS: Investigator-Derived Independent Outcome Measure Score</p>											
									Three deaths related to intravenous access in MED group. None in GES.	Potential for bias: Small patient size.	



Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
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Case Series Studies

Abell *et al.* 2002

Patients:

Total 33. Idiopathic (24), diabetes mellitus (9), post-surgical (5).

Follow up:

Phase I, between 2 and 4 weeks.

Phase II, 3, 6, 12 and > 12 month follow up.

Selection criteria:

Highly symptomatic documented gastroparesis and refractory to drugs for at least 1 year, significant weight loss prior to study.

	Baseline	Phase I	Phase II
Solid gastric emptying T50	4.4 (range -2.1 to 9.1)	Improvement in only 8 patients.	At 1 year normalised in 7, no change in 6 and worsened in 2.
Weekly vomiting frequency	21	0	Average reduction of more than 90%. Maintained for at least 1 year.
Weekly nausea frequency	21	2	At 1 year fell to 1 episode per week.
Median weight	59	-	At 1 year 64 kg
Enteral or parenteral nutritional support	14/23	-	At 1 year 5/23
Medication usage	-	-	Statistically significant reduction
Deactivation of device for 1 week at 6 months	-	-	8 reported increased symptoms, 8 no change, 2 improved symptoms and 7 required re-activation before week was complete.

No cardiac effects detected.

Deactivation of device apparently caused by stray magnetic fields (10), sudden increase in symptoms due to inadvertent deactivation of device (8), removal of device due to infection (4), total gastrectomy (2). Various other adverse events also reported.

Potential for bias:

Other than selection criteria no statement regarding patient selection was presented. Small sample size.



Study Details	Key Efficacy Findings						Key Safety Findings	Appraisal/Comments																																																																																										
<p>Abell et al. 2003a</p> <p><i>Patients:</i> Total 12. Diabetes mellitus (3), idiopathic.</p> <p><i>Follow up:</i> Short term (0-12 months), intermediate term (1-2 years), long term (5 years).</p> <p><i>Selection criteria:</i> Symptoms of gastroparesis, history of hospitalisations for gastroparesis and refractory or intolerant to at least 2 classes of prokinetics and 2 classes of antiemetics.</p>	<p><i>Short term:</i></p> <table border="1" data-bbox="432 363 1350 691"> <thead> <tr> <th></th> <th>Baseline</th> <th>3 months</th> <th>6 months</th> <th>12 months</th> <th>ANOVA</th> </tr> </thead> <tbody> <tr> <td>TSS*</td> <td>35.6 ± 1.9</td> <td>16.3 ± 4.3</td> <td>12.3 ± 3.3</td> <td>16.6 ± 5.4</td> <td>P < 0.01</td> </tr> <tr> <td>Weight</td> <td>68.1 ± 4.0</td> <td>72.3 ± 4.9</td> <td>73.6 ± 5.3</td> <td>73.6 ± 5.3</td> <td>P < 0.05</td> </tr> <tr> <td>Body mass index</td> <td>23.9 ± 1.4</td> <td>25.4 ± 1.6</td> <td>25.4 ± 1.8</td> <td>25.7 ± 2.3</td> <td>P = 0.05</td> </tr> <tr> <td>Albumin</td> <td>3.5 ± 0.2</td> <td>3.7 ± 0.3</td> <td>3.32 ± 0.3</td> <td>3.5 ± 0.2</td> <td>P > 0.3</td> </tr> <tr> <td>Cholesterol</td> <td>180.6 ± 13.2</td> <td>216.8 ± 19.7</td> <td>217.6 ± 19.9</td> <td>186.2 ± 31.8</td> <td>P = 0.16</td> </tr> <tr> <td>Complete blood count</td> <td>6.63 ± 0.4</td> <td>7.03 ± 0.7</td> <td>7.9 ± 1.1</td> <td>7.02 ± 0.6</td> <td>P > 0.3</td> </tr> <tr> <td>Lymphocyte</td> <td>29.21 ± 4.4</td> <td>32.46 ± 3.3</td> <td>28.5 ± 3.6</td> <td>32.58 ± 5.9</td> <td>P > 0.3</td> </tr> </tbody> </table> <p><i>Intermediate and long term:</i></p> <table border="1" data-bbox="432 754 1350 1098"> <thead> <tr> <th></th> <th>Baseline</th> <th>Intermediate Term</th> <th>Long Term</th> <th>Improvement (%)</th> <th>p from Baseline</th> </tr> </thead> <tbody> <tr> <td>TSS*</td> <td>37.1</td> <td>15.75</td> <td>20.3</td> <td>51</td> <td>< 0.05</td> </tr> <tr> <td>Weekly vomiting frequency score</td> <td>3.9 ± 0.1</td> <td>1.4 ± 0.6</td> <td>1.7 ± 0.5</td> <td>61.6</td> <td>< 0.01</td> </tr> <tr> <td>Weight</td> <td>69.9 ± 3.6</td> <td>72.7 ± 6.4</td> <td>71.4 ± 5.9</td> <td>< 5</td> <td>< 0.8</td> </tr> <tr> <td>Body mass index</td> <td>24.1 ± 1</td> <td>25.6 ± 2</td> <td>24.6 ± 2</td> <td>< 5</td> <td>< 0.8</td> </tr> <tr> <td>Nutrition quality of life</td> <td>-</td> <td>-</td> <td>Median/Mean (+2/+1.2)</td> <td>-</td> <td>-</td> </tr> <tr> <td>Overall quality of life</td> <td>-</td> <td>-</td> <td>Median/Mean (+3/+2.1)</td> <td>-</td> <td>-</td> </tr> </tbody> </table> <p>Results reported as mean ± standard error of the mean, or median values. *TSS: Total Symptom Score</p>							Baseline	3 months	6 months	12 months	ANOVA	TSS*	35.6 ± 1.9	16.3 ± 4.3	12.3 ± 3.3	16.6 ± 5.4	P < 0.01	Weight	68.1 ± 4.0	72.3 ± 4.9	73.6 ± 5.3	73.6 ± 5.3	P < 0.05	Body mass index	23.9 ± 1.4	25.4 ± 1.6	25.4 ± 1.8	25.7 ± 2.3	P = 0.05	Albumin	3.5 ± 0.2	3.7 ± 0.3	3.32 ± 0.3	3.5 ± 0.2	P > 0.3	Cholesterol	180.6 ± 13.2	216.8 ± 19.7	217.6 ± 19.9	186.2 ± 31.8	P = 0.16	Complete blood count	6.63 ± 0.4	7.03 ± 0.7	7.9 ± 1.1	7.02 ± 0.6	P > 0.3	Lymphocyte	29.21 ± 4.4	32.46 ± 3.3	28.5 ± 3.6	32.58 ± 5.9	P > 0.3		Baseline	Intermediate Term	Long Term	Improvement (%)	p from Baseline	TSS*	37.1	15.75	20.3	51	< 0.05	Weekly vomiting frequency score	3.9 ± 0.1	1.4 ± 0.6	1.7 ± 0.5	61.6	< 0.01	Weight	69.9 ± 3.6	72.7 ± 6.4	71.4 ± 5.9	< 5	< 0.8	Body mass index	24.1 ± 1	25.6 ± 2	24.6 ± 2	< 5	< 0.8	Nutrition quality of life	-	-	Median/Mean (+2/+1.2)	-	-	Overall quality of life	-	-	Median/Mean (+3/+2.1)	-	-	<p>Infection requiring removal of device at 1 year (1). Unrelated death (1).</p>	<p><i>Potential for bias:</i> Small sample size. Patient overlap with Abell et al. 2002.</p> <p><i>Other comments:</i> Study sponsored in part by Medtronic Inc.</p>
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Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments																																																				
<p>Abell et al. 2003b</p> <p><i>Patients:</i> Total 33. Diabetic (17), idiopathic (16).</p> <p><i>Follow-up:</i> Phase I, 2 month randomised, placebo-controlled, double-blind crossover trial. Phase II, 10 month open label period (follow up, 6 and 12 months post implantation).</p> <p><i>Selection criteria:</i> Gastroparetic patients, over 7 vomiting episodes weekly, delayed gastric emptying, symptoms for over 12 months, refractory or intolerant to 2 of 3 classes of prokinetic and antiemetic drugs.</p>	<p><i>Phase I:</i></p> <table border="1" data-bbox="427 357 1487 501"> <thead> <tr> <th></th> <th>Baseline</th> <th>Device OFF</th> <th>Device ON</th> </tr> </thead> <tbody> <tr> <td>Median weekly vomiting frequency (interquartile range)</td> <td>17.3 (11.8-45.7)</td> <td>13.5 (5.5-25.4)</td> <td>6.8 (3.9-16.5)*</td> </tr> <tr> <td>Total Symptom Score (mean ± standard error)</td> <td>16.8 ± 0.9</td> <td>13.9 ± 1.1</td> <td>12.5 ± 1.0</td> </tr> <tr> <td>Patient preference</td> <td>-</td> <td>7</td> <td>21</td> </tr> </tbody> </table> <p><i>Phase II:</i></p> <table border="1" data-bbox="427 608 1487 959"> <thead> <tr> <th></th> <th>Baseline</th> <th>6 Months</th> <th>12 Months</th> </tr> </thead> <tbody> <tr> <td>Median weekly vomiting frequency (interquartile range)</td> <td>17.3 (11.8-45.7)</td> <td>2.6 (0.6-12.0)*</td> <td>4.8 (0.1-7.6)*</td> </tr> <tr> <td>Mean vomiting severity score</td> <td>3.3 ± 0.1</td> <td>2.0 ± 0.3†</td> <td>2.0 ± 0.3†</td> </tr> <tr> <td>Mean nausea severity score</td> <td>3.5 ± 0.1</td> <td>2.4 ± 0.2†</td> <td>2.4 ± 0.3†</td> </tr> <tr> <td>Delayed gastric emptying at 2 hours % (interquartile range)</td> <td>78 (67-84)</td> <td>65 (53-80)*</td> <td>56 (45-74)*</td> </tr> <tr> <td>Delayed gastric emptying at 4 hours % (interquartile range)</td> <td>34 (26-57)</td> <td>27 (14-54)</td> <td>22 (11-37)</td> </tr> <tr> <td>Enteral/parenteral nutrition requirement</td> <td>14</td> <td>-</td> <td>7</td> </tr> <tr> <td>Physical Composite Score (mean ±standard error)</td> <td>25.8 ± 1.5</td> <td>33.5 ± 2.0‡</td> <td>32.4 ± 2.2‡</td> </tr> <tr> <td>Physical Composite Score (mean ±standard error)</td> <td>36.1 ± 2.2</td> <td>43.7 ± 2.4‡</td> <td>45.1 ± 2.1‡</td> </tr> </tbody> </table> <p>*P < 0.05, †P < 0.005, ‡P < 0.025</p>		Baseline	Device OFF	Device ON	Median weekly vomiting frequency (interquartile range)	17.3 (11.8-45.7)	13.5 (5.5-25.4)	6.8 (3.9-16.5)*	Total Symptom Score (mean ± standard error)	16.8 ± 0.9	13.9 ± 1.1	12.5 ± 1.0	Patient preference	-	7	21		Baseline	6 Months	12 Months	Median weekly vomiting frequency (interquartile range)	17.3 (11.8-45.7)	2.6 (0.6-12.0)*	4.8 (0.1-7.6)*	Mean vomiting severity score	3.3 ± 0.1	2.0 ± 0.3†	2.0 ± 0.3†	Mean nausea severity score	3.5 ± 0.1	2.4 ± 0.2†	2.4 ± 0.3†	Delayed gastric emptying at 2 hours % (interquartile range)	78 (67-84)	65 (53-80)*	56 (45-74)*	Delayed gastric emptying at 4 hours % (interquartile range)	34 (26-57)	27 (14-54)	22 (11-37)	Enteral/parenteral nutrition requirement	14	-	7	Physical Composite Score (mean ±standard error)	25.8 ± 1.5	33.5 ± 2.0‡	32.4 ± 2.2‡	Physical Composite Score (mean ±standard error)	36.1 ± 2.2	43.7 ± 2.4‡	45.1 ± 2.1‡	<p>Device related, required surgical intervention: infection of neurostimulator pocket (2), pain related to lead perforation of stomach (1), pulse generator erosion through skin (1), discomfort from migration of pulse generator (1).</p>	<p><i>Potential for bias:</i> Other than selection criteria no statement regarding patient selection was presented. Attrition levels varied between the centres.</p> <p><i>Other comments:</i> Multi-centre study. Study partly supported by Medtronic Inc.</p>
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Study Details	Key Efficacy Findings			Key Safety Findings	Appraisal/ Comments																																							
<p>Forster <i>et al.</i> 2003</p> <p><i>Patients:</i> Total 55. Diabetic (39), post-surgical (9), idiopathic (7).</p> <p><i>Follow up:</i> 6 and 12 months.</p> <p><i>Intervention:</i> Enterra Therapy implantation</p> <p><i>Selection criteria:</i> Prolonged gastric retention.</p>	<table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>6 Months</th> <th>12 Months</th> </tr> </thead> <tbody> <tr> <td>Gastric emptying</td> <td>45% ± 3.7</td> <td>33% ± 4.0*</td> <td>38% ± 5.3</td> </tr> <tr> <td>Total Symptom Score (severity)</td> <td>20 ± 0.68</td> <td>10 ± 1.1*</td> <td>9.1 ± 1.2*</td> </tr> <tr> <td>Total Symptom Score (frequency)</td> <td>21 ± 0.66</td> <td>11 ± 1.1*</td> <td>10 ± 1.2*</td> </tr> <tr> <td>Physical Composite Score</td> <td>24 ± 1.1</td> <td>32 ± 1.5*</td> <td>33 ± 1.7*</td> </tr> <tr> <td>Mental Composite Score</td> <td>37 ± 1.6</td> <td>48 ± 2.0*</td> <td>48 ± 1.6*</td> </tr> <tr> <td>Body weight (kg)</td> <td>64.5 ± 2.1</td> <td>65.1 ± 2.0</td> <td>65.4 ± 1.9*</td> </tr> <tr> <td>Body Mass Index</td> <td>22.9 ± 0.7</td> <td>22.3 ± 0.7</td> <td>23.3 ± 0.6*</td> </tr> <tr> <td>Haemoglobin A1C</td> <td>9.8% ± 0.49</td> <td>9.0% ± 0.56</td> <td>8.5% ± 0.45*</td> </tr> <tr> <td>Jejunal feeding tube requirement</td> <td>25</td> <td>-</td> <td>8</td> </tr> </tbody> </table>		Baseline	6 Months	12 Months	Gastric emptying	45% ± 3.7	33% ± 4.0*	38% ± 5.3	Total Symptom Score (severity)	20 ± 0.68	10 ± 1.1*	9.1 ± 1.2*	Total Symptom Score (frequency)	21 ± 0.66	11 ± 1.1*	10 ± 1.2*	Physical Composite Score	24 ± 1.1	32 ± 1.5*	33 ± 1.7*	Mental Composite Score	37 ± 1.6	48 ± 2.0*	48 ± 1.6*	Body weight (kg)	64.5 ± 2.1	65.1 ± 2.0	65.4 ± 1.9*	Body Mass Index	22.9 ± 0.7	22.3 ± 0.7	23.3 ± 0.6*	Haemoglobin A1C	9.8% ± 0.49	9.0% ± 0.56	8.5% ± 0.45*	Jejunal feeding tube requirement	25	-	8	<p>Data presented as means ± standard error of the mean *P < 0.05</p>	<p>Post operative infection requiring removal (2), inflammation, infection and pushing of device against rib cage and skin as a result of placing device without being sutured to fascia requiring removal (1), small bowel volvulus about wires requiring removal (1). 3 patients required device to be moved or replaced.</p>	<p><i>Potential for bias:</i> Other than selection criteria no statement regarding patient selection was presented. Patient overlap of some subjects with Abell <i>et al.</i> (2003b).</p> <p><i>Other comments:</i> Partly supported by Medtronic Inc.</p>
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Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
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Lin et al. 2004b
Patients:
48 diabetic patients.

Follow up:
6 and 12 month follow up.

Selection Criteria:
Documented diagnosis of gastroparesis for over 1 year, refractoriness to antiemetics and prokinetics, over 7 emetic episodes per week, delayed gastric emptying.

Health related quality of life:
Both physical and mental composite scores significantly (P < 0.05) increases improved at 6 months' follow up, compared to baseline. The effect was maintained at 12 months' follow up.

Gastric retention:
Both 2-hour and 4-hour gastric retention times significantly (P < 0.05) decreased at 6 months' follow up, compared to baseline. The effect was not maintained at 12 months.

Symptom relief:

		Baseline	6 Months	12 Months
Severity scores	Vomiting	3.3 ± 0.1	1.5 ± 0.2*	1.3 ± 0.3*
	Nausea	3.6 ± 0.1	1.9 ± 0.2*	1.7 ± 0.3*
	Early satiety	2.9 ± 0.1	1.4 ± 0.2*	1.2 ± 0.3*
	Bloating	2.7 ± 0.2	1.3 ± 0.2*	1.1 ± 0.2*
	Postprandial fullness	2.8 ± 0.2	1.0 ± 0.2*	1.4 ± 0.2*
	Epigastric pain	2.6 ± 0.2	1.4 ± 0.2*	1.1 ± 0.2*
	Total Symptom Score of severity (0 to 24)	17.6 ± 0.6	8.5 ± 0.9*	7.9 ± 1.3*
Frequency scores	Vomiting	3.4 ± 0.1	1.5 ± 0.2*	1.4 ± 0.3*
	Nausea	3.6 ± 0.1	1.9 ± 0.2*	1.9 ± 0.3*
	Early satiety	3.1 ± 0.2	1.6 ± 0.2*	1.6 ± 0.3*
	Bloating	2.8 ± 0.2	1.4 ± 0.2*	1.4 ± 0.3*
	Postprandial fullness	3.0 ± 0.2	1.3 ± 0.2*	1.6 ± 0.3*
	Epigastric pain	2.8 ± 0.2	1.4 ± 0.2*	1.1 ± 0.3*
	Total Symptom Score of frequency (0 to 24)	18.5 ± 0.6	8.9 ± 1.0*	8.9 ± 1.4*

Data are presented as means ± standard error
*P < 0.05 compared to baseline

Infection at pulse generator site requiring removal (2), skin penetration and infection requiring removal (1), volvulus about wires requiring removal of device (1).

Potential for bias:
Small sample size. Patient overlap with Forster et al. (2003) of 39 diabetic patients.

Other comments:
Study partly supported by Medtronic Inc.



Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments																																						
<p>Lin et al. 2005</p> <p><i>Patients:</i> Total 37. Type 1 diabetic (24), idiopathic (8) and postsurgical (5).</p> <p><i>Follow up:</i> 1 year follow up.</p> <p><i>Selection criteria:</i> Delayed gastric emptying, over 7 vomiting episodes per week, gastroparesis symptoms for over a year. Refractoriness or intolerance to 2 of 3 classes of prokinetic and antiemetic drugs.</p>	<p><i>Medication use:</i> At 1 year follow up the mean number of prokinetics used daily decreased from baseline levels (not statistically significant). Mean number of antiemetics used daily significantly ($P < 0.05$) decreased at 1 year follow up. The number of patients requiring antiemetics, at least 1 prokinetic and a combination of prokinetics and antiemetics decreased in all cases at 1 year follow up, however, this was not statistically significant.</p> <p><i>Gastric Emptying:</i> No significant effects on gastric emptying at 1 year follow up.</p> <p><i>Total Symptom Score:</i></p> <table border="1" data-bbox="430 678 1473 928"> <thead> <tr> <th></th> <th>Baseline</th> <th>1 year</th> </tr> </thead> <tbody> <tr> <td>Pts on prokinetics (n = 19)</td> <td>18.1 ± 0.9</td> <td>7.4 ± 1.3*</td> </tr> <tr> <td>Pts off prokinetics (n = 8)</td> <td>17.0 ± 0.8</td> <td>2.6 ± 1.1*†</td> </tr> <tr> <td>Pts on antiemetics (n = 17)</td> <td>19.1 ± 0.7</td> <td>9.9 ± 1.8*</td> </tr> <tr> <td>Pts off antiemetics (n = 9)</td> <td>17.7 ± 1.3</td> <td>5.0 ± 2.1*</td> </tr> <tr> <td>Pts on both medications (n = 9)</td> <td>19.4 ± 0.9</td> <td>7.7 ± 1.6*</td> </tr> <tr> <td>Pts reducing use of medications (n = 11)</td> <td>16.6 ± 1.0</td> <td>3.9 ± 1.4*†</td> </tr> </tbody> </table> <p><i>Physical/Mental Composite Score:</i></p> <table border="1" data-bbox="430 986 1473 1168"> <thead> <tr> <th></th> <th>Baseline</th> <th>1 year</th> </tr> </thead> <tbody> <tr> <td rowspan="2">Physical Composite Score</td> <td>Patients on both medications (n = 9)</td> <td>21.3 ± 1.2</td> <td>33.8 ± 24*</td> </tr> <tr> <td>Patients decreasing use of medications (n = 11)</td> <td>23.7 ± 2.3</td> <td>38.4 ± 3.9*</td> </tr> <tr> <td rowspan="2">Mental Composite Score</td> <td>Patients on both medications (n = 9)</td> <td>36.4 ± 3.0</td> <td>50.2 ± 24*</td> </tr> <tr> <td>Patients decreasing use of medications (n = 11)</td> <td>36.4 ± 3.8</td> <td>50.1 ± 3.7*</td> </tr> </tbody> </table> <p>Data expressed as means ± standard error. *$P < 0.05$ †$P < 0.05$ compared to patients on antiemetics at 1 year of gastric electrical stimulation.</p>		Baseline	1 year	Pts on prokinetics (n = 19)	18.1 ± 0.9	7.4 ± 1.3*	Pts off prokinetics (n = 8)	17.0 ± 0.8	2.6 ± 1.1*†	Pts on antiemetics (n = 17)	19.1 ± 0.7	9.9 ± 1.8*	Pts off antiemetics (n = 9)	17.7 ± 1.3	5.0 ± 2.1*	Pts on both medications (n = 9)	19.4 ± 0.9	7.7 ± 1.6*	Pts reducing use of medications (n = 11)	16.6 ± 1.0	3.9 ± 1.4*†		Baseline	1 year	Physical Composite Score	Patients on both medications (n = 9)	21.3 ± 1.2	33.8 ± 24*	Patients decreasing use of medications (n = 11)	23.7 ± 2.3	38.4 ± 3.9*	Mental Composite Score	Patients on both medications (n = 9)	36.4 ± 3.0	50.2 ± 24*	Patients decreasing use of medications (n = 11)	36.4 ± 3.8	50.1 ± 3.7*	<p>Infection at generator site pocket requiring removal of device (3).</p>	<p><i>Potential for bias:</i> Small sample size. Patient overlap. Eight patients overlapped with Abell et al. 2003a and 29 with Forster et al. 2003.</p>
	Baseline	1 year																																							
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Study Details	Key Efficacy Findings		Key Safety Findings	Appraisal/ Comments																					
<p>Mason et al. 2005</p> <p><i>Patients:</i> Total 29. Type I diabetic (24), idiopathic (5).</p> <p><i>Follow up:</i> Median follow up period of 20 months.</p> <p><i>Selection criteria:</i> Refractory gastroparesis referred for gastrectomy, vomiting episodes for over 7 per week, duration of vomiting of over 12 months, refractoriness or intolerance of antiemetic and prokinetic drugs, delayed gastric emptying.</p>	<table border="1"> <thead> <tr> <th></th> <th>Preoperatively</th> <th>Postoperatively</th> </tr> </thead> <tbody> <tr> <td>Total parenteral nutrition requirement</td> <td>12</td> <td>0</td> </tr> <tr> <td>Enteral nutrition requirement</td> <td>3</td> <td>0</td> </tr> <tr> <td>Enteral and total parenteral nutrition requirement</td> <td>4</td> <td>0</td> </tr> <tr> <td>Clinical outcome of stimulator placement</td> <td>-</td> <td>Good to excellent (70%) Fair to poor (30%)</td> </tr> <tr> <td>Body Mass Index</td> <td>22.9 ± 7.5</td> <td>25.1 ± 7.45*</td> </tr> <tr> <td>Gastric emptying rate (per minute)</td> <td>0.17% ± 0.54%</td> <td>0.38% ± 0.26%†</td> </tr> </tbody> </table> <p>Data presented as median ± interquartile ranges. *P = 0.006 †P < 0.001</p>			Preoperatively	Postoperatively	Total parenteral nutrition requirement	12	0	Enteral nutrition requirement	3	0	Enteral and total parenteral nutrition requirement	4	0	Clinical outcome of stimulator placement	-	Good to excellent (70%) Fair to poor (30%)	Body Mass Index	22.9 ± 7.5	25.1 ± 7.45*	Gastric emptying rate (per minute)	0.17% ± 0.54%	0.38% ± 0.26%†	<p>No 30 day mortality. Postoperative morbidity occurred in 4 patients.</p> <p>Erosion of gastric stimulator leads through the gastric mucosa at 6 months postoperatively requiring replacement of leads (1); removal of device due to pain at subcutaneous pocket site (1); total gastrectomy for failure to improve with treatment (1).</p>	<p><i>Potential for bias:</i> Other than selection criteria no statement regarding patient selection was presented. Small sample size.</p> <p><i>Other comments:</i> Two of the authors were consultants for Medtronic Inc. at time of writing and one had received honoraria for presentations on the device.</p>
	Preoperatively	Postoperatively																							
Total parenteral nutrition requirement	12	0																							
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<p>Oubre et al. 2005</p> <p><i>Patients:</i> Six post-surgical gastroparesis in total.</p> <p><i>Follow up:</i> Temporary phase, 3, 6 and 12 months. Plus longer follow up period (varied between patients).</p> <p><i>Selection criteria:</i> Documented gastroparesis after gastric surgery.</p>	<table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>Temp</th> <th>3 Months</th> <th>6 Months</th> <th>12 Months</th> <th>Latest</th> </tr> </thead> <tbody> <tr> <td>Vomiting Frequency Score</td> <td>3.2 ± 0.6</td> <td>0.4 ± 0.4*</td> <td>0.9 ± 0.5</td> <td>1.3 ± 0.4</td> <td>0.3 ± 0.3*</td> <td>1.4 ± 0.6</td> </tr> <tr> <td>Total Symptom Score</td> <td>36.5 ± 2.7</td> <td>12.3 ± 5.7</td> <td>10.4 ± 3.8*</td> <td>12.5 ± 6.6</td> <td>8.5 ± 4.8</td> <td>20.5 ± 4</td> </tr> <tr> <td>Health-related Quality of Life</td> <td>13.2 ± 2</td> <td>-</td> <td>7.7 ± 2</td> <td>7.2 ± 2</td> <td>6 ± 1</td> <td>7.3 ± 1</td> </tr> <tr> <td>Gastric emptying at 2h, solid</td> <td>76.8 ± 13</td> <td>52 ± 14</td> <td>67 ± 11</td> <td>54.7 ± 22</td> <td>50 ± 20</td> <td>63.7 ± 9</td> </tr> <tr> <td>Gastric emptying at 4h, solid</td> <td>71.4 ± 14</td> <td>41.6 ± 16</td> <td>41 ± 9</td> <td>36.7 ± 31</td> <td>15 ± 11</td> <td>30 ± 4</td> </tr> <tr> <td>Gastric emptying at 1h, liquid</td> <td>73.6 ± 7</td> <td>52.6 ± 11</td> <td>63.3 ± 7</td> <td>42.3 ± 19</td> <td>40.7 ± 9</td> <td>-</td> </tr> <tr> <td>Gastric emptying at 2h, liquid</td> <td>60.2 ± 9</td> <td>27 ± 6.5</td> <td>46.3 ± 10</td> <td>30.7 ± 16</td> <td>24.7 ± 11</td> <td>-</td> </tr> </tbody> </table>		Baseline	Temp	3 Months	6 Months	12 Months	Latest	Vomiting Frequency Score	3.2 ± 0.6	0.4 ± 0.4*	0.9 ± 0.5	1.3 ± 0.4	0.3 ± 0.3*	1.4 ± 0.6	Total Symptom Score	36.5 ± 2.7	12.3 ± 5.7	10.4 ± 3.8*	12.5 ± 6.6	8.5 ± 4.8	20.5 ± 4	Health-related Quality of Life	13.2 ± 2	-	7.7 ± 2	7.2 ± 2	6 ± 1	7.3 ± 1	Gastric emptying at 2h, solid	76.8 ± 13	52 ± 14	67 ± 11	54.7 ± 22	50 ± 20	63.7 ± 9	Gastric emptying at 4h, solid	71.4 ± 14	41.6 ± 16	41 ± 9	36.7 ± 31	15 ± 11	30 ± 4	Gastric emptying at 1h, liquid	73.6 ± 7	52.6 ± 11	63.3 ± 7	42.3 ± 19	40.7 ± 9	-	Gastric emptying at 2h, liquid	60.2 ± 9	27 ± 6.5	46.3 ± 10	30.7 ± 16	24.7 ± 11	-						<p>Device removal due to fistula (1).</p>	<p><i>Potential for bias:</i> Other than selection criteria no statement regarding patient selection was presented. Small sample size.</p> <p><i>Other comments:</i> Patients in this study were already involved in humanitarian and investigational trials (5 included in Abell et al. (2002)).</p>
	Baseline	Temp	3 Months	6 Months	12 Months	Latest																																																										
Vomiting Frequency Score	3.2 ± 0.6	0.4 ± 0.4*	0.9 ± 0.5	1.3 ± 0.4	0.3 ± 0.3*	1.4 ± 0.6																																																										
Total Symptom Score	36.5 ± 2.7	12.3 ± 5.7	10.4 ± 3.8*	12.5 ± 6.6	8.5 ± 4.8	20.5 ± 4																																																										
Health-related Quality of Life	13.2 ± 2	-	7.7 ± 2	7.2 ± 2	6 ± 1	7.3 ± 1																																																										
Gastric emptying at 2h, solid	76.8 ± 13	52 ± 14	67 ± 11	54.7 ± 22	50 ± 20	63.7 ± 9																																																										
Gastric emptying at 4h, solid	71.4 ± 14	41.6 ± 16	41 ± 9	36.7 ± 31	15 ± 11	30 ± 4																																																										
Gastric emptying at 1h, liquid	73.6 ± 7	52.6 ± 11	63.3 ± 7	42.3 ± 19	40.7 ± 9	-																																																										
Gastric emptying at 2h, liquid	60.2 ± 9	27 ± 6.5	46.3 ± 10	30.7 ± 16	24.7 ± 11	-																																																										

Data presented as means ± standard deviation
*p < 0.01



Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/ Comments														
<p>Jones <i>et al.</i> 2003 (Small preliminary observation from Editorial)</p> <p><i>Patients:</i> Total 13. Diabetic (12), idiopathic (1).</p> <p><i>Follow up:</i> 6 months.</p> <p><i>Selection criteria:</i> Delayed gastric emptying not responsive to prokinetics or antiemetics.</p>	<table border="1"> <thead> <tr> <th colspan="2" data-bbox="913 363 1368 400">Effects at 6 month follow up</th> </tr> </thead> <tbody> <tr> <td data-bbox="427 400 913 451">Disease specific quality of life (SF-36 health survey and Nepean Dyspepsia Index)</td> <td data-bbox="913 400 1368 451">No significant difference to baseline.</td> </tr> <tr> <td data-bbox="427 451 913 488">Psychological distress (Symptom Check List 90R)</td> <td data-bbox="913 451 1368 488">No significant difference to baseline.</td> </tr> <tr> <td data-bbox="427 488 913 525">Nausea scores</td> <td data-bbox="913 488 1368 525">No significant difference to baseline.</td> </tr> <tr> <td data-bbox="427 525 913 561">Vomiting scores</td> <td data-bbox="913 525 1368 561">No significant difference to baseline.</td> </tr> <tr> <td data-bbox="427 561 913 598">Water load volume in ml (mean ± standard error)</td> <td data-bbox="913 561 1368 598">No significant difference to baseline.</td> </tr> <tr> <td data-bbox="427 598 913 643">Percentage of subjects with normal electrogastrographies</td> <td data-bbox="913 598 1368 643">80% at baseline, 40% at 6 months.</td> </tr> </tbody> </table>	Effects at 6 month follow up		Disease specific quality of life (SF-36 health survey and Nepean Dyspepsia Index)	No significant difference to baseline.	Psychological distress (Symptom Check List 90R)	No significant difference to baseline.	Nausea scores	No significant difference to baseline.	Vomiting scores	No significant difference to baseline.	Water load volume in ml (mean ± standard error)	No significant difference to baseline.	Percentage of subjects with normal electrogastrographies	80% at baseline, 40% at 6 months.	<p>Pain at implant site requiring removal of the device (2).</p>	<p><i>Potential for bias:</i> Small sample size.</p>
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