



**North East Treatment
Advisory Group**

Gastroelectrical stimulation for gastroparesis

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Summary

- Gastroelectrical stimulation (GES) is a treatment in which a neuromodulating electrical stimulator is surgically inserted under the abdominal skin sending high-frequency low-power electrical impulses to the lower portion of the stomach.
- It is indicated for the symptomatic relief of severe gastroparesis refractory to conventional medical management.
- Gastroparesis is a condition characterised by reduced or absent gastric motility leading to gastric retention and symptoms of nausea, vomiting, and oesophageal reflux. Patients are often underweight and experience poorer quality of life than patients without gastroparesis.
- Conventional management includes lifestyle and dietary changes, and use of prokinetic and anti-emetic medication. A proportion of patients, estimated at about 2%, will be refractory to these measures.
- The evidence base for GES with the Enterra™ device is substantial however the majority of the evidence is of low quality with few comparative studies. There is only one comparative study that utilised patient blinding. Results consistently demonstrate significant effects on symptomatic relief, with smaller effects on gastric emptying rates. Healthcare utilisation, such as non-oral feeding methods, hospital appointments, and medication use, is often reduced following GES. Improvements in quality of life scores have been reported.
- GES requires surgery under general anaesthesia. About 10% of devices require removal. Battery life is expected to be at least seven years, to a likely maximum of 12 years. Safety complications are known and commonly consist of implant-site infections and lead migration.
- The presence of an Enterra™ implant will impose certain constraints on patients due to potential interference or damage to the device.
- GES is a costly treatment, estimated at about £16,000 to £18,000 per patient including all pre- peri- and post-operative care and hardware costs. Additional costs may be incurred if complications arise. There may be opportunities for significant off-set costs if patients are able to reduce or withdraw from non-oral feeding or reduce their need for medical care. Reductions in use of medication for gastroparesis are unlikely to realise important savings. Patient numbers have been estimated at about one or two patients per PCT per annum.

Introduction and background

The North East Treatment Advisory Group has been requested by the North East Specialised Commissioning Team (NESCT) to conduct an appraisal of, and advise, the North East Specialised Commissioning Group concerning gastroelectrical stimulation (GES) for gastroparesis. NESCT has received an application from a NHS North East acute trust for the commissioning of a service for implantation of GES devices.

GES involves abdominal surgery to implant a neurostimulating device into the abdomen. The application specifically refers to the use of a device called the Enterra™ (Medtronic Incorporated, USA). The Enterra™ implant has two intramuscular leads which are fixed to the muscle of the lower stomach. The neurostimulator delivers high-frequency low-powered electrical impulses and the stimulation rates and amplitude can be varied using an external programmer.¹⁻⁶

GES is a technique used to manage gastroparesis, a chronic disorder in which food empties from the stomach much more slowly than normal in the absence of any type of mechanical obstruction. The condition may be asymptomatic although in many patients it can cause significant morbidity. The most common symptoms are severe nausea and protracted vomiting. Other symptoms include abdominal bloating, pain and oesophageal reflux. Gastroparesis is a common complication of diabetes, or may occur following surgery particularly gastrointestinal or abdominal surgery, or in association with other disorders such as anorexia nervosa or abdominal migraine. In severe cases patients may be hospitalised due to the effects of dehydration and excessive weight loss and require nutritional support.¹⁻⁵

Conventional management will utilise dietary adaption with smaller and more frequent meals advocated, and the importance of maintaining adequate fluid intake highlighted. More severe dietary adaption may involve a shift towards a greater consumption of calories in liquid form (for example the consumption of soups and sugary drinks) and reduction in consumption of fat and fibre.¹⁻⁵

Pharmacological treatments are effective for the majority of patients. The drugs that are typically used have low acquisition costs and established efficacy and safety records. These include prokinetic agents such as metoclopramide and domperidone, the antibiotic erythromycin, and antiemetic agents such as prochlorperazine and ondansetron. Other drug therapy may involve antisecretory drugs such as histamine antagonists and proton-pump inhibitors.¹⁻⁵

About 2 to 5% of patients with gastroparesis are not able to obtain sufficient relief through simple dietary changes with or without drug therapy.¹⁻⁵

For medically refractory and severe cases major gastrointestinal surgery such as total gastrectomy is sometimes indicated.¹⁻⁵

GES is a potential alternative treatment to surgical management of gastroparesis. The operation to implant the device is often performed via laparoscopy under general anaesthesia and is estimated to take between one and two hours. A small subcutaneous pouch is prepared into which the control unit and battery pack is inserted.⁷ The combined mass is 42 grams and the device measures 55 by 60 mm with a depth of 10 mm. From this two leads, each 35 cm long, are connected deep into the muscle of the lower portion of the stomach. The device settings can be adjusted externally using a digital programmer which can also switch the device on or off. Battery power duration depends on device settings and is officially estimated at between five and ten years although in practice a range of seven to twelve years is more realistic.^{6,8}

Currently there are six centres in the UK that provide GES implantation, with the first UK patients receiving treatment in 2003. The centres are located in Scotland (two), the south east of England (two), Liverpool (since 2008) and Leeds (since 2009). The manufacturer of the Enterra™ device estimates that between 80 and 100 UK patients have received an Enterra™ implant to date.⁸

In December 2004 the National Institute for Health and Clinical Excellence (NICE) issued guidance on gastroelectrical stimulation for gastroparesis which stated:⁹

‘Current evidence on the safety and efficacy of gastroelectrical stimulation for gastroparesis does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research.’

‘There is little evidence that the procedure improves gastric emptying. Further research will be useful, and the Institute may review the procedure upon publication of further evidence.’

The evidence supporting the guidance was obtained up to and including June 2003. Since this time a considerable amount of new evidence has become available and this appraisal report is intended to serve as an update to the NICE appraisal.¹

Clinical evidence

Search method

The search strategy used by NICE in their 2003-4 appraisal ¹ was recreated in Embase and Medline accessed via the current NHS Evidence interface, with two additional limitations; year of publication = 2003 to current, and subjects = human. Searches were also made using the trade name of the device that is included in the proposal, 'Enterra'. Additional information was derived from internet searches and cross-referencing of other retrieved articles and review articles.

Results: Clinical evidence review

One hundred and sixty articles were screened from Medline and 196 from Embase. Retrieved articles met the following the criteria:

- Number of participants ≥ 6
- Principal use of the Enterra™ device made by Medtronic
- The intention of permanent implantation and the absence of prior use of a temporary implant

Nineteen studies met these criteria, including a total of 682 patients although some patients may have been counted in more than one report and outcomes are not reported for all. Key results are summarised in table 1.

As can be seen from the data in table 1, none of the relevant reports published since the NICE evidence review ¹ include a suitable comparator group and they amount to a collection of prospective and retrospective case series reports. To date only one study has attempted to blind patients to treatment. The results were based on short-term follow-up of a small number of patients and showed that at two months self-reported vomiting frequency was significantly lower in patients receiving stimulation than in patients in control groups. ¹⁰

In addition, a significant proportion of the evidence originates from only a few research teams, and many of the authors have affiliations with the manufacturer of the Enterra™ device. ^{1,11} In some examples a temporary device has been used prior to implantation of a permanent device thus introducing a degree of selection bias. Despite attempting to screen out evidence derived from such cases they may still be present in the data in table 1. In addition, not all patients received implantation with an Enterra™ device specifically despite attempting to identify evidence only relating to that device. However all patients did at least receive a device made by the same manufacturer which emitted high-frequency low-energy impulses. The most frequently encountered alternative device is the Itrel-3™, also manufactured by Medtronic. This is reported to be identical to the Enterra™ device although marketed for pain relief. ⁸

Table 1. Summary of key studies for the use of gastroelectrical stimulation published since 2003*

| Reference | Number of patients with outcomes (recruited) | Patients | Duration (time point at which outcomes derived unless indicated) | Key outcomes reported | Safety |
|--|--|---|--|---|---|
| Gourcerol G et al. Gastric electrical stimulation in intractable nausea and vomiting: Assessment of predictive factors of favorable outcomes. <i>Journal of the American College of Surgeons</i> 2009;209:215-21 | 33 (33) | Diabetic (12), idiopathic (11), post-surgery (10). Female (21), mean age 48 years. | Six months | Improvement was noted for 24 patients (73%) and no improvement for 9%. Mean total gastrointestinal quality of life index score (combined symptom and quality of life measure with a range from 0 to 100) increased from 64 to 85 ($p < 0.0001$). Mean weight (kg) increased from 61.6 to 62.4 ($p = 0.08$). Proportion of patients using prokinetic drugs decreased from 100% to 36% ($p < 0.0001$). There was no change in the mean time to achieve 50% gastric emptying (211 minutes). | None reported |
| McKenna D et al. Gastric electrical stimulation is an effective and safe treatment for medically refractory gastroparesis. <i>Surgery</i> 2008;144(4):566-74 | 9 (19) | Diabetic (10), idiopathic (6), post-surgery (3). Female (14) mean age 49 years. | Mean 38 weeks (range 1 to 35 months) | Mean 12-month total symptom score (range 0 to 24): Pre-GES score 17.1, 12-month post-GES score 7.7 ($p = 0.01$). 20% of patients did not report clinically significant changes in symptom scores. Gastric emptying times normalised in 5 out of 11 patients. | No changes in quality-of-life scores |
| Lin Z et al. Association between changes in symptoms and gastric emptying in gastroparetic patients treated with gastric electrical stimulation. <i>Neurogastroenterology and Motility</i> 2008;20:464-70 | 63 (63) | Diabetic (38), idiopathic (11), post-surgery (14). Female (51), mean age 41 years. | Twelve months | Mean total symptom score (range 0 to 28): Pre-GES score 19.9, post-GES score 9.1 ($p < 0.001$). Gastric retention at two hours reduced by 10% ($p = 0.02$), and at four hours reduced by 7% ($p = 0.10$) from baseline. Each symptom sub-measure demonstrated significant ($p < 0.05$) changes post-GES. Fourteen patients had normal gastric emptying after one year (22%). | None reported |
| Velanovich V. Quality of life and symptomatic response to gastric neurostimulation for gastroparesis. <i>Journal of Gastrointestinal Surgery</i> 2008;12:1656-63 | 42 (42) | Diabetic (24), idiopathic (17), post-surgery (1). Female 29, mean age 41 years. | Median follow-up 12 months (range 1 to 42) | 31 patients responded to GES to varying degrees, 11 (26%) had no response or worsening symptoms. Of six patients with feeding tubes, five were able to have them removed. Of the patients who responded the median time to response was 1.5 weeks (range 0 to 32) including eight with an immediate response. Of the patients with no response, the median time to determining this was 15 months (range 4 to 22). Quality of life results are only reported for responders and demonstrate significant improvements in all parameters. | Nine devices required removal with three subsequently re-implanted. Five devices were removed from confirmed non-responders. Two deaths occurred, neither related to GES. |
| Filichia LA et al. Small case series of gastric stimulation for the management of transplant-induced gastroparesis. <i>Journal of Surgical Research</i> 2008;148:90-3 | 13 (13) | Diabetic (5), idiopathic (5), post-lung transplant (3). | Mean twelve months | Eleven patients reported an improvement in quality of life, including all three transplant patients. Worse outcomes observed for diabetic patients compared with non-diabetic patients. | None reported |

| Reference | Number of patients with outcomes (recruited) | Patients | Duration (time point at which outcomes derived unless indicated) | Key outcomes reported | Safety |
|--|--|---|--|--|---|
| Maranki JL et al. Predictive factors for clinical improvement with Enterra gastric electric stimulation treatment for refractory gastroparesis. <i>Digestive Diseases and Sciences</i> 2008;53:2072-8 | 28 (29) | Diabetic (12), idiopathic (16) Female (24), mean age 40 years | Mean follow-up five months (maximum twelve months) | Fourteen patients reported symptom improvement, eight reported no change, and six reported worsening. Other results reported by sub-group. General trend was for modest improvements in symptom scores. | Two devices removed. Other reported sequelae appear unrelated to implantation or device. Four patients had enteral feeding tubes inserted. |
| Brody F et al. Gastric electrical stimulation for gastroparesis. <i>Journal of the American College of Surgeons</i> 2008;207:533-8 | 30 (50) | Diabetic (20), idiopathic (25), post-surgery (2), other (3). Female (45) Mean age 41 years | Mean follow-up 22 months; although one-year outcomes only available for 30 patients | All results reported are 12 month outcomes: Symptom outcomes (n = 30): Mean total symptom severity score (range 0 to 36) reduced from 19 to 14 (p ≤ 0.01). Mean total symptom frequency score (range 0 to 36) reduced from 20 to 16 points (p ≤ 0.05). Gastric retention (n = 27): Two-hour rate decreased from 66% to 50% (p ≤ 0.05) and four-hour rate from 35% to 21% (p > 0.05). | No post-op infections or erosions. Mean hospital stay 1.7 days (range 1 to 4). Three patients died 'several months post-operatively' with none considered related to GES. |
| Anand C et al. Gastric electrical stimulation is safe and effective: A long-term study in patients with drug-refractory gastroparesis in three regional centers. <i>Digestion</i> 2007;75:83-9 | 156 patients implanted with GES (not all Enterra™, 47 received prior temporary device) plus controls consisting of 25 consented but not implanted and 33 implanted with a temporary device only. | Of permanent devices (156): Idiopathic (107), diabetic (32), post-surgery (17). Of all patients (214): female (169), mean age at time of consent 42 years. | Median follow-up 4 years | For patients with a permanent implant compared with baseline: mean vomiting frequency score (range 0 to 4) reduced from 2.9 to 1.9, mean total symptom score (range 0 to 20) reduced from 15.6 to 10.9, mean quality of life score (range 0 to 30) improved from 16.3 to 10.6 (all p < 0.05). Small but significant improvements for 2h (55 to 42%) and 4h (26 to 17%) gastric emptying rates (both p < 0.05). No overall effect on survival for implanted vs. control patients (which includes some temporary implants). | 11 of 156 permanent devices removed, 7 due to infection and 4 for technical reasons. 10 subsequently re-implanted successfully. No deaths considered related to GES. |
| Lin Z et al. Symptom responses, long-term outcomes and adverse events beyond 3 years of high-frequency gastric electrical stimulation for gastroparesis. <i>Neurogastroenterology and Motility</i> 2006;18:18-27 | 37 (55) | Of the 37 patients with 3 year follow-up: Diabetic (23), idiopathic (9), post-surgery (5). | Of the 37 who completed three year follow-up the mean duration of device in situ was 45 months (range 36 to 79). | Results based on intention to treat (n = 55) with last observation carried forward for missing data: Mean total symptom severity score (range 0 to 28) reduced from 21 to 8 and mean total symptom frequency score (range 0 to 28) reduced from 23 to 9 (both p < 0.05). Median numbers of days in hospital reduced from 31 to 2. Median weight (kg) increased from 63 to 68. Median use of drugs remained at 1 per patient. All p < 0.05. Of the 37 patients with 3 year follow-up, (par)enteral nutrition requirements were reduced from 15 to 5 patients with none receiving total parenteral nutrition. | Of the initial 55 patients, 10 died of non-GES complications and six had the device removed with four due to infection at the implant site and two due to total gastrectomy. One re-implantation due to external trauma. |

| Reference | Number of patients with outcomes (recruited) | Patients | Duration (time point at which outcomes derived unless indicated) | Key outcomes reported | Safety |
|--|--|--|---|---|--|
| de Csepel J et al. Electrical stimulation for gastroparesis: Gastric motility restored. Surgical Endoscopy 2006;20(2):302-6 | 10 (16) | Diabetic (7), idiopathic (7), other (2). Twelve female, mean age 38 years. | Six months | Mean nausea and vomiting symptom scores (range 0 to 16): pre-GES score 11.2 reduced to 4.85 post-GES (p = 0.004). SF-36 health survey: Pre-GES mean score 39.5%, post-GES mean score 57.8% (p = 0.039). | None reported |
| Andersson S et al. Gastric electrical stimulation for intractable vomiting in patients with chronic intestinal pseudo-obstruction. Neurogastroenterology and Motility 2006;18:823-30 | 15 (16) | Four female with chronic intestinal pseudo-obstruction (CIP). Twelve (eight female) with diabetic gastroparesis included as a control group. | Twelve months | Five patients had temporary devices implanted initially. Mean weekly vomiting frequency decreased from 24 to 6.9 post-GES for CIP patients and from 23 to 3.5 for diabetic patients. No overall reduction in hospital admissions but clear reduction in admissions related to gastroparesis. No recorded reductions in requirements for parenteral nutrition. | One re-implantation required due to device fault and one re-implantation required due to skin erosion. One implant required additional surgical intervention to correct complications and one fault was managed without surgery. |
| Abidi N et al. An energy algorithm improves symptoms in some patients with gastroparesis and treated with gastric electrical stimulation. Neurogastroenterology and Motility 2006;18:334-8 | 22 (22) | Idiopathic (12), diabetic (4), post-surgery (6). Female (17), mean age 35 years. | Median 4.3 years | Patients were selected for this report because they did not achieve a satisfactory response with standard GES device settings. The report describes the results obtained when settings were adjusted according to a defined algorithm which resulted in adjustments to the power and frequency of electrical impulses: mean total symptom scores improved in patients, with 18 of 22 achieving at least a 50% improvement in symptoms from baseline. Average symptom score change from baseline was 36% with standard settings and 59% with optimal settings. 10% of patients demonstrated no change, none demonstrated worsening. | None reported |
| Gray J, Fullarton GM. Gastric electrical stimulation in severe gastroparesis – the Scottish experience. Neurogastroenterology and Motility 2006;18:493 | 7 (7) | Diabetic (5), idiopathic (2) Female (5), median age 30. | Six months | Median weekly vomiting frequency reduced from 25 to 4 episodes (p < 0.001). Median weight (kg) increased from 49 to 54 (p > 0.05). Three patients demonstrated improved gastric emptying. Six patients required supplemental enteral feeding prior to surgery. None have required enteral feeding since surgery (follow-up between 11 and 34 months). | One patient died six months post implant due to unrelated sepsis. |

| Reference | Number of patients with outcomes (recruited) | Patients | Duration (time point at which outcomes derived unless indicated) | Key outcomes reported | Safety |
|---|--|--|---|--|---|
| Mason RJ et al. Gastric electrical stimulation: An alternative surgical therapy for patients with gastroparesis. Archives of Surgery 2005;140:841-8 | 29 (29) | Female (22) median age 39 years. Diabetic (24), idiopathic (5) | Median follow-up 20 months (range 4 to 37) | Good to excellent outcomes for 70% of patients, fair to poor outcomes for 30%. Absence of solid food from the diet was reduced from 19 patients to 0 (zero) patients at follow-up. 46% patients normalised gastric emptying. Mean gastric emptying rate (% min ⁻¹) changed from 0.17% to 0.38% from baseline to post-GES. Median body mass index increased by 2.2 points (p = 0.006) against a background of previous decreases. | No deaths at 30 days post-surgery. Four post-surgical incidents, none related to the subcutaneous pocket for the device. Three patients had died at follow-up, none directly related to the device. |
| McCallum R et al. Clinical response to gastric electrical stimulation in patients with postsurgical gastroparesis. Clinical Gastroenterology and Hepatology 2005;3:49-54 | 16 (16) | Female (15), mean age 46 years. All post-surgery. | Twelve months | Mean total symptom severity score (range 0 to 24) reduced from 17.1 to 8.6. Mean total symptom frequency score (range 0 to 24) reduced from 19.2 to 9.8 (both p < 0.05). Mean health-related quality of life scores (range 0 to 100) increased from 28.6 to 37.7 for physical components, and from 39.7 to 49.6 for mental components (both p < 0.05). Mean two-hour gastric retention rate reduced from baseline 81% to 66%, and mean four-hour gastric retention rate reduced from 52% to 40% (both p > 0.05). Of seven patients at baseline receiving tube feeding, three were still receiving tube feeds at 12 months and four had discontinued tube feeds. Mean body mass increased from 61 to 65 kg (p < 0.05). | Two devices removed; one due to pocket infection and the other due to unrelated external trauma with device later replaced. |
| Lin Z et al. Chronic gastric electrical stimulation for gastroparesis reduces the use of prokinetic and/or antiemetic medications and the need for hospitalizations. Digestive Diseases and Sciences 2005;50(7):1328-34 | 37 (37) | Diabetic (24), idiopathic (8), post-surgery (5). Female (29) mean age 41 years. | Twelve months | Mean number of antiemetic medications used daily reduced from 1.0 to 0.6, and prokinetic medications from 1.2 to 0.8 (both p < 0.05). Eight of 27 patients not taking any prokinetic medication and 9 of 26 patients not taking any antiemetics. 20 patients receiving (par)enteral nutrition at baseline reduced to 7 after one year with none receiving parenteral nutrition. Mean days in hospital reduced from 50 to 14 (p < 0.05). Symptom scores and quality of life scores demonstrated significant improvements. No overall change in gastric emptying rates. 22% patients normalised at one year, 35% demonstrated increased retention. | Three devices removed due to related infections in subcutaneous pocket. |

| Reference | Number of patients with outcomes (recruited) | Patients | Duration (time point at which outcomes derived unless indicated) | Key outcomes reported | Safety |
|--|--|--|---|---|--|
| Cutts TF et al. Is gastric electrical stimulation superior to standard pharmacologic therapy in improving GI symptoms, healthcare resources, and long-term healthcare benefits? Neurogastroenterology and Motility 2005;17:35-43 | 18 (18) | Nine patients treated with GES and nine treated with intensive medical therapy. GES patients: female (6), mean age 39 years. Diabetic (1), idiopathic (8). Control group: All female, mean age 40 years. Diabetic (1), idiopathic (8). | All patients had three year outcomes (except three who died in the control group) | Mean total symptom score (range 0 to 50) reduced from 38 to 23 in GES patients and from 39 to 35 in control patients. Mean quality of life score (range 0 to 30) improved from 13 to 6 in GES patients and worsened from 11 to 14 in control patients. Mean annual cost per patient decreased from \$84,000 to \$22,000 in GES patients and from \$80,000 to \$63,000 in control patients (all between group $p < 0.05$). Mean annual hospital days decreased from 25 to 3 for GES patients and from 27 to 6 for control patients (between group $p > 0.05$). | Three deaths in the control group and none in the GES group. No other safety data reported. |
| Lin Z et al. Treatment of diabetic gastroparesis by high-frequency gastric electrical stimulation. Diabetes Care 2004;27:1071-6 | 28 (48) | All diabetic. Female 33, mean age 38 years. | Twelve months | Mean total symptom score (severity) decreased from 17.6 to 7.9. Mean total symptom score (frequency) decreased from 18.5 to 8.9 (both range 0 to 24). Physical and mental components of quality of life scores both increased significantly. Gastric retention (% standardised meal retained): 2 hours retention decreased from 76% to 75%, and 4 hour retention from 50% to 38% (both $p > 0.05$). Use of parenteral and/or enteral nutrition decreased from 22 to 5 patients, with none requiring total parenteral nutrition. | Implant subsequently removed in four patients at range 3 to 16 months post-insertion. Nine patients died with follow-up < 63 months. One post-surgery due to embolus, the other eight deaths are not obviously related to GES. |
| Jones MP et al. Enterra for gastroparesis. American Journal of Gastroenterology 2003;98:2578 | 10 (13) | Diabetic (12), idiopathic (1) | Six months | No significant differences observed with respect to health survey (SF-36) scores, psychological distress scores, nausea or vomiting scores. Modest and significant improvements in scores for dyspepsia-related quality of life. Actual values not stated. Mean water load volumes increased from baseline 306 to 358 millilitres ($p > 0.05$). Proportion of patients with normal electrogastronomy reduced from 80% to 40% ($p > 0.05$). | Two patients had device removed due to pain at implant site |

* : Not included in the evidence overview for NICE Interventional Procedure Guidance 103 (i.e. from new evidence published since June 2003)
GES: gastroelectrical stimulation

In addition to the studies that have been reviewed in table 1 a relevant meta-analysis has recently been published which was independent of the manufacturers of the Enterra™ device. The literature search was conducted up to August 2008 and with rigorous criteria applied the authors identified thirteen studies, of which only one had a control group. Ten of the studies have been published since the NICE review. In total, the thirteen studies recruited 302 patients (range 7 to 48 per study) although outcomes were often available from fewer patients than were recruited. Nine of these studies are also described in table 1 and two were included in the NICE appraisal.¹ Of the remaining two, an updated report with a greater number participants is reported in table 1 and the other did not use the Enterra™ device. Study quality was rated as 'low' for twelve studies. Four outcomes were assessed: symptom improvement, nutritional outcome, gastric emptying, and device complications. The results are summarised in table 2.¹²

Table 2. Summary results of a meta-analysis of gastroelectrical stimulation with the Enterra™ device for gastroparesis¹²

| Outcome | Number of studies (patients*) | Mean difference (95% CI) |
|--|-------------------------------|-------------------------------------|
| Total symptom score (mean difference, range 0 to 24) | Three (77) | 6.5 (1.3 to 11.7) [p < 0.05] |
| Requirement for (par)enteral support (odds ratio) | Eight (184) | 5.5 (2.8 to 11.1) [p < 0.05] |
| Change in weight (mean, kg) | Four (96) | 3.7 (-0.2 to 7.6) [p = 0.07] |
| Change in 2-hr gastric emptying (mean proportion [%] of patients with delayed gastric emptying) | Four (90) | 23.1 (7.9 to 38.4) [p < 0.05] |
| Change in 4-hr gastric emptying (mean proportion [%] of patients with delayed gastric emptying) | Five (86) | 12.7 (9.8 to 15.6) [p < 0.05] |

* Number of patients on which the outcome has been assessed

Safety

As demonstrated by the data in table 1, adverse effects and other post-operative treatment sequelae are often poorly reported. The frequency of device removal with or without subsequent re-implantation ranges from 0% to about 20%, with a typical value of about 10%. The most common complication appears to be infection at the site of device implantation. Other complications include migration of the neurostimulator leads or device malfunction. One serious complication led to infarction of the small bowel following bowel volvulus around the device wires.

The systematic review previously referred to found a rate of device removal and/or replacement of 8.3% (22 out of 265 patients where the relevant outcome was reported; approximately 1 in 12 patients). Amongst the reasons given were infection (eight cases), erosion of device through skin (six), pain (four), and stomach perforation by device leads (two).¹²

Specific safety reports include a case report of gastric wall perforation due to a gastric electrical stimulator device, although not specifically the Enterra™ device. The patient required an emergency hospital admission for epigastric pain 41 months after the device had been implanted. It was subsequently found that the cause of the pain was gastric perforation from one of the leads from the stimulator device. Both leads were replaced, and the device remained *in situ* and remained active.¹³

One other report describes two cases of erosion of leads from Enterra™ devices. The patients presented 16 and 21 months after device implantation with upper gastric erosion. In both cases the devices and leads were removed and in one case a new device was re-implanted seven months later. Both patients initially presented with severe pocket site infections with gastric erosion of the leads only identified incidentally. Both patients survived.¹⁴

Cost analysis

All hardware costs include VAT at 17.5%

Each Enterra™ device costs £5,170. Each neurostimulator lead costs £1,410 and two are required with each device. Therefore the total hardware costs associated with an Enterra™ device are £7,990.⁸

Implantation of an Enterra™ device requires laparoscopic surgery of between one and two hours duration under general anaesthesia. The HRG-4 tariff price for laparoscopic procedures is typically between £3,000 and £4,000 although this does not relate to gastrointestinal surgery.¹⁵ The business case submission reports that other UK centres charge between £16,000 and £18,000 per patient including hardware, which is reported as being correct.⁸ This suggests the cost of medical care alone and ancillary consumables including pre-, peri- and post-operative care and assessment is between £8,000 and £10,000 per patient.

There are potential off-set costs. For example, the evidence demonstrates that there is a significant reduction in the proportion of patients who require enteral or parenteral nutrition.¹² The cost of supplemental enteral nutrition provided via homecare arrangements has been estimated at about £3,500 per patient per annum for the feeds, hardware, and delivery alone (based on 2004-05 prices and exchange rates).¹⁶ Enteral feeding will also be associated with specific healthcare labour resources although there is no evidence that the net effect is any different for gastroparesis patients who are not receiving enteral feeding.

Although no reliable recent cost estimate for total parenteral nutrition in the UK was identified, parenteral feeding is typically substantially more expensive to provide than enteral feeding and the off-set costs will be greater than with enteral feeding.¹⁷ Parenteral feeding is also considered to present significant clinical risk due to complications associated with intravenous access (e.g. infection and thrombosis).

Although parenteral and enteral feeding techniques are considered higher risk compared with oral feeding due to risk of infection it should be remembered that use of the Enterra™ device will also present a risk of surgical complications and an ongoing risk of infection at the site of the subcutaneous pocket and lead migration. There is no reliable evidence to estimate the cost impact of these factors, nor any useful comparisons of use of the Enterra™ device compared with non-oral feeding techniques.

There is evidence that the total use of drugs can be reduced however the off-set costs of this are likely to be relatively small because commonly used drugs to manage gastroparesis are of low cost (see table 3).

Table 3. Cost of commonly used drugs to manage gastroparesis

| Treatment ¹⁸ | Annual drug cost (primary care) ¹⁹ |
|--|---|
| Metoclopramide 10 mg three times daily | £43 |
| Domperidone 20 mg three times daily | £91 |
| Erythromycin 250 mg three times daily | £80 |

Where GES is used as an alternative to major gastrointestinal surgery such as total gastrectomy there may also be further off-set costs as this procedure is likely to be costly with a considerable recovery period. Patients with gastrectomy will require enteral or parenteral nutrition for life.

The business case submission estimates that the proposed service will implant a maximum of 24 devices per annum based on a maximum of four patient assessments per month of which only half will be considered suitable for GES. It is expected that referrals from outside of NHS North East will initially be low at about 10% per annum, gradually increasing to 50% over time. Therefore the majority of patients for the proposed service are expected to be derived from within NHS North East.

If twelve patients per annum are treated from NHS North East (i.e. approximately one per PCT) the total annual cost to NHS North East will be about £200,000. This does not include costs associated with adverse effects, device removal or replacement, and other care that patients may be receiving.

Patient impact

The following aspects will all have an impact on patients to varying degrees. ¹⁻⁸

- The surgical procedure for implantation is estimated to take between one and two hours and is performed under general anaesthesia.
- The device will be visible as a small raised area under the skin.
- The device has a limited lifespan dictated principally by battery life, officially estimated at five to ten years, although in practice seven to twelve years is the norm. When the device has expired it will require surgery to be removed or replaced.
- There is a risk of electromagnetic interference with the device from other electrical equipment especially radio wave emitting devices, magnets, and electrical amplifiers. Patients are advised to avoid security scanners and theft scanners such as those found at airports and in department stores.
- Some particular types of physical activity are not advised, for example those that require excessive stretching or twisting. Any activity that exposes the patient to excessive pressures, such as underwater diving, is not recommended.
- Most medical imaging techniques are considered safe except magnetic resonance imaging scans.
- Caution is expressed with numerous other medical and cosmetic interventions such as dental drills and ultrasonic probes, cardioversion and defibrillation, laser therapy, radiation therapy, and others.
- Currently the nearest centres that offer surgical implantation of Enterra™ devices to treat gastroparesis are in Leeds and Glasgow. Therefore development of a service within NHS North East should make the treatment more convenient for local patients who receive the implant.
- About 10% of patients will subsequently require the device to be removed at further risk and inconvenience and a proportion will derive no benefit.
- GES is proposed as an alternative to gastrointestinal surgery for patients with severe symptoms of gastroparesis and refractory to conventional medical management.

Points to consider

- Development of this service within NHS North East will lead to development of nationally recognised clinical expertise with associated training and research opportunities.
- The service is likely to draw income from purchasers outside of NHS North East and is unlikely to be entirely dependent on patients from the local population.
- The concluding statements in the NICE guidance were: ^{1,9}
 - Current evidence on the safety and efficacy of gastroelectrical stimulation for gastroparesis does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research.
 - Clinicians wishing to undertake gastroelectrical stimulation for gastroparesis should take the following actions: 1. Inform the clinical governance leads in their Trusts. 2. Ensure that patients understand the uncertainty about the procedures safety and efficacy and provide them with clear, written information. 3. Audit and review clinical outcomes of all patients having gastroelectrical stimulation for gastroparesis.
 - The procedure should only be performed in specialist gastroenterology units with expertise in gastrointestinal motility disorders.
 - Current evidence on the efficacy of the procedure relates mainly to relief from nausea and vomiting, which occurs in some patients. There is little evidence that the procedure improves gastric emptying. Further research will be useful, and the Institute may review the procedure upon publication of further evidence.
- A large volume of evidence has been published since the NICE evidence overview, ¹ however it is all of low methodological quality, largely consisting of non-comparative case series reports. Only one comparator study, a placebo-controlled 'n-of-one' study, has been performed using an Enterra™ device. This study used a small number of patients with only short follow-up. All other evidence originates from non-comparative case series reports which include a mixture of prospective and retrospective data collection.
- Nonetheless, the evidence is consistently in favour of significant symptomatic relief. In addition, there are small but statistically significant improvements in two- and four-hour gastric emptying rates. There are attendant reductions in healthcare use such as enteral and parenteral nutrition, medical appointments, and drug use. Patients demonstrate modest but significant weight gain. A significant proportion of patients report no benefit.
- GES implantation with Enterra™ is a costly therapy, estimated at a total of £16,000 to £18,000 per patient. Ongoing and recurrent care will be required. Significant off-set costs may be achievable for some patients, especially those receiving non-oral nutritional support and those with a high rate of hospital admission. There is a lack of data to reliably estimate the costs of these effects.
- The complication rate requiring removal of the original implant is about 10%, with rates of up to 20% reported in some series. The most common complication is pocket-site infection. Many of the removed devices have been replaced.

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References

1. National Institute for Clinical Excellence. Interventional procedure overview gastroelectrical stimulation for gastroparesis. September 2003.
2. Park M-I, Camilleri M. Gastroparesis: Clinical update. *American Journal of Gastroenterology* 2006;101:1129-39
3. Gumaste V, Baum J. Treatment of gastroparesis: An update. *Digestion* 2008;78:173-9
4. Syed AA, Rattansingh A, Furtado SD. Current perspectives on the management of gastroparesis. *Journal of Postgraduate Medicine* 2005;51:54-60
5. Waseem S, Moshiree B, Draganov PV. Gastroparesis: Current diagnostic challenges and management considerations. *World Journal of Gastroenterology* 2009;15(1):25-37
6. Medtronic UK limited. Enterra™ product literature (various)
7. Pinto DA, Kaidar-Person O, Cho M et al. Laparoscopic placement of a gastric stimulator for the treatment of gastroparesis. *Surgical Laparoscopy, Endoscopy and Percutaneous Techniques* 2008;18(2):144-50
8. Personal communication with representative of Medtronic. April 2010
9. National Institute for Clinical Excellence. Gastroelectrical stimulation for gastroparesis: Interventional procedure guidance 103. December 2004
10. Reference 9 referring to Abell T et al. Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology* 2003;125:421-8
11. Jones MP. Is gastric electrical stimulation an effective therapy for patients with drug-refractory gastroparesis? *Nature Clinical Practice Gastroenterology and Hepatology* 2008;5(7):368-70
12. O'Grady G, Egbuji JU, Du P, Cheng LK, Pullan AJ, Windsor JA. High-frequency gastric electrical stimulation for the treatment of gastroparesis: A meta-analysis. *World Journal of Surgery* 2009;33:1693-701
13. Becker JC, Dietl KH, Konturek JW, et al. Gastric wall perforation: a rare complication of gastric electrical stimulation. *Gastrointestinal Endoscopy* 2005;59(4):584-6
14. Liu RC, Sabnis AA, Chand B. Erosion of gastric electrical stimulator electrodes: Evaluation, management, and laparoscopic techniques. *Surgical Laparoscopy, Endoscopy and Percutaneous Techniques* 2007;17(5):438-41
15. Department of Health. 2010-11 National Tariff Information. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_112284
16. Elia M, Stratton RJ. A cost-utility analysis in patients receiving enteral tube feeding at home and in nursing homes. *Clinical Nutrition* 2008;27:416-23
17. Richards DM, Irving MH. Cost-utility analysis of home parenteral nutrition. *British Journal of Surgery* 1996;83:1226-9
18. NHS Clinical Knowledge Summaries. Diabetes type 2 – management: Gastroparesis. www.cks.nhs.uk/diabetes_type_2/management/detailed_answers/managing_neuropathy/autonomic_neuropathy_including_erection_dysfunction
19. NHS Dictionary of medicines and devices. April 2010. <http://dmd.medicines.org.uk>