NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of electrical stimulation of the lower oesophageal sphincter for treating gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease, or GORD, causes symptoms such as heartburn, regurgitation, chest pain and nausea. It is caused by several conditions, such as hiatus hernia, that disturb the function of the lower oesophageal sphincter. This is the ring of muscle separating the oesophagus from the stomach. Electrical stimulation of the lower oesophageal sphincter involves applying low energy electrical impulses to the sphincter in repeated sessions. The aims are to strengthen the sphincter and reduce acid reflux. In this procedure, small electrodes are implanted in the sphincter using keyhole surgery and connected to a stimulator, which is placed under the skin of the abdomen.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in December 2014 and updated in June 2015.

Procedure name

- Electrical stimulation of the lower oesophageal sphincter for treating gastro-oesophageal reflux disease.

Specialist societies

- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland

- British Society of Gastroenterology.

Description

Indications and current treatment

Gastro-oesophageal reflux disease (GORD) is a common problem. It is caused by several conditions that disturb the sphincter function at the lower end of the oesophagus, such as hiatus hernia. Symptoms of GORD can be broadly grouped into those directly related to reflux episodes, such as heartburn, regurgitation, chest pain and nausea, and those symptoms caused by complications of reflux disease, including dysphagia and respiratory difficulties. Repeated episodes of GORD can damage the lining of the oesophagus and lead to oesophageal ulceration, oesophageal stricture and Barrett's oesophagus.

The standard treatments for patients with symptomatic GORD are lifestyle modification and drug therapy. Patients who have refractory symptoms, who develop complications despite medication or who develop intolerance to medication may be considered for anti-reflux surgery (usually laparoscopic fundoplication). Several endoscopic techniques (such as endoscopic radiofrequency ablation or endoscopic injection of bulking agents) have also been used.

What the procedure involves

Electrical stimulation of the lower oesophageal sphincter aims to strengthen a weak or improperly functioning lower oesophageal sphincter muscle, to restore the anti-reflux barrier between the stomach and oesophagus, by using low energy electrical impulses. With the patient under general anaesthesia, 2 electrodes and a lead are implanted into the sphincter muscle using a laparoscope under endoscopic guidance. The lead is passed through the abdominal wall and is secured to a stimulator, which is implanted in a subcutaneous pocket in the abdominal wall. The stimulator automatically delivers impulses of about 3 mA to 8 mA to the electrodes in repeated 30-minute sessions. The patient does not feel the stimulation. The stimulator is programmed and controlled wirelessly to adapt it to specific patient needs (for example, related to diet and lifestyle).

Outcome measures

Improvement in quality of life; the gastro-oesophageal reflux disease health-related quality of life (GORD-HRQL) scale assesses patient symptoms and effects on daily living using 10 questions. Scores of 0–50 are recorded; from best to worst.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to electrical stimulation of the lower oesophageal sphincter for treating gastro-oesophageal reflux disease. The following databases were searched, covering the period from their start to 4 June 2015: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with gastro-oesophageal reflux disease.
Intervention/test	Electrical stimulation of the lower oesophageal sphincter.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 69 patients from 4 case series.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on electrical stimulation of the lower oesophageal sphincter for the treatment of gastro-oesophageal reflux disease

Study 1 Kappelle WFW (2015)

Details

Study type	**Prospective study**
Country	International multicentre trial (10 sites in 8 countries)
Recruitment period	Not reported
Study population and number	n=**44** patients with chronic GORD partially responsive to PPIs
Age and sex	Mean 50 years; 57% (24/42) male (baseline patients' characteristics only presented for 42 patients).
Patient selection criteria	Inclusion criteria: age 21-80 years, history of heartburn or acid regurgitation or both, continued daily use of PPI for ≥ 12 months before enrolment, continued symptoms in spite of acid suppression therapy prompted consideration of alternative therapy for GORD, baseline GORD-HRQL score of ≥20 following 10–14 days off-PPI, and at least 5 points higher than the on-PPI score, excessive oesophageal acid exposure during 24-h pH monitoring of acid suppression therapy (pH <4 for ≥5% of total time), resting LOS end-expiratory pressure ≥5 mmHg. Exclusion criteria: history of previous oesophageal or gastric surgery, including Nissen fundoplication, history of gastroparesis, History of significant multisystem diseases, known autoimmune or connective tissue disorder requiring therapy in the preceding 2 years, Barrett's epithelium (> M2; >C1) or any grade of dysplasia, hiatal hernia >3 cm, oesophagitis Grade D (LA classification) on upper endoscopy performed within 6 months of enrolment, ASA Physical Status Classification >II, BMI greater than 35 kg/m2, T1DM or uncontrolled T2DM defined as HbA1c ≥9.5 in the previous 6 months, or T2DM for ≥10 years, history of suspected or confirmed oesophageal or gastric cancer, history of any other malignancy in the last 2 years, oesophageal or gastric varices or dysphagia or oesophageal peptic stricture, significant cardiac arrhythmia or significant cardiovascular disease, existing implanted electrical stimulator or those requiring chronic anticoagulant therapy, pregnant women or women intending to become pregnant during the trial period, patients currently enrolled in other potentially confounding research, patients with any condition that, at the discretion of the investigator, would prevent participation in the trial.
Technique	Bipolar stitch electrodes and a pulse generator (EndoStim BV) were implanted laparoscopically. A commercially available 10-mm electrode was used in most patients and an investigational 5-mm electrode was used in a subgroup of patients to facilitate electrode placement. All patients were initiated on a standard stimulation protocol consisting of 30-minute sessions with 90-minute breaks, 12 times daily at 5 mA, 20 Hz, 220 µs pulse width. Stimulation settings were altered if patients had either persistent symptoms or persistent acid exposure at follow-up visit. First, the stimulating electrode was changed (only 1 of the 2 electrodes is stimulating). If that did not resolve the problem, the number of sessions was increased and the amplitude was increased. A crural repair was performed during the implantation procedure in patients with a hiatal hernia to restore normal anatomy at the discretion of the team on-site. Patients were taken off acid suppressive therapy at discharge and told to take H2-receptor antagonists if needed; patients were allowed to take PPIs if residual or recurrent symptoms were present despite optimisation of LOS-EST. All patients were discharged within 1 day after the procedure.
Follow-up	**6 months**
Conflict of interest/source of funding	The study was funded by Endostim BV. Most of the authors declared personal or funding interests.

Analysis

Follow-up issues:

- 110 patients were screened. Laparoscopy was performed in 44 patients but the characteristics were presented for 42 patients and 41 completed the 6-month follow-up. One patient was excluded after the decision was made to perform a Toupet procedure because a hiatal hernia of greater than 3 cm was found during the procedure. A second patient had a trocar perforation of the intestine during the implant procedure (reported in the safety section of the table); the device was removed and the patient was withdrawn from the study. A third patient was lost to follow-up.

Study design issues:

- Stimulation started within 48 hours of implant in 88% (37/42) of patients or after 2 weeks in 12% (5/42) of patients who had a hiatal repair procedure to allow for electrode implant site healing after oesophageal hiatus dissection.
- The stimulating electrode was swapped in 50% (21/42) of patients, followed by altering of the number of daily sessions in 40% (17/42) of patients and increasing pulse amplitude in 17% (7/42) of patients.
- Oesophageal pH measurement systems varied between centres. Oesophageal manometry was performed and interpreted by each centre using either the Medical Measurement System or the Sierra Instruments system.

Study population issues:

- 3 patients did not take the prescribed dose of PPI at time of inclusion because of side effects or a fear of side effect.
- A hiatal hernia was present in 61% (25/41) of patients available at 6 months.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **42, but 41 patients completed the 6-month follow-up period.**

GORD-HRQL

	GORD-HRQL Median (IQR)	Change from baseline on-PPI (IQR)	Change from baseline off-PPI (IQR)
Before the procedure (baseline) on-PPI (n=42)	16.5 (9.0 to 22.8)		
Baseline off-PPI (n=42)	31.0 (26.2 to 36.8)		
3 months after the procedure (n=41)	4.0 (1.0 to 8.0)	−11 (−18 to −5)*	−27 (−33 to −21)*
6 months after the procedure (n=41)	5.0 (3.0 to 9.0)	−8 (−16 to −1)*	−22 (-32 to −17)*

*p<0.0001

- Before the procedure and while on PPI:
  - 7% (3/42) of patients reported in a daily symptom diary that they were 'satisfied' with their condition.
  - 74% (31/42) reported that they were 'unsatisfied' with their condition.
- 6 months after the procedure:
  - 54% (21/39) of patients available for the analysis were 'satisfied' with their condition (p<0.001 for the difference with those who were 'unsatisfied' at baseline (on PPI) (31/42)
  - 26% (10/39) were neutral
  - 21% (8/39) were 'unsatisfied'
- Median improvement of 44% of all 'unsatisfied' patients versus baseline off-PPI score.

% 24-hour distal oesophageal pH<4.0

	% 24-hour distal oesophageal pH<4.0 Median (IQR)	Change from baseline off-PPI (IQR)	p value
Baseline (n=42)	9.9 (7.5 to 12.9)		
3 months (n=28)	3.8 (1.9 to 12.3)	−5.1 (−9.0 to −1.0)	0.0027
6 months (n=40)	4.4 (2.2 to 7.2)	−5.5 (−10.2 to −2.5)	<0.0001

- Oesophageal acid exposure was assessed using 24-hour oesophageal pH monitoring after patients were off-PPI for at least 5 days.
- 1 patient did not have oesophageal pH testing at 6 months.
- 8% (3/40) of patients had worsening in their oesophageal acid exposure at 6 months.
- Patients with a hiatal hernia of 2 cm or more who did not have it repaired (n=6) had significantly less improvement in oesophageal acid exposure compared against patients with a hernia of less than 2 cm and no significant hiatal defect on laparoscopy (p=0.04).
- There was a trend for less improvement in oesophageal acid exposure in patients with an unrepaired hiatal hernia ≥ 2 cm compared against patients with a repaired hiatal hernia ≥ 2 cm (p=0.09).

Safety

Type of adverse effects	Detail	Number of adverse events	Number of patients
Serious adverse events (n=3)			
Procedure-related	Trocar perforation of the small bowel	1	1/41
Procedure- or device-related	Lead erosion (investigational 5-mm lead)	1	1/41
Not related to device or procedure	Paroxysmal atrioventricular nodal re-entrant tachycardia	1	1/41
Non-serious adverse events related to the procedure (n=52)			
Pain/discomfort		24	46% (19/41)
Weight loss/anorexia		5	12% (5/41)
Dysphagia		5	10% (4/41)
Nausea/vomiting		4	7% (3/41)
Bloating/belching		3	7% (3/41)
Hiccups		3	5% (2/41)
Inability to vomit		2	5% (2/41)
Impedance out of range		2	5% (2/41)
Constipation		1	1/41
Epigastric pain		1	1/41
Fever		1	1/41
Mesh repair hernia cicatricialis		1	1/41
Non-serious adverse events not related to the procedure (n=55)			
Gastrointestinal		15	32% (13/41)
	Nausea/vomiting	3	7% (3/41)
	Inability to vomit	2	5% (2/41)
	Diarrhoea	1	1/41
	Other	9	17% (7/41)
Pain discomfort		15	32% (13/41)
	Abdomen/chest	11	22% (9/41)
	Other	4	10% (4/41)
Respiratory		14	32% (13/41)
	Cough	4	10%

DeMeester score

	DeMeester score Median (IQR)	Change from baseline off-PPI (IQR)	p value
Baseline (n=42)	35.1 (27.1 to 51.9)		
3 months (n=26)	16.2 (9.6 to 37.6)	−16.5 (−28.8 to −5.2)	0.0102
6 months (n=40)	17.5 (10.9 to 23.4)	−19.7 (−37 to −6.9)	<0.0001

Daily symptoms

	Median (IQR)	p value
% days with heartburn		
Baseline off-PPI (n=35)	86 (64 to 100)	
3 months (n=34)	21 (0 to 64)	<0.0001
6 months (n=34)	17 (0 to 93)	<0.0001
% nights with heartburn		
Baseline off-PPI (n=35)	64 (43 to 86)	
3 months (n=34)	0 (0 to 14)	<0.0001
6 months (n=34)	0 (0 to 8)	<0.0001
% days with regurgitation		
Baseline off-PPI (n=35)	79 (54 to 100)	
3 months (n=32)	4 (0 to 21)	<0.0001
6 months (n=34)	0 (0 to 21)	<0.0001
% nights with regurgitation		
Baseline off-PPI (n=35)	50 (15 to 79)	
3 months (n=32)	0 (0 to 7)	<0.0001
6 months (n=34)	0 (0 to 7)	<0.0001

Status of erosive oesophagitis (% of patients with oesophagitis evaluated by endoscopy)

	Baseline (n=39)	6 months (n=39)
No oesophagitis	41% (16/39)	51% (20/39)
LA grade A oesophagitis	31% (12/39)	31% (12/39)
LA grade B oesophagitis	23% (9/39)	18% (7/39)
LA grade C oesophagitis	5% (2/39)	0% (0/39)

- Significant improvement in oesophagitis grade at 6 months of follow-up (p=0.02).
- In 5% (2/41) of patients, no oesogastro-duodenoscopy was performed at 6 months of follow-up.
- 28% (11/39) of patients had no oesophagitis at baseline or 6 months after the procedure.
- When only considering patients with erosive oesophagitis at baseline, improvement was not significant (p=0.07).

		(4/41)
Pneumonia	3	7% (3/41)
Sore throat	2	1/41
Other	5	12% (5/41)
Other	10	24% (10/41)

- The trocar perforation of the small bowel occurred during the implantation and was repaired laparoscopically. The device was removed and the patient recovered fully.
- The lead erosion was found at a 6-month endoscopy. The implantable pulse generator and the lead were removed and a Toupet fundoplication was performed during the same procedure.
- Mild or moderate dysphagia resolved without intervention in the 4 patients. All of them had a crural repair during the device implantation.

Quality of life scores

	Median (IQR)	Change from baseline on-PPI (IQR)	p value	Change from baseline off-PPI (IQR)	p value
SF-12 quality of life mental health score					
Baseline on-PPI (n=39)	48 (41 to 56)				
Baseline off-PPI (n=41)	45 (37 to 55)				
6 months (n=41)	52 (45 to 57)	2.5 (−4 to 8.0)	0.1147	2 (−3.5 to 12)	0.0253
SF-12 quality of life physical health score					
Baseline on-PPI (n=39)	45 (37 to 50)				
Baseline off-PPI (n=41)	39 (30 to 45)				
6 months (n=41)	52 (46 to 55)	7 (1 to 14)	<0.0001	11 (5.5 to 21)	<0.0001
Pittsburgh Sleep Quality Index (PSQI)*					
Baseline on-PPI (n=29)	7 (5 to 10)				
Baseline off-PPI (n=30)	8 (6 to 11)				
6 months (n=36)	5 (3 to 7)	−2 (−3 to −1)	<0.001	−4 (−5 to 0)	<0.001
Work time missed due to GORD (%)					
Baseline on-PPI (n=25)	0 (0 to 8.6)				
Baseline off-PPI (n=23)	3.9 (0 to 15)				
6 months (n=22)	0 (0 to 0)	0 (−5 to 0)	0.4063	0 (−15 to 0)	0.0801
Impairment while working due to GORD (%)					
Baseline on-PPI (n=26)	20 (0 to 40)				
Baseline off-PPI (n=24)	60 (25 to 80)				
6 months (n=23)	0 (0 to 0)	−10 (−30 to 0)	0.0063	−60 (−70 to −15)	<0.0001
Overall work impairment due to GORD (%)					
Baseline on-PPI (n=25)	20 (0 to 55.5)				
Baseline off-PPI (n=23)	64.5 (30 to 82.2)				
6 months (n=22)	0 (0 to 10)	−15 (−52.5 to 0)	0.045	−60 (−78.6 to −13.5)	<0.0001
Activity impairment due to GORD (%)					
Baseline on-PPI (n=37)	20 (0 to 50)				
Baseline off-PPI (n=37)	60 (30 to 80)				
6 months (n=39)	0 (0 to 10)	−15 (-40 to 0)	0.0003	−35 (−70 to −20)	<0.0001

*Sleep quality was assessed using the PSQI score (from 0 to 21 with 0 indicating

a better sleep quality and 21 a worse sleep quality) during 1 month.

A score greater than 5 is associated with poor sleep quality and a score equal or less than 5 is associated with good sleep quality.

PPI use

- At the 6-month follow-up, 90% (37/41) of patients were completely off PPI, 5% (2/41) reported intermittent PPI use and 7% (3/41) reported regular PPI use (p<0.001).

LOS mean pressure

	LOS mean pressure (mm Hg) Median (IQR)	**Change from baseline**	**p value**
Baseline off-PPI (n=35)	13.1 (10 to 15.9)		
6 months (n=30)	15 (10.2 to 27.1)	0.7 (−3.0 to 5.0)	0.2195

LOS end-expiratory pressure

	LOS end-expiratory pressure (mm Hg) Median (IQR)	**Change from baseline**	**p value**
Baseline off-PPI (n=38)	8.0 (5 to 12)		
6 months (n=35)	9.9 (5.2 to 15)	−0.4 (−2.0 to 5.0)	0.7332

LOS residual pressure

	LOS residual pressure (mm Hg) Median (IQR)	**Change from baseline**	**p value**
Baseline off-PPI (n=42)	2.8 (0.3 to 6.7)		
6 months (n=37)	2.7 (1.0 to 5.2)	0.0 (−2.0 to 0.9	0.8018

Abbreviations used: ASA, American society of anaesthesiologists; BMI, body mass index; EST, electrostimulation; GORD, gastro-oesophageal reflux disease; HRQL, health-related quality of life; IQR, interquartile range; LA, Los Angeles; LOS, lower oesophageal sphincter; PPIs, proton pump inhibitors; PSQI, Pittsburgh sleep quality index**;** SF-12, short form (12 items) health survey.

Study 2 Rodriguez L (2013)

Details

Study type	**Case series**
Country	Chile
Recruitment period	Not reported
Study population and number	n=**25** patients with GORD who were at least partially responsive to PPIs and who had hiatal hernia and oesophagitis.
Age and sex	Mean 52 years; 56% (14/25) male
Patient selection criteria	Inclusion criteria: age 21–65 years; heartburn, regurgitation or both for more than 6 months necessitating daily use of PPI; baseline GORD–HRQL heartburn score of more than or equal to 20 off PPI with at least 10-point improvement on PPI; ASA physical status classification below or equal to 2; distal oesophageal pH of less than 4 on 24-hour pH-metry off anti-secretory therapy for more than 5% of the 24-hour period; resting LOS end expiratory pressure of more than or equal to 5 mmHg and of less than or equal to 15 mmHg; oesophageal body contraction amplitude over 30 mmHg for more than 70% of swallows and more than 50% peristaltic contractions; oesophagitis of less or equal to grade C (LA classification of reflux oesophagitis). Exclusion criteria: non-GORD oesophageal motility disorders or gastroparesis; significant multi-system diseases; Barrett's or any dysplasia; hiatus hernia of more than 3 cm; BMI of more than 35kg/m^2; type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus; oesophageal or gastric malignancy or varices; significant cardiac arrhythmia, ectopy, significant cardiovascular disease; implanted electromedical device; pregnancy; oesophageal or gastric surgery, including anti-reflux surgery.
Technique	The Endostim LES stimulation system was used. LOS stimulation was delivered at 20 Hz, 215µs, 3–8 mA in multiple 30-minute sessions. Up to 12 sessions were delivered per day pre-meal and pre-reflux event. LOS stimulation was initiated on day 1 after the implantation and PPI therapy was stopped. Patients with residual or recurrent symptoms were allowed to take rescue GORD medications. Electrical stimulation was initiated at a median of 4 sessions per day (IQR 3-5) at a median amplitude of 3.5 mA (IQR 3.2–3.9).
Follow-up	**12 months**
Conflict of interest/source of funding	The study was funded by Endostim BV. One of the authors is a consultant for Endostim Inc. and the chair of its data monitoring Committee. Another author is a stock holder of Endostim Inc.

Analysis

Follow-up issues:

The study was initially designed with a 6-month follow-up period but this was extended to 2 years.

Successful implantation was completed in 25 patients but 1 patient withdrew consent 2 weeks after the implantation because of the anxiety related to the device and the multiple invasive tests required by the protocol. The patient had an uneventful removal of the device under local anaesthesia 6 weeks after implantation. The leads were left in situ inside the abdomen of the patient and no device or procedure-related adverse effects were reported through the 1-year follow-up.

One patient was not enrolled in the extension trial beyond 6 months because of a planned Roux-en-Y gastric bypass surgery for uncontrolled Type 2 diabetes; the patient had excellent symptom control, normal distal oesophageal acid exposure and was off PPI medication at the 6-month follow-up.

Study design issues:

The pH data were scored by a reviewer who was blinded to all patient identification and visit data.

Oesophageal manometry at baseline was performed using the MMS system in 25% (6/24) of patients and in 75% (18/24), the Sierra scientific instruments system (Given imaging) was used at baseline and at 3-month follow-up. All 12-month manometry was performed using the MMS system because of equipment malfunction.

Symptoms were assessed at baseline while the patient was on PPI, after 2 weeks off PPI therapy and at follow-up while treated by electrical stimulation.

All comparisons were made using related-samples Wilcoxon sign rank test.

SF-12 quality of life physical health used (higher score means better quality of life).

Study population issues:

This study reported that 13% (3/24) of patients had a normal BMI, 58% (14/24) were overweight and 29% (7/24) were obese.

88% (21/24) of patients had no hiatal hernia, 4% (1/24) had a hiatal hernia of less than 2 cm and 8% (2/24) had a hiatal hernia of more than 2 cm.

Other issues: Discrepancies between the paper reporting on the 2-year follow-up (study 2, using same study population) and this paper were noted for the GORD-HRQL sleep scores at baseline and the SF-12 scores at baseline.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **25 implantations but 23 patients completed the 12-month follow-up period.**

Median increase in the number of sessions delivered between baseline and month 12: 3 sessions per day (IQR 1-7).

Median increase in the stimulation current from baseline to month 12: 19 mA (IQR 1.2-2.8).

GORD-HRQL

GORD-HRQL Median (IQR)	Baseline	12 months	p value
On-PPI (n=22)	9 (6 to 10)	2.0 (0 to 3.0)	0.002
Off-PPI (n=24)	23.5 (21.0 to 25.8)		<0.001

- Composite baseline GORD-HRQL scores after 12 months compared with baseline on-PPI scores improved in 74% (17/23) of patients.
- Dissatisfaction with GORD control while on PPI therapy was reported in 71% (17/24) of patients and in 92% (22/24) of patients off-PPI at baseline.
- At 12-month follow-up, dissatisfaction was reported in 13% of patients (absolute numbers not given, p<0.001 for both groups of patients).

% of patients who reported that GORD impacted their sleep

GORD-HRQL sleep	Baseline	12 months	p value
On-PPI	33% (8/24)	4% (1/24)	0.001
Off-PPI	88% (21/24)		<0.001

% of patients who reported dysphagia/odynophagia caused by GORD

GORD-HRQL dysphagia	Baseline	12 months	p value
On-PPI	13% (3/24)	4% (1/24)	0.3
Off-PPI	58% (14/24)		0.001

SF-12

SF-12 quality of life physical health (median [IQR])

SF-12 physical health	Baseline	12 months	p value
On-PPI (n=22)	47.0 (41.8 to 52.8)	52.0 (43.0 to 55.0)	0.191
Off-PPI (n=24)	46.5 (39.8 to 51.0)		0.041

SF-12 quality of life mental health (median [IQR])

SF-12 mental health	Baseline	12 months	p value
On-PPI (n=22)	45.0 (41.5 to 55.0)	50.0 (45.0 to 58.0)	0.281
Off-PPI (n=24)	49.0 (37.8 to 54.8)		0.375

PPI use

- At baseline all (24/24) patients were on PPIs for GORD.
- At the 12-month follow-up, 96% (22/23) of patients were not using any PPIs and 1 patient reported occasional PPI use.

Safety

- 60% (15/25) of patients who had the device implanted reported 44 adverse effects during the 12 months following implantation.
- 1 serious adverse effect not related to the device or treatment was reported: an episode of chest discomfort with mild sinus tachycardia not temporally associated with LOS stimulation sessions.
- 43 non-serious adverse effects reported:

Type of adverse effects	Detail	Number of adverse effects
Adverse effects possibly or definitely related to the device (reported in 5 patients)	Implantation site pain	3
	Skin infection	1
	Dyspepsia	1
	Anxiety	1
Adverse effects related to the laparoscopic procedure (reported in 6 patients)	Implantation site pain	3
	Post-operative nausea	3
	Skin infection	1

Daily symptom diaries (n=21 patients)*

Diary days, median (IQR), %	None	Mild	Moderate	Severe	Nocturnal	Daytime	Antacid/day
Regurgitation							
Baseline off-PPI	7 (4 to 65)	8 (7 to 26)	31 (4 to 57)	0 (0 to 22)	29 (0 to 78)	67 (16 to 93)	0.4 (0.1 to 1.2)
6 months	100 (93 to 100)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0-0)	0 (0 to 7)	0.1 (0 to 0.2)
12 months	100 (91 to 100)	0 (0 to 7)	0 (0 to 0)	0 (0 to 0)	0 (0-2)	0 (0 to 2)	0 (0 to 0.1)
Heartburn							
Baseline off-PPI	0 (0 to 14)	14 (8 to 29)	50 (30 to 69)	7 (0 to 29)	64 (21 to 86)	92 (73 to 93)	N/A
6 months	79 (50 to 93)	14 (0 to 50)	0 (0 to 7)	0 (0 to 0)	0 (0 to 14)	14 (7 to 36)	N/A
12 months	83 (48 to 100)	0 (0 to 27)	0 (0 to 14)	0(0 to 0)	0 (0 to 14)	8 (0 to 50)	N/A

*****Evaluation used the 14-day symptom diaries

Authors state that all comparisons with baseline were statistically significant except mild heartburn at 12 months compared with baseline (no p values reported).

% 24-hour distal oesophageal pH<4.0 (total)

Time	Median % of the 24-h period with pH<4.0	p value versus baseline
Baseline	10%	
3 months (n=23)	6%	0.002
6 months (n=23)	5%	<0.001
12 months (n=22)	3%	<0.001

- The distal oesophageal acid exposure was normalised (<4% of 24-hour recording) in 64% (14/22) and improved by >50% in a further 5% (1/22) at 12 months.
- Both patients with missing pH data at 12 months had either a normal or significantly improved distal oesophageal pH at their 6-month follow-up.
- All patients (24/24) had abnormal distal oesophageal pH (<4 for >4%) at baseline and 39% (8/22) after 12 months (p<0.001).

% 24-hour proximal oesophageal pH<4.0 (total)

- Median 0.4% (0.1-1.45) at baseline versus 0% (0-0%) after 12 months (p=0.001).
- 33% (7/21) of patients had abnormal proximal oesophageal pH (<4 for >1.1%) at baseline versus none after 12 months (p=0.008).

Healing of erosive oesophagitis (% of patients with oesophagitis evaluated by endoscopy)

	Baseline	3 months*	12 months**
No oesophagitis	0	48% (11/23)	31% (7/23)
LA Grade A oesophagitis	67% (16/24)	30% (7/23)	52% (12/23)
LA Grade B oesophagitis	25% (6/24)	17% (4/23)	13% (3/23)
LA Grade C oesophagitis	8% (2/24)	4% (1/23)	4% (1/23)

*****p=0.003; related-samples Wilcoxon Sign Rank test

**p=0.01; related-samples Wilcoxon Sign Rank test

- Oesophagitis improved by at least 1 grade in 58% (14/24) of patients at 3 months and in 57% (13/23) of patients at 12 months compared with baseline.

Abbreviations used: ASA, American society of anaesthesiologists; BMI, body mass index; GORD, gastro-oesophageal reflux disease; HRQL, health-related quality of life; IQR, interquartile range; LA, Los Angeles; LOS, lower oesophageal sphincter; PPIs, proton pump inhibitors; SF-12, short form (12 items) health survey.

Study 3 Rodriguez L (2015)

Details

Study type	**Case series.** Same study population as in Rodriguez (2013) paper but with a 2-year follow-up.
Country	Chile
Recruitment period	Not reported
Study population and number	n=**25** patients with GORD who were at least partially responsive to proton pump inhibitors (PPIs) and who had hiatal hernia and oesophagitis.
Age and sex	Mean 52 years; 56% (14/25) male
Patient selection criteria	Inclusion criteria: age 21-65 years; heartburn, regurgitation or both for more than 6 months necessitating daily use of PPI; baseline GORD-HRQL heartburn score of more than or equal to 20 off PPI with at least 10-point improvement on PPI; ASA physical status classification below or equal to 2; distal oesophageal pH of less than 4 on 24-hour pH-metry off anti-secretory therapy for more than 5% of the 24-hour period; resting LOS end expiratory pressure of more than or equal to 5 mmHg and of less than or equal to 15 mmHg; oesophageal body contraction amplitude over 30 mmHg for more than 70% of swallows and more than 50% peristaltic contractions; oesophagitis of less or equal to grade C (LA classification of reflux oesophagitis). Exclusion criteria: non-GORD oesophageal motility disorders or gastroparesis; significant multi-system diseases; Barrett's or any dysplasia; hiatus hernia of more than 3 cm; BM) of more than 35 kg/m2; type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus; oesophageal or gastric malignancy or varices; significant cardiac arrhythmia, ectopy, significant cardiovascular disease; implanted electromedical device; pregnancy; oesophageal or gastric surgery, including anti-reflux surgery.
Technique	The Endostim LES stimulation system was used. LOS stimulation was delivered at 20 Hz, 215µs, 3 to 8 mA in multiple 30-minute sessions. Up to 12 sessions were delivered per day pre-meal and pre-reflux event. LOS stimulation was initiated on day 1 after the implantation and PPI therapy was stopped. Patients were allowed to take antacid medications as needed per-protocol for residual GORD symptoms during the study. Those with persistent symptoms on electrical stimulation therapy despite antacids were allowed PPI medications. Electrical stimulation was initiated at a median of 4 sessions per day (IQR 3-5) at a median amplitude of 3.5 mA (IQR 3.2-3.9).
Follow-up	**2 years**
Conflict of interest/source of funding	The study was funded by Endostim BV. Two of the authors are consultants for Endostim Inc. Another author is a stock holder in Endostim Inc.

Analysis

Follow-up issues:

The study was initially designed with a 6-month follow-up period but this was extended to 2 years.

75 patients consented and enrolled in the study. 26 patients were found to be eligible and had a laparoscopic procedure. One patient was excluded because of a large (5 cm) hiatal hernia and did not have the device implanted. Successful implantation was completed in 25 patients but 1 patient withdrew consent 4 weeks after the implantation. The patient had an uneventful removal of the device under local anaesthesia 6 weeks after implantation.

One patient was not enrolled in the extension trial beyond 6 months because of a planned Roux-en-Y gastric bypass surgery for uncontrolled Type 2 diabetes; the patient had excellent symptom control, normal distal oesophageal acid exposure and was off PPI medication at the 6-month follow-up.

96% (22/23) of patients had oesophageal pH testing at the 12-month follow-up visit. One patient refused the 12-month pH test. Of the 21 patients who completed the 24-month visit (1 patient voluntary withdrew after 18-month visit and 1 patient was lost to follow-up), 18 had oesophageal pH testing. Three patients refused the 24-month pH test.

Study design issues:

All comparisons were made using pairs Wilcoxon tests.

SF-12 quality of life physical health used (higher score means better quality of life).

Symptoms were assessed at baseline while the patient was on PPI, after 2 weeks off PPI therapy and at follow-up while treated by electrical stimulation.

Oesophageal acid exposure was assessed using 24-hour oesophageal pH-metry with the patient off PPI therapy for at least 5 days.

As part of a substudy, 3 patients with no GORD symptoms or medication use and normal oesophageal acid exposure at 12-month had blinded turn-off of the device after their 18-month follow-up. Additionally, 1 patient also with no GORD symptoms or medication use and normal 12-month oesophageal pH had her therapy turned off accidentally at month 15 by inadvertent use of magnet therapy for her arthritis. These patients had their oesophageal pH tested after cessation of electrical stimulation of the LOS for ≥3 months to evaluate the effect of stopping electrical stimulation on oesophageal acid exposure.

Study population issues:

20% (5/25) of patients had a normal BMI, 52% (13/25) were overweight and 28% (7/25) were obese.

88% (22/25) of patients had no hiatal hernia, 8% (2/25) had a hiatal hernia of less than 2 cm and 4% (1/25) had a hiatal hernia of more than 2 cm.

All patients were on chronic, daily PPI therapy and 24% (6/25) were on twice daily PPI before implantation.

Median duration of GORD diagnosis was 10.6 years.

Median duration of PPI use of 5.5 years before enrolment.

Other issues: Discrepancies between the paper reporting on the 1-year follow-up and this paper were noted for the GORD-HRQL sleep scores at baseline and the SF-12 scores at baseline.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **25 implantations but 21 patients completed the 24-month follow-up visit.**

GORD-HRQL

GORD-HRQL Median (IQR)	Baseline (n=24)	6 months	12 months	18 months	24 months (n=21)	p value
On PPI	9 (6 to 10)	2	2	0	0 (0-3)	0.002
Off PPI	23.5 (21 to 25.3)					<0.0001

- Dissatisfaction with GORD control while on PPI therapy was reported in 71% (17/24) of patients and in 92% (22/24) of patients off-PPI at baseline.
- At 24-month follow-up, dissatisfaction was reported in none (0/21) of the patients (p<0.001 for both on-PPI and off-PPI baseline satisfaction).

% of patients who reported that GORD impacted their sleep

GORD-HRQL sleep	Baseline (n=24)	12 months (n=23)	24 months (n=21)
On-PPI	71% (17/24)	17%	10% (2/21)
Off-PPI	96% (23/24)		

- Sleep quality, assessed by questionnaire evaluating the effect of heartburn on sleep, improved from a baseline median of 1 on PPI and 2.5 off PPI to a median of 0 at the 6-, 12-, and 24-month follow-up visits.

% of patients who reported dysphagia caused by GORD*

GORD-HRQL	Baseline (n=24)	12 months (n=23)	24 months (n=21)
On-PPI	38% (9/24)	13%	5% (1/21)
Off-PPI	71% (17/24)		

*****individual GORD-HRQL scores ≥ 1

% of patients who reported odynophagia caused by GORD*

GORD-HRQL	Baseline (n=24)	12 months (n=23)	24 months (n=21)
On-PPI	21% (5/24)	9%	10% (2/21)
Off-PPI	83% (20/24)		

*individual GORD-HRQL scores ≥1

Safety

- 76% (19/25) of patients who had the device implanted reported 65 adverse events (AE) within 2 years following implantation.
- 2 serious AE were reported in 8% (2/25) of patients, both not related to the device or procedure:
  - An episode of acute, retrosternal chest pain occurring 2 months after implantation. The patient had a negative cardiac evaluation and was diagnosed with non-cardiac chest pain. The patient reported experiencing similar events before enrolment in the study and continued with the treatment without recurrence of chest pain.
  - The other patient was hospitalised for an elective thyroidectomy 3 months after implantation.
- 63 non-serious AE reported:

Type of AE	Detail	Number of AE
AE related to the procedure	Nausea or vomiting on or the day after the procedure and resolving in ≤1 day	3 in 3 patients
	Pain or discomfort in the shoulder the day after the procedure lasting for 1 day	1 in 1 patient
	'Hypertensive episode' the day after the procedure lasting for 1 day	1 in 1 patient
	Superficial skin infection at the pocket site	1 in 1 patient
AE related to the device	Pain or discomfort in the abdomen	6 in 5 patients
AE possibly related to the device or procedure	'Psychotic disturbance'	1 in 1 patient
	'Nervous breakdown'	1 in 1 patient (same patient as above)
AE not	AE involving	19 in 13

SF-12

SF-12 quality of life physical health (median [IQR])

SF-12 physical health	Baseline	24 months (n=21)	p value
On-PPI	47.0 (42.5 to 51.5)*	55 (53 to 57)	0.0007
Off-PPI	46.5 (41.2 to 49.0)**		0.0001

*n=22

** n=24

SF-12 quality of life mental health (median [IQR])

SF-12 mental health	Baseline	24 months (n=21)	p value
On-PPI	43 (40.5 to 53.0)*	56 (44 to 62)	0.058
Off-PPI	49 (39.2 to 54.2)**		0.082

*n=22

** n=24

PPI use

- At baseline all (24/24) patients were taking daily PPIs for GORD and 25% (6/24) were taking twice daily PPIs.
- PPI use on <50% of the daily diary days was defined as ‘‘occasional use’’ and PPI use on ≥50% of the daily diary days was defined as ‘‘regular use.’’
- At the 12-month follow-up, 95% (20/21) of patients were not taking any PPIs and 5% (1/21) of patients reported occasional PPI use.
- At the 24-month follow-up, 76% (16/21) of patients were not taking any PPIs, 14% (3/21) of patients reported occasional PPI use and 10% (2/21) reported regular use of PPIs.

Median PPI use	Baseline (n=24)	3 months	6 months	12 months	24 months (n=21)
On-PPI	1 pill per day	<0.1 pills per day	<0.1 pills per day	<0.1 pills per day	<0.1 pills per day

p <0.001 by Wilcoxon paired test at each time point

Daily symptom diaries*

	Baseline (n=24)	6 months	12 months	24 months (n=18)
Heartburn				
Median % of days with heartburn off PPIs	92%	14%	13%	7%
Median % of nights with heartburn off PPIs	71%	0%	0%	0%

related to the device or procedure	the respiratory system	patients (cold was reported in 17/19 episodes)
	Others	32

Regurgitation				
Median % of days with regurgitation off PPIs	66%	0%	0%	0%
Median % of nights with regurgitation off PPIs	31%	0%	0%	0%

p < 0.001 for all times versus baseline off PPIs for heartburn and % of days with regurgitation.

p < 0.01 for all times versus baseline off PPIs for % of nights with regurgitation.

*****Evaluation used a 14-day symptom diary

- Patients reported none or mild heartburn symptoms for a median 17% of diary days at baseline off PPI, which increased to 93% after 24 months of treatment.
- Patients reported none or mild regurgitation symptoms for a median 18% of diary days at baseline off PPI, which increased to 100% after 6 months of treatment and stayed at 100% through 24 months of treatment.

% 24-hour distal oesophageal pH<4.0 (total)

	Per-protocol continuous therapy		**Intent-to-treat analysis***		**Patients with stimulation interrupted for ≥ 3 months before 24-month follow-up**	
	Median % of the 24-hour period with pH<4.0 (IQR)	p value versus baseline	Median % of the 24-hour period with pH<4.0 (IQR)	p value versus baseline	Median % of the 24-hour period with pH<4.0 (IQR)	p value versus baseline
Baseline	11% (8.0 to 16.8%) (n=20)		10% (7.8 to 13.0%) (n=24)		7% (6.3 to 8.2%) (n=4)	
12 months	4% (2.6 to 7.0%) (n=18)	<0.001			2% (1.4 to 2.0%) (n=4)	
24 months	4% (2 to 6.9%) (n=14)	0.001	5% (3.4 to 7.0%) (n=18)	0.001	5% (5.0 to 6.6%) (n=4)	

*4 patients with normal oesophageal pH at 12 months had LOS stimulation turned off for at least 3 months before the 24-month follow-up; all had abnormal oesophageal pH at 24 months. Their results are included in the ITT analysis.

- The distal oesophageal acid exposure was normalised (<4 for < 4% of 24-hour recording) in 50% of patients and improved by >50% in a further 21% at 24 months.
- Three patients refused objective pH testing at their 24-month follow-up. Of these 3 patients, 2 had an improvement of ≥50% compared against both on-PPI and off-PPI GORD-HRQL scores; 1 patient had suboptimal (<50%) symptom improvement. One of these 3 patients used PPIs occasionally at their 2-year follow-up, whereas the other 2 were using PPIs regularly (≥50% of diary days).
- 96% (23/24) of patients had abnormal distal oesophageal pH (<4 for >4% of 24 hour recording) at baseline versus 61%

(11/18) at 24 months.

DeMeester score

	Per-protocol continuous therapy	ITT analysis	
	Median score	Median score (IQR)	p value versus baseline
Baseline	37.5 (n=20)	36.6 (29.6-50.2) (n=24)	
12 months	17.7 (n=18)		
24 months	14.6 (n=14)	16.1 (12.2-29.1) (n=18)	0.002

DeMeester score includes 6 parameters: total per cent time pH less than 4.0, per cent time pH less than 4.0 in the upright period, per cent time pH less than 4.0 in the recumbent period, the total number of reflux episodes, the total number of reflux episodes longer than 5 minutes, and the duration of the longest reflux episode. A score of more than 14.7 is considered abnormal.

% 24-hour proximal oesophageal pH<4.0 (total)

- Median 0.4% (IQR 0.1-1.3%, n=21) at baseline versus 0% (IQR 0-0.1%, n=18) after 24 months (p=0.001).
- 33% (7/21) of patients had abnormal proximal oesophageal pH (<4 for >1.1%) at baseline versus 0% (0/18) at 24 months.

Effect of blinded turn off of electrical stimulation of the LOS

- 25% (1/4) of patients reported recurrence of GORD symptoms 3 months after blinded turn off.
- Oesophageal pH testing: 100% (4/4) of patients had worsening in their distal oesophageal acid exposure compared against their on-therapy 12-month acid exposure.

Abbreviations used: AE, adverse events; BMI, body mass index; GORD, gastro-oesophageal reflux disease; HRQL, health-related quality of life; IQR, interquartile range; ITT, intent-to-treat; LOS, lower oesophageal sphincter; PPIs, proton pump inhibitors; SF-12, short form (12 items) health survey.

Study 4 Rodriguez L (2015) – Manufacturer registry

Details

Study type	**Case series.** Same study population as in Rodriguez (2013) paper but with a 3-year follow-up.
Country	Chile
Recruitment period	Not reported
Study population and number	n=**15** patients with GORD from the Rodriguez (2013) study
Age and sex	Mean 56 years; 53% (8/15) male
Patient selection criteria	Inclusion criteria: GORD patients with partial response to PPI, hiatal hernia ≤3 cm and oesophagitis ≤ grade C.
Technique	The Endostim LES stimulation system was used.
Follow-up	**3 years**
Conflict of interest/source of funding	The study was funded by Endostim BV. One of the authors is a consultant for Endostim Inc. Another author is a stock holder in Endostim Inc.

Analysis

Follow-up issues:

- 25 patients were originally implanted, 72% (18/25) were enrolled in the registry trial and 60% (15/25) were available for evaluation at 3 years.
- 80% (12/15) of patients had an endoscopy at their 3-year follow-up.

Study design issues:

- All comparisons were made using pairs Wilcoxon tests.
- SF-12 quality of life physical health used (higher score means better quality of life).
- Symptoms were assessed at baseline while the patient was on PPI, after 2 weeks off PPI therapy and at follow-up while treated by electrical stimulation.
- Change in % time distal oesophageal pH was lower than 4 was assessed by comparing the results at baseline against the 3-year follow-up.
- At the end of the 2-year follow-up study (Rodriguez 2015), patients were asked if they wanted to be included in this registry trial which planned a maximum follow-up of 5 years.

Study population issues:

- 20% (3/15) of patients had a normal BMI, 60% (9/15) were overweight and 20% (3/15) were obese.
- 93% of patients had no hiatal hernia, none had a hiatal hernia of less than 2 cm and 7% had a hiatal hernia of 2 cm or more.
- All patients were on daily PPI therapy before implantation.
- Median duration of GORD diagnosis was 10 years.
- Mean ± SD duration of PPI use of 5.9±3.3 years at baseline.

Other issues: none.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 15

GORD-HRQL
<table>
<tr><th>GORD-HRQL Median (IQR)</th><th>Baseline (n=15)</th><th>3 years (n=15)</th><th>p value</th></tr>
<tr><td>On-PPI</td><td>9 (6 to 10)</td><td rowspan="2">1 (0 to 2)</td><td><0.001</td></tr>
<tr><td>Off-PPI</td><td>23.5 (21 to 25)</td><td><0.001</td></tr>
</table>

All patients (15/15) reported clinically significant (more than 50%) improvement in their composite GORD-HRQL score versus both their ‘baseline off-PPI’ and ‘baseline on-PPI’ scores.

SF-12
The SF-12 scores for both physical and mental health improved numerically compared against ‘baseline on-PPI’ and ‘baseline off-PPI’ scores, but did not reach statistical significance (no further details reported).

PPI use

At baseline all (15/15) patients were taking daily PPIs for GORD.
At 3-year follow-up, 73% of patients were free from PPI dependence (defined as 50% or more diary days with PPI use).

Median (IQR) % 24-hour distal oesophageal pH<4.0 (total)
<table>
<tr><th></th><th>All patients (n=15)</th><th>Patients treated per-protocol (continuous therapy, n=12)</th><th>Patients with stimulation interrupted for ≥ 3 months between 1- and 2-year follow-up (n=3)**</th></tr>
<tr><td>Baseline</td><td>10 (8 to 12)</td><td>11 (8 to 13)</td><td>6 (6 to 8)</td></tr>
<tr><td>1 year</td><td>3 (2 to 7)</td><td>4 (3 to 7)</td><td>2</td></tr>
<tr><td>2 years</td><td>5 (3 to 9)</td><td>4 (2 to 9)</td><td>6 (5 to 8)</td></tr>
<tr><td>3 years</td><td>3 (2 to 5)*</td><td>3 (2 to 5)</td><td>3 (3 to 4)</td></tr>
</table>
*p<0.001 for the comparison against baseline scores.
**4 patients with normal oesophageal pH at 12 months had LOS stimulation turned off for at least 3 months before the 24-month follow-up; all had abnormal oesophageal pH at 24 months. All these patients had their stimulation turned back after their 2-year visit and 3/4 had oesophageal pH testing at 3-year follow-up. All 3 patients had significantly improved or normalised their distal oesophageal acid exposure suggesting a causal association between improvement in oesophageal acid exposure and LES stimulation.

The distal oesophageal acid exposure was normalised (<4 for < 4% of 24-hour recording) in (11/15) 73% of patients.
The remaining 4 patients had 39-48% improvement in their distal oesophageal acid exposures.

</td><td>There were no additional adverse events reported between year 2 and year 3 of follow-up.</td></tr>
</table>

DeMeester score

	Baseline (n=15)	3 years (n=15)	p value
DeMeester score Median (IQR)	36.9 (30.8 to 44.3)	12.8 (7.2 to 18.8)	0.0003

DeMeester score includes 6 parameters: total per cent time pH less than 4.0, per cent time pH less than 4.0 in the upright period, per cent time pH less than 4.0 in the recumbent period, the total number of reflux episodes, the total number of reflux episodes longer than 5 minutes, and the duration of the longest reflux episode. A score of more than 14.7 is considered abnormal.

Healing of erosive oesophagitis

- All patients in the cohort had erosive oesophagitis at baseline.
- Twelve patients had an endoscopy at their 3-year follow-up with 50% (6/12) patients showing improvement in their oesophagitis by more than 1 grade.
- 25% (3/12) of patients had stable grade A.
- 25% (3/12) of patients had worsening (grade A to grade B) oesophagitis.
- Two of the 3 patients that had worsening oesophagitis and all 3 patients with stable oesophagitis had normal oesophageal acid exposure at their 3-year evaluation.
- None of the patients had developed Barrett oesophagus at their 3-year follow-up on LOS stimulation therapy.

Abbreviations used: BMI, body mass index; GORD, gastro-oesophageal reflux disease; HRQL, health-related quality of life; IQR, interquartile range; LOS, lower oesophageal sphincter; PPIs, proton pump inhibitors; SD, standard deviation; SF-12, short form (12 items) health survey.

Efficacy

GORD symptoms

A case series of 44 patients with GORD treated by electrostimulation of the LOS reported median (interquartile range; IQR) percentages of days with heartburn of 86% (64–100%, n=35) at baseline and 17% (0–93%, n=34) at 6 months (p<0.0001). Median (IQR) percentages of nights with heartburn were 64% (43–86%, n=35) at baseline and 0% (0–8%, n=34) at 6 months (p<0.0001). Median (IQR) percentages of days with regurgitation were 79% (54–100%, n=35) before the procedure and 0% (0–21%, n=34) at 6 months (p<0.0001). Median (IQR) percentages of nights with regurgitation were 50% (15%–79%, n=35) at baseline and 0% (0%–7%, n=34) at 6 months (p<0.0001). The evaluations used a symptom diary kept by the patients.[1]

A case series of 25 patients with GORD with a 1-year follow-up reported that the median (IQR) percentages of diary days with no symptoms of heartburn at baseline were 0% (0–14%), with mild symptoms 14% (8–29%), with moderate symptoms 50% (30–69%) and with severe symptoms 7% (0–29%). Six months after implantation, the median (IQR) percentages of diary days with no symptoms of heartburn improved to 79% (50–93%), with mild symptoms to 14% (0–50%), with moderate symptoms to 0% (0–7%) and with severe symptoms to 0% (0–0%). Twelve months after implantation, a median of 83% (48–100%) of diary days were free of symptoms of heartburn, with no diary days with mild, moderate or severe symptoms of heartburn. Authors stated that all comparisons with baseline were statistically significant except mild heartburn at 12 months compared with baseline (no p values reported)[2].

A publication about the case series of 25 patients with GORD treated by electrostimulation of the LOS, with a 2-year follow-up, reported median percentages of days and nights with heartburn at 'baseline off proton pump inhibitors (PPIs)' (defined as 10 days after the patients had started electrostimulation and had stopped taking PPIs) and at follow-up. Median percentages of days with heartburn were 92% at 'baseline off PPIs', 14% at 6 months, 13% at 12 months and 7% at 24 months (p<0.001 for all times versus 'baseline off PPIs'). Median percentages of nights with heartburn were 71% at 'baseline off PPIs', and 0% at 6, 12 and 24 months (p<0.001 for all times versus 'baseline off PPIs')[3].

The case series of 25 patients reported median percentages of days with symptoms of regurgitation of 66% at 'baseline off PPIs', and 0% at 6, 12 and 24 months (p<0.001 for all times versus 'baseline off PPIs'). Median percentages of nights with regurgitation were 31% at 'baseline off PPIs', and 0% at 6, 12 and 24 months (p<0.01 for all times versus 'baseline off PPIs')[2].

The case series of 25 patients reported dysphagia caused by GORD in 38% (9/24) of patients at 'baseline on PPIs' and in 71% (17/24) at 'baseline off PPIs'.

Dysphagia was reported in 13% (n=23) of patients at 12-month follow-up, and in 5% (1/21) patient at 24-month follow-up (level of significance not stated)[3].

The case series of 25 patients with a 2-year follow-up reported odynophagia caused by GORD (individual GORD-HRQL scores ≥1) in 21% (5/24) of patients 'on PPI' at baseline and in 83% (20/24) 'off PPI' at baseline. At 12-month follow-up, odynophagia was reported in 9% (n=23) of patients and in 10% (2/21) at 24 months[3].

In the case series of 25 patients with a 2-year follow-up, 1 patient reported recurrence of GORD symptoms 3 months after blinded turn-off of electrical stimulation of the LOS (the device was turned off at least 3 months before the 2-year follow-up)[3].

Quality of life

The case series of 44 patients reported median GORD–HRQL scores (IQR) at baseline of 16.5 (9.0–22.8) when patients (n=42) were still taking PPIs and of 31.0 (26.2-36.8) when patients (n=42) had stopped taking PPIs. The scores improved significantly to 5.0 (3.0-9.0) at 6 months, (n=41, p<0.0001 for the comparison against 'baseline on PPI' and 'baseline off PPI' scores). In this study, 74% (31/42) of patients reported dissatisfaction with GORD control at 'baseline on PPIs' and 21% (8/39) reported it 6 months after the procedure. Median (IQR) SF-12 mental health scores of 48 (41–56) were reported at baseline when patients (n=39) were still using PPIs and of 45 (37–55) when patients (n=41) had stopped using PPIs. At 6 months, the score was 52 (45–57; n=41; p value not significant versus 'baseline on PPIs' and p=0.0253 for the comparison against 'baseline off PPIs'). Median (IQR) SF-12 physical health scores of 45 (37–50) were reported at baseline when patients (n=39) were still using PPIs and of 39 (30–45) when patients (n=41) had stopped using PPIs. At 6 months, the score was 52 (46–55; n=41; p<0.0001 for the comparisons against 'baseline on PPIs' and 'baseline off PPIs').[1]

The case series of 25 patients reported median GORD-HRQL scores (IQR) at baseline of 9.0 (6.0–10.0) when patients (n=24) were still taking PPIs, and of 23.5 (21.0–25.8) when patients (n=24) had stopped taking PPIs. The scores improved significantly to 2.0 at 12 months (IQR and number of patients not given) and to 0 (0–3.0) at 24 months (n=21; p≤0.002 versus 'baseline on PPI' and 'baseline off PPI' scores for 12- and 24-month follow-up respectively)[3].

The case series of 25 patients with the 1-year follow-up reported that composite baseline GORD-HRQL scores after 12 months compared with 'baseline on PPI' scores improved in 74% (17/23) of patients[2].

A publication reporting on 15 patients from the case series of 25 patients with GORD treated by electrostimulation of the LOS after 3 years of follow-up, reported median GORD-HRQL scores (IQR) at baseline of 9 (6–10) when

patients were still taking PPIs and of 23.5 (21–25) when patients had stopped taking PPIs. The scores improved significantly to 1 (0–2) at 3 years (p<0.001).[4]

The case series of 25 patients reported median SF-12 mental health scores (IQR) of 43.0 (40.5–53.0) at baseline when patients (n=22) were still using PPIs and of 49.0 (39.2–54.2) when patients (n=24) had stopped using PPIs. At 24 months, the score was 56 (44–62; p values not significant versus 'baseline on PPIs' and 'baseline off PPIs')[3].

The case series of 25 patients reported median SF-12 physical health scores (IQR) of 47.0 (42.5–51.5) at baseline when patients (n=22) were still using PPIs and of 46.5 (41.2–49.0) when patients (n=24) had stopped using PPIs. At 24 months, the score was 55 (53–57; p=0.0007 versus 'baseline on PPIs' and p=0.0001 versus 'baseline off PPIs')[3].

In the case series of 25 patients, 71% (17/24) of patients reported dissatisfaction with GORD control at 'baseline on PPIs' and 92% (22/24) reported dissatisfaction at 'baseline off PPIs'. At 24-month follow-up, dissatisfaction was reported in none (0/21) of the patients (p<0.001 for both groups of patients)[3].

The case series of 25 patients reported that GORD had an impact on their sleep in 71% (17/24) of patients at 'baseline on PPIs' and in 96% (23/24) of patients at 'baseline off PPIs'. At 12-month follow-up, GORD was reported to have an impact on their sleep by 17% of patients (n=23; absolute numbers not given) and, at 24-month follow-up, by 10% (2/21) of patients[3].

The case series of 25 patients reported that sleep quality improved from a baseline median GORD-HRQL score of 1 'on PPI' and of 2.5 'off PPI' to a median score of 0 at the 6-, 12-, and 24-month follow-up visits[3].

Oesophageal pH

The case series of 44 patients reported that the median (IQR) percentages of the 24-hour period for which there was a distal oesophageal pH of less than 4 was 10% (8-13%, n=42) before the procedure compared against 4% (2-7%) after 6 months (p<0.0001).[1]

The case series of 25 patients reported that the median percentage of the 24-hour period for which there was a distal oesophageal pH of less than 4 was 10% (IQR 8–13%) at baseline (n=24; defined for this measure as at least 5 days after the patients had started electrostimulation and had stopped taking PPIs) compared against 5% (3–7%) at 24 months (n=18; p=0.001 versus baseline). At baseline, 96% (23/24) of patients had an abnormal distal oesophageal pH (less than 4 for more than 4% of a 24-hour recording) and, at 24 months, 61% (11/18) had an abnormal pH[3].

The case series of 25 patients reported that the median percentage of the 24-hour period with proximal oesophageal pH<4 was 0.4% at baseline versus 0%

after 24 months (p=0.001). At baseline, 33% (7/21) of patients had abnormal proximal oesophageal pH (<4 for >1.1%) versus 0% at 24 months[3].

The publication reporting on 15 patients from the case series of 25 patients with a 3-year follow-up reported that the median (IQR) percentages of the 24-hour period with distal oesophageal pH of less than 4 was 10% (8–12%) at baseline compared against 3% (2–5%) at 3 years (p<0.001 for the comparison against baseline scores).[4]

The case series of 44 patients reported median (IQR) DeMeester scores (including 6 parameters with a score of more than 14.7 indicating reflux) of 35.1 (27.1-51.9, n=42) at baseline and 17.5 (10.9-23.4, n=40) at 6 months (p<0.0001).[1]

The case series of 25 patients with the 2-year follow-up reported median DeMeester scores of 37.5 (n=20) at baseline, 17.7 (n=18) at 12 months and 14.6 (n=14) at 24 months in the group of patients treated with the continuous therapy per-protocol. In the intent-to-treat population, median DeMeester scores were 36.6 (29.6–50.2, n=24) at baseline and 16.1 (12.2–29.1, n=18) at 24 months (p=0.002)[3].

The publication reporting on 15 patients from the case series of 25 patients with a 3-year follow-up reported median (IQR) DeMeester scores of 36.9 (30.8–44.3) at baseline and 12.8 (7.2-18.8) at 3 years (p<0.0003).[4]

Reduction in medication use

In the case series of 44 patients, 90% (37/41) of patients were completely off PPI, 5% (2/41) reported intermittent use of PPIs and 7% (3/41) reported regular use of PPIs at 6 months (p<0.001).[1]

In the case series of 25 patients, all patients still included in the study (24/24) were taking PPIs for GORD after implantation. At 24 months, 76% (16/21) of patients were not taking any PPIs, 14% (3/21) reported occasional PPI use and 10% (2/21) reported regular PPI use[3].

The publication reporting on 15 patients from the case series of 25 patients with a 3-year follow-up reported that 73% of patients were free from PPI dependence (defined as 50% or more diary days with PPI use) at 3 years.[4]

The case series of 25 patients up reported a median PPI use of 1 pill per day at baseline and of less than 0.1 pill per day at 3, 6, 12 and 24 months (p<0.001 at each time point versus baseline)[3].

Long-term sequelae

The case series of 44 patients reported that, at baseline, 41% (16/39) of patients had no oesophagitis, 31% (12/39) had Los Angeles classification (LA) grade A oesophagitis (grades A to D range from less severe to more severe oesophagitis

assessed by endoscopy), 23% (9/39) had LA grade B oesophagitis and 5% (2/39) had LA grade C oesophagitis. At 6 months, 51% (20/39) of patients had no oesophagitis, 31% (12/39) had LA grade A, 18% (7/39) had LA grade B and none (0/39) had LA grade C oesophagitis (p=0.02 for the improvement in oesophagitis grade at 6 months)[1].

The case series of 25 patients with 1-year follow-up reported that, at baseline, (within 6 months before enrolment), 67% (16/24) of patients had LA grade A oesophagitis, 25% (6/24) had LA grade B and 8% (2/24) had LA grade C oesophagitis. At 12 months, 31% (7/23) of patients had no oesophagitis, 52% (12/23) had LA grade A, 13% (3/23) had LA grade B and 4% (1/23) had LA grade C oesophagitis (p=0.01). Oesophagitis had improved by at least 1 grade in 58% (14/24) of patients at 3 months and in 57% (13/23) of patients at 12 months compared against baseline[2].

The publication reporting on 15 patients from the case series of 25 patients with a 3-year follow-up reported that 50% (6/12) of the patients who had an endoscopy at 3 years showed an improvement in their oesophagitis by more than 1 grade.[4]

Safety

Perforation of the small bowel

Trocar perforation of the small bowel during laparoscopy was reported in 1 patient in a case series of 44 patients with GORD treated by electrostimulation of the LOS. This was repaired and the device was removed to avoid the possibility of subsequent complications.[1]

Pain

Pain or discomfort was reported on 24 occasions in 46% (19/41) of patients in the case series of 44 patients; the adverse events were reported as related to the procedure (no details on timing given).[1]

Pain or discomfort in the abdomen was reported on 6 occasions in 6 patients in a case series of 25 patients with GORD treated by electrostimulation of the LOS with a 2-year follow-up; the adverse events were reported as related to the device (no details on timing given). In addition, 1 patient had transient discomfort in the shoulder.[3]

Epigastric pain was reported once in 1 patient in the case series of 44 patients; the adverse event was reported as related to the procedure (no details on timing given).[1]

Dysphagia

Mild or moderate dysphagia related to the procedure was reported on 5 occasions in 10% (4/41) of patients in the case series of 44 patients; it resolved

without intervention. It was reported that crural repair was done in all 4 patients during device implantation (no details on timing given).[1]

Nausea

Nausea or vomiting was reported on 4 occasions in 7% (3/41) of patients in the case series of 44 patients; the adverse events were reported as related to the procedure (no details on timing given).[1]

Nausea or vomiting on the day or the day after the procedure was reported on 3 occasions in 3 patients in the case series of 25 patients with 2-year follow-up[3].

Bloating

Bloating or belching was reported on 3 occasions in 7% (3/41) of patients in the case series of 44 patients; the adverse events were reported as related to the procedure (no details on timing provided).[1]

Hiccups

Hiccups was reported on 3 occasions in 5% (2/41) of patients in the case series of 44 patients; the adverse events were reported as related to the procedure (no details on timing provided).[1]

Inability to vomit

Inability to vomit was reported on 2 occasions in 5% (2/41) of patients in the case series of 44 patients; the adverse events were reported as related to the procedure (no details on timing provided).[1]

Constipation

Constipation was reported on 1 occasion in 1 patient in the case series of 44 patients; the adverse event was reported as related to the procedure (no details on timing provided).[1]

Weight loss

Weight loss or anorexia was reported on 5 occasions in 12% (5/41) of patients in the case series of 44 patients; the adverse events were reported as related to the procedure (no details on timing given).[1]

Fever

Fever was reported once in 1 patient in the case series of 44 patients; the adverse event was reported as related to the procedure (no details on timing provided).[1]

Skin infection

Superficial skin infection at the abdominal wall pocket site was reported in 1 patient in the case series of 25 patients.[3]

Mesh repair hernia cicatricalis

Mesh repair hernia cicatricalis was reported once in 1 patient in the case series of 44 patients; the adverse event was reported as related to the procedure (no details on timing given).[1]

Hypertension

A hypertensive episode was reported on 1 occasion in the case series of 25 patients with 2-year follow-up; the episode lasted for 1 day.[3]

Anxiety

Anxiety was reported in 1 patient in a publication about the case series of 25 patients after only 1-year follow-up. The case series of 25 patients with 2-year of follow-up described this episode as a 'psychotic disturbance' and a 'nervous breakdown'.[2,3]

Device failure

Lead erosion was reported in 1 patient at the 6-month endoscopy in the case series of 44 patients. The device was removed and the patient was treated by fundoplication performed during the same procedure.[1]

Out-of-range impedance was reported on 2 occasions in 5% (2/41) of patients in the case series of 44 patients; the adverse events were reported as related to the procedure (no details on timing given).[1]

Validity and generalisability of the studies

- Very limited evidence base: only 1 multicentre trial of 44 patients[1] and 1 study[2,3,4] including 25 patients with published clinical results at 1-year, 2-year and 3-year of follow-up, no comparative studies.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Transcutaneous neuromuscular electrical stimulation for oropharyngeal dysphagia. NICE interventional procedure guidance 490 (2014). Available from http://www.nice.org.uk/guidance/ipg490

- Gastroelectrical stimulation for gastroparesis. NICE interventional procedure guidance 489 (2014). Available from http://www.nice.org.uk/guidance/ipg489

- Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease. NICE interventional procedure guidance 461(2013). Available from http://www.nice.org.uk/guidance/ipg461

- Laparoscopic insertion of a magnetic bead band for gastro-oesophageal reflux disease. NICE interventional procedure guidance 431(2012). Available from http://www.nice.org.uk/guidance/ipg431

- Endoluminal gastroplication for gastro-oesophageal reflux disease. NICE interventional procedure guidance 404 (2011). Available from http://www.nice.org.uk/guidance/ipg404

- Endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease. NICE interventional procedure guidance 222 (2007). Available from http://www.nice.org.uk/guidance/ipg222

- Catheterless oesophageal pH monitoring. NICE interventional procedure guidance 187 (2006). Available from http://www.nice.org.uk/guidance/ipg187

- Endoscopic injection of bulking agents for gastro-oesophageal reflux disease. NICE interventional procedure guidance 55 (2004). Available from http://www.nice.org.uk/guidance/ipg55

NICE guidelines

- Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people. NICE clinical guideline 1 (2015). Available from http://www.nice.org.uk/guidance/ng1
- Dyspepsia and gastro-oesophageal reflux disease: Investigation and management of dyspepsia, symptoms suggestive of gastro‑oesophageal

reflux disease, or both. NICE clinical guideline 184 (2014). Available from http://www.nice.org.uk/guidance/cg184

- Barrett's oesophagus: Ablative therapy for the treatment of Barrett's oesophagus. NICE clinical guideline 106 (2010). Available from http://www.nice.org.uk/guidance/cg106

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Specialist Advisor Questionnaires for electrical stimulation of the lower oesophageal sphincter for the treatment of GORD were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

Ongoing study:

- NCT01574339 Effect of long-term electrical stimulation on LES pressure and oesophageal acid exposure in patients with GORD. Locations: Germany, Holland, Chile, India. Enrolment: 45 patients. Estimated Completion Date: July 2016.

References

1. Kappelle WFW, Bredenoord AJ, Conchillo JM et al. (2015) Electrical stimulation therapy of the lower oesophageal sphincter for refractory gastro-oesophageal reflux disease – interim results of an international multicentre trial. Alimentary Pharmacology and Therapeutics. 42(5):614-25. doi: 10.1111/apt.13306.
2. Rodriguez L, Rodriguez P, Gomez B et al. (2013) Long-term results of electrical stimulation of the lower esophageal sphincter for the treatment of gastroesophageal reflux disease. Endoscopy 45:595-604.
3. Rodrıguez L, Rodriguez P, Gomez B et al. (2015) Two-year results of intermittent electrical stimulation of the lower esophageal sphincter treatment of gastroesophageal reflux disease. Surgery 157(3):556-567.
4. Rodriguez L, Rodriguez P, Gomez B et al. Electrical Stimulation Therapy of the Lower Esophageal Sphincter is successful in treating GERD – Long-term 3-Year Results. Surgical Endoscopy. doi: 10.1007/s00464-015-4539-5.

Appendix A: Additional papers on electrical stimulation of the lower oesophageal sphincter for the treatment of gastro-oesophageal reflux disease

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Banerjee R, Pratap N, Kalpala R et al. (2014) Effect of electrical stimulation of the lower oesophageal sphincter using endoscopically implanted temporary stimulation leads in patients with reflux disease. Surgical Endoscopy 28:1003-1009.	Case series n=6 Follow-up= 7 days	In patients with GORD, short-term electrical stimulation therapy delivered using electrodes endoscopically implanted in the LOS results in a significant increase in LOS pressure without affecting patients' swallow function or causing any adverse symptoms or cardiac rhythm disturbances. Electrical stimulation therapy may offer a novel therapy to patients with GORD.	Study reports short-term effects on sphincter pressure and function. No clinical outcomes reported.
Eypasch E. (2014) Electrical stimulation of the lower oesophageal sphincter: An emerging therapy for treatment of GORD. European Surgery - Acta Chirurgica Austriaca.46 (2) (pp 57-64).	Review	Enhancement of the anti-reflux function of the lower oesophageal sphincter using electrical stimulation is a safe and effective GORD treatment and can potentially address the unmet need of patients who are unsatisfied with PPIs. Additional data will help in a wider adoption of this technology.	Narrative review with no meta-analysis.
Hoppo T, Rodriguez L, Soffer E et al. (2014) Long-term results of electrical stimulation of the lower oesophageal sphincter for treatment of proximal GERD. Surgical Endoscopy 28:3293-3301.	Case series n=19 Follow-up=1 year	Electrical stimulation of the LOS is associated with normalisation of proximal oesophageal pH in patients with GORD and may be useful in treating those with proximal GORD. Electrical stimulation of the LOS is safe without typical side effects associated with traditional antireflux surgery.	Subgroup of patients from Rodriguez 2013 (which is included in Table 2) and results already reported in Rodriguez 2013 paper.
Rodriguez L, Rodriguez P, Neto MG et al. (2012) Short-term electrical stimulation of the lower esophageal sphincter increases sphincter pressure in patients with gastroesophageal reflux disease. Neurogastroenterology & Motility 24:446-450.	Case series n=10 Follow-up=5 days	Short-term stimulation of the LOS in patients with GORD significantly increases resting LOS pressure without affecting oesophageal peristalsis or LOS relaxation. Electrical stimulation of the LOS may offer a novel therapy for patients with GORD.	Study reports short-term effects on sphincter pressure. No clinical outcomes reported.
Rodriguez L,	Case	Median GORD-HRQL scores at 6 months: 2.0 (IQR = 0-	Same study

Rodriguez P, Gomez B et al. (2013) Electrical stimulation therapy of the lower oesophageal sphincter is successful in treating GERD: final results of open-label prospective trial. Surgical Endoscopy 27:1083-1092.	series n=24 Follow-up=6 months	5.5) significantly better than both baseline on-PPI [9.0 (range = 6.0-10.0); p < 0.001] and off-PPI [23 (21-25); p < 0.001] GORD-HRQL. Median% 24-h oesophageal pH < 4.0 at baseline: 10.1 and improved to 5.1 at 6 months (p < 0.001). At their 6-month follow-up, 91 % (21/23) of the patients were off PPI and had significantly better median GORD-HRQL on LOS stimulation compared to their on-PPI GORD-HRQL at baseline (9.0 vs. 2.0; p < 0.001). There were no unanticipated implantation- or stimulation-related adverse events or untoward sensation due to stimulation. There were no reports of treatment-related dysphagia, and manometric swallow was also unaffected.	population as in other Rodriguez 2013 study (which is included in Table 2) but follow-up of 6 months only (while follow-up in other Rodriguez 2013 study is 1 year).

Appendix B: Related NICE guidance for electrical stimulation of the lower oesophageal sphincter for the treatment of gastro-oesophageal reflux disease

Guidance	Recommendations
Interventional procedures	**Endoscopic injection of bulking agents for gastro-oesophageal reflux disease. NICE interventional procedure guidance 55 (2004)** 1.1 Current evidence on the safety and efficacy of endoscopic injection of bulking agents for gastro-oesophageal reflux disease does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake endoscopic injection of bulking agents for gastro-oesophageal reflux disease should take the following action. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. Use of the Institute's information for the public is recommended. • Audit and review clinical outcomes of all patients having endoscopic injection of bulking agents for gastro-oesophageal reflux disease. 1.3 Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. The Institute may review the procedure upon publication of further evidence.
Interventional procedures	**Catheterless oesophageal pH monitoring. NICE interventional procedure guidance 187 (2006)** 1.1 Current evidence on the safety and efficacy of catheterless oesophageal pH monitoring appears adequate to support the use of this technique provided that normal arrangements are in place for consent, audit and clinical governance.
Interventional procedures	**Endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease. NICE interventional procedure guidance 222 (2007)** 1.1 There is limited evidence of short-term efficacy on endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease (GORD). This evidence also raises concerns about the procedure's safety. Therefore, this procedure should not be used without special arrangements

	for consent and for audit. 1.2 Clinicians wishing to undertake endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of GORD should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, use of the Institute's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of all patients having endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of GORD (see section 3.1). 1.3 Any adverse events resulting from the procedure should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA).
Interventional procedures	**Endoluminal gastroplication for gastro-oesophageal reflux disease. NICE interventional procedure guidance 404 (2011)** 1.1 The evidence on endoluminal gastroplication for gastro-oesophageal reflux disease (GORD) raises no major safety concerns. Evidence from a number of randomised controlled trials (RCTs) shows a degree of efficacy in terms of reduced medication requirement in the short term, but changes in other efficacy outcomes are inconsistent and there is no good evidence of sustained improvement in oesophageal pH measurements. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake endoluminal gastroplication for GORD should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's efficacy, particularly in the long term, and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/guidance/IPG404/publicinfo). • Audit and review clinical outcomes of all patients having endoluminal gastroplication for GORD (see section 3.1). 1.3 Any further studies should include measurements of oesophageal pH and report long-term outcomes.

Interventional procedures	**Laparoscopic insertion of a magnetic-bead band for gastro-oesophageal reflux disease. NICE interventional procedure guidance 431(2012)** 1.1 The evidence on the safety and efficacy of laparoscopic insertion of a magnetic bead band for gastro-oesophageal reflux disease (GORD) is limited in quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake laparoscopic insertion of a magnetic bead band for GORD should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. • Audit and review clinical outcomes of all patients having laparoscopic insertion of a magnetic bead band for GORD (see section 3.1). 1.3 NICE encourages further research and collaborative data collection on laparoscopic insertion of a magnetic bead band for GORD. Clear descriptions of patient selection are particularly important. Perioperative and long-term complications should be reported, together with details of long-term efficacy, including the need for further procedures and medication to control symptoms of GORD. NICE may review the procedure on publication of further evidence.
Interventional procedures	**Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease. NICE interventional procedure guidance 461(2013)** 1.1 The evidence on the safety of endoscopic radiofrequency ablation for gastro-oesophageal reflux disease (GORD) is adequate in the short and medium term but there is uncertainty about longer-term outcomes. With regard to efficacy, there is evidence of symptomatic relief but objective evidence on reduction of reflux is inconclusive. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake endoscopic radiofrequency ablation for GORD should take the following actions. • Inform the clinical governance leads in their NHS trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. • Audit and review clinical outcomes of all patients

	having endoscopic radiofrequency ablation for GORD (see section 7.1). 1.3 Future review of the guidance might consider evidence from research that includes objective outcome measures such as oesophageal pH, long-term follow-up data, comparison with Nissen fundoplication, information about patient selection and further insight into the mechanism of action of the procedure.
Interventional procedures	**Gastroelectrical stimulation for gastroparesis. NICE interventional procedure guidance 489 (2014)** 1.1 Current evidence on the efficacy and safety of gastric electrical stimulation for gastroparesis is adequate to support the use of this procedure with normal arrangements for clinical governance, consent and audit. 1.2 During the consent process, clinicians should inform patients considering gastric electrical stimulation for gastroparesis that some patients do not get any benefit from it. They should also give patients detailed written information about the risk of complications, which can be serious, including the need to remove the device. 1.3 Patient selection and follow-up should be done in specialist gastroenterology units with expertise in gastrointestinal motility disorders, and the procedure should only be performed by surgeons working in these units. 1.4 Further publications providing data about the effects of the procedure on symptoms in the long term and on device durability would be useful.
Interventional procedures	**Transcutaneous neuromuscular electrical stimulation for oropharyngeal dysphagia. NICE interventional procedure guidance 490 (2014)** 1.1 Current evidence on the efficacy of transcutaneous neuromuscular electrical stimulation (NMES) for oropharyngeal dysphagia is limited in quality. The evidence on safety is limited in both quality and quantity but there were no major safety concerns. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake transcutaneous NMES for oropharyngeal dysphagia should take the following actions. • Inform the clinical governance leads in their NHS trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. • Audit and review clinical outcomes of all patients

	having transcutaneous NMES for oropharyngeal dysphagia (see section 7.1). 1.3 NICE encourages further research into transcutaneous NMES for oropharyngeal dysphagia, which should clearly document the indications for treatment and the details of patient selection. Research should document the timing of initiation of treatment after onset of symptoms, as well as precise information about the procedure technique. Outcome measures should include freedom from tube feeding, quality of life and duration of treatment effect. NICE may review the procedure on publication of further evidence.
Clinical guidelines	**Barrett's oesophagus: Ablative therapy for the treatment of Barrett's oesophagus. NICE clinical guideline 106 (2010).** 1.1 List of all recommendations Before considering endoscopic therapy as an alternative to surgery, a confirmed diagnosis of high-grade dysplasia or intramucosal cancer in Barrett's oesophagus should be agreed by a designated specialist multidisciplinary team for oesophago-gastric cancer. **Key principles of care** 1.1.1 All treatments for high-grade dysplasia and intramucosal cancer in Barrett's oesophagus should be performed by specialist oesophago-gastric cancer teams with the experience and facilities to deliver the treatments recommended in this guideline. **Endoscopic therapies** 1.1.2 Consider offering endoscopic therapy as an alternative to oesophagectomy to people with high-grade dysplasia and intramucosal cancer (T1a), taking into account individual patient preferences and general health. Endoscopic therapy is particularly suitable for patients who are considered unsuitable for surgery or who do not wish to undergo oesophagectomy. **Endoscopic mucosal resection** 1.1.3 Consider using endoscopic mucosal resection alone to treat localised lesions. 1.1.4 Use circumferential endoscopic mucosal resection with care because of the high incidence of stricture formation. 1.1.5 If residual or recurrent disease is suspected, consider additional or repeated therapy with appropriate follow-up using: • endoscopic mucosal resection with further pathological assessment **or** • ablative therapy (radiofrequency ablation or photodynamic therapy) **or** • endoscopic mucosal resection and ablative therapy

	(radiofrequency ablation, argon plasma coagulation or photodynamic therapy). **Ablative therapies** 1.1.6 Consider using radiofrequency ablation alone or photodynamic therapy alone for flat high-grade dysplasia, taking into account the evidence of their long-term efficacy, cost and complication rates. 1.1.7 Do not use argon plasma coagulation, laser ablation or multipolar electrocoagulation alone, or in combination with each other, unless as part of a clinical trial. **Endoscopic mucosal resection in combination with ablative therapies** 1.1.8 If using endoscopic mucosal resection, consider following with an additional ablative therapy (radiofrequency ablation, argon plasma coagulation or photodynamic therapy) to completely remove residual flat dysplasia, taking into consideration the side-effect profiles. **Patient and carer support and information** 1.1.9 Give patients verbal and written information about their diagnosis, available treatments, patient support groups and the uncertainty of the long-term outcomes of ablative therapies. Give patients time to consider this information when making decisions about their care. 1.1.10 Discuss the multidisciplinary team's views on the range of appropriate treatments with the patient. 1.1.11 Offer patients the opportunity to see the same specialist healthcare team more than once to agree treatment. 1.1.12 Advise patients who have endoscopic therapy that they will need lifelong care and repeated endoscopies.
Clinical guidelines	**Dyspepsia and gastro-oesophageal reflux disease: Investigation and management of dyspepsia, symptoms suggestive of gastro‑oesophageal reflux disease, or both. NICE clinical guideline 184 (2014)** 1.10 Laparoscopic fundoplication 1.10.1 Consider laparoscopic fundoplication for people who have: • a confirmed diagnosis of acid reflux and adequate symptom control with acid suppression therapy, but who do not wish to continue with this therapy long term • a confirmed diagnosis of acid reflux and symptoms that are responding to a PPI, but who cannot tolerate acid suppression therapy. [new 2014]
Clinical guidelines	**Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people.**

	NICE guideline 1 (2015) 1.5 Surgery for GORD 1.5.1 Offer an upper GI endoscopy with oesophageal biopsies for infants, children and young people before deciding whether to offer fundoplication for presumed GORD. 1.5.2 Consider performing other investigations such as an oesophageal pH study (or combined oesophageal pH and impedance monitoring if available) and an upper GI contrast study for infants, children and young people before deciding whether to offer fundoplication. 1.5.3 Consider fundoplication in infants, children and young people with severe, intractable GORD if: • appropriate medical treatment has been unsuccessful or • feeding regimens to manage GORD prove impractical, for example, in the case of long-term, continuous, thickened enteral tube feeding.

Appendix C: Literature search for electrical stimulation of the lower oesophageal sphincter for the treatment of gastro-oesophageal reflux disease

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	04/06/2015	Issue 6 of 12, June 2015
HTA database (Cochrane Library)	04/06/2015	Issue 2 of 4, April 2015
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	04/06/2015	Issue 5 of 12, May 2015
MEDLINE (Ovid)	04/06/2015	1946 to May Week 5 2015
MEDLINE In-Process (Ovid)	04/06/2015	June 03, 2015
EMBASE (Ovid)	04/06/2015	1974 to 2015 Week 22
PubMed	04/06/2015	n/a
JournalTOCS	04/06/2015	n/a

Trial sources searched on 24/10/2014 – IP Scoping page

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- WHO International Clinical Trials Registry

Websites searched on 24/10/2014 – IP Scoping page

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Gastroesophageal Reflux/ (22062)
2 ((gastro-?esophageal* or gastro?esophageal*) adj4 reflux*).ti,ab. (14653)
3 (GORD or GERD).ti,ab. (5963)
4 regurgitat*.ti,ab. (27067)
5 ((acid* or gastric*) adj4 reflux*).ti,ab. (4520)
6 Heartburn/ (1719)
7 (heartburn* or heart-burn* or (heart adj4 burn*)).ti,ab. (3993)
8 Dyspepsia/ (7382)
9 dyspepsia*.ti,ab. (8227)
10 Esophageal motility disorders/ (1473)
11 (?esophageal adj4 motilit* adj4 disorder*).ti,ab. (572)
12 Esophageal Sphincter, Lower/ (751)
13 (low* adj4 ?esophageal* adj4 sphinct*).ti,ab. (3606)
14 or/1-13 (66537)
15 Electric Stimulation/ (107227)
16 Electric Stimulation Therapy/ (17474)
17 Electrodes, implanted/ (17095)
18 ((LES or (low* adj4 ?esophageal* adj4 sphinct*)) adj4 stimulat*).ti,ab. (116)
19 (Electr* adj4 (stimulat* or impuls*) adj4 (LES or (low* adj4 ?esophageal* adj4 sphinct*))).ti,ab. (33)
20 (EST or (electr* adj4 stimulat* adj4 therap*)).ti,ab. (9123)
21 (electr* adj4 (low-energ* or (low* adj4 energ*))).ti,ab. (1301)
22 or/15-21 (145388)
23 14 and 22 (380)
24 (endostim* or endo-stim*).ti,ab. (5)
25 23 or 24 (383)
26 animal/ not humans/ (3961836)
27 25 not 26 (208)
28 limit 27 to ed=20141114-20150630 (9)