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, which is the ring of muscle separating the oesophagus from the stomach. Electrical stimulation of the lower oesophageal sphincter applies low energy electrical impulses to the sphincter in repeated sessions, with the aims of strengthening it and reducing 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 March 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 (LOS) for treating gastro-oesophageal reflux disease (GORD). The following databases were searched, covering the period from their start to 19 December 2014: 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 58 patients from 3 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 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 (6-10)	2.0 (0-3.0)	0.002
Off-PPI (n=24)	23.5 (21.0-25.75)		<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 (41.8-52.8)	52.0 (43.0-55.0)	0.191
Off-PPI (n=24)	46.5 (39.8-51.0)		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 (41.5-55.0)	50.0 (45.0-58.0)	0.281
Off-PPI (n=24)	49.0 (37.8-54.8)		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 (4-65)	8 (7-26)	31 (4-57)	0 (0-22)	29 (0-78)	67 (16-93)	0.4 (0.1-1.2)
6 months	100 (93-100)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-7)	0.1 (0-0.2)
12 months	100 (91-100)	0 (0-7)	0 (0-0)	0 (0-0)	0 (0-2)	0 (0-2)	0 (0-0.1)
Heartburn							
Baseline off-PPI	0 (0-14)	14 (8-29)	50 (30-69)	7 (0-29)	64 (21-86)	92 (73-93)	N/A
6 months	79 (50-93)	14 (0-50)	0 (0-7)	0 (0-0)	0 (0-14)	14 (7-36)	N/A
12 months	83 (48-100)	0 (0-27)	0 (0-14)	0(0-0)	0 (0-14)	8 (0-50)	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 2 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 35kg/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, 3-8 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 (6-10)	2	2	0	0 (0-3)	0.002
Off-PPI	23.5 (21-25.3)					<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 related to the device or procedure	AE involving the respiratory system	19 in 13 patients (cold was reported in 17/19 episodes)
	Others	32

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 (42.5-51.5)*	55 (53-57)	0.0007
Off-PPI	46.5 (41.2-49.0)**		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 (40.5-53.0)*	56 (44-62)	0.058
Off-PPI	49 (39.2-54.2)**		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 /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%
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-h period with pH<4.0 (IQR)	p value versus baseline	Median % of the 24-h period with pH<4.0 (IQR)	p value versus baseline	Median % of the 24-h period with pH<4.0 (IQR)	p value versus baseline
Baseline	11% (8.0-16.8%) (n=20)		10% (7.8-13.0%) (n=24)		7% (6.3-8.2%) (n=4)	
12 months	4% (2.6-7.0%) (n=18)	<0.001			2% (1.4-2.0%) (n=4)	
24 months	4% (2-6.9%) (n=14)	0.001	5% (3.4-7.0%) (n=18)	0.001	5% (5.0-6.6%) (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 3 Siersema PD (2014) [conference abstract only]

Details

Study type	**Case series**
Country	International multicentre trial.
Recruitment period	Not reported
Study population and number	n=**33** patients with GORD
Age and sex	Median 49.8 years; 55% (18/33) male
Patient selection criteria	GORD patients partially responsive to PPI with off-PPI GORD-HRQL >20 and >5 point improvement on-PPI, LOS end-expiratory pressures of >5 mmHg, % 24-hour oesophageal pH<4 for >5%, hiatal hernia <3cm and oesophagitis <LA Grade C.
Technique	Bipolar stitch electrodes and a pulse generator (EndoStim BV) were implanted laparoscopically. Electrical stimulation at 20Hz, 220usec, 5mAmp in twelve 30-minute sessions was initiated post-implant. Stimulation sessions were optimised based on residual symptoms and oesophageal pH testing.
Follow-up	**6 months**
Conflict of interest/source of funding	Financial support for research from Endostim.

Analysis

Follow-up issues: 24 patients completed their 3-month and 22 their 6-month visits.
Study design issues: None.
Study population issues: None.
Other issues: None.

Key efficacy and safety findings

Efficacy	Safety

Efficacy findings from conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview.	89 adverse events were reported in 27 patients:
	• 38 were device, procedure, or therapy related
	• 2 serious adverse events were reported in 2 patients
	  ○ 1 had a **procedure-related trocar perforation of the small bowel** during laparoscopy that was successfully treated and the device was prophylactically explanted.
	  ○ 1 had **atrioventricular (AV) nodal re-entrant tachycardia not device or procedure related** successfully treated with AV nodal ablation.
	• Other device or procedure related events were typical of surgical implant procedures, such as post-op nausea and pocket pain.
	• 3 instances of **mild dysphagia** in 2 patients (both with a hiatal closure at time of implantation) resolved without intervention.

Abbreviations used: AV, atrioventricular; GORD, gastro-oesophageal reflux disease; HRQL, health-related quality of life; LA, Los Angeles; PPIs, proton pump inhibitors.	

Efficacy

GORD symptoms

A case series of 25 patients with GORD with a 1-year follow-up reported that the median interquartile range (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)[1].

A publication about the case series of 25 patients with GORD treated by electrostimulation of the LOS after 2 years of 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. The evaluations used a 14-day symptom diary kept by the patients. 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')[2].

The case series of 25 patients with a 2-year follow-up 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 with a 2-year follow-up 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)[2].

The case series of 25 patients with a 2-year follow-up reported odynophagia caused by GORD (individual gastro-oesophageal reflux disease health-related quality of life [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[2].

In the case series of 25 patients with a 2-year follow-up, 1 patients 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)[2].

Quality of life

The case series of 25 patients with a 2-year follow-up reported median GORD-HRQL scores (IQR range) at baseline of 9.0 (6.0–10.0) when patients (n=24) were still taking PPIs and of 23.5 (21.0–25.3) 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 'off PPI' score for 12- and 24-month follow-up respectively)[2].

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[1].

The case series of 25 patients with a 2-year follow-up 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 'off PPIs')[2].

The case series of 25 patients with 2-year follow-up 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)[2].

The case series of 25 patients with 2-year follow-up reported dissatisfaction with GORD control in 71% (17/24) of patients at baseline 'on PPIs' and in 92% (22/24) of patients 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)[2].

The case series of 25 patients with 2-year follow-up 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[2].

The case series of 25 patients with a 2-year follow-up 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[2].

Oesophageal pH

The case series of 25 patients with 2-year follow-up 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 24-hour recording) and, at 24 months, 61% (11/18) had an abnormal pH[2].

The case series of 25 patients with the 2-year follow-up 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[2].

The case series of 25 patients with the 2-year follow-up reported median DeMeester scores (including 6 parameters with a score of more than 14.7 indicating reflux) 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)[2].

Reduction in medication use

In the case series of 25 patients with 2-year follow-up, 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[2].

The case series of 25 patients with a 2-year follow-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)[2].

Long-term sequelae

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 (Los Angeles classification) Grade A oesophagitis (Grade A to D from less severe to more severe oesophagitis assessed by endoscopy), 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[1].

Safety

Perforation of the small bowel

Trocar perforation of the small bowel during laparoscopy was reported in 1 patient in a case series of 33 patients with GORD treated by electrostimulation of the LOS (results only reported in a conference abstract). It was successfully treated and the device was prophylactically explanted[3].

Pain

Pain or discomfort in the abdomen was reported on 6 occasions in 6 patients in the 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 provided). In addition, 1 patient had transient discomfort in the shoulder.

Nausea

Nausea or vomiting on 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[2].

Skin infection

Superficial skin infection at the abdominal wall pocket site was reported in 1 patient in the case series of 25 patients with 2-year follow-up[,2].

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[2].

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’ [1,2].

Validity and generalisability of the studies

- Very limited evidence base: only 1 study[1,2] including 25 patients with published clinical results at 1-year and 2-year of follow-up, no comparative studies.
- One conference abstract[3] was included in table 2 for safety data.

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

- 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
- Catheterless oesophageal pH monitoring. NICE interventional procedure guidance 187 (2006). Available from http://www.nice.org.uk/guidance/ipg187
- 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
- Endoluminal gastroplication for gastro-oesophageal reflux disease. NICE interventional procedure guidance 404 (2011). Available from http://www.nice.org.uk/guidance/ipg404
- 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
- Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease. NICE interventional procedure guidance 461(2013). Available from http://www.nice.org.uk/guidance/ipg461
- Gastroelectrical stimulation for gastroparesis. NICE interventional procedure guidance 489 (2014). Available from http://www.nice.org.uk/guidance/ipg489
- Transcutaneous neuromuscular electrical stimulation for oropharyngeal dysphagia. NICE interventional procedure guidance 490 (2014). Available from http://www.nice.org.uk/guidance/ipg490

NICE guidelines

- 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
- 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
- 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

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 (LOS) for the treatment of gastro-oesophageal reflux disease (GORD) were submitted and can be found on the NICE website [INSERT HYPER LINK TO MAIN IP PAGE].

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. 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.
2. 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.
3. Siersema PD, Bredenoord AJ, Conchillo JM et al. (2014) Electrical stimulation therapy (EST) of the lower esophageal sphincter (LES)-an effective therapy for refractory gerd-interim results of an international multicenter trial. Gastroenterology.Conference: Digestive Disease Week 2014, DDW 2014 Chicago, IL United States.Conference Start: 20140503 Conference End: 20140506.Conference Publication: (var.pagings).146 (5 SUPPL.1) (pp S-167).

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

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 (LOS) for the treatment of gastro-oesophageal reflux disease (GORD)

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 clinical 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 (LOS) for the treatment of gastro-oesophageal reflux disease (GORD)

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	22/12/2014	Issue 12 of 12, December 2014
Database of Abstracts of Reviews of Effects – DARE (Cochrane)	22/12/2014	Issue 4 of 4, October 2014
HTA database (Cochrane)	22/12/2014	Issue 4 of 4, October 2014
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	22/12/2014	Issue 11 of 12, November 2014
MEDLINE (Ovid)	19/12/2014	1946 to November week 3 2014
MEDLINE In-Process (Ovid)	19/12/2014	December 11, 2014
EMBASE (Ovid)	19/12/2014	1974 to 2014 Week 50
PubMed	22/12/2014	n/a
BLIC (Dialog DataStar)	22/12/2014	n/a
Databases	Date searched	Version/files

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/ (22231)
2	((gastro-?esophageal* or gastro?esophageal*) adj4 reflux*).ti,ab. (14734)
3	(GORD or GERD).ti,ab. (6000)
4	regurgitat*.ti,ab. (26851)
5	((acid* or gastric*) adj4 reflux*).ti,ab. (4590)
6	Heartburn/ (1738)
7	(heartburn* or heart-burn* or (heart adj4 burn*)).ti,ab. (4053)
8	Dyspepsia/ (7498)
9	dyspepsia*.ti,ab. (8361)
10	Esophageal motility disorders/ (1489)
11	(?esophageal adj4 motilit* adj4 disorder*).ti,ab. (583)
12	Esophageal Sphincter, Lower/ (737)
13	(low* adj4 ?esophageal* adj4 sphinct*).ti,ab. (3643)
14	or/1-13 (66726)
15	Electric Stimulation/ (111702)
16	Electric Stimulation Therapy/ (17897)
17	Electrodes, implanted/ (17883)
18	((LES or (low* adj4 ?esophageal* adj4 sphinct*)) adj4 stimulat*).ti,ab. (113)
19	(Electr* adj4 (stimulat* or impuls*) adj4 (LES or (low* adj4 ?esophageal* adj4 sphinct*))).ti,ab. (31)
20	(EST or (electr* adj4 stimulat* adj4 therap*)).ti,ab. (9113)
21	(electr* adj4 (low-energ* or (low* adj4 energ*))).ti,ab. (1317)
22	or/15-21 (150673)
23	14 and 22 (378)
24	(endostim* or endo-stim*).ti,ab. (4)
25	23 or 24 (381)
26	animal/ not humans/ (4004886)
27	25 not 26 (206)