National Institute for Health and Care Excellence

IP1244 – Electrical stimulation of the lower oesophageal sphincter for treating gastro-oesophageal reflux disease

Consultation Comments table

IPAC date: Thursday 10th September 2015

An administrative error was identified during the consultation process and stakeholders may not have been able to comment. A second period of consultation was run to ensure that all consultees were able to comment on the draft guidance. The first consultation was run from 01/06/2015 to 26/06/2015 and the second consultation from 10/07/2015 to 06/08/2015. Consultee comments from the first and second consultation are both presented below, starting with the comments from the first consultation.

FIRST CONSULTATION				
Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
1	Consultee 1 Overseas health care professional	**1**	I have read your guidelines on EndoStim® electrical stimulation of the LOS for treatment of GORD with great interest. It seems to me that your conclusions are too restrictive based on existing evidence with this technology and more importantly the existing knowledge in the field of GORD. Let me express my concern in that your guidelines will significantly hinder our ability to take care of the patients. I am the Director of the Esophageal Institute at Hospital Universitario Fundacion Favaloro in Buenos Aires, Argentina with oesophageal surgery as the main focus of my research and practice. We are the first hospital in Argentina offering neurostimulation therapy to selected GORD patients who are not good candidates for traditional therapy. This therapy has exceptional results documented by objective measurements for GORD. In my practice in addition to simple GORD, we have successfully treated patients with severe oesophageal dysmotility including complete aperistalsis who would have had a suboptimal outcome with a fundoplication or would have required partial resections and complex digestive reconstructions to avoid dysphagia.	Thank you for your comment which outlines your own clinical experience and identifies certain groups of patients where you feel this treatment may have a particular role. No data on patients with severe oesophageal dysmotility, post-lung transplant GORD or post-laparoscopic sleeve gastrectomy GORD is available in the published evidence on electrical stimulation of the lower oesophageal sphincter for treating GORD. Section 1.2 of the guidance now states that 'NICE encourages clinicians to enter patients into controlled clinical trials. These could include crossover and cohort studies which would allow inclusion of patients for whom other surgical options are unsuitable.'

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	Consultee 1 Overseas health care professional		The results have been documented by the post-operative oesophageal high resolution manometry and MII/pH testing. This is only possibly because the EndoStim data "conclusively" shows that electric stimulation therapy has no effect on LES relaxation and oesophageal body function. A testimonial from one such patient is available at our website at ffavaloro.org. We have also successfully treated a patient with post-lung transplant GORD and objectively documented our success in this case. We will shortly be treating our second lung transplant patient. We all know that in those patients, GORD will lead to transplant failure and death. Finally, a large growing patient population of post laparoscopic sleeve gastrectomy GORD cannot be treated with antireflux surgery: options in these patients are a more invasive laparoscopic roux-en-Y gastric bypass surgery or continued suffering from GORD. We have been successfully able to treat such patients and objectively document elimination of GORD.	

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2	Consultee 1 Overseas health care professional	**4**	I have been involved with clinical investigation and evidence generation for various oesophageal therapies and treatment guidelines development. I understand the importance for objective analysis of data. Oesophageal acid exposure is the gold-standard biomarker for GORD. Based on this biomarker we classify patients as diseased or not in routine practice, and are willing to subject them to invasive surgery based on the results of this one test. LES electrical stimulation has been able to demonstrate long-term control of oesophageal acid exposure in two independent open-label trials, indicating that the majority of these patients have either been cured of their condition or have had successful control of their disease. I strongly welcome the value of sham-control data. However, a >60% improvement in an objectively measured biomarker of GORD - oesophageal acid exposure - cannot possibly be a sham response. A sham response of this magnitude and sustained for 3 years has never been reported.	Thank you for your comment and for drawing the attention of the committee to the evidence regarding the objectively measured oesophageal acid exposure. The Rodriguez (2015) paper with a follow-up of 3 years has been added to the main extraction table (Table 2).

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3	Consultee 1 Overseas health care professional	**1**	My concern by the proposed NICE recommendations, regardless of my personal feeling that patients in UK should not be denied the option of a safe and effective, minimally-invasive therapy for GORD, is the global impact they may have on other health care systems. I am seriously concerned that these restrictive guidelines will impact our ability to take care of our patients here in Argentina. I request that the NICE committee take a practical view of the results of studies and make a recommendation that allows physicians to offer this therapy in clinical practice to well-selected, well-informed patients for whom existing treatment options are very unsatisfactory. Treatment development is a shared responsibility and our patients are willing to participate in such an endeavor outside of clinical trials as long as they are informed of the limitations during consultation with their treating physician and the pre-procedure informed consent process. This suggests that a 'special arrangements' recommendation would be appropriate.	Thank you for your comment. The NICE IP programme considers the safety and efficacy of procedures, and makes recommendations as to what arrangements should be in place for clinicians wishing to do the procedure. It does not produce clinical guidelines which determine the place of this procedure in clinical practice in the UK or elsewhere. Section 1.2 of the guidance now states that 'NICE encourages clinicians to enter patients into controlled clinical trials. These could include crossover and cohort studies which would allow inclusion of patients for whom other surgical options are unsuitable.' The Committee considered this comment but decided not to change the main recommendations.

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Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
4	Consultee 2 Specialist Adviser	**4**	Thank you for the opportunity to provide feedback regarding the proposed NICE advice on the use of the EndoStim Electrical stimulation of the Lower Oesophageal sphincter. As I had been consulted as a Specialist Advisor during the initial consideration by NICE earlier this year I would like to add some additional considerations due to on-going research outcomes and new publications. Since my advice was given in March a further publication of the outcome of the EndoStim treatment has been accepted for publication in the Journal Alimentary Pharmacology and Therapeutics and this describes the Interim results of an International multicenter trial. This paper not only broadens the clinical experience of the therapy (previously only published from single institution studies) but it also adds information on the range of patient types that can be treated, such as those with hiatal hernia as well as those without. The combination of hiatal hernia repair with electrical stimulation has now been established. The additional multicenter patients have also shown that the device is safe in a broader clinical setting, supporting the data from the initial study centres.	Thank you for your comment. The Kappelle (2015) paper has been added to the main extraction table (Table 2).

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Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
5	Consultee 2 Specialist adviser	**1**	Because of this accumulating data I believe that the NICE advice now should be that the procedure be used with special arrangements for patients who might not be suitable for standard anti reflux surgery, as well as in the setting of clinical trials or registry studies. There are a wide range of circumstances where a standard anti reflux operation is either not possible (such as after sleeve gastrectomy for obesity where there is no fundus left to plicate) or in patients with disordered motility of the oesophagus where the non obstructive nature of this device allows for control of reflux without dysphagia. Indeed it is clear from the studies that the electrical stimulation therapy has the lowest degree of dysphagia of any anti reflux procedure with no new dysphagia seen in any of the studies. This contrasts with other anti reflux procedures – whether endoscopic or laparoscopic – where post procedure dysphagia is a problem for patients with disordered motility . Allied to the broader indications is its documented excellent quality of measured pH improvement. I now advise that the NICE recommendation be made to allow the EndoStim therapy to be used for patients under special arrangements as well as in research and registry studies, to permit the care of patients in clinical need while the data from controlled or sham studies and follow up through 5 – 10 years is collected.	Thank you for your comment. There is no published evidence on patients who might not be suitable for standard anti-reflux surgery. The Committee considered this comment but decided not to change the main recommendations. Section 1.2 of the guidance now states that 'NICE encourages clinicians to enter patients into controlled clinical trials. These could include crossover and cohort studies which would allow inclusion of patients for whom other surgical options are unsuitable.'

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Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
6	Consultee 3 Manufacturer and overseas healthcare professional	**1**	I would like to thank you for the opportunity to respond formally on behalf of EndoStim Inc. on proposed guidance for electrical stimulation of the lower oesophageal sphincter for treating GORD. I am a [redacted]. I have also been involved with Health Technology Assessment in the past ([redacted]) and know the rigors of the HTA reviews. The proposed recommendation of 'research only' is too restrictive and could significantly affect the access of GORD patients to this highly safe and effective therapy. A 'special arrangements' recommendation would be more appropriate. Access to this therapy should be available on a case-by-case basis to patients who are not well treated with maximal medical therapy and do not want or cannot have traditional antireflux surgery for multitude of reasons and are left to suffer while more conclusive evidence is being gathered.	Please note that this comment has been updated by the Consultee during the second round of consultation.

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Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
7	Consultee 3 Manufacturer and overseas healthcare professional	**4**	I am in a unique position to have knowledge of the most up-to-date data on electrical stimulation of the LOS including information about its efficacy in highly unique patient populations who other than EndoStim have no good options for treatment of their GORD. A paper by Kappelle W et al. describing the interim results of an n = 42 multicentre trial of electrical stimulation therapy of the lower oesophageal sphincter for refractory gastro-oesophageal reflux disease has recently been accepted for publication in Alimentary Pharmacology and Therapeutics. Results are reported for 41/42 (97.6%) enrolled patients. In respect of efficacy, Kappelle and colleagues report that GORD-HRQL improved significantly, and oesophageal acid exposure normalised. Of the 42 enrolled patients, 37 (88.1%) were off PPI at 6 months and the mean acid exposure time was <5% in 35 patients (85%). At 6 months post-procedure, three SAEs had been reported: one device-related: an asymptomatic lead erosion was encountered at the 6-month endoscopy in a patient implanted with an investigational lead with a 5-mm electrode. Treatment consisted of explant of the IPG and lead, followed by fundoplication performed during the same procedure;	Please note that this comment has been updated by the Consultee during the second round of consultation.

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	Consultee 3 Manufacturer and overseas healthcare professional		one procedure-related: a trocar perforation of the small bowel, which occurred during the implant procedure and was successfully repaired laparoscopically. The device was prophylactically removed immediate post-op, no therapy was delivered and the patient recovered fully; a case of paroxysmal atrioventricular nodal re-entrant tachycardia several months after the procedure. Based on the sequence of events, the stimulation parameters, and the distance of the electrodes from the heart, the event was considered NOT to be device- or stimulation-related by the treating cardiologist Kappelle and colleagues concl ude that the results show that the procedure has an acceptable safety record and good short-term efficacy in GORD patients who are partially responsive to PPI therapy. They consider that "…A remarkable reduction in regurgitation symptoms, without the risk of intervention-requiring dysphagia may prove to be an advantage compared with other anti-reflux procedures." The Committee should include the Kappelle paper in the evidence base it uses to determine its final advice to NICE.	

FIRST CONSULTATION				
Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
8	Consultee 3 Manufacturer and overseas healthcare professional	**4**	In respect of the Rodriguez n = 25 trial whose results are included in the present overview, an abstract has been published by Rodriguez et al (S080. Electrical Stimulation Therapy (EST) of the Lower Oesophageal Sphincter (LES) Is Successful in Treating GORD – Long-Term 3 Year Results. Surg Endosc (2015) 29:S340). A manuscript is expected to be published very shortly per the SAGES process of publishing a full manuscript following accepted abstracts which are presented at the SAGES podium. The cohort of patients who completed the 2-year open-label trial are being followed up over a 5-year follow-up period, as part of a registry study. The abstract reports the results of this cohort at 3-year follow-up. 18/25 (72%) of patients completed a 3-year evaluation. Three patients were not receiving stimulation at 3 years. Results in the other 15 patients confirm that the significant improvement in GERD-HRQL and oesophageal pH was maintained at three years. 14/15 (93.3%) reported cessation of regular PPI use, a remarkable result in a cohort of patients whose symptoms were resistant to optimal medical therapy. No unanticipated device- or stimulation-related adverse events or untoward sensations were reported between the 2- and 3-year follow-up period. There were no complaints of dysphagia. The authors conclude that the procedure is safe and effective for treating GORD over a 3-year period.	Please note that this comment has been updated by the Consultee during the second round of consultation.

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Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
9	Consultee 3 Manufacturer and overseas healthcare professional	**General comment**	The Committee should postpone further consideration of this procedure for a short period to allow inclusion of the 3-year results of the n = 25 trial in the evidence base it uses to determine its final advice to NICE. The results of the two published trials are consistent in demonstrating both statistically significant and clinically meaningful improvement in all major GORD patient outcomes. Both trials revealed a significant improvement in oesophageal acid exposure, out to 3 years (n = 25) and 6 months (n = 42), respectively with almost two-thirds of the patients showing either normalisation or > 50% improvement in their distal oesophageal acid exposure. Normalisation of proximal oesophageal acid exposure has been reported in 100% of patients at 2 years.	Please note that this comment has been updated by the Consultee during the second round of consultation.

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Please respond to all comments</th></tr>
<tr><td>10</td><td>Consultee 3
Manufacturer and overseas healthcare professional</td><td>4</td><td>Oesophageal acid exposure is the hallmark feature of GORD and the most objective and robust biomarker for this disease. The most unique feature of LOS electrical stimulation is its safety and tolerability and paucity of long-term side-effects. In 67 patients whose results have been reported to date, only two serious procedure- or device-related AEs have been observed.
This compares very favourably to SAE rates of 5-15% with traditional antireflux surgery and significant long-term complications (see graphic below).
Table 1. Prevalence of Medical and Surgical Complications of Antireflux Surgery
Mortality (<30 days) 1% or less
Perioperative and immediate postoperative morbidity 8%–17%
Open conversion rate 0%–24%
Early postoperative complications
Bowel perforation 0%–4%
Bleeding and splenic injury <1%
Pneumothorax 0%–10%
Severe postoperative nausea and vomiting 2%–5%
Late postoperative complications
Gas-bloat syndrome 1%–85%
Dysphagia
Early 10%–50%
Late 3%–24%
Diarrhea 18%–33%
Recurrent heartburn 10%–62%
Need for revisional surgery
Laparoscopic Nissen fundoplication 0%–15%
Laparoscopic Toupet fundoplication 4%–10%
Richter JE. Clin Gastroenterol Hepatol. 2013 May; 11(5): 465-71</td><td><u>Please note that this comment has been updated by the Consultee during the second round of consultation.</u>
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11	Consultee 3 Manufacturer and overseas healthcare professional	**4**	The long-term effectiveness of this procedure is also being seen in the international post-marketing registry which is prospectively collecting data from patients treated outside clinical trials. Importantly, our global clinical experience shows SAE rates <2% which is far superior to traditional antireflux surgery.	Please note that this comment has been updated by the Consultee during the second round of consultation.

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12	Consultee 3 Manufacturer and overseas healthcare professional	**4**	The unique feature of LOS electrical stimulation therapy is its non-disruptive approach to LOS function restoration which does not affects LOS relaxation or oesophageal body function. This phenomenon has been documented in thousands of high resolution manometry swallows, the gold-standard test for evaluation of oesophageal function. This unique feature allows EndoStim to treat some specific patient populations whose needs are not adequately met by traditional antireflux surgery. Such populations include patients with i severe oesophageal dysmotility including aperistalsis, post-myotomy GORD and post lung-transplant GORD which is commonly associated with severe oesophageal dysmotility. Another rapidly growing severe GORD population without effective clinical options is those patients who suffer from GORD after laparoscopic sleeve gastrectomy (LSG): these patients are not candidates for traditional antireflux surgery. With the exception of LSG, the evidence for efficacy of LOS stimulation for these unique indications is highly unlikely to come from clinical trials and can only be obtained from its use in routine clinical practice. Many such patients are currently safely and successfully treated around the world using LOS stimulation and the results continue to be objectively documented.	Please note that this comment has been updated by the Consultee during the second round of consultation. .

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			We are continuing to accumulate more evidence of safety and efficacy of LOS stimulation in both clinical trials and in clinical practice. However, we believe that there is adequate evidence for the safety of this procedure in > 200 patients treated with longest follow-up approaching 5 years. A similar safety profile is seen in patients undergoing gastric electric stimulation which has very similar technical and treatment characteristics. The significant and sustained improvement in oesophageal acid exposure, the hallmark of GORD, is a strong evidence for efficacy of LOS stimulation in long-term control of GORD. A 'research only' recommendation will deny many GORD sufferers in need of this procedure, given the lack of effective treatment options for the group for whom the procedure is intended. The evidence reviewed by the Committee, together with the new papers by Kappelle and Rodriguez merit a 'special arrangements' recommendation.	

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13	Consultee 4 British Society of Gastroenterology NHS Professional	**General comment**	Many thanks for the information on the Electrical Stimulation of the lower oesophageal sphincter for treating GORD. I've limited experience of this area of work. From my limited understanding and reading of the current data there is a need for large randomised studies for this technology as have been noted by all 3 reviewers. There are some interesting initial observations which if replicated in large studies would make this a widely used technology with a significant impact on how we manage GORD. As a potential referrer for this type of procedure in the future it would certainly be something to consider. Would be interested to see some data on larger hiatus hernia related GORD.	Thank you for your comment and for drawing the attention of the Committee to the need of large randomised controlled trials.

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14	Consultee 5 British Society of Gastroenterology Chair of the BSG Oesophageal Section Committee	**General comment**	There has been 1 response from the oesophageal section membership (see e mail trail below) endorsing the need for randomised comparative studies. I understand that a study od EndoStim versus sham procedure is about to start in the US and this will be very important. However, there are 2 reports of observational studies (Rodrguez 2013 and Siersema 2014) indicating sustained reductions in oesophageal exposure a year after implant. One of the potential benefits of the procedure is virtually no dissection or disruption of the anatomy at the gastro-oesophageal junction which would be a big advantage in patients unable to undergo a fundoplication (eg previous sleeve gastrectomy), and no mechanical tightening of the GO junction (as occurs with laparoscopic fundoplication or LINX device insertion). This would therefore be a very interesting option to try in patients with severely compromised oesophageal motility in whom traditional antireflux surgery may well increase the risk of severe dysphagia. It does also seem to have an excellent safety record so far though the number of devices inserted so far is limited.	Thank you for your comment which identifies certain groups of patients where you feel this treatment may have a particular role. The committee noted the US sham-controlled trial, and your comments about the safety profile. Please also refer to response to comment 1.

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15	Consultee 5 British Society of Gastroenterology Chair of the BSG Oesophageal Section Committee	**General comment**	Unfortunately I've tried twice to access the draft recommendations via the link below (yesterday and today) and have both times been frustrated by a NICE Server error.	Thank you for your comment and for notifying us of a website access problem during consultation. Following the Consultee's comment, an administrative error was identified during the consultation process and stakeholders may not have been able to comment. A second period of consultation was run to ensure that all consultees were able to comment on the draft guidance.
16	Consultee 5 British Society of Gastroenterology Chair of the BSG Oesophageal Section Committee	**1**	I understand however that NICE are proposing to recommend this procedure for research only, whereas I would wish to support a 'special arrangements' recommendation so that there is the opportunity for selected patients (eg the types of cases outlined above) to be offered this procedure, rather than wait for RCT evidence. I would have thought that the results of observational study demonstration of efficacy in the medium term, and safety would support this.	Thank you for your comment. The Committee considered this comment but decided not to change the main recommendations. Section 1.2 of the guidance now states that 'NICE encourages clinicians to enter patients into controlled clinical trials. These could include crossover and cohort studies which would allow inclusion of patients for whom other surgical options are unsuitable.'
17	Consultee 6 Royal College of Physicians	**General comment**	Please take this email as confirmation that the RCP wishes to endorse the comments submitted by the BSG for this consultation. I would be grateful if you could confirm receipt.	Thank you for your comment.

SECOND CONSULTATION				
Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
18	Consultee 3 Manufacturer and overseas healthcare professional	**1**	I would like to thank you for the opportunity to respond formally on behalf of EndoStim Inc. on proposed guidance for electrical stimulation of the lower oesophageal sphincter for treating GORD. I am a [redacted] I have also been involved with Health Technology Assessment in the past ([redacted]) and know the rigours of the HTA reviews. The proposed recommendation of 'research only' is too restrictive and would significantly affect the access of GORD patients to this very safe and highly effective therapy. A 'special arrangements' recommendation would be more appropriate. Access to this therapy should be available on a case-by-case basis to patients who are not well treated with maximal medical therapy and do not want—or cannot have—traditional antireflux surgery for a multitude of reasons and continue to suffer very significant symptoms.	<u>Please note that this comment replaces the previous comments sent by the Consultee during the first round of consultation.</u> Thank you for your comment. It is not within the remit of the IP programme to determine what treatments are or are not made available by the NHS. The Committee considered this comment but decided not to change the main recommendations. Section 1.2 of the guidance now states that 'NICE encourages clinicians to enter patients into controlled clinical trials. These could include crossover and cohort studies which would allow inclusion of patients for whom other surgical options are unsuitable.'

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19	Consultee 3 Manufacturer and overseas healthcare professional	**4**	I am in a unique position to have knowledge of the most up-to-date data on electrical stimulation of the LOS including information about its efficacy in highly unique patient populations who other than EndoStim have no good options for treatment of their GORD. A paper by Kappelle W et al. describing the interim results of an n = 42 multicentre trial of electrical stimulation therapy of the lower oesophageal sphincter for refractory gastro-oesophageal reflux disease has now been published (Kappelle WF et al. Electrical stimulation therapy of the lower oesophageal sphincter for refractory gastro-oesophageal reflux disease – interim results of an international multicenter trial. Alimentary Pharmacology and Therapeutics July 8 2015, doi:10.1111/apt.13306). This publication provides significant new data collected from 10 additional sites worldwide (including one site in the UK) amongst multiple operators validating the safety and efficacy of EndoStim LOS stimulation therapy in reflux patients who are not satisfied with medical therapy with proton pump inhibitors. Results are reported for 41/42 (97.6%) enrolled patients.	Please note that this comment replaces the previous comments sent by the Consultee during the first round of consultation. Thank you for your comment. The Kappelle (2015) paper has been added to the main extraction table (Table 2).

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			In respect of efficacy, Kappelle and colleagues report that GORD-HRQL improved significantly, and oesophageal acid exposure normalised. Of the 42 enrolled patients, 37 (88.1%) were off PPI at 6 months and the mean acid exposure time was <5% in 35 patients (85%). At 6 months post-procedure, three SAEs had been reported: one device-related: an asymptomatic lead erosion was encountered at the 6-month endoscopy in a patient implanted with an investigational lead with a 5-mm electrode. Treatment consisted of explant of the IPG and lead, followed by fundoplication performed during the same procedure; one procedure-related: a trocar perforation of the small bowel, which occurred during the implant procedure and was successfully repaired laparoscopically. The device was prophylactically removed immediate post-op, no therapy was delivered and the patient recovered fully; a case of paroxysmal atrioventricular nodal re-entrant tachycardia several months after the procedure. Based on the sequence of events, the stimulation parameters, and the distance of the electrodes from the heart, the event was considered not to be device- or stimulation-related by the treating cardiologist.	

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			Kappelle and colleagues conclude that the results show that the procedure has an acceptable safety record and good short-term efficacy in GORD patients who are partially responsive to PPI therapy. They consider that "…A remarkable reduction in regurgitation symptoms, without the risk of intervention-requiring dysphagia may prove to be an advantage compared with other anti-reflux procedures." A copy of the paper is attached for ease of reference. The Committee should include the Kappelle paper in the evidence base it uses to determine its final advice to NICE.	

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Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
20	Consultee 3 Manufacturer and overseas healthcare professional	**4**	In respect of the Rodriguez n = 25 trial whose results are included in the present overview, an abstract has been published by Rodriguez et al (S080. Electrical Stimulation Therapy (EST) of the Lower Oesophageal Sphincter (LES) Is Successful in Treating GORD – Long- Term 3 Year Results. Surg Endosc (2015) 29:S340). A copy of the abstract is attached. A manuscript is currently in press and will be published in Surgical Endoscopy within the next 30 to 60 days. The cohort of patients who completed the 2-year open-label trial are being followed up over a 5-year period as part of a registry study. The abstract reports the results of this cohort at 3-year follow-up. 18/25 (72%) of patients completed a 3-year evaluation. Three patients were not receiving stimulation at 3 years. Results in the other 15 patients confirm that the significant improvement in GERD- HRQL and oesophageal pH was maintained at three years. 14/15 (93.3%) reported cessation of regular PPI use, a remarkable result in a cohort of patients whose symptoms were resistant to optimal medical therapy. Eleven of fifteen (73%) patients had normalised their distal oesophageal acid exposure at three years. All remaining patients had improved their distal oesophageal acid exposure by between 39% and 48% from baseline.	Please note that this comment replaces the previous comments sent by the Consultee during the first round of consultation. Thank you for your comment. The Rodriguez (2015) paper has been added to the main extraction table (Table 2).

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Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
		4	No unanticipated device- or stimulation-related adverse events or untoward sensations were reported between the 2- and 3-year follow-up period. There were no complaints of dysphagia. The authors conclude that the procedure is safe and effective for treating GORD over a 3-year period.	

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Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
21	Consultee 3 Manufacturer and overseas healthcare professional	**General comment**	The Committee should postpone further consideration of this procedure for a short period to allow inclusion of the 3-year results of the n = 25 trial in the evidence base it uses to determine its final advice to NICE. The 4-year results with LOS stimulation show a similar profile and is expected to be published within the next 60 days as a supplement to the Surgical Endoscopy paper. The Committee should postpone further consideration of this procedure for a short period to allow inclusion of the 4-year results of the n = 25 trial in the evidence base it uses to determine its final advice to NICE.	Please note that this comment replaces the previous comments sent by the Consultee during the first round of consultation. Thank you for your comment. The Rodriguez (2015) paper has been added to the main extraction table (Table 2). The paper with a 4-year follow-up has not been accepted for publication yet; therefore it is not considered adequate to support decisions on efficacy.

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Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
22	Consultee 3 Manufacturer and overseas healthcare professional	**4**	The figure below shows the cumulative results on oesophageal acid control from all available data of patients treated in our clinical trials. [Graph]	Please note that this comment replaces the previous comments sent by the Consultee during the first round of consultation. Thank you for your comment. The Consultee refers to a graph from a study which has not been published yet. The NICE IP Methods Guide highlights that efficacy outcomes from non-published studies are not normally presented to the Committee, unless they contain important safety data.
23	Consultee 3 Manufacturer and overseas healthcare professional	**4**	The results of the two published trials are consistent in demonstrating both statistically significant and clinically meaningful improvement in all major GORD patient outcomes. Both trials revealed a significant and comparable improvement in oesophageal acid exposure, out to 3 years (n =25) and 6 months (n = 42), respectively with almost two-thirds of the patients showing either normalisation or > 50% improvement in their distal oesophageal acid exposure. Normalisation of proximal oesophageal acid exposure has been reported in 100% of patients at 2 years. Oesophageal acid exposure is the hallmark feature of GORD and the most objective and robust biomarker for this disease. Elimination of abnormal oesophageal acid exposure conclusively confirms successful control of the disease.	Please note that this comment replaces the previous comments sent by the Consultee during the first round of consultation. Thank you for your comment. The Rodriguez (2015) and the Kappelle (2015) papers have been added to the main extraction table (Table 2).

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<tr><th colspan="4">SECOND CONSULTATION</th></tr>
<tr><th>Com. no.</th><th>Consultee name and organisation</th><th>Sec. no.</th><th>Comments</th><th>Response
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<tr><td>24</td><td>Consultee 3
Manufacturer and overseas healthcare professional</td><td>4</td><td>The most unique feature of LOS electrical stimulation is its safety and tolerability and
paucity of long-term side-effects. In 67 patients in clinical trials whose results have been
reported to date, only two serious procedure- or device-related AEs have been observed.
This compares very favourably to SAE rates of 5-15% with traditional antireflux surgery
and significant long-term complications (see graphic below).
Table 1. Prevalence of Medical and Surgical Complications of Antireflux Surgery
Mortality (<30 days) 1% or less
Perioperative and immediate postoperative morbidity 8%–17%
Open conversion rate 0%–24%
Early postoperative complications
Bowel perforation 0%–4%
Bleeding and splenic injury <1%
Pneumothorax 0%–10%
Severe postoperative nausea and vomiting 2%–5%
Late postoperative complications
Gas-bloat syndrome 1%–85%
Dysphagia
Early 10%–50%
Late 3%–24%
Diarrhea 18%–33%
Recurrent heartburn 10%–62%
Need for revisional surgery
Laparoscopic Nissen fundoplication 0%–15%
Laparoscopic Toupet fundoplication 4%–10%
Source: Richter JE. Clin Gastroenterol Hepatol. 2013 May; 11(5): 465-71</td><td><u>Please note that this comment replaces the previous comments sent by the Consultee during the first round of consultation.</u>

Thank you for your comment.

The Committee noted the published data on long-term outcomes including side effects. The Committee noted the adverse event rates with traditional antireflux surgery. The IP programme does not assess the efficacy and safety of comparator interventions.</td></tr>
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25	Consultee 3 Manufacturer and overseas healthcare professional	**4**	The long-term effectiveness of this procedure is also being seen in the international postmarketing registry which is collecting data prospectively from patients treated outside clinical trials. Results from this registry study were accepted and will be presented at the October 2015 United European Gastroentrology Week (UEGW) in Barcelona. Attached is the accepted abstract. Our global clinical experience shows SAE rates < 2% which is far superior to traditional antireflux surgery.	Please note that this comment replaces the previous comments sent by the Consultee during the first round of consultation. Thank you for your comment. The Endostim registry data have not been published yet so they are not considered adequate to support decisions on efficacy unless they contain important safety data.
26	Consultee 3 Manufacturer and overseas healthcare professional	**4**	Additionally, a paper (attached) summarizing post-hoc analysis of the single centre trial by Prof. Edy Soffer is currently in review for publication in World Journal of Gastroenterology. Publication is expected within 60-90 days. The trial demonstrated that LOS stimulation was equally effective in controlling GERD symptoms and oesophageal acid exposure in patients with partial response to PPI compared to those with adequate response to PPI. These partial PPI responders are the target EndoStim population.	Please note that this comment replaces the previous comments sent by the Consultee during the first round of consultation. Thank you for your comment. The paper from E. Soffer has not been accepted for publication yet; therefore it is not considered adequate to support decisions on efficacy.

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27	Consultee 3 Manufacturer and overseas healthcare professional	**4**	Another unique feature of LOS electrical stimulation therapy is its non-disruptive approach to LOS function restoration which does not affects LOS relaxation or oesophageal body function. This phenomenon has been consistently documented in thousands of high resolution manometry swallows, the gold-standard test for evaluation of oesophageal function. This unique attribute allows EndoStim to treat some specific patient populations whose needs are not adequately met by traditional antireflux surgery. Such populations include patients with severe oesophageal dysmotility including aperistalsis, post-myotomy GORD and post lung-transplant GORD which is commonly associated with severe oesophageal dysmotility. Another rapidly growing severe GORD population without effective clinical options is those patients who suffer from GORD after laparoscopic sleeve gastrectomy (LSG): these patients are not candidates for traditional antireflux surgery. With the exception of LSG, the evidence for efficacy of LOS stimulation for these unique indications is highly unlikely to come from clinical trials and can only be obtained from its use in routine clinical practice. Many such patients are currently safely and successfully treated around the world using LOS stimulation and the results continue to be objectively documented.	Please note that this comment replaces the previous comments sent by the Consultee during the first round of consultation. Thank you for your comment. Please refer to responses to comments 1 and 5.

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			We are continuing to accumulate more evidence of safety and efficacy of LOS stimulation in both clinical trials and in clinical practice. However, we believe that there is already adequate evidence for the safety of this procedure in > 200 patients treated with longest follow-up approaching 5 years. A similar safety profile is seen in patients undergoing gastric electric stimulation which has very similar technical and treatment characteristics. The significant and sustained improvement in oesophageal acid exposure, the hallmark of GORD, is a strong evidence for efficacy of LOS stimulation in long-term control of GORD. A 'research only' recommendation will deny many GORD sufferers in need of this procedure, given the lack of effective treatment options for the group for whom the procedure is intended. The evidence reviewed by the Committee, together with the new papers by Kappelle, Rodriguez and Soffer merit a 'special arrangements' recommendation so that this highly effective therapy can be offered to carefully selected GORD patients in the UK for whom medical therapy is unsatisfactory and who are not candidates for traditional antireflux surgery or do not wish to have such surgery.	

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28	Consultee 7 Overseas healthcare professional	**General comment**	I am [redacted] at the [redacted]. I have performed over a thousand surgeries for GERD and have worked with many device-based therapies for GERD. Since 2013, I have personally performed about 30 EndoStim implant procedures under standard care setting with excellent safety and efficacy outcomes with the longest patient follow-up now over two years. I am also an investigator in the ongoing international multi-center registry study. To the best of my knowledge, the device has been used in regular clinical practice in Germany by at least 10 hospitals who also participate in the international multi-center registry study and the system is covered under the NUB reimbursement program.	Thank you for your comment which outlines your own clinical experience and the use of this procedure in Germany.

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29	Consultee 7 Overseas healthcare professional	**1**	Based on the data collected in my own clinical experience I believe that EndoStim therapy is a significant advance in GERD management and is serving an important and expanding role in addressing the therapy gap in management of GERD patients. I see EndoStim therapy, in my practice, as an excellent complement to existing surgical anti-reflux techniques which are specifically useful for patients who are not a good fit for traditional anti-reflux surgery. Those include, for example: - Patients who underwent sleeve gastrectomy for weight loss and developed severe reflux. This group can no longer undergo fundoplication because of the anatomical alteration done during the sleeve gastrectomy procedure - Patients with esophageal dysmotility which could at high likelihood of suffering from dysphagia post-op - Patients with small or no hiatal hernia who are worried about the side effects and complications of fundoplication and prefer a reversible procedure - High risk patients who suffer from severe respiratory problem (for example post lung-transplant patients) in whom I prefer to avoid the major anatomical change associated with fundoplication	Thank you for your comment which outlines your own clinical experience and identifies certain groups of patients where you feel this treatment may have a particular role.

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30	Consultee 7 Overseas healthcare professional	**General comment**	Most importantly, the fact that the EndoStim implant procedure preserves the natural anatomy, is reversible and seems to avoid the typical side effects of fundoplication makes it an excellent first line therapy. The growing concern with long-term risks associated with life-long use of acid suppressive medications such as the proton pump inhibitors creates a growing need for such a less invasive solution.	Thank you for your comment. The NICE IP programme considers the safety and efficacy of procedures, and makes recommendations as to what arrangements should be in place for clinicians wishing to do the procedure. It does not produce clinical guidelines which determine the place of this procedure in clinical practice in the UK or elsewhere.
31	Consultee 7 Overseas healthcare professional	**4**	The long term, three year esophageal acid-exposure results reported in the first pilot study support a true anti-reflux mechanism and were recently also corroborated by the results of the international multi-center trial as well with my own patients (which I expect to publish later this year). An interview with one of our patients can be found at https://www.youtube.com/watch?v=EIDj5QHH6g8 .	Thank you for your comment. Tthe Rodriguez (2015) and the Kappelle (2015) papers have been added to the main extraction table (Table 2). The Committee very much welcomes hearing from patients who have undergone this procedure and considers their experience and views in their deliberations.

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32	Consultee 7 Overseas healthcare professional	**1**	To summarize, I encourage you to provide access to this therapy for well selected patients in the UK in standard practice, preferably as part of a registry study. In cases were fundoplication is not an appropriate option EndoStim should be available also outside a clinical trial.	Thank you for your comments. The NICE IP programme considers the safety and efficacy of procedures, and makes recommendations as to what arrangements should be in place for clinicians wishing to do the procedure. It does not produce clinical guidelines which determine the place of this procedure in clinical practice in the UK or elsewhere. The Committee considered this comment and decided to change section 1.2 of the guidance to: 'NICE encourages clinicians to enter patients into controlled clinical trials. These could include crossover and cohort studies which would allow inclusion of patients for whom other surgical options are unsuitable. These should provide a clear description of patient selection, and details of adjunctive medical and surgical treatments. Outcomes should include GORD symptoms, quality of life and objective measurements of gastric reflux. Efficacy, device durability, the need for surgical treatment for GORD in the longer term (at least 2 years) and all complications should be reported. NICE may update the guidance on publication of further evidence.'

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."