Interventional procedure overview of laparoscopic insertion of an inactive implant for gastro-oesophageal reflux disease

Contents

Table 1 Abbreviations

Abbreviation	Definition
GERD-HRQL	Gastro-oesophageal reflux disease – health related quality of life questionnaire
GORD	Gastro-oesophageal reflux disease
HH	Hiatus hernia
IOM	Ineffective oesophageal motility
LOS	Lower oesophageal sphincter
OMD	Oesophageal motility disorder
PPI	Proton pump inhibitor

Indications and current treatment

Gastro-oesophageal reflux disease (GORD) is when stomach acid and other contents flow back (reflux) into the oesophagus (food pipe). This can cause symptoms such as heartburn, chest pain, hoarseness, difficult swallowing, cough, wheezing and dental erosions, and can impair quality of life. GORD can occur when the lower oesophageal sphincter (LOS, the ring of muscle at the bottom of the oesophagus) does not work properly, or if the LOS moves above the diaphragm into the thoracic cavity. In some cases, part of the top of the stomach (the fundus) can also push up through the diaphragm. This is called a hiatus hernia (HH).

The standard treatments for symptomatic GORD are lifestyle modification and drug therapy. If these do not work or are not appropriate, people could be offered surgery. One option is laparoscopic insertion of a magnetic ring at the gastro-oesophageal junction (see NICE's interventional procedures guidance). Another surgical option is laparoscopic fundoplication, a procedure that involves wrapping the top part of the stomach around the lower oesophagus (see NICE's guideline on the investigation and management of gastro-oesophageal reflux disease and

dyspepsia). For those with more complex cases, such as GORD with oesophageal motility disorders, there are limited treatment options.

Unmet need

GORD is usually a chronic condition that affects between 10% and 30% of people in developed countries. In England, according to Hospital Episode Statistics (admitted patient care), there were approximately 98,102 finished consultant episodes for people with a primary diagnosis of GORD in 2022 to 2023.

Unlike other options, this procedure does not involve implanting materials in the LOS or a full fundoplication around the LOS. This may be beneficial because encircling or implanting materials into the LOS can lead to side effects such as swallowing difficulties (dysphagia), painful swallowing (odynophagia) and inability to vomit or belch, which impact quality of life.

This procedure could provide a minimally invasive option for people with chronic GORD whose symptoms have not responded adequately to lifestyle modification and drug therapy. There are also limited treatment options for those with more complex cases, such as those with oesophageal dysmotility (such as IOM disorders), larger HH or preoperative dysphagia. This is because people in this group may have a higher risk of postoperative dysphagia, so are often treated more conservatively.

What the procedure involves

The procedure involves placing an implant on the outside of the upper part of the stomach wall. The procedure is done using keyhole (laparoscopic) surgery. The implant is considered inactive because it does not move or release any chemical or biological substances. The aim is to keep the LOS in the abdominal cavity and

maintain the angle between the stomach entrance and the LOS, to restore normal anatomy.

For the device implant procedure, a section of the upper part of the stomach wall is attached to the LOS. Then, at the top of the stomach (fundus) and parallel to the oesophagus, the device is sewn into a pocket of fundus wall (on the outside of the stomach) and sutured in place. This should be above the LOS. The device is made from medical-grade silicone and is inactive.

This is a laparoscopic procedure done under general anaesthesia and includes repair of a hiatus hernia if present.

Outcome measures

The main efficacy outcomes include:

- Gastro-oesophageal reflux disease – health related quality of life (GERD-HRQL) questionnaire score
- Heartburn subscore (within GERD-HRQL questionnaire)
- Regurgitation subscore (within GERD-HRQL questionnaire)
- Dysphagia reduction (within GERD-HRQL questionnaire)
- Odynophagia
- Proton pump inhibitor (PPI) usage
- 24-hour pH monitoring, mean reduction in percentage of time in a pH less than 4
- Gas bloating subscore (within GERD-HRQL questionnaire)
- Patient satisfaction subscore (within GERD-HRQL questionnaire)

Safety measures

- Clavien–Dindo scale

The measures used are detailed in the following paragraphs.

GERD-HRQL score

The GERD-HRQL questionnaire produces a total score to measure and grade the severity of GORD. It is a patient-reported outcome measure which includes questions and subscores on symptoms such as heartburn and regurgitation.

There are 2 versions of the questionnaire that have been used by different studies. In one version, the highest possible score is 50, indicating the worst symptoms, and the lowest possible score is 0, indicating no symptoms (Velanovich 1996). This version is used in Bjelovic (2020) and Harsanyi (2024).

In the second version of the questionnaire, the highest possible score is 75, indicating the worst symptoms, and the lowest possible score is 0, indicating no symptoms. This version is used in Fringeli (2024a, 2024b, 2024c).

Heartburn subscore

The heartburn subscore can be calculated from the GERD-HRQL questionnaire. The highest possible score is 30, indicating the worst heartburn symptoms, and the lowest possible score is 0, indicating no heartburn symptoms. Scores of less than 12 and each individual question not exceeding 2 indicates no heartburn.

Regurgitation subscore

The regurgitation subscore can be calculated from the GERD-HRQL questionnaire. The highest possible score is 30, indicating the worst regurgitation symptoms, and the lowest possible score is 0, indicating no regurgitation symptoms. Scores of less than 12 and each individual question not exceeding 2 indicates no regurgitation.

Foregut questionnaire

The Foregut questionnaire is a symptom-oriented questionnaire used to measure the severity and frequency of dysphagia, heartburn and regurgitation. The questionnaire was used to assess regurgitation scores in 2 papers (Bjelovic 2020 and Harsanyi 2024). The grading system ranges from 0 to 4, where 0 indicates no regurgitation and 4 indicates very severe continuous regurgitation (Makris 2012).

Dysphagia

The GERD-HRQL questionnaire has a question relating to dysphagia. Scores can be between 0 and 5. 0 indicates no symptoms and 5 indicates that symptoms are incapacitating.

Patient satisfaction relating to GORD

In the GERD-HRQL questionnaire people were asked how satisfied they were with their current quality of life relating to GORD. Possible responses include ‘satisfied’, ‘neutral’ or ‘dissatisfied’.

Clavien–Dindo scale

The Clavien–Dindo scale is a classification system used for grading adverse events in surgical procedures. It is graded from 1 (mild) to 5 (death).

Evidence summary

Population and studies description

This interventional procedures overview is based on a total of around 130 people from 3 studies across 6 papers. The studies include 1 prospective observational study (Bjelovic 2020) and 2 retrospective cohort studies (Feka 2024 and Fringeli 2024c). The remaining 3 articles include 2 retrospective chart reviews associated with Fringeli (2024c), (Fringeli, 2024a and 2024b; further analysis on subgroups

within the sample in Fringeli [2024c]) and 1 follow-up article from the Bjelovic (2024) study (Harsanyi 2024). All participants in all studies had the procedure. This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 3 studies as the key evidence in table 2 and table 3.

The prospective study was a single-arm, multicentre study of 50 people by Bjelovic (2020). This was based in Hungary, Serbia and Switzerland. Follow-up time was 6 weeks, 3 months, 6 months and 12 months. The aim of the study was to assess the safety and effectiveness of the procedure in those experiencing GORD, with small HH and no IOM. It was also to obtain CE marking. The 4-year follow-up results are reported in Harsanyi (2024). There are 2 unpublished papers for the 3-year and 5-year follow-up results. These manuscripts have not yet been accepted for publication so cannot be included in this overview.

The first retrospective observational single-arm study of 40 people was published by Feka (2024). This is a multicentre trial from 2 hospitals, one based in the UK and the other in Austria. Follow-up time was 3 months. The aim of this study was to assess safety and effectiveness in those experiencing GORD and who have IOM.

The second retrospective cohort study and 2 retrospective chart reviews by Fringeli (2024a, 2024b, 2024c) were based in Switzerland. These studies include a significant overlap of people, but with a variation in follow-up length and clinical characteristics.

The retrospective cohort study by Fringeli (2024c) included 40 people who were followed up for 3 months. The study included those with HH less than 10 cm in size. Some people (77.5%) had IOM but not all. Fringeli (2024c) reports the initial overall analysis of this study. Following this, further analysis was carried out in 2

subgroups of 20 people and 30 people in 2 retrospective chart reviews (Fringeli 2024a, 2024b).

The Fringeli (2024a) study is a retrospective chart review that included 20 people who had IOM and a 12-month follow-up. The population included in this review were also part of the Fringeli (2024c) study. The aim of the review was to assess effectiveness and safety outcomes in this group of people.

The second retrospective chart review included 30 people (Fringeli 2024b). The aim of the study was to assess the safety and effectiveness of the procedure in those with large HH (between 4 cm and 10 cm in size). Follow-up time was up to 6 months after the procedure. They almost entirely overlap with those in the Fringeli (2024c) study as well as some in the Fringeli (2024a) study.

Table 2 presents study details.

Figure 1 Flow chart of study selection

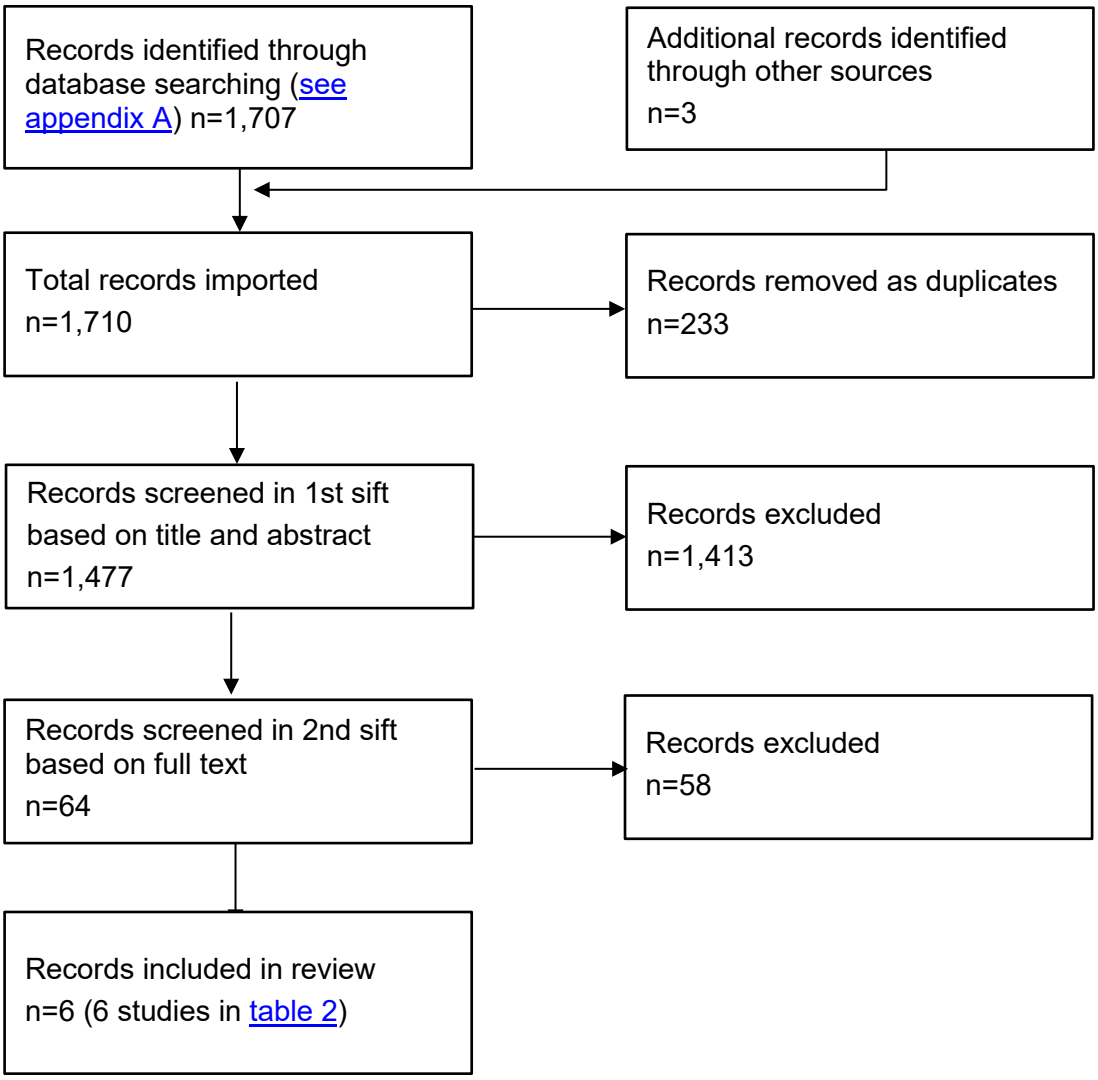

Table 2 Study details

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow-up
1	Bjelovic, 2020 Hungary, Serbia, Switzerland	N=50 (n=47 at 1-year follow-up) Mean age: 51.5 years (SD 11.8). Female: 22 (44%)	Prospective, single-arm, multicentre study (Surgery performed at 4 hospitals)	• People aged 18 to 75 • Documented typical GORD symptoms, present for more than 6 months, that respond to PPIs • Requires daily PPI • Subject has a 24-hour pH monitoring proven GORD performed while off any anti-reflux medication or after discontinuation for at least 7 days before testing • Total distal oesophageal pH must be more than 4 for more than 4.5% of the time during a 24-hour monitoring **Exclusion criteria include:** • A history of gastroesophageal surgery • HH larger than 3 cm • Oesophageal dysmotility disorder (IOM)	RefluxStop device	6 weeks, 3 months, 6 months, 12 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow-up
				• Oesophagitis grade C or D, according to the Los Angeles classification. The Los Angeles classification system is a method for diagnosing and grading reflux oesophagitis. There are 4 grades, A to D, with grade A indicating the most mild and grade D indicating the most severe oesophagitis. • BMI over 35 kg/m^2		
2	Harsanyi, 2024 (follow-up of Bjelovic 2020)	N=44 at 4 years Baseline characteristics same as described in Bjelovic (2020)	Prospective, single-arm, multicentre study (Surgery performed at 4 hospitals)	Inclusion criteria same as described in Bjelovic (2020)	RefluxStop device	Effectiveness results: 4 years. Safety results: years 1 to 4 and at any additional visits
3	Feka, 2024 Austria and UK	N=40 Female: 15 (37.5%) Mean age: 48.93 years (SD 4.59)	Retrospective, observational, single-arm study	• People aged 18 years and older • More than 1 year of GORD • History of PPI usage • Have IOM (as diagnosed according to criteria according to Chicago classification v4.0).	RefluxStop device	3 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow-up
				The Chicago classification version 4.0 is a system for classifying oesophageal motility disorders • GORD diagnosis via 24-hour impedance pH testing • BMI less than 35 m^2/kg **Exclusion criteria include:** • History of oesophageal or gastric malignancies • Oesophageal strictures or stenosis		
4	Fringeli, 2024c Switzerland	N=40 Female: 16 (40%) Mean age: 60 years (SD 51 to 71) Mean BMI (kg/m^2): 26.3 (24.6 to 28.9)	Retrospective single-arm cohort study	Included all people who underwent surgery between May 2020 and April 2022. To be eligible for surgery people must: • be aged 18 years or older • with documented GORD or typical symptoms of GORD • with HH smaller than 10 cm • no previous gastric or oesophageal surgery	RefluxStop device	4 weeks, 3 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow-up
				• no long-segment Barrett's oesophagus		
5	Fringeli, 2024a Switzerland (subgroup of Fringeli 2024c)	N=20 Female: 10 (50%) Mean age: 57.4 years (SD 12.6). Has IOM Mean BMI (kg/m^2): 26.5 (SD 4.8)	Retrospective chart review	This review included the first cohort of people with the criteria below who had RefluxStop in the Fringeli (2024c) study. • those with 12-month follow-up data • aged 18 years or older • with documented GORD • concurrent with IOM (identified via video-oesophagram with inefficient or slow emptying of the oesophagus or on manometry with less than 70% contractile waves or an amplitude of less than 30 mmHg) **Exclusion criteria include:** • HH larger than 10 cm • Long-segment Barrett's oesophagus • History of oesophageal or gastric surgery	RefluxStop device	4 weeks, 3 months, 12 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow-up
6	Fringeli, 2024b, Switzerland (subgroup of Fringeli 2024c)	N=30 Female: 14 (46.7%) Mean age: 61 years (SD 15) Has HH between 4 cm and 10 cm Mean BMI (kg/m^2): 26.8 (SD 4.3)	Retrospective chart review	This review included people with the criteria below, many of whom had RefluxStop in the Fringeli (2024c) study. • Those with 6-month follow-up data • Aged 18 years and older • With documented GORD • Require daily PPI • Diagnosed with a large HH (defined as an axial hernia length of 4 cm to 10 cm) • Diagnosis of HH was made preoperatively by gastroscopy, high-resolution oesophageal manometry or video-oesophagram **Exclusion criteria include:** • History of oesophageal or gastric surgery • Long-segment Barrett's oesophagus • HH larger than 10 cm	RefluxStop device	Day 1, 4 weeks, 3 months 6 months

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Bjelovic, 2020	**Primary efficacy outcome:** **GERD-HRQL scores (0 to 50 points)** Baseline: 28.8 (SD 7.3) 6 months: 3.4 (SD 6.0; p<0.0001) – improvement of 88%. 45 out of 47 people had more than 50% improvement of GERD-HRQL total score at 6 months. 12 months: 44 people had more than 50% improvement in GORD symptoms compared with baseline. 3 people had less than 50% improvement. **Secondary efficacy outcomes:** **Median heartburn subscores:** Median baseline: 4.0 (range 0 to 5) Median 12 months: not provided **Daily regurgitation (Foregut questionnaire):** Baseline: 88% (out of 50 people) had daily regurgitation 12 months: 97.8% (out of 47 people) had no or minimal occasional episodes of regurgitation. Statistically significant reduction (p<0.001).	**Primary safety outcome:** **No serious device-related adverse events** No serious adverse events related to RefluxStop device reported during the 6-month and 1-year follow-up. **6 serious procedure-related adverse events** Occurred in 4 people: • Infection – included both mediastinal abscess and empyema, probably due to the infected mediastinal haematoma • Bleeding • Release of fundoplication sutures occurred in 1 person at 6 months. They had a second operation which was successful. **Secondary safety outcome:** **No device-related adverse events** No non-serious adverse events related to RefluxStop device reported during the 6-month and 1-year follow-up. No device deficiencies and no removal of device. **Procedure-related adverse events**

First author, date	Efficacy outcomes	Safety outcomes
	Changes in dysphagia Baseline: 15 (30%) people had dysphagia (n=50) 6 months: 11 (22%) people had resolved dysphagia. 4 (9%) people continued minimal to moderate dysphagia (p<0.001; n=47) 12 months: 2 (4%) people reported minimal dysphagia (p<0.001; n=47) **Odynophagia** Baseline: 13 (26%) people had odynophagia (n=50) 6 months: 0 (0%) people (p<0.001; n=47) 12 months: 1 (2%) person (p<0.001; n=47) **PPI medication** Baseline: Everyone took daily PPI medication 6 months: 0 people took PPI. 12 months: 1 person took PPIs (device position was too low) **24-hour pH monitoring** This was measured as the mean percentage of overall time (within 24 hours) with a pH less than 4. Baseline: 16.35%	**Postoperative dysphagia** No new cases of dysphagia or odynophagia at 6 months or 12 months

First author, date	Efficacy outcomes	Safety outcomes
	6 months: 0.8% (p<0.001). 98% of people had a normal 24-hour pH result. This is a 95% improvement of mean value. **Gas bloating (those with a score above 2 in the related GERD-HRQL survey):** Baseline: 84%, median: 4.0 (0 to 5) 12 months: 19% (p<0.0001), Median: not provided At 12 months, gas bloating: Disappeared: 30 people Improved: 7 people Unchanged: 2 people Worsened: 0 people **Patient satisfaction relating to GORD:** Baseline: 1 (2%) person was satisfied. 45 (90%) were dissatisfied 6 months: 44 (94%) people were satisfied, 2 (4%) were dissatisfied 12 months: 43 (91%) people were satisfied, 1 (2%) was dissatisfied. 2 (4%) further people were dissatisfied, and the authors suggest that this was unrelated to GORD due to their normal 24-hour pH monitoring results at 4-year follow-up.	

First author, date	Efficacy outcomes	Safety outcomes
	5 out of 6 people who did not have 4-year follow-up data were satisfied at their last visit. Further information was not provided.	
Harsanyi, 2024 (Follow-up from Bjelovic 2020 paper)	At 4 years, follow-up data were available in 44 out of 50 people. In addition, they reported outcomes from 3 people at 3 years carried forward. **Primary efficacy outcome:** **Median GERD-HRQL score (IQR) (0 to 50 points):** Baseline: 29.5 (24 to 33) 4 years: 3.0 (0 to 9.2) This is a 90% reduction compared with baseline. **Secondary efficacy outcome:** **Daily regurgitation (Foregut questionnaire):** Baseline: 43 out of 50 (86%) people had daily regurgitation. At 4 years they report the inverse: 42 out of 44 (95.5%) had no or minimal regurgitation. 3 people with missing 4-year follow-up data reported no regurgitation at 3 years. So 45 out of 47 had no or minimal regurgitation. Everyone experienced improvement in regurgitation.	**Missing data:** • 1 person died from COVID-19 • 2 people missed 4-year follow-up • 1 person terminated within the first year of the study after a broken needle was left subcutaneously. This was removed under local anaesthesia. They terminated dissatisfied, with a high GERD-HRQL score, no regular daily PPI at 6 months and no regurgitation. They refused 24-hour pH testing. • 2 people terminated within the first year of study. Both were satisfied, did not take PPIs had a low average GERD-HRQL score of 2.5, no regurgitation. **Primary safety outcomes:** **No serious device related adverse events** • No adverse events related to RefluxStop device • No device deficiencies • No migration or erosion • No oesophageal dilation required

First author, date	Efficacy outcomes	Safety outcomes
	Changes in dysphagia **1 report of dysphagia:** Baseline: 1 person reported severe dysphagia (score 5) 3 years: Same person reported mild dysphagia at 3-year follow-up (score 2). Their dysphagia score was improved from baseline. 46 out of 47 people reported no dysphagia. **Changes in odynophagia** 0 reports of odynophagia **PPI use:** Baseline: Everyone used daily PPIs (n=50) 4 years: 2 out of 44 (4.5%) people used daily PPIs. Both had normal 24-hour pH monitoring results. **Gas bloating** Baseline: (data not provided, but reported in Bjelovic 2020) 4 years: • Disappeared: 30 (68%) • Improved: 11 (25%) • Unchanged: 2 (5%) • Worsened: 1 (2%)	**2 serious procedure-related adverse events occurred following surgery which were reported in Bjelovic 2020:** 1. Infection with abscess 2. Haematoma Both treated to resolution. No other serious adverse events were reported in the follow-up period. **Postoperative dysphagia** No new cases of dysphagia or odynophagia at 4 years. **Secondary safety outcomes:** **No device related adverse event** **1 procedure related adverse event:** Recurrence of acid reflux symptoms in 1 person who had a 24-hour pH of less than 4. Device was found to be positioned too low. This position was categorised as a 'failure risk' after surgery and at 4 year follow-up. Events relating to dysphagia and odynophagia are reported in the efficacy outcomes section.

First author, date	Efficacy outcomes	Safety outcomes
	Patient satisfaction relating to GORD: Baseline: reported in Bjelovic 2020 4 years: 2 out of 44 (4.5%) were dissatisfied. Both had normal 24-hour pH monitoring results, suggesting that GORD was unlikely to be the reason for dissatisfaction	
Feka, 2024 (Austria and UK) Aim: assess safety and effectiveness in those with GORD and IOM	**Primary efficacy outcome:** **GERD-HRQL total score (they do not clarify which version of the questionnaire they used or range for scores)** Baseline (SD): 32.83 (5.08) 3 months (SD): 6.6 (3.71; p<0.001) **Secondary efficacy outcomes:** **Mean heartburn subscore** Baseline mean (SD): 17.4 (2.07) 3 months mean (SD): 3.83 (1.88; p<0.001) **Mean regurgitation subscore** Baseline mean (SD): 10.85 (2.85) 3 months mean (SD): 1.63 (1.68; p<0.001) **Changes in dysphagia (%)** Baseline: 4 (10%) people 3 months: 1 (2.5%) people (p-value not provided) **Percentage of people using PPIs daily**	**There were 2 (5%) serious adverse events** 1. 1 serious adverse event occurred in 1 person and was classified as Clavien–Dindo 3b in surgical severity. The newly reconstructed His angle and RefluxStop device had reherniated into the thoracic cavity and required revisional surgery at the first postoperative day. During the laparoscopic revision, the device was removed and a Dor fundoplication was performed. They believe it was due to high BMI causing high intra-abdominal pressure. 2. In 1 person, device migration occurred 1 month after surgery. They experienced epigastric pain for 3 days before the device was retrieved. The study suggests this could have been caused by a small haematoma where the device was implanted. **Postoperative dysphagia** No new cases of dysphagia at 3 months.

First author, date	Efficacy outcomes	Safety outcomes
	Baseline: 31 (77.5%) people 3 months: 5 (12.5%; p<0.001) people 35 (87.5%) people no longer required PPI **Patient satisfaction relating to GORD** Baseline: 40 (100%) reported dissatisfied or neutral. 0 reported satisfied. 3 months: 4 (10%) reported dissatisfied or neutral. 36 (90%) reported satisfied. Dissatisfaction reduction of 90%. P-value not provided. **Operative practice** Median hospital stay was 3 days	
Fringeli, 2024c Switzerland Aim: To assess safety and effectiveness outcomes	**Primary efficacy outcome:** Feasibility of the procedure, measured by the proportion of people who had the device implanted in the correct position. Everyone had the device implanted in the correct position. **Secondary efficacy outcomes:** **Median GERD-HRQL scores (0 to 75 points) (n=38)** Baseline (IQR): 35 (28.5 to 49) 3 months (IQR): 2 (0 to 3; p<0.0001) **Heartburn subscore**	**Secondary outcomes:** **Operative practice** Conversion to laparotomy, n (%): 1 (2.5%) Intraoperative complication, n (%): 1 (2.5%) **6 postoperative complications within 3 months graded to Clavien–Dindo classification system:** Grade 2: 1 (2.5%) Grade 3a: 3 (7.5%) Grade 3b: 2 (5%) **Description of postoperative complications:**

First author, date	Efficacy outcomes	Safety outcomes
	Statistically significant reduction (p<0.0001). Scores not provided (from figure 3) **Regurgitation subscore** Statistically significant reduction (p<0.0001). Scores not provided (from figure 3) **Changes in dysphagia** 3 months: The 20 people who had previously suffered from dysphagia showed a reduction in severity or complete resolution of symptoms. No p-values provided. **Patient satisfaction relating to GORD (n=38)** Baseline: 28 (73.7%) reported either dissatisfaction or neutral 3 months: 100% reported improvement No further figures or p-values provided. **Operative practice** Median operating time: 57.5 minutes (IQR, 51.75 to 64.25 minutes). Median hospital stay: 4 days (IQR 3 to 5). 3 months: RefluxStop device was in correct location in everyone. No device-related complications were observed.	1. 1 person underwent urgent laparoscopic reoperation the same day due to postoperative haemorrhage caused by dissection of the short gastric vessels at the fundus 2. 1 person reported persistent fatigue due to pericardial effusion 3. 1 person developed a trocar hernia in the epigastric area. They underwent direct open closure of the trocar hernia defect 4. 3 people had dysphagia. Events relating to dysphagia are reported in the efficacy outcomes section. No device-related complications or re-operations during 4-week and 3-month follow-up. **Postoperative dysphagia** The author reports no new onset of dysphagia at 3 months. They also report that after surgery 3 people (7.5%) had severe, persistent dysphagia with frequent vomiting and inability to eat a normal diet. Due to the severity of the symptoms, early dilations were performed 3 to 4 weeks following surgery. These people had IOM prior to surgery and 2 had preoperative dysphagia. 1 was new onset after the follow-up period of 3 months. Due to the severity of the symptoms they performed early dilations 3 to 4 weeks after

First author, date	Efficacy outcomes	Safety outcomes
		surgery. In 1 person 18 mm to 20 mm balloons were successful. The other 2 people required further endoscopic dilations with the endoflip balloon to 25 mm.
Fringeli, 2024a, Switzerland Aim: To assess safety and effectiveness in those with IOM There is overlap in people and their respective outcomes in this article and those in the Fringeli (2024c and 2024b article)	**Mean GERD-HRQL score (SD) (0 to 75 points):** Baseline SD: 40.7 (16.0) 3 months: 4.8 (8.3; p<0.001) 12 months: 5.7 (7.7; p<0.001) No worsening of GORD symptoms reported at 12-month follow-up in anyone. 12-month outcomes categorised as: Excellent: 13 people (65%) Good: 2 people (10%) Fair: 3 people (15%) Poor: 2 people (10%) Of the 2 people with poor outcomes: • 1 person had recurrence of GORD within 12 months. They attributed this to weight gain of 10 kg • 1 person had persistence of symptoms, particularly heartburn. They could not identify a cause and was considered multifactorial in nature	• 1 person (5%) required a second operation during 12-month follow-up, due to persistent left-sided thoracic pain, which was considered unrelated to the device. • 1 person (5%) had a procedural complication. An implant that had split into 5 parts and had migrated from its initial position. It is thought this was due to insufficient surgical closure of the passageway where the deployment tool was used to hold the device in place during the procedure. It was not due to pressure-induced tissue damage, so it is considered a procedural complication rather than device malfunction. • No device related reoperations or complications at surgery during 12-month follow-up • For 1 person, the procedure was converted to open surgery due to adhesions and bleeding when trying to establish access laparoscopically. They had had previous open surgery. Once bleeding was controlled, the intended procedure was performed as described in Methods.

First author, date	Efficacy outcomes	Safety outcomes
	Mean heartburn subscores (SD): Baseline: 17.4 (8.3) 12 months: 2.4 (3.7; p<0.001) **Mean regurgitation subscores (SD):** Baseline: 17.7 (7.5) 12 months: 1.6 (3.5; p<0.001) **Changes in dysphagia** Changes in scores for the whole cohort (n=20) were not statistically significant. 12 people experienced dysphagia before surgery. Mean baseline scores (SD): 2.7 (1.4) Mean 12-month scores (SD): 1.0 (1.0; p<0.005) **PPI usage:** 16 people were able to completely discontinue use of PPIs **Patient satisfaction relating to GORD** Baseline: 25% satisfied 12 months: 90% satisfied	**Postoperative dysphagia** • Among the 8 people without dysphagia before the procedure, 3 developed dysphagia after 12 months. Change in dysphagia scores for the 8 people were not statistically significant (p<0.075). • The 3 people (15%) who had dysphagia experienced persistent severe dysphagia requiring endoscopic dilation after surgery. 2 people had dysphagia before surgery and 1 person developed dysphagia after surgery. All 3 people had successful repeated endoscopic dilations with complete resolution of dysphagia.

First author, date	Efficacy outcomes	Safety outcomes
	Operative practice RefluxStop procedure was feasible in all 20 people. In everyone, video-oesophagram confirmed the device was in the right location and adequate reduction in HH. • Median operating time: 59.5 minutes (IQR 50.25 to 64 minutes). • Median hospital stay: 3.5 days (IQR 3 to 4 days)	
Fringeli, 2024b, Switzerland Aim: To assess safety and effectiveness in those with a larger HH (between 4 to 10 cm). There is overlap in people and their respective outcomes in this article and those in the Fringeli (2024c and 2024a article)	**Primary outcomes:** The RefluxStop procedure was feasible in everyone in the chart review. **Secondary outcomes:** **Mean GERD-HRQL total scores (SD; 0 to 75 points)** Mean baseline scores (SD): 37.6 (15.5) Mean 6-month scores (SD): 3.1 (5.4; p<0.001) 6-month outcomes (n=29) categorised as: Excellent: 26 people (89.7%) Fair: 1 person (3.5%) Poor: 2 people (6.9%) Both people with poor results showed improvement in symptoms.	**Primary outcomes:** **Device related complications** No device-related complications during 3- and 6-month follow-up. No device-related reoperations for anyone. **Secondary outcomes:** **Postoperative complications within 90 days** • 1 person experienced persistent fatigue at 4 weeks due to pericardial effusion. • 1 person had persistent dysphagia 12 weeks after operation and required endoscopic dilations **Postoperative dysphagia** Of the 15 people who did not have dysphagia at baseline, 10 had IOM (66.7%).

First author, date	Efficacy outcomes	Safety outcomes
	Mean heartburn subscores (SD) Baseline: 16.5 (8.1) 6 months: 1.1 (2.3; p<0.001) **Mean regurgitation subscores (SD)** Baseline:16.5 (7.2) 6 months: 0.9 (2.0; p<0.001) **Mean dysphagia subscores (SD)** Changes in subscores for the whole cohort were not statistically significant. At baseline, 15 (50%) people had dysphagia. Among them, 14 (93.3%) people had IOM. Mean dysphagia subscores of those with dysphagia at baseline (n=15) Baseline: 2.7 (1.5) 6 months: 0.6 (0.9; p<0.001) **Patient satisfaction relating to GORD** Baseline: 8 (27%) people were satisfied. 17 (57%) were dissatisfied 6 months: 28 (97%) people were satisfied, 0 (0%) were dissatisfied	New onset dysphagia occurred in 5 people. 4 people had no intervention and had changes in diet only. **Recurrence of hiatus hernia** 3 months: No recurrence of HH 6 months: 1 person had recurrence of HH (3.3%). The person had a large HH measuring 8 cm. It is thought to have been a consequence of severe vomiting from food poisoning. The upper third of the stomach and RefluxStop device had slipped through the hiatus. They received emergency surgery outside the institution to reposition the fundus and RefluxStop device. **Operative practice** • 29 out of 30 people: surgery was performed laparoscopically • 1 person had a procedure that was converted to open surgery, due to adhesions and bleeding. They had had open surgery previously

First author, date	Efficacy outcomes	Safety outcomes
	Operative practice • Median operating time: 56 minutes (IQR 52 to 63). • Median hospital stay: 4 days (IQR 3 to 5) • Adequate reduction in HH and correct location of device in everyone (100%)	

Procedure technique

All 6 papers detailed the procedure technique and devices used. There were no significant variations in technique or devices used.

Only 1 device was used for this procedure (RefluxStop, Implantica, Zug, Switzerland).

The procedure

Hiatus hernia reduction

In 5 papers, HH was treated first before implanting the device (Bjelovic 2020, Fringeli 2024a, 2024b, 2024c, Harsanyi 2024). Feka (2024) did not specify treatment of HH in their methods, but this step was implied. HH was reduced and the sac was excised (if present) in the studies by Bjelovic (2020) and Fringeli (2024a, 2024c). The HH was closed, avoiding compression of the oesophagus. Excessive fat pads at the angle between the LOS and the stomach were removed in all studies (Bjelovic 2020, Fringeli 2024a, 2024b, 2024c, Feka 2024, Harsanyi 2024).

Implantation of device

In all articles, everyone had the operation using a standardised surgical technique, similar to other laparoscopic anti-reflux procedures (LARs). All studies highlighted the importance of high placement of the device above the upper edge of the LES for successful treatment (Bjelovic 2020, Fringeli 2024a, 2024b, 2024c, Feka 2024, Harsanyi 2024).

All studies dissected quite extensively around the oesophagus in the mediastinum and as high as possible. Fringeli (2024a) described that they aimed to have an intra-abdominal length of at least 4.5 cm with a small traction on the oesophagus. Similarly, Bjelovic (2020) described that optimal placement of the device is more than 1 time the device size above the upper edge of the LOS. In

all studies, the device was introduced laparoscopically using a specially made trocar and deployment tool (Implantica, Zug, Switzerland) (Bjelovic 2020, Fringeli 2024a, 2024b, 2024c, Feka 2024, Harsanyi 2024).

Efficacy

GERD-HRQL questionnaire scores

All 6 papers reported data on GERD-HRQL questionnaire scores. All studies showed reduction in GERD-HRQL scores from baseline to follow-up. A high GERD-HRQL score indicates worse GORD symptoms and a low GERD-HRQL score indicates minimal GORD symptoms. 5 out of 6 papers reported statistical significance in reduction. Only the 4-year follow-up study did not provide a p-value (Harsanyi 2024).

In the prospective single-arm study of 50 people, mean GERD-HRQL scores were 28.8 (SD 7.3) at baseline, which decreased at 6 months follow-up to 3.4 (SD 6.0; $p<0.0001$) (Bjelovic 2020). In the follow-up study, the score had remained reduced at 4 years. At year 1, the median had been 29.5 (IQR 24 to 33) which decreased to 3.0 (IQR 0 to 9.2) by year 4. The p-value for the 4-year result was not provided (Harsanyi 2024). The GERD-HRQL questionnaire used in these 2 articles had a score range of 0 to 50.

In the retrospective observational single-arm study of 40 people, mean GERD-HRQL scores decreased from 32.83 (SD 5.08) before surgery to 6.60 (SD 3.71) at 3 months ($p<0.001$; Feka 2024). The authors did not clarify the range or the version of the GERD-HRQL questionnaire they used.

In the retrospective cohort study of 40 people, median GERD-HRQL score at baseline was 35 (IQR 28.5 to 49). At 3 months this decreased to 2 (IQR 0 to 3; $p<0.0001$). In both retrospective chart reviews there were statistically significant reductions in GERD-HRQL scores. In Fringeli (2024a) with 20 people with IOM,

the mean baseline score was 40.7 (SD 16.0). This decreased to 4.8 (SD 8.3) at 3 months and to 5.7 (SD 7.7) at 12 months ($p<0.001$) for both. In Fringeli (2024b), made up of 30 people with larger HH, the mean baseline score was 37.6 (SD 15.5). At 6 months this reduced to 3.1 (SD 5.4). The GERD-HRQL questionnaire used in these 3 articles had a score range of 0 to 75. As previously discussed, populations in the 2024a and 2024b studies almost entirely overlap with the 2024c study. All results were statistically significant.

Heartburn – subscore of GERD-HRQL questionnaire

All 6 papers measured changes in heartburn symptoms using subscores of components of the GERD-HRQL questionnaire, but not all studies reported the heartburn scores separately.

In the retrospective observational single-arm study of 40 people, mean heartburn scores decreased from 17.4 (SD 2.07) before surgery to 3.83 (SD 1.88) at 3 months ($p<0.001$; Feka 2024).

In a retrospective chart review of 20 people (with IOM), the mean baseline score was 17.4 (SD 8.3). At 12 months, this decreased to 2.4 (SD 3.7; $p<0.001$) (Fringeli 2024a).

In Fringeli (2024b) the retrospective chart review of 30 people (with larger HH) had a baseline heartburn score of 16.5 (SD 8.1). At 6 months, this had reduced to 1.1 (SD 2.3; $p<0.001$).

In the retrospective cohort study with 40 people, heartburn scores were not provided, but they noted that the reduction was statistically significant ($p<0.0001$; Fringeli 2024c). There was significant overlap between populations in the 2024a, 2024b and 2024c studies.

In the prospective single-arm study of 50 people, by Bjelovic (2020) and 4-year follow-up study (Harsanyi 2024) heartburn scores were not provided.

Regurgitation – subscore of GERD-HRQL questionnaire

All 6 papers reported changes in regurgitation symptoms using subscores of components of the GERD-HRQL questionnaire.

In the prospective single-arm study of 50 people, 88% of participants experienced daily regurgitation. At 12 months, 98% of people had no or minimal regurgitation episodes ($p<0.001$; Bjelovic 2020). In the 4-year follow-up study, 42 out of 44 participants (96%) had no or minimal regurgitation (Harsanyi 2024).

In the retrospective observational single-arm trial of 40 people, mean regurgitation scores decreased from 10.85 (SD 2.85) before surgery to 1.63 (SD 1.68) at 3 months ($p<0.001$; Feka 2024).

In a retrospective chart review of 20 people (with IOM), the mean baseline score was 17.7 (SD 7.5). At 12 months, this decreased to 1.6 (SD 3.5; $p<0.001$; Fringeli 2024a).

In Fringeli (2024b), the retrospective chart review of 30 people (with larger HH), had a baseline regurgitation score of 16.5 (SD 7.2). At 6 months, this had reduced to 0.9 (SD 2.0; $p<0.001$).

In the retrospective cohort study, regurgitation scores were not provided, but they noted that the reduction was statistically significant ($p<0.0001$; Fringeli 2024c). There was significant overlap between subjects in the 2024a, 2024b and 2024c studies.

Changes in dysphagia (difficulty swallowing)

All 6 papers measured changes in dysphagia. This section reports changes in symptoms in those who had preoperative dysphagia. New onset and postoperative dysphagia are described in the safety section below.

In a prospective single-arm study of 50 people, 15 (30%) people experienced dysphagia. At 6 months, 4 (9%) people reported minimal to moderate dysphagia ($p<0.001$). At 12 months, 2 (4%) people reported minimal dysphagia ($p<0.001$) (Bjelovic 2020). In the follow-up study, 1 person reported mild dysphagia (a score of 2 in the GERD-HRQL questionnaire) at 3-year follow-up. This was an improvement from their baseline score of 5 (severe). At 4 years 46 out of 47 people reported no dysphagia (Harsanyi, 2024).

In the retrospective observational single-arm trial of 40 people, 4 (10%) people had dysphagia at baseline. At 3 months, 1 (2.5%) person had dysphagia. A p-value was not provided (Feka 2024).

In the retrospective cohort study with 40 people, 20 out of 40 (50%) reported preoperative dysphagia (Fringeli 2024c). At 3 months, there was a reduction in severity or complete resolution of symptoms in those who had dysphagia. A p-value was not provided. 2 of those who reported preoperative dysphagia required treatment (dilations) after the procedure. They also had IOM. Due to the severity of the symptoms, early dilations were performed 3 to 4 weeks after surgery (Fringeli 2024c).

In the retrospective chart review of 20 people (with IOM), changes in dysphagia scores for the whole cohort were not statistically significant. In the 12 people who had dysphagia before surgery the mean dysphagia score reduced from 2.7 (SD 1.4) at baseline to 1.0 (SD 1.0) at 12 months ($p<0.005$) (Fringeli 2024a).

In the retrospective chart review of 30 people (with larger HH), changes in the whole cohort were not statistically significant. 15 out of 30 (50%) people had dysphagia at baseline, with a mean dysphagia score of 2.7 (SD 1.5). At 6 months, this had reduced to 0.6 (SD 0.9; $p<0.001$).

There was significant overlap between subjects in the Fringeli 2024a, 2024b and 2024c studies.

Odynophagia (pain swallowing)

Changes in odynophagia were reported in 2 papers (1 study) (Bjelovic 2020, Harsanyi 2024).

At baseline 13 out of 50 (26%) of people had odynophagia. At 6 months, no-one reported odynophagia and at 12 months 1 person (2%) reported odynophagia ($p<0.001$ for both time periods; Bjelovic 2020). In the 4-year follow-up, 0 out of 50 people reported odynophagia between the years of 1 and 4 (Harsanyi 2024). Of the 50, 3 people did not have 4-year follow-up data so their 3-year data was carried forward (Harsanyi, 2024).

The Harsanyi (2024) paper reports 2 events of odynophagia that were not reported in the Bjelovic (2020) paper. 1 person complained of odynophagia 1 day after surgery. At 6 months they were verified to have a motility disorder. For the second person with odynophagia, symptoms disappeared within a few months after surgery (Harsanyi 2024).

No other papers reported odynophagia outcomes.

Proton pump inhibitor (PPI) usage

All 6 papers measured changes in usage of proton pump inhibitor medication before and after the procedure.

In the prospective single-arm study of 50 people, everyone took daily PPI medication preoperation. At 6 months, 0 people took PPI and at 12 months 1 person was taking PPIs. In the person who started taking PPIs at 12 months, the device had been implanted too low and had been at risk of failure surgically (Bjelovic 2020). In the 4-year follow-up study, 2 out of 44 (5%) people were using daily PPIs. Both had normal 24-hour pH monitoring results (Harsanyi 2024).

In the retrospective observational single-arm trial of 40 people, 31 (78%) people took daily PPIs. At 3 months, this reduced to 5 (13%) people ($p<0.001$) (Feka 2024).

In a retrospective chart review of 20 people, at baseline everyone used PPI. At 12 months, 16 people were able to completely discontinue use of PPIs (Fringeli 2024a).

The 2 other studies by Fringeli (2024b and 2024c) did not report changes in PPI usage.

24-hour pH monitoring

1 paper reported changes in 24-hour pH monitoring scores. This was measured as the mean percentage of overall time (within 24 hours) with a pH less than 4.

In the prospective single-arm study of 50 people, at baseline the mean percentage of time with a pH less than 4 was 16%. At 6 months, this reduced to 1% ($p<0.001$). 98% of people had a normal 24-hour pH result. This was a 95% improvement of the mean value (Bjelovic 2020).

In the 4-year follow-up study, 24-hour pH monitoring only occurred in those whose operation was considered at risk of failure. Potential failure operations included those in people who were dissatisfied with their quality of life relating to GORD, taking daily PPIs or had GERD-HRQL questionnaire results with less than 50% improvement. Of those who had an operation that was at risk of failure, 1 person had a pathologic pH test result. The paper considers this an objectified failed operation and is thought to be due to the device being positioned too low (Harsanyi 2024).

No other papers reported changes in 24-hour pH monitoring.

Gas bloating

2 papers reported changes in gas bloating (Bjelovic 2020 and Harsanyi 2024). Both report percentages of people who experienced gas or bloating as identified through the GERD-HRQL questionnaire.

In the prospective single-arm study of 50 people, 84% of people experienced gas bloating (a median score of 4.0, range 0 to 5). At 12 months, this had reduced to 19% of people ($p<0.0001$). After 12 months, gas bloating had disappeared in 30 people, improved in 7 people, remained unchanged in 2 people and did not worsen in anyone (Bjelovic 2020).

In the 4-year follow-up study, gas bloating had disappeared in 30 (68%) people, improved in 11 (25%) people, remained unchanged in 2 (5%) people and worsened in 1 (2%) person (Harsanyi 2024).

Patient satisfaction relating to GORD – score of additional question in GERD-HRQL questionnaire

All 6 papers measured patient satisfaction relating to GORD by adding a question to the GERD-HRQL questionnaire. The question was 'How satisfied are you with your current quality of life related to GERD?'. Possible responses included 'satisfied', 'neutral' or 'dissatisfied'.

In the prospective single-arm study of 50 people, baseline results showed that 1 (2%) person was satisfied and 45 (90%) were dissatisfied with their quality of life related to GORD. At 6 months, 44 (94%) people were satisfied and 2 (4%) were dissatisfied. At 12 months, 43 (91%) were satisfied, 1 (2%) was dissatisfied (Bjelovic 2020). 2 (4%) more people were dissatisfied for reasons that Bjelovic (2020) have suggested are not related to GORD as they had normal 24-hour pH monitoring results. In the 4-year follow-up study, 2 out of 44 (5%) people were dissatisfied due to reasons unrelated to GORD. 42 out of 44 (96%) people were either satisfied or neutral at 4 years after the procedure (Harsanyi 2024).

In the retrospective observational single-arm trial of 40 people, all subjects were either dissatisfied or neutral about their quality of life relating to GORD. No-one was satisfied. At 3 months post-procedure, this had decreased to 4 (10%) people who were dissatisfied or neutral. 36 (90%) of people were satisfied. This is a dissatisfaction reduction of 90%. P-values were not provided (Feka 2024).

In the retrospective cohort study of 40 people, 28 (74%) reported dissatisfaction or neutrality when asked about their quality of life relating to GORD. At 3 months, 100% reported improvement and no-one was dissatisfied. No further information or p-values were provided (Fringeli 2024c).

In the retrospective chart review of 20 people (with IOM), 25% of people were satisfied preoperation, compared with 90% satisfied at 12-month follow-up (Fringeli 2024a).

In the retrospective chart review of 30 people (with larger HH) had 8 (27%) satisfied people compared with 28 (97%) satisfaction at 6 months (Fringeli 2024b).

There was significant overlap between subjects in the 2024a, 2024b and 2024c studies.

Safety

Postoperative dysphagia

This section describes postoperative dysphagia. Most studies describe this as new onset dysphagia which developed following the procedure (Bjelovic 2020, Harsanyi 2024, Feka 2024, Fringeli 2024a, Fringeli 2024b). 1 study was not clear about whether the postoperative dysphagia was new onset or if the participants experienced dysphagia before the operation (Fringeli 2024c).

In the retrospective cohort study with 40 people, the authors report that there was no new onset of dysphagia recorded after 3 months. They report that 3 people had postoperative dysphagia requiring dilations (see section 'Changes in dysphagia'). All 3 people had IOM and 2 of them had experienced dysphagia preoperatively (Fringeli, 2024c). The authors do not clarify whether the third person had preoperative dysphagia, or if they developed new onset dysphagia postoperatively. Due to the severity of the symptoms, early dilations were performed 3 to 4 weeks after surgery (Fringeli, 2024c).

In the retrospective chart review of 20 people (with IOM), there were 8 people who did not report preoperative dysphagia. Of those people, 3 developed dysphagia after 12 months following the procedure. Change in dysphagia scores for these 8 people were not statistically significant (Fringeli 2024a).

In the retrospective chart review of 30 people (with larger HH), new-onset dysphagia occurred in 5 people, 4 of whom had no intervention and only changes in diet (Fringeli 2024b).

There was significant overlap between participants in the Fringeli 2024a, 2024b and 2024c studies.

There were no new cases of dysphagia after surgery in the prospective single-arm study of 50 people at 12 months, or during the 4-year follow-up in the subsequent article (Bjelovic 2020 and Harsanyi 2024). There were no new cases of dysphagia in the retrospective observational single-arm trial of 40 people (Feka 2024).

Recurrence of HH

Recurrence of HH occurred in 2 people in 2 different studies.

In the retrospective observational single-arm study of 40 people, 1 person had recurrence of HH where the newly reconstructed oesophageal and stomach

angle and the device had herniated into the thoracic cavity. This was classified as a Clavien–Dindo grade 3b. They had a second operation the day after where the device was removed and they had a Dor fundoplication (Feka 2024).

In the retrospective chart review of 30 people (with larger HH), 1 person had recurrence of HH. Their pre-existing hernia was 8 cm in size. The reherniation occurred after the person experienced severe vomiting caused by food poisoning, resulting in the upper third of the stomach and device to enter the thoracic cavity. They required emergency surgery to reposition the stomach and device (Fringeli 2024b).

Device migration

Device migration occurred in 2 people in 2 different studies (Feka 2024 and Fringeli 2024a).In the retrospective observational single-arm study of 40 people, device migration occurred in 1 person 1 month after the operation. The device entered the stomach cavity and left the body naturally. They experienced epigastric pain for 3 days before the device was removed. The paper suggests that it could have been caused by a small haematoma where the device had been implanted (Feka 2024). In the retrospective chart review of 20 people, 1 person experienced device migration. The device did not migrate into the stomach cavity. The device had split into 5 parts: 3 parts were sitting close to the stomach and 2 parts were close to the spleen and greater omentum. All 5 parts were recovered by diagnostic laparoscopy. It is thought the migration was due to insufficient closure of the passageway where the deployment tool was used to hold the device in place during the operation (Fringeli 2024a).

Haemorrhage or bleeding (haematoma)

2 people experienced postoperative bleeding in 2 different studies (Bjelovic 2020 and Fringeli 2024c).

In the prospective single-arm study of 50 people, 1 person experienced bleeding which was categorised as a severe adverse event. They believed it was probably caused by the short gastric vessels. The person had clot evacuation and drainage (Bjelovic 2020).

In the retrospective cohort study of 40 people, 1 person experienced a haemorrhage caused by dissection of the short gastric vessels at the top of the stomach (fundus). This required urgent laparoscopic operation on the same day (Fringeli 2024c).

Infection

Infection occurred in 1 person in the prospective single-arm study of 50 people (Bjelovic 2020). The infection occurred 3 times in the same person and resulted in both a mediastinal abscess and empyema. The authors report this was probably caused by an infected mediastinal haematoma. The infection did not spread to the pouch with the device. Once the subject had healed from the infection the study claim they had an excellent treatment result (Bjelovic 2020).

Recurrence of acid reflux symptoms

1 person in 1 study experienced recurrence of acid reflux symptoms as verified by a pathological 24-hour pH monitoring result. The device was found to be positioned too low and was categorised as a failed operation during follow-up (Harsanyi 2024).

Release of sutures

In the prospective single-arm study of 50 people, fundoplication sutures released in 1 person between the 6 and 12 month visit. This was classified as a serious adverse event. Reoperation was performed and they had a successful 12-month follow-up (Bjelovic 2020).

Persistent left-sided thoracic pain

1 person in 1 study experienced persistent left-sided thoracic pain at 12 months. It required a second operation. The pain was considered unrelated to the device (Fringeli 2024a).

Persistent fatigue due to pericardial effusion

There were 2 reports of a person experiencing persistent fatigue due to pericardial effusion. This was reported in the retrospective cohort study by Fringeli (2024c) and the retrospective chart review by Fringeli (2024b). It is unclear if this is the same event reported twice or 2 separate events.

Incisional hernia

1 person experienced a hernia at the insertion site for laparoscopic surgery (trocar hernia) (Fringeli 2024c). 1 person experienced an incisional hernia twice (Bjelovic 2020).

Death

1 person died in 1 study due to COVID-19 (Harsanyi 2024).

Other adverse events

The prospective single-arm study of 50 people further reported 1 moderate adverse event of pleuritis in 1 person, and 4 mild adverse events including the removal of part of a broken needle that had been left subcutaneously in 1 person, 1 accidental intraoperative hepatic lesion, 1 postoperative delayed gastrointestinal paralysis for 1 day and 1 procedural pneumothorax (Bjelovic 2020).

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about

(anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following anecdotal and theoretical adverse events:

- silicone allergies or induced hypersensitivity
- foreign body reaction
- erosion risk
- oesophagus dilation.

6 professional expert questionnaires for this procedure were submitted. Full details of what the professional experts said about the procedure are in the specialist advice questionnaires for this procedure.

Validity and generalisability

- Evidence is mainly from small studies, with each study having 50 people or fewer. Sample size calculations were reported and sufficient numbers of people participated in 1 study (Bjelovic 2020). The remaining 4 papers (2 studies) did not report sample size calculations or said that they did not calculate them (Feka 2024, Fringeli 2024a, 2024b, 2024c).
- In the 4-year follow-up study, there was missing data for 6 out of 50 people. The sample size calculation (reported in Bjelovic 2020) mentioned a sample size of 45 was necessary. Of those who terminated the trial early:
  - 1 person died from COVID-19
  - 2 people had 3-year follow-up data which showed they were satisfied, not low GERD-HRQL scores (average 1.3), no PPI usage and no regurgitation
  - 2 people left the study within the first year. Both were satisfied, did not take PPIs, had a low GERD-HRQL score (2.5) and no regurgitation

  - 1 person had a broken needle left under the skin that required removal under local anaesthesia. They were dissatisfied, had a high GERD-HRQL score, no PPI usage and no regurgitation.
- Of the 3 studies, 1 was based in Hungary, Serbia and Switzerland, another was based in Switzerland, and 1 was based in Austria and the UK.
- The retrospective cohort study of 40 people had significant overlap in sample with those in the retrospective chart reviews (Fringeli 2024a, 2024b, 2024c). The retrospective chart review of 20 people (Fringeli 2024a) is entirely a subgroup of the retrospective cohort study (Fringeli 2024c). The second retrospective chart review (Fringeli 2024b) is almost entirely a subgroup of the retrospective cohort study (Fringeli 2024c). There is also some overlap of people in the chart reviews (Fringeli 2024a, 2024b).
- There are some potential sources of bias in these studies. As all studies were single arm and were not comparative studies, principles of randomisation cannot be applied. Due to the nature of the procedure, blinding could also not be applied, leading to selection bias. Sham procedures would not have been feasible. In the retrospective chart review of 30 people, the authors report selection bias towards people with ineffective or weak oesophageal motility (Fringeli 2024b).
- Follow-up time for 5 out of 6 papers was 12 months or less. 1 paper was a 4-year follow-up (Harsanyi, 2024).
- There was very little variability in the person inclusion and exclusion criteria across the 6 papers. The main variation was that in the retrospective chart review of 20 people, they selected those with IOM (Fringeli 2024a). In the retrospective chart review of 30 people, they selected those with larger HH (4 to 10 cm in size; Fringeli 2024b).
- There was little variability in the procedure technique. The same device was used in every procedure.

- 1 study (2 papers) was funded by the device manufacturer, Implantica (Zug, Switzerland) (Bjelovic 2020, Harsanyi 2024). Feka (2024) reports that 2 of their authors received travel grants and speaker honoraria but do not say from who. In the Fringeli papers, 1 author, Joerg Zehetner, received reimbursement from Implantica for educational activities. There are also overlaps in authors in different studies. Joerg Zehetner, who was an author in the Fringeli (2024a, 2024b, 2024c) papers was also an author on the Feka (2024) paper.

Any ongoing trials

- NCT05870163 Post-Market Registry for the Evaluation of RefluxStop in GERD Treatment. This is a single-arm, prospective, open-label, multicentre study. There are 91 enrolled people: 43 in Germany, 24 in Switzerland, 19 in Italy and 5 in Norway. Estimated study completion date is 31 December 2029.
- RXI005/RENEW RCT (RCT RefluxStop vs. Nissen): to be conducted in Austria (submitted to Ethical Committee and waiting for approval), Switzerland (submitted to Ethical Committee and waiting for approval), Germany (submitted to Ethical Committee and waiting for approval), Italy (under preparation), Spain (under preparation), the UK (under preparation).
- RXI008/IM REVOLUTION RCT (RCT RefluxStop vs.PPI): under preparation and to be conducted in Austria, Switzerland, Germany, Italy, Spain and the UK.

Existing assessments of this procedure

No recent publications were identified.

Related NICE guidance

Interventional procedures

- Endoluminal gastroplication for gastro-oesophageal reflux disease (2023) Interventional procedures guidance 753 - *research only*
- Laparoscopic insertion of a magnetic ring for gastro-oesophageal reflux disease (2023) Interventional procedures guidance 749 - *standard arrangements*
- Electrical stimulation of the lower oesophageal sphincter for treating gastro-oesophageal reflux disease (2015) NICE interventional procedure guidance 540 – *research only*
- Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease (2013) NICE interventional procedure guidance 461 – *special arrangements*
- Endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease (2007) NICE interventional procedure guidance 222 – *special arrangements*
- Endoscopic injection of bulking agents for gastro-oesophageal reflux disease (2004) NICE interventional procedure guidance 55 - *special arrangements*

NICE guidelines

- Gastro-oesophageal reflux disease in children and young people: diagnosis and management (updated in 2019) NICE guideline NG1
- Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management (updated in 2019) NICE clinical guideline CG184

Professional societies

- Association of Upper Gastrointestinal Surgeons for Great Britain and Ireland (AUGIS)
- British Society of Gastroenterology (BSG)

Evidence from people who have had the procedure and patient organisations

NICE received 1 submission from patient organisations about laparoscopic insertion of an inactive implant (RefluxStop) for gastro-oesophageal reflux disease from Heartburn Cancer UK. At the time of writing, we are awaiting a final submission from OPA Cancer Charity.

NICE received 6 questionnaires from people who have had the procedure (or their carers).

1 person who has had the procedure raised the following issues about the safety and efficacy of the procedure, which was not in the published evidence or the opinions of professional experts:

- They had shoulder pain for a few weeks after the operation. This has almost resolved 4 months after the operation.

Otherwise, the patient survey results from those who had the procedure were very positive about the efficacy and impact of the procedure. See the patient commentary summary for more information.

Company engagement

NICE asked the company who manufacture the device relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the interventional procedures technical team and any relevant points have been taken into consideration when preparing this overview.

References

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2. Feka J, Saad M, Boyle N, Paireder M, Kristo I, Rieder E, Asari R, Schoppmann SF, (2024) Multicentric short term and safety study of ineffective esophageal motility patients treated with RefluxStop device. Scientific Reports, 14:15425
3. Fringeli Y, Linas I, Kessler U, Zehetner J (2024a) Short-term results of laparoscopic anti-reflux surgery with the RefluxStop device in patients with gastro-esophageal reflux disease and ineffective esophageal motility. Langenbecks Arch Surg 29;409(1):78
4. Fringeli Y, Linas I, Kessler U, Zehetner J (2024b) Laparoscopic Large Hiatal Hernia Repair With RefluxStop: Outcomes of Six Months Follow-up in Thirty Patients. Surg Laparosc Endosc Percutan Tech, 1;34(2):143-149
5. Fringeli Y, Linas I, Kessler U, Zehetner J (2024c) Exploring the feasibility and safety of laparoscopic anti-reflux surgery with the new RefluxStopTM device: a retrospective cohort study of 40 patients, Swiss Med Wkly [Internet]. 154(7):3365
6. Harsányi L, Kincses Z, Zehetner J, Altorjay A, (2024) Treating acid reflux without compressing the food passageway: 4-year safety and clinical outcomes 3 with the RefluxStop device in a prospective multicenter study. Surg Endosc.
7. Velanovich V, Vallance SR, Gusz JR, Tapia VF, Harkabus MA (1996) Quality of life scale for gastroesophageal reflux disease. J Am Coll Surg, 183(3):217-24.
8. Makris KI, Cassera MA, Kastenmeier AS, Dunst CM, Swanström LL, (2012) Postoperative dysphagia is not predictive of long-term failure after laparoscopic antireflux surgery, Surg Endosc 26, 451–457.

Appendix A: Methods and literature search strategy

Methods and literature search strategy

NICE has identified studies and reviews relevant to laparoscopic insertion of an inactive implant for gastro-oesophageal reflux disease from the medical literature. Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

Search strategy design and peer review

This search report is informed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension (PRISMA-S). A NICE information specialist ran the literature searches on 03 June 2024. See the search strategy history for the full search strategy for each database. The principal search strategy was developed in MEDLINE ALL (Ovid interface). It was adapted for use in each of the databases listed in table 4a, taking into account the database's size, search functionality and subject coverage. The MEDLINE ALL strategy was quality assured by a NICE senior information specialist. All translated search strategies were peer reviewed to ensure their accuracy. The quality assurance and peer review procedures were adapted from the Peer Review of Electronic Search Strategies (PRESS) 2015 evidence-based checklist.

Review management

The search results were managed in EPPI Reviewer version 5 (EPPIR5). Duplicates were removed in EPPIR5 using a 2-step process. First, automated deduplication was done using a high-value algorithm. Second, manual deduplication was used to assess low-probability matches. All decisions about inclusion, exclusion and deduplication were recorded and stored.

Limits and restrictions

IP overview: Laparoscopic insertion of an inactive implant for gastro-oesophageal reflux disease

The search was not limited by date or language. The CENTRAL database search removed trial registry records and conference material. The limit to remove animal studies in the searches is standard NICE practice, which has been adapted from Dickersin K, Scherer R, Lefebvre C (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ 309(6964): 1286.

Main search

Table 4a Main search results

Database	Date searched	Database platform	Database segment or version	Number of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	03/06/2024	Wiley	Issue 6 of 12, June 2024	218
Cochrane Database of Systematic Reviews (CDSR) Protocols	03/06/2024	Wiley	Issue 6 of 12, June 2024	7 2
Embase Embase Conferences	03/06/2024	Ovid Ovid	1974 to 2024 May 31	335 171
INAHTA International HTA Database	03/06/2024	https://database.inahta.org/	-	141
MEDLINE ALL	03/06/2024	Ovid	1946 to May 30, 2024	833

Search strategy history

MEDLINE ALL search strategy

1 , exp Gastroesophageal Reflux/ , 29,987

2 , ((gastro-esophag* or gastro-oesophag* or gastro?esophag* or oesophag* or esophag*) adj4 reflux*).tw. , 32,987

3 , Esophageal Motility Disorders/ , 2,261

4 , ((oesophag* or esophag*) adj4 (motilit* or dysmotilit* or disorder* or funct*)).tw. , 9,274

5 , (gord or gerd).tw. , 11,641

6 , Heartburn/ , 2,323

7 , ((heart adj1 burn) or heartburn or pyros?s or (water adj1 brash) or waterbrash or (acid adj1 brash) or acidbrash).tw. , 6,183

8 , Barrett Esophagus/ , 8,880

9 , (barrett* adj4 (esophag* or oesophag* or dysplas* or syndrom*)).tw. , 10,274

10 , Esophageal Sphincter, Lower/ , 1,907

11 , (lower adj4 (gastro-esophag* or gastro-oesophag* or gastro?esophag* or oesophag* or esophag*) adj4 sphincter*).tw. , 6,003

12 , (gastric adj4 (reflux* or regurgitat* or acid* or juice*)).tw. , 25,048

13 , ((acid or bile) adj4 (reflux* or indigest* or flow-back or flowback or back-flow or backflow)).tw. , 5,523

14 , Dyspepsia/ , 9,412

15 , dyspepsi*.tw. , 12,815

16 , Hernia, Hiatal/ , 7,001

17 , ((oesophag* or esophag* or para?esophag* or hiat*) adj4 hernia*).tw. , 8,844

18 , deglutition disorder/ , 24,703

19 , (Deglutit* adj4 disord*).tw. , 341

20 , dysphag*.tw. , 36,177

21 , or/1-20 , 143,991

22 , "Prostheses and Implants"/ , 50,486

23 , Prosthesis Implantation/ , 15,741

24 , Prosthesis Design/ , 61,937

25 , (prosthe* adj4 (design* or implant*)).tw. , 22,984

26 , (implantable adj2 device).tw. , 2,961

27 , ((anti-reflux or non-active) adj4 implant*).tw. , 24

28 , or/22-27 , 138,552

29 , 21 and 28 , 870

30 , refluxstop.tw. , 6

31 , 29 or 30 , 873

32 , animals/ not humans/ , 5,192,576

33 , 31 not 32 , 833

Embase search strategy

1, exp gastroesophageal reflux/, 80,534

2, ((gastro-esophag* or gastro-oesophag* or gastro?esophag* or oesophag* or esophag*) adj4 reflux*).tw., 51,332

3, esophagus function disorder/, 3,016

4, ((oesophag* or esophag*) adj4 (motilit* or dysmotilit* or disorder* of funct*)).tw., 8,340

5, (gord or gerd).tw., 24,694

6, heartburn/, 17,717

7, ((heart adj1 burn) or heartburn or pyros?s or (water adj1 brash) or waterbrash or (acid adj1 brash) or acidbrash).tw., 11,398

8, Barrett esophagus/, 20,102

9, (barrett* adj4 (esophag* or oesophag* or dysplas* or syndrom*)).tw., 17,658

10, lower esophagus sphincter/, 14,133

11, (lower adj4 (gastro-esophag* or gastro-oesophag* or gastro?esophag* or oesophag* or esophag*) adj4 sphincter*).tw., 9,433

12, (gastric adj4 (reflux* or regurgitat* or acid* or juice*)).tw., 29,181

13, ((acid or bile) adj4 (reflux* or indigest* or flow-back or flowback or back-flow or backflow)).tw., 9,349

14, Dyspepsia/, 40,639

15, dyspepsi*.tw., 20,118

16, hiatus hernia/, 15,657

17, ((oesophag* or esophag* or para?esophag* or hiat*) adj4 hernia*).tw., 13,006

18, dysphagia/, 95,461

19, (Deglutit* adj4 disord*).tw., 356

20, dysphag*.tw., 63,413

21, or/1-20, 283,966

22, prosthesis/, 34,291

23, prosthesis implantation/, 3,383

24, prosthesis design/, 8,182

25, (prosthes* adj4 (design* or implant*)).tw., 20,535

26, (implantable adj2 device).tw., 4,797

27, ((anti-reflux or non-active) adj4 implant*).tw., 35

28, or/22-27, 65,776

29, 21 and 28, 499

30, refluxstop.tw,dv,dm., 25

31, 29 or 30, 514

32, Nonhuman/ not human/, 5,456,142

33, 31 not 32, 506

34, (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su., 5,959,494

35, 33 not 34, 335

36, 33 and 34, 171

(CDSR and CENTRAL) search strategy

#1 MeSH descriptor: [Gastroesophageal Reflux] explode all trees 2561

#2 ((gastro-esophag* or gastro-oesophag* or gastro?esophag* or oesophag* or esophag*) near/4 reflux*) 6553

#3 MeSH descriptor: [Esophageal Motility Disorders] explode all trees 2794

#4 ((oesophag* or esophag*) near/4 (motilit* or dysmotilit* or disorder* of funct*)) 11154

#5 (gord or gerd) 2471

#6 MeSH descriptor: [Heartburn] explode all trees 467

#7 ((heart near/1 burn) or heartburn or pyros?s or (water near/1 brash) or waterbrash or (acid near/1 brash) or acidbrash) 2937

#8 MeSH descriptor: [Barrett Esophagus] explode all trees 347

#9 (barrett* near/4 (esophag* or oesophag* or dysplas* or syndrom*)) 798

#10 MeSH descriptor: [Esophageal Sphincter, Lower] explode all trees 101

#11 (lower near/4 (gastro-esophag* or gastro-oesophag* or gastro?esophag* or oesophag* or esophag*) near/4 sphincter*) 1018

#12 gastric near/4 (reflux* or regurgitat* or acid* or juice*) 4362

#13 ((acid or bile) near/4 (reflux* or indigest* or flow-back or flowback or back-flow or backflow)) 1107

#14 MeSH descriptor: [Dyspepsia] explode all trees 1437

#15 dyspepsi* 6542

#16 MeSH descriptor: [Hernia, Hiatal] explode all trees 135

#17 ((oesophag* or esophag* or para?esophag* or hiat*) near/4 hernia*) 501

#18 MeSH descriptor: [Deglutition Disorders] explode all trees 4107

#19 (Deglutit* near/4 disord*) 1514

#20 dysphag* 6190

#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 31305

#22 MeSH descriptor: [Prostheses and Implants] explode all trees 25963

#23 MeSH descriptor: [Prosthesis Implantation] explode all trees 11818

#24 MeSH descriptor: [Prosthesis Design] explode all trees 3527

#25 (prosthes* near/4 (design* or implant*)) 9295

#26 (implantable near/2 device) 379

#27 (anti-reflux or non-active) near/4 implant* 6

#28 #22 or #23 or #24 or #25 or #26 or #27 34255

#29 #21 AND #28 230

#30 refluxstop 2

#31 #29 or #30 231

#32 "conference":pt or (clinicaltrials or trialsearch):so 750874

#33 #31 NOT #32 227

INAHTA HTA search strategy

1 , "Gastroesophageal Reflux"[mhe] , 47

2 , ((gastro-esophag* or gastro-oesophag* or gastro?esophag* or oesophag* or esophag*) AND reflux*) , 36

3 , "Esophageal Motility Disorders"[mh] , 0

4 , (oesophag* or esophag*) AND (motilit* or dysmotilit* or disorder* of funct*)) , 21

5 , (gord or gerd) , 36

6 , "Heartburn"[mh] , 3

7 , (heart AND burn) or heartburn or pyros?s or (water AND brash) or waterbrash or (acid AND brash) or acidbrash) , 8

8 , "Barrett Esophagus"[mh] , 30

9 , (barrett* AND (esophag* or oesophag* or dysplas* or syndrom*)) , 38

10 , "Esophageal Sphincter, Lower"[mh] , 6

11 , (lower AND (gastro-esophag* or gastro-oesophag* or gastro?esophag* or oesophag* or esophag*) AND sphincter*) , 7

12 , gastric AND (reflux* or regurgitat* or acid* or juice*) , 14
13 , (acid or bile) AND (reflux* or indigest* or flow-back or flowback or back-flow or backflow)) , 13
14 , "Dyspepsia"[mh] , 16
15 , dyspepsi* , 29
16 , "Hernia, Hiatal"[mh] , 0
17 , (oesophag* or esophag* or para?esophag* or hiat*) AND hernia*) , 5
18 , "Deglutition Disorders"[mh] , 22
19 , (Deglutit* AND disord*) , 1
20 , dysphag* , 37
21 , #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 , 183
22 , "Prostheses and Implants"[mh] , 154
23 , "Prosthesis Implantation"[mh] , 169
24 , "Prosthesis Design"[mh] , 39
25 , (prosthes* AND (design* or implant*)) , 78
26 , (implantable AND device) , 48
27 , (anti-reflux or non-active) AND implant* , 2
28 , #27 OR #26 OR #25 OR #24 OR #23 OR #22 , 417
29 , #28 AND #21 , 141
30 , refluxstop , 1
31 , #30 OR #29 , 141

Inclusion criteria

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not

report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events not available in the published literature.

- People with: gastro-oesophageal reflux disease.
- Intervention or test: Laparoscopic insertion of an inactive implant (RefluxStop)
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Find out more about how NICE selects the evidence for the committee.