# Health Policy Advisory Committee on Technology

## Technology Brief Update

## LINX® Reflux Management System

## August 2016


Australian Safety and Efficacy Register of New Interventional Procedures – Surgical

Royal Australasian College of Surgeons

HealthPACT

*emerging health technology*

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## 2016 Summary of findings

The findings of this Technology Brief Update suggest that the LINX® Reflux Management System may be a viable treatment for patients with gastro-oesophageal reflux disease (GORD); however there are still considerable issues with the evidence base. Long-term follow-up of a small number of patients implanted with the LINX device indicate that the device's effectiveness and safety maybe maintained up to five years. Since the original 2013 Technology Brief two cases of device erosion have been identified, an outcome that should be monitored if the device is more widely introduced.

Retrospective non-randomised comparative studies suggest that LINX implantation is as effective as the laparoscopic Nissen fundoplication procedure; with equivalent rates of adverse events. The LINX device can be successfully removed if required. The comparative studies are at risk of selection bias as patients with advanced or complicated GORD were more likely to be offered fundoplication than a LINX device. The exact effect that this bias has on the results of the studies is not known, but they may overestimate the comparative effectiveness of the LINX device.

Recently published trials have included a broader range of patients, including those with advanced GORD and patients who have previously undergone bariatric surgery. Where published, these trials are preliminary and further research is warranted before any conclusions can be drawn for these populations. Identified ongoing trials suggest that there will be new evidence available with expanded inclusion criteria in the future.

It should also be noted that all included studies and ongoing trials are sponsored by the device manufacturer or have been run by clinicians who have consulted for the device manufacturer.

Future studies should be randomised controlled trials comparing surgical approaches for reflux that evaluate the ability of the LINX device to reduce the complications of GORD as well as quality of life outcomes and comprehensive cost analyses. Introduction of the device into Australia does not appear to be imminent, and the cost of the device is likely to be a barrier to its use.

## 2016 HealthPACT assessment

The evidence base supporting the use of the LINX® Reflux Management system appears to be unchanged since the original brief was written in 2013. There is insufficient evidence demonstrating the superiority of other methods, such as laparoscopic Nissen fundoplication. In addition, the LINX is unlikely to be a cost-effective option for the treatment of reflux.

HealthPACT does not support public investment in the LINX® Reflux Management system in clinical practice, and recommends no further review of the evidence is warranted at this time.

## Technology, Company and Licensing

| | |
|---|---|
| **Register ID** | **WP128** |
| **Technology name** | **LINX® Reflux Management System** |
| **Patient indication** | **Patients with gastro-oesophageal reflux disease** |

**Reason for assessment**

In 2013 a Technology Brief was completed to investigate the LINX® Reflux Management System for treatment of gastro-oesophageal reflux disease (GORD). While the LINX system showed promising initial results, the Brief recommended the technology be monitored for 36 months to allow time for the evidence base to develop. The purpose of this Update is to consider the evidence that has emerged since 2013 and to determine whether this new evidence provides additional information to inform policy and funding decision making.

**Description of the technology**

The LINX Reflux Management System consists of a small flexible and expandable 'bracelet' of titanium beads, with magnetic cores linked by independent titanium wires.[1, 2] The device is placed laparoscopically at the gastro-oesophageal junction (Figure 1) to help the lower oesophageal sphincter (LOS) resist opening, thereby preventing stomach contents from entering the LOS.[2, 3] The LINX device permits natural physiologic function to enable swallowing or release of elevated gastric pressure (associated with belching or vomiting).[1] This is achieved when the peristaltic pressure of the food bolus, for example, is greater than the magnetic attraction between adjacent beads of the LINX System, causing them to expand and 'open' the device. As the food moves through the oesophagus into the stomach and the peristaltic pressure drops below that of the magnetic attraction between beads, the beads are magnetically drawn together and the device 'closes'.[3] The attractive force between the beads ranges from 40 G (closed) to 7 G (fully expanded).[1] The device comes in different sizes ranging from 12 to 16 beads; the device size to be determined during surgery, using specialised sizing equipment to measure the outer diameter of the oesophagus.[1]

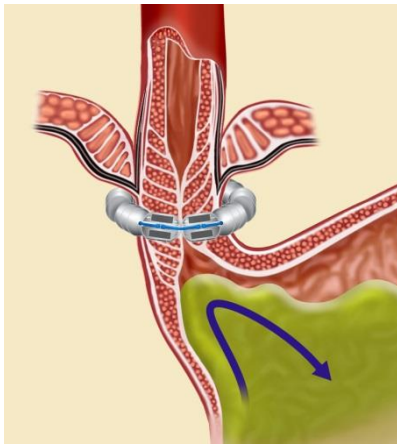

**Figure 1 LINX device implanted around the oesophagus to assist lower oesophageal sphincter closure (printed with permission).[2]**

Typically, placement of the device occurs under general anaesthesia via five laparoscopic ports. Dissection takes place so that a tunnel is formed between the posterior oesophageal wall and the posterior vagus nerve. A drain is placed within the tunnel, encircling the oesophagus, to maintain access for the sizing tool and then the LINX device. Following the insertion of a correctly-sized LINX device, its ends are secured at the anterior surface of the oesophagus. Implantation of the LINX device takes approximately 30 minutes and patients are generally discharged from hospital on the same or the following day. Patients are advised to continue a normal diet, as tolerated, and cease taking acid suppression medication.[1]

The LINX system is a novel treatment for gastro-oesophageal reflux disease (GORD) in that it is reversible (i.e. it can be surgically removed) and does not alter the hiatal or gastric anatomy or physiology of the patient. Consequently, future treatments with other therapies, such as fundoplication, are possible if required.

**2016 Stage of development in Australia**

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

**2016 Licensing, reimbursement and other approval**

Licencing and approvals for the LINX system do not appear to have changed since the original brief was prepared. The LINX Reflux Management System received CE Mark approval in April 2010[4] and United States Food and Drug Administration (FDA) pre-market approval in March 2012 (approval umber P100049).[5]

**2016 Australian Therapeutic Goods Administration approval**

- ☐ Yes — ARTG number (s) Not applicable
- ☒ No
- ☐ Not applicable

**2016 Diffusion of technology in Australia**

The LINX device is not available in Australia and a search of the Australian Register of Therapeutic Goods (ARTG) did not identify any listing for the device.

The device manufacturer, Torax® Medical, Inc. (Minnesota, United States of America) was contacted and has confirmed that they have no immediate plans to introduce the device into Australia.

## 2016 International utilisation

| Country | Level of Use | | |
|---|---|---|---|
| | Trials underway or completed | Limited use | Widely diffused |
| Austria | ✓ | ✓ | |
| France | ✓ | | |
| Germany | ✓ | ✓ | |
| Italy | ✓ | ✓ | |
| The Netherlands | ✓ | | |
| Switzerland | ✓ | ✓ | |
| United Kingdom | ✓ | ✓ | |
| United States of America | ✓ | ✓ | |

## 2016 Cost infrastructure and economic consequences

In the United States of America the LINX device is reported to cost approximately $6,800[a].[6]

The total cost for a LINX procedure at one centre in the United Kingdom is approximately $15,720; in comparison, a Nissen fundoplication procedure is reported to cost from $13,245[b].[7] These costs do not include reflux diagnosis or pre-operative consultation charges.[7] No further information on training requirements for device implantation was identified for this update.

## 2016 Evidence and Policy

### Safety and effectiveness

Since the Technology Brief in 2013 there have been a number of studies published on the use of the LINX system to treat GORD. This update includes five studies: three comparative studies[10-12] comparing LINX to the laparoscopic Nissen fundoplication (LNF) procedure and two case series studies[8, 9] reporting results from long-term follow-up of patients receiving the device. An overview of the included studies is provided in Table 1. The patients included in Reynolds et al (2015) are a subset of those included in Warren et al (2015) therefore the former study has only been discussed in the economic section of the report. It is possible that some patients included in the retrospective case series conducted by Warren et al and Riegler et al were also included in Ganz et al (2016) and in the studies included in the 2013 Technology Brief. This potential overlap, could not be conclusively confirmed.

a AUD = 0.735 USD, currency conversion performed on 11 May 2016, source XE Currency Converter
bAUD =0.509 GBP, currency conversion performed on 11 May 2016, source XE Currency Converter

**Table 1 Study profile of included studies**

| Study ID<br>Design | Inclusion criteria | Exclusion criteria | Length of follow-up and number of patients | Conflict of interest |
|---|---|---|---|---|
| Riegler et al (2014)[11]<br>Level III-2 evidence<br>(Prospective case-control study)<br>Multicentre (22 institutions in Austria, Germany, Italy and the United Kingdom) | All patients who were candidates for surgical anti-reflux procedures, including those with moderate (abnormal oesophageal pH, reflux symptoms despite medication) and advanced (hiatal hernia >3cm, Barrett's oesophagus, motility disorder and/or Grade C or D oesophagitis by the Los Angeles Classification[13]) GORD. | Patients with known conditions that would make them unlikely to complete a 3-year follow-up. | 12 months<br>LINX: 202<br>LNF: 47<br>Lost to follow-up NA | Torax Medical, Inc sponsored and partially funded this study. Two authors are consultants for Torax Medical, Inc. |
| Warren et al (2016)[12]<br>Level III-2 evidence<br>(Retrospective case-control study)<br>Multicentre (3 institutions USA) | Patients aged 18-85 years with a documented history of GORD and at least partially responsive to PPI treatment who were eligible for LINX implantation and/or laparoscopic Nissen fundoplication. | Prior gastric or oesophageal surgery, hiatal hernia >3cm in size, oesophageal dysmotility (<70% effective swallowing on manometry and/or distal oesophageal amplitude <35 mmHg) or the presence of endoscopically visible Barrett's or oesophageal stricture. | Minimum 12 months<br>LINX: 201<br>LNF: 214<br>Lost to follow-up:<br>LINZ: N = 32<br>LNF: N = 29<br>Propensity matched comparison<br>LINX: 114<br>LNF: 114 | Three authors are consultants for Torax Medical, Inc. |
| Ganz et al (2016)[8]<br>Level IV evidence<br>(Prospective case series study)<br>Multicentre (13 centres in USA, 1 centre in The Netherlands) | Patients 18 to 75 years of age, ≥ 6-month history of GORD, partial response to daily PPIs, increased exposure to oesophageal acid confirmed by pH monitoring | Evidence of hiatal hernia >3 cm, oesophagitis grade C or D (Los Angeles classification[13]), BMI >35, Barrett's oesophagus or motility disorder | 5 years<br>100 patients initially enrolled,<br>Loss to follow-up at 5 years: N = 15 | Study designed and supported by Torax Medical, Inc. |
| Lipham et al (2014)[9]<br>Level IV evidence<br>(Retrospective case review)<br>Multicentre (82 institutions in USA and Europe) | First 1048 patients implanted with LINX device. | NR | Median follow-up 274 days 1048<br>N=1048<br>Lost to follow-up: NA | No funding or grant support* |

BMI: body mass index; GORD: gastro-oesophageal reflux disease; LA: Los Angeles; LNF: laparoscopic Nissen fundoplication; NA: not applicable (only patients who completed follow-up were included); NR: not reported; PPI: proton-pump inhibitor.

Riegler et al (2015)[11]

Riegler et al (2015) reported the results of a prospective observational study of patients undergoing LINX implantation (N = 202) or LNF (N = 47). This study had a broader inclusion criteria compared to other available evidence and included patients with advanced GORD (hiatal hernia >3 cm, Barrett's oesophagus, motility disorders or grade C/D oesophagitis as defined by the Los Angeles classification[13]) as well as those with moderate GORD. Patients undergoing the LNF procedure had significantly higher rates of advanced GORD at baseline than those undergoing LINX implantation. Baseline characteristics are reported in Table 2.

**Table 2 Baseline characteristics of patients in Riegler et al (2015)[11]**

| Characteristic | LINX | LNF<br>Baseline | P value (between-group comparison) |
|---|---|---|---|
| Age, years (mean ± SD) | 46.6 ± 13.9 | 52.8 ± 12.8 | 0.007 |
| Men (%) | 61.7 | 60.0 | NR |
| BMI, kg/m$^2$ (mean ± SD) | 25.7 ± 3.8 | 26.1 ± 5.3 | 0.611 |
| Advanced GORD (%) | 6.4 | 61.7 | NR |

BMI: body mass index; GORD: gastro-oesophageal reflux disease; LNF: laparoscopic Nissen fundoplication; SD: standard deviation.

*Safety*

No significant differences were observed in the rate of intraoperative or procedure-related complications between the two groups up to 12 months post-implantation.

One patient in each group experienced an injury to the pleura (membrane around the lungs). In the intervention group two patients experienced minor bleeding (< 300 mL) with no clinical consequences, one patient had dysphagia and there was one case of pneumothorax (air between the lungs and the chest wall). In the comparator group one patient underwent laparoscopic revision for herniation.

*Effectiveness*

At the 12-month follow-up both groups showed improvement in GORD-HRQL score compared with baseline. There was no significant difference between the groups. Similarly, both groups were observed to have improvements in heartburn causing waking, reflux interfering with sleep, sleep with upper body elevated and extra-oesophageal, symptoms with no differences observed between groups. LINX implantation was associated with significantly better outcomes with respect to moderate/ severe regurgitation, discontinuation of proton-pump inhibitors (PPIs), bloating/gassy feeling and, ability to burp or vomit (Table 3). No subgroup analysis was undertaken on patients with advanced GORD and it was not reported whether effectiveness outcomes differed between these patients and those with moderate GORD. The authors noted that it was unclear to what extent the baseline differences between the two groups may have affected their results; however, they

suggested that differences in outcomes relating to ability to burp or vomit are direct surgical outcomes and therefore are not likely to be influenced by baseline characteristics.

**Table 3 Summary of effectiveness data reported in Riegler et al (2015)[11]**

| Outcome | LINX Baseline | LINX 12 months | LNF Baseline | LNF 12 months | P value (between-group comparison) |
|---|---|---|---|---|---|
| GORD-HRQL score (median) | 20.0 | 3.0 | 23.0 | 3.5 | 0.2 |
| Heartburn waking from sleep (%) | 31 | 4 | 40 | 9 | 0.2 |
| Reflux interfering with sleep (%) | 62 | 12 | 73 | 17 | 0.3 |
| Sleep with upper body elevated (%) | 48 | 7 | 47 | 9 | 0.5 |
| Moderate or severe regurgitation (%) | 58 | 3 | 60 | 13 | 0.01 |
| Extra-oesophageal symptoms (%) | 64 | 22 | 53 | 17 | 0.6 |
| Discontinuation of PPIs (%) | NA | 82 | NA | 63 | 0.009 |
| Bloating and gassy feeling | NR | 10 | NR | 32 | <0.001 |
| Difficulty swallowing | NR | 7 | NR | 11 | 0.4 |
| Ability to burp | NR | 98 | NR | 89 | 0.0007 |
| Ability to vomit | NR | 91 | NR | 44 | <0.001 |

GORD: gastro-oesophageal reflux disease; GORD-HRQL: GORD-health related quality of life; LNF: laparoscopic Nissen fundoplication.

## Warren et al (2015)[12]

Warren et al (2015) reported the results of a retrospective comparison of LINX implantation and LNF. All patients who underwent either procedure at three centres in the United States of America between April 2007 and December 2014 and who met the inclusion criteria outlined in Table 1 were identified. Of the 455 identified patients, 21 who had undergone LINX implantation and 19 who had undergone LNF were excluded due to a lack of follow-up data. Patients in the LINX group had a median age of 54 years (range 42-64) and 32 per cent had a body mass index (BMI) greater than 30 kg/$m^2$. In the LNF group the median age of patients was 52 years (range 43-64) and 40 per cent had a BMI greater than 30 kg/$m^2$. The safety analysis included 201 patients in the LINX group and 214 in the LNF group. The effectiveness analysis included all patients with 12 months' (minimum) follow-up data available (LINX, N = 169, and LNF, N = 185). The authors performed a propensity analysis of 114 patients in the intervention group matched to 114 patients in the comparator group. This examined the baseline characteristics relating to the presence of oesophagitis and Barrett's oesophagus, hiatal hernia size, Hill grade and BMI. No differences in baseline characteristics were reported for this subgroup of patients. Outcomes for the propensity analysis were measured at a mean follow-up time of 11 months for the LINX group and 16 months for the LNF group. It should be noted that a minimum follow-up of 12 months was an inclusion criteria for the trial; no reason for this discrepancy was provided.

*Safety*

No significant differences in 30-day post-operative complications were observed between the groups. One major complication was observed in the LINX group (a gastro-oesophageal junction obstruction required reoperation). Three patients in the LNF group experienced major complications including one gastro-oesophageal junction obstruction requiring reoperation and two cases of retro-oesophageal abscesses necessitating surgical drainage. Minor complications were experienced by 14 patients in the LINX group and 18 patients in the LNF group; the nature of these complications was not reported.

Two patients required removal of the LINX device; one due to device erosion and the second due to failure of the device to control reflux, as evidenced by positive pH test results and presence of symptoms. Two patients required revision of LNF due to recurrence of hiatal hernia with symptomatic GORD.

*Effectiveness*

Effectiveness outcomes were measured 12 months post-surgery. Patients in the LINX group were more likely to retain the ability to burp (96% versus 69%, $p < 0.001$) and vomit (95% versus 43%, $p < 0.001$). Incidence of moderate or severe gas bloat and dysphagia were similar between the two groups. Equivalent numbers of patients in both groups reported satisfaction with the procedure (85% versus 91%, $p = 0.09$) and likelihood of undergoing the procedure again (90% versus 89%, $p = 0.75$).

Results of the propensity analysis of 114 matched patients showed that more patients in the LINX group retained the ability to burp (88% versus 40%, $p < 0.001$) and vomit (97% versus 66%, $p < 0.001$). More patients in the LINX group reported that they would undergo the procedure again than in the LNF group (93% versus 83%, $p = 0.01$). No significant differences were found in rates of moderate or severe gas bloat, dysphagia or patient satisfaction.

Ganz et al (2016)[8]

Ganz et al (2016) reported the five-year follow-up data of an industry sponsored, prospective, multicentre case series trial of 100 patients implanted with the LINX system. Results from the first three years of follow-up of this trial were included in the 2013 Technology Brief; 82 patients were available for the five-year follow-up endoscopy. Patients had a median age of 53 years (range 18-75 years) and a median body mass index of 28 $kg/m^2$ (range 20-35 $kg/m^2$). Primary effectiveness outcomes for the five-year follow-up were a 50 per cent reduction in the GORD-health related quality of life (GORD-HRQL) questionnaire compared with baseline (score from 0-50 with higher score representing worse symptoms) and number of patients experiencing a reduction in PPI dosage of at least 50 per cent. The criteria for long-term efficacy were met if at least 60 per cent of patients achieved the primary outcomes. No additional oesophageal pH monitoring was performed beyond the 12-month follow-up.

*Safety*

No new safety concerns have emerged since the results of the three-year follow-up were published in 2013. In total, seven patients required device removal during the trial. Four removals were due to persistent dysphagia (difficulty swallowing) (at 21, 31, 93 and 1,807 days after implantation), one patient required device removal at 357 days post implantation due to intermittent vomiting, one patient required removal at 489 days due to persistent reflux symptoms and one device was removed after 1,062 days following persistent chest pain. Three of these patients subsequently underwent uneventful LNF.

Oesophagitis was present in 34 patients before implantation. By the five-year follow-up this had healed in 26 patients (77%). Of the eight patients with ongoing oesophagitis, six had grade A and one had grade B (remaining patient not categorised by authors). During the course of the study, five additional patients developed: four grade A and one grade B. No patients developed Barrett's oesophagus.

Patients reported less diarrhoea ($p = 0.1$), constipation ($p = 0.008$) and nausea/vomiting ($p = 0.003$) five years after treatment compared with baseline measures.

*Effectiveness*

A 50 per cent reduction in GORD-HRQL score was reported in 70 patients (83%) at five years. Median GORD-HRQL scores (with PPI use) dropped from 11 out of 50 at baseline to 4 out of 50 at the five-year follow-up. A reduction (≥ 50%) in daily PPI use occurred in 76 patients (89%). Based on these results criteria for long-term efficacy were met.

In addition to the primary outcomes, the number of patients with moderate or severe heartburn decreased from 89 per cent to 12 per cent ($p < 0.001$) and patients with moderate or severe regurgitation decreased from 57 per cent to one per cent ($p < 0.001$). Patient dissatisfaction decreased from 95 per cent to seven per cent at five years post-implantation ($p < 0.001$). Daily use of PPIs was 100 per cent at baseline compared with 15 per cent at five years; 75 per cent of patients had complete cessation of PPI use while nine per cent did not require daily medication.

After five years implantation all patients reported being able to belch and vomit if required.

'Bothersome' swallowing was reported by five patients both at baseline and at five-years post-implantation. Symptoms of bloating and/or gas were reported in 52 patients at baseline (52%) and seven patients at five years (8%, $p < 0.001$).

Lipham et al (2014)[9]

Lipham et al (2014) presented a summary of all safety-related events that occurred in the first 1,048 devices implanted world-wide at 82 institutions in the United States of America and Europe between February 2007 and July 2013. The median implant duration was 274 days. Adverse events were identified from the published clinical literature, the FDA's

Summary of Safety Effectiveness Data and from information provided by the device manufacturer. Events included in the analysis were any patient related experience that resulted in complications during or after surgery, an inability to implant the device, a device malfunction that harmed a patient, a device related event that required intervention and any hospital readmission or reoperation.

*Safety*

A total of 111 events occurring in 82 patients at 26 medical centres were identified. Events were categorised as intra- or peri-operative complications (occurring in 0.1% of patients), readmission (1%), oesophageal dilation (6%), device removal (3%) and device erosion (0.1%).

No intraoperative complications were reported. One patient had an acute respiratory arrest immediately following device implantation which was considered to be unrelated to the device. Readmission was required in 14 patients, all of whom reported minor morbidity such as dysphagia, pain, nausea and vomiting. All readmissions but one occurred within 90 days of the implantation. Oesophageal dilation was required in 59 patients, 45 of which were required in the first 90 days of treatment. Two patients were found to have oesophageal candidiasis at the time of dilation, which was treated with antifungal therapy. Device removal was required in 36 (3%) patients; median implant duration at the time of removal was 94 days (range 6-1,302 days). All removals were non-emergency procedures by a laparoscopic approach without conversion to laparotomy or any complications. In these 36 patients reasons for removal were dysphagia (23 patients, 64%), GORD symptoms (7 patients, 19%), pain (3 patients, 8%), vomiting (1 patient, 3%) and a planned MRI (1 patients (3%). One patient was reported to have device erosion into the oesophageal lumen. The erosion was identified by oesophagogastroduodenoscopy performed to investigate persistent dysphagia. The device was removed in two procedures; an endoscopy to remove the eroded portion of the device followed by a laparoscopy to remove the remainder of the device. The patient made a full recovery with no complications.

*Effectiveness*

No effectiveness outcomes were reported in this study.

**2016 Economic evaluation**

One study was identified that analysed the cost of LINX implantation compared to LNF.[10] Reynolds et al (2015) included a cost analysis on a subset of patients from the multicentre study reported by Warren et al (2015). Patients undergoing a LINX implantation or LNF procedure performed by a single surgeon at two centres between January 2010 and June 2013 were included in the retrospective analysis. All hospital charges were obtained for each patient. Physician charges were not included in the analysis as they were reported to represent a fixed cost regardless of procedure type or patients and were billed separately.

Length of stay information was obtained from hospital records and was calculated from the time the patient was admitted to the pre-operative area until the discharge was recorded in the computer. Baseline characteristics were equivalent between the two groups except that there were more men in the LINX group (62% versus 46%).

Overall, there was no significant difference in the charges associated with LINX implantation and LNF. The mean total charges associated with LINX implantation were $65,974 (SD $22,423) and the mean total charges associated with the LNF procedure were $68,178 (SD $23,640).[c] While LINX was associated with higher charges for supplies (due primarily to the cost of the device), this was offset by higher charges for LNF in all other categories (pharmacy, laboratory, radiology, operating room services, anaesthesia, hospital board).

The authors noted that the information provided in this study represents the charges set by the hospital, not the cost of the procedure, which is dependent on the type of insurance and vendor and payer contracts. As such, the data presented in this study enables comment on comparative charges but should not be taken to represent the actual cost of the procedure. In addition, as this is a USA-based study the differences in health systems and funding arrangements compared to the Australian and New Zealand health systems may make limit the applicability of this study to the Australasian context.

Reigler et al (2015) provided a comparison of the healthcare utilisation between patients undergoing LINX implantation compared to those undergoing LNF.[11] The authors reported that the number of patients requiring an unscheduled office visit, outpatient intervention or testing was comparable between the two groups. Visits to the emergency room were reported for four per cent of patients in the LINX group compared to two per cent of patients in the LNF group. Readmission to hospital was reported in five per cent and four per cent of LINX and LNF patients, respectively. Reoperation was required in four per cent of the LINX patients and six per cent of the LNF group. No statistical analysis of these results was reported, and again it should be noted that patients in the LNF group were more likely to have advanced GORD than those in the intervention group.

**2016 Ongoing research**

Four ongoing clinical trials were identified from searches of ClinicalTrials.gov and the Australian and New Zealand Clinical Trials Registry (Table 4). One trial is a multicentre randomised controlled trial comparing LINX to proton pump inhibitor therapy (NCT02505945). Two trials are of case series design to evaluate the LINX device in patients who have undergone laparoscopic sleeve gastrectomy (NCT02429830 and NCT02762487). The final trial is an ongoing post-approval study of the device (NCT01940185). All trials are sponsored by the device manufacture (Torax Medical, Inc.).

c AUD = 0.735 USD, currency conversion performed on 11 May 2016, source XE Currency Converter

**Table 4 Ongoing clinical trials for the LINX Reflux Management System**

| Study<br>Location | Study Design | Number of patients<br>Indication | Intervention | Primary outcomes | Trial status<br>(Estimated completion date) |
|---|---|---|---|---|---|
| NCT02505945<br>USA | RCT<br>Multicentre (22 centres) | 150 patients aged ≥ 21 years who have unsatisfactory symptom response to single-dose proton pump inhibitors and who have abnormal distal oesophageal pH. | LINX versus double-dose proton pump inhibitors | Percentage of subjects with resolution of GORD symptom | Currently recruiting<br>(April 2017) |
| NCT02762487<br>Germany, Italy | Case series<br>Multicentre (3 centres Germany, 1 centre Italy) | 100 patients aged ≥ 21 years who have undergone laparoscopic sleeve gastrectomy >12 months prior to device implantation (with at least 30% EWL) who have documented pathologic oesophageal acid exposure. | LINX | Change in GORD-HRQL score<br>Number of patients with serious complications<br>Change in total distal acid exposure | Currently recruiting (August 2017) |
| NCT02429830<br>USA | Case series<br>NR if multicentre | 100 patients aged ≥ 21 years who have undergone laparoscopic sleeve gastrectomy >12 months prior to device implantation (with at least 30% EWL) who have documented pathologic oesophageal acid exposure. | LINX | Change in GORD-HRQL score<br>Number of patients with serious complications<br>Change in total distal acid exposure<br>Percentage of patients with esophagitis | Not yet open for recruitment, estimate start date July 2016<br>August 2017 |
| NCT01940185<br>USA | Case series<br>Multicentre (19 centres) | 200 patients with the LINX device. Post-approval study to monitor safety and efficacy. | LINX | Successful reduction of total GORD-HRQL score<br>Serious, device-related adverse events | Ongoing, not recruiting<br>(September 2019) |

EWL: % of excess weight lost; GORD: gastro-oesophageal reflux disease; GORD-HRQL: GORD-health-related quality of life; NR: not reported; RCT: randomised controlled trial; USA: United States of America.

## 2016 Other issues

All included studies in this update had at least one author who had served as a consultant to the device manufacturer. All identified ongoing clinical trials are sponsored by Torax Medical, Inc. This may reflect the emerging stage of development of the device.

Incidences of device erosion have now been reported. The first, reported in Lipham et al (2014) and Warren et al (2015) were identified 21 months post-implantation.[9, 12] The device was removed in two stages. The second incidence was reported in a case report by Bauer et al (2015).[14] Erosion occurred at two years post-implantation and the device was removed in a single endoscopic procedure. In both cases patients experienced complete healing of the

erosion without further complication. These cases demonstrate that erosion of the LINX device can occur around two years after implantation and this issue should continue to be monitored as post-approval studies progress.

Due to the retrospective nature of the available comparative evidence, it is likely that some patients included in the intervention (LINX) arms of these studies were included in the two case series trials identified in the 2013 Technology brief. It is not clear from any of the studies how many patients have been included in other studies.

Since the original 2013 Technology Brief, preliminary evidence on a wider patient population has been published. Riegler et al (2015) included patients with advanced GORD (hiatal hernia >3 cm, Barrett's oesophagus, motility disorders or grade C/D oesophagitis), although no subgroup analysis was performed on these patients so it is not clear if the effectives of the device is maintained in this group.[11] There is emerging evidence (two case series studies with <10 patients and ongoing clinical trials) of patients who have undergone bariatric surgery. The expansion of the inclusion criteria in recent trials likely reflects the population of patients who may be treated with the device in practice and results from these trials may be more applicable to decision makers assessing the device.[15, 16]

MRI safety is a still a concern with the device; however, newer iterations of the device are more compatible with MRI imaging than the first generation LINX systems. Torax Medical, Inc. reported that devices implanted prior to May 22, 2015 cannot undergo MRI imaging above 0.7 T. Devices implanted after this date may be able to undergo imaging up to 1.5 T, depending on which generation device was implanted.[17]

**2016 Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

| | |
|---|---|
| Total number of studies | 5 |
| Total number of Level III-2 studies | 3 |
| Total number of Level IV studies | 2 |

**Search terms used [MeSH terms]**

LINX reflux management system (keyword)

Magnetic AND gastroesophageal reflux

Magnetic AND sphincter augmentation (keyword)

Sphincter augmentation AND gastroesophageal reflux

**Search date**

3/5/2016

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## Technology, Company and Licensing

| | |
|---|---|
| **Register ID** | **WP128** |
| **Technology name** | **LINX® Reflux Management System** |
| **Patient indication** | **Patients with gastro-oesophageal reflux disease** |

### Description of the technology

The LINX® Reflux Management System consists of a small flexible and expandable 'bracelet' of titanium beads, with magnetic cores that are linked by independent titanium wires.[1, 2] The device is placed laparoscopically at the gastro-oesophageal junction (Figure 2) to help the lower oesophageal sphincter (LOS) resist opening, thereby preventing stomach contents from entering the oesophagus without affecting the natural physiologic function of the LOS.[1, 3] The LINX® device permits the expansion of the LOS so that swallowing or the release of elevated gastric pressure (associated with belching or vomiting) may take place.[2] This is achieved when the peristaltic pressure of the food bolus, for example, is greater than that of the magnetic attraction between adjacent beads of the LINX® System, causing them to expand and 'open' the device. As the food moves through the oesophagus into the stomach and the peristaltic pressure drops below that of the magnetic attraction between the beads, they are drawn back together and the device 'closes'.[3] The attractive force between the beads comprising the LINX® device range from 40 G (closed) to 7 G (fully expanded).[2] The device comes in different sizes ranging from 12 to 16 beads; the size of the device implanted is determined at the time of placement, using specialised sizing equipment to measure the outer diameter of the oesophagus.[2]

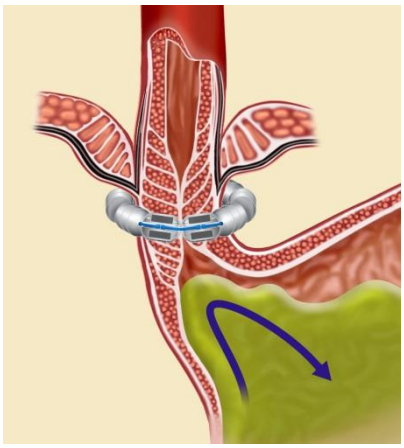

**Figure 2** **LINX® device implanted around the oesophagus to assist lower oesophageal sphincter closure (printed with permission).[1]**

Typically, placement of the device occurs under general anaesthesia via five laparoscopic ports. Dissection takes place so that a tunnel may be formed between the posterior

oesophageal wall and the posterior vagus nerve. A drain is placed within the tunnel, encircling the oesophagus, to maintain access for the sizing tool and then the LINX® device. Following the insertion of a correctly-sized LINX® device, its ends are secured at the anterior surface of the oesophagus. Implantation of the LINX® device takes approximately 30 minutes and patients are generally discharged from hospital on the same or the following day. Patients are advised to continue a normal diet, as tolerated, and cease taking acid suppression medication.[2]

The LINX® system is a novel treatment for gastro-oesophageal reflux disease (GORD) in that it is reversible and does not alter the hiatal or gastric anatomy or physiology of the patient. This means that future treatments with other therapies, such as fundoplication, are possible if required.

**Company or developer**

Torax® Medical, Inc., Minnesota, United States of America.

**Reason for assessment**

A novel surgical treatment alternative with potentially fewer side effects for managing GORD, a condition which causes a large patient group significant morbidity.

**Stage of development in Australia**

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

**Licensing, reimbursement and other approval**

The LINX® Reflux Management System received CE Mark approval in April 2010[4] and United States Food and Drug Administration (FDA) pre-market approval in March 2012 (approval umber P100049).[5] The device is not listed on the Australian Register of Therapeutic Goods (ARTG) at this time. Correspondence with Torax® Medical, Inc. indicated that they currently do not plan to seek Therapeutic Goods Administration (TGA) approval.

**Australian Therapeutic Goods Administration approval**

- ☐ Yes — ARTG number (s) Not applicable
- ☒ No
- ☐ Not applicable

**Technology type** **Device**

**Technology use** **Therapeutic**

## Patient Indication and Setting

### Disease description and associated mortality and morbidity

The oesophagus carries food from the mouth to the stomach. The LOS is a ring of muscle at the bottom of the oesophagus which acts to keep stomach contents from refluxing back into the oesophagus.[6] In some people, the LOS does not work correctly and stomach acids are able to enter the oesophagus causing a burning sensation in the chest or throat known as heartburn.[6] GORD is a common and chronic gastrointestinal disorder where patients experience frequent acid reflux. The main symptoms of GORD are heartburn and acid regurgitation. Other symptoms include nausea, hoarseness, laryngitis, chronic dry cough, asthma, 'lump-in-throat' feeling, sudden excessive saliva, bad breath and chest pain or discomfort.[7] In some cases, GORD may be caused by or associated with hiatal hernia, which occurs when part of the stomach herniates through the diaphragmatic hiatus (the opening in the diaphragm that separates the chest from the abdomen).[8] It is thought that a hiatal hernia may weaken the LOS resulting in GORD.[8] These types of hernia may be repaired at the time of anti-reflux surgery if necessary. Patients with GORD whose symptoms are not well-managed are at risk of developing erosive oesophagitis, Barrett's oesophagus, stricture and adenocarcinoma.[2]

### Number of patients

It has been estimated that 10 to 20 per cent of the Western population suffer from chronic GORD.[9] In Australia, it is estimated that approximately nine per cent of the population suffer from GORD, which corresponds to approximately 2.1 million people.[10] A population-based study (n=1,000) conducted in Wellington, New Zealand found that, over a 12-month period, 34 per cent of people had suffered from dyspepsia, 30 per cent had reflux and 45 per cent had both symptoms.[11] The frequency of these symptoms ranged from once a month (48% of people) to several times a week (19%) or daily (6%).[11]

According to the Australian Statistics on Medicines 2010 report, the number of prescriptions for the following PPIs issued in 2010 was as follows: approximately 6.5 million for Esomeprazole, 600, 000 for Lansoprazole, 3.2 million for Omeprazole, 4.3 million for Pantoprazole and 2.5 million for Rabeprazole.[12]

Between 2006 and 2007, 61,049 patients were admitted to hospital with GORD (with or without oesophagitis) in Australia.[13] In addition, GORD is one of the ten most frequently managed problems in general practice.[14] In New Zealand, from 1 July 2010 to 30 June 2011, there were 3,741 discharges from publically-funded hospitals and 202 from privately-funded hospitals for patients with GORD.[15]

A number of patient-related factors have been identified that potentially increase the risk of developing GORD. These include obesity (body mass index, BMI, >30kg/$m^2$), alcohol consumption (>7 standard drinks per week), chronic airway disease, intellectual disability, spending prolonged periods in a supine position, and having a first-degree relative who has reflux symptoms.[16]

| | |
|---|---|
| **Speciality** | **Upper gastrointestinal surgery** |
| **Technology setting** | **General Hospital** |

## Impact

### Alternative and/or complementary technology

The LINX® Reflux Management System is an alternative technology to the current surgical treatment strategies available for patients with GORD. The LINX® system is a reversible surgical intervention that does not interfere with the anatomical or physiological function of the patient's digestive system. ENREF 2

### Current technology

Current treatment options for patients with GORD generally include long-term pharmaceutical intervention or surgical alteration of the gastric anatomy.[2] Long-term acid suppression medications, often in the form of proton pump inhibitors (PPIs), work by suppressing the acid produced in the stomach through blocking enzymes on the surface of the acid-producing cells.[17] These drugs are usually an effective first-line therapy; however, a considerable proportion of patients with GORD (up to 40%) have only partial symptom response, particularly those with a mechanically defective LOS.[2, 18]

Surgical intervention for GORD typically involves adding to the bulk of or tightening the LOS.[3] The most common (gold standard) surgical treatment for GORD is Nissen fundoplication.[18] Nissen fundoplication is a surgical procedure whereby the fundus (upper curve of the stomach) is wrapped around the oesophagus so that the lower oesophagus passes through a tunnel of stomach muscle.[19] This acts to reinforce the LOS and restrict the reflux of stomach contents into the oesophagus. The side effects associated with surgical treatments for GORD, which have led to their limited acceptance, include abdominal bloating, increased flatulence, the inability to belch or vomit, and persistent difficulty swallowing.[18]

### Diffusion of technology in Australia

The LINX® Reflux Management System is not in use in Australia at this time, and the manufacturer has no plans to seek listing on the ARTG. There are no clinical trials of the device being conducted in an Australian healthcare setting.

### International utilisation

| Country | Level of Use | | |
|---|---|---|---|
| | Trials underway or completed | Limited use | Widely diffused |
| Austria | ✓ | | |
| France | ✓ | | |
| Germany | ✓ | | |
| Italy | ✓ | | |
| Switzerland | ✓ | | |
| United Kingdom | ✓ | | |
| United States | ✓ | | |

The LINX® Reflux Management System was first used in Europe in 2007 as part of a multicentre feasibility trial.[2] Continued use of the device, on a registry basis, beyond the completion of the trial has taken place.[2] Use of the device in the United States, in two clinical trials, occurred originally under a United States FDA investigational device exception.[2] Correspondence with Torax® Medical, Inc. indicated that approximately 1,000 LINX® systems have been implanted to date, about half of these in Europe and the other half in the USA.

### Cost infrastructure and economic consequences

The cost of the LINX® Reflex Management System is A$5,045[4] for the 12 to 16 bead device and A$673 for a pack of five laparoscopic sizing tools. Additional costs would include those related to operative facilities, staff, anaesthesia and hospital stay.

There would also be costs associated with the initial training of surgical staff to undertake the implantation procedure. The LINX® system offers an alternative surgical intervention to patients with GORD, with the potential for fewer side effects. Therefore, it may offer greater economic impact on the healthcare system, with respect to burden of disease, compared with present clinical practice because it gives patients who would otherwise not have considered surgical intervention an option. Despite this, current surgical interventions for GORD are considerably less expensive than the LINX® system. A standard laparoscopic fundoplication procedure (without hernia repair) has a Medicare Benefits Schedule (MBS) fee of $871.30 (75% benefit = $653.50) (MBS item number 31464).[20]

### Ethical, cultural or religious considerations

No ethical, cultural or religious issues where identified in the literature.

[4] 1 AUD = 1.68 GBP

## Evidence and Policy

A total of four case series studies (level IV Intervention evidence) were eligible for inclusion in this Technology Brief[3, 18, 21, 22], three of which provided short- (3- and 6-month)[22], medium- (1- and 2-year)[21] and long-term (3- and 4-year)[3] follow-up data for the same patient population. Overall, the safety and effectiveness of the LINX® Reflux Management System was evaluated in 144 patients with GORD (Table 5).

**Table 5 Study profile of included studies**

| Study | Ganz et al. 2013[18] | Bonavina et al 2008[22], Bonavina et al 2010[21], Lipham et al 2012[3] |
|---|---|---|
| **Level of evidence** | IV | IV |
| **Number of patients** | 100 | 44 |
| **Patient details** | Patients 18 to 75 years of age, ≥ 6-month history of GORD, partial response to daily PPIs, increased exposure to oesophageal acid confirmed by pH-monitoring | Patients 18 to 75 years of age, candidates for anti-reflux surgery, ≥ 6 months documented history of GORD, incomplete symptom response to daily PPIs, confirmed abnormal oesophageal acid exposure whilst on PPIs, normal contraction amplitude and wave form in oesophageal body |
| **Intervention** | LINX System | LINX System |
| **Characteristics of patient population** | 52% male; median age 53 years; median symptom duration 5 years; median DeMeester score* 36.6. | 59% male; mean age 42.3 years; mean BMI 25.7 kg/m$^2$; primary symptom of heartburn; no hernia, n=18; <3 cm sliding hiatal hernia, n=26. |
| **Losses to follow-up** | 1-year, n=2<br>2-year, n=10<br>3-year, n=15 | Median 895 days, n=1 |
| **Follow-up (time points)** | 1 week; 3 and 6 months; 1, 2 and 3 years | 3 and 6 months; 1, 2, 3 and 4 years |
| **Conflict of interest** | Study designed and supported by Torax® Medical, Inc. | Four authors were/are consultants for Torax® Medical, Inc. |

GORD: gastro-oesophageal reflux disease; PPIs: proton pump inhibitors; BMI: body mass index.

*DeMeester score: composite score of factors measured during 24 to 48 hour pH study; including percentage of time pH < 4 in various positions, total number of reflux episodes, number of reflux episodes lasting >5 minutes and duration of longest reflux episode. A score ≥14.7 indicates abnormal reflux.

### Safety and effectiveness

#### Ganz et al 2013[18]

This industry-sponsored, prospective, multicentre (13 centres in the USA and one centre in the Netherlands) case series study enrolled 100 patients with GORD between January and September 2009 to be implanted with the LINX® device. Patients were excluded if they had evidence of a large hiatal hernia, oesophagitis of Los Angeles classification[5] Grade C or D, BMI > 35 kg/m$^2$, Barrett's oesophagus, a motility disorder, dysphagia more than three times per week, or an allergy to any of the materials in the LINX® device. Baseline screening of patients included endoscopy, pH monitoring (off PPIs), barium oesophagography and manometry. These tests, along with chest radiography, were repeated at the 1- and 2-year

[5] **Los Angeles classification of oesophagitis[18]**
Grade A: ≥1 mucosal break(s) ≤5 mm in length; Grade B: ≥ 1 mucosal break(s) >5 mm in length; Grade C: mucosal breaks that extend between ≥2 mucosal folds but involve <75 per cent of the circumference of the oesophagus; Grade D: mucosal breaks involving ≥ 75 per cent of the circumference of the oesophagus.

follow-up. The use of PPIs was assessed at baseline, one week after treatment, three and six months after treatment, and yearly thereafter. Quality of life (QoL) was measured using the Gastroesophageal Reflux Disease–Health Related QoL Questionnaire (range 0 [good]–50 [poor]). The LINX® device was implanted laparoscopically, but the exact surgical technique was not described.

The primary effectiveness endpoint reported was the proportion of patients with either normalised oesophageal acid exposure (≤4.5% of a 24-hour period with pH <4) or at least a 50 per cent reduction in the proportion of time pH was less than 4 (without PPIs), compared with baseline. Secondary endpoints included at least a 50 per cent reduction in QoL questionnaire score and daily PPI dose, compared with baseline measurements. Inclusion criteria and baseline patient demographics are summarised in Table 5.

*Safety*

There were no intraoperative or device-related complications reported. All adverse events and incidences of device removal are reported in Table 6.

Major complications occurred in six of the 100 patients (6%), four of whom required device removal. Three of the four device removals occurred in the early postoperative period due to persistent dysphagia (at 21, 31 and 93 days after implantation), while the fourth device removal occurred 357 days after treatment due to intermittent vomiting, which continued after the removal of the device. The remaining two patients experienced nausea and vomiting that required hospitalisation; both cases were resolved with conservative treatment. Two additional devices were removed as part of each patient's "disease management": one patient experienced persistent reflux symptoms, while the other had persistent chest pain. Three of the six patients who had their devices removed underwent uncomplicated Nissen fundoplication.

Oesophageal dilation was undertaken in 19 patients to treat the most common complication of dysphagia, which occurred in a total of 68 patients (68%). Eighty-four per cent (16/19) of these patients experienced improvement in their dysphagia symptoms. The proportion of patients with Grade A and B oesophagitis decreased significantly, from 40 per cent at baseline to 12 per cent at the 1-year follow-up and 11 per cent at the 2-year follow-up ($p<0.001$).

**Table 6 Adverse events reported by Ganz et al. (2013)[18]**

| Adverse event | Patients (n=100) | Level of intensity (%) | | | Device removal |
|---|---|---|---|---|---|
| | | Mild | Moderate | Severe | |
| Dysphagia | 68 | 47 | 16 | 5 | 3 |
| Bloating | 14 | 12 | 2 | 0 | 0 |
| Pain | 25 | 7 | 13 | 5 | 1 |
| Painful swallowing | 8 | 4 | 3 | 1 | 0 |
| Hiccups | 8 | 7 | 1 | 0 | 0 |
| Nausea | 7 | 3 | 2 | 2 | 0 |
| Inability to belch or vomit | 6 | 5 | 1 | 0 | 0 |
| Decreased appetite | 4 | 4 | 0 | 0 | 0 |
| Flatulence | 2 | 2 | 0 | 0 | 0 |
| Belching | 2 | 2 | 0 | 0 | 0 |
| Weight loss | 2 | 2 | 0 | 0 | 0 |
| Food impaction | 1 | 0 | 1 | 0 | 0 |
| 'Lump in throat' sensation | 1 | 1 | 0 | 0 | 0 |
| Irritable bowel syndrome or dyspepsia | 1 | 1 | 0 | 0 | 0 |
| Regurgitation of sticky mucus | 1 | 0 | 1 | 0 | 0 |
| Uncomfortable feeling in chest | 1 | 1 | 0 | 0 | 0 |
| Vomiting | 1 | 0 | 1 | 0 | 1 |
| Persistent gastro-oesophageal reflux disease symptoms | 1 | 0 | 1 | 0 | 1 |

*Effectiveness*

The median time taken to implant the LINX® device (measured from placement of the last laparoscopic port to removal of the first laparoscopic port) was 36 minutes (range 7–125 minutes). All patients were discharged within one day of the operation.

The primary effectiveness endpoints of normalised oesophageal acid exposure or a reduction of at least 50 per cent in oesophageal acid exposure (compared with baseline) was achieved in 67 per cent (64/96 patients) and 58 per cent (56/96) of patients, respectively. Collectively, 67 per cent of patients achieved the primary effectiveness endpoint. All components of the DeMeester score/pH monitoring (described previously) were significantly improved at 1-year follow-up ($p$<0.001 for all components), compared with baseline.

The secondary effectiveness endpoints of at least a 50 per cent reduction in QoL score and daily PPI dose was achieved in 92 per cent (95% confidence interval [CI] [85, 97]) and 93 per cent (95% CI [86, 97]) of patients respectively. Statistical analyses found significant improvements in median QoL scores after LINX® implantation at 1-, 2- and 3-year follow-up, with or without PPIs, compared with baseline ($p$<0.005). Eighty-seven per cent of patients

reported continued PPI cessation at 3-year follow-up. Regurgitation symptoms, measured using the Foregut Symptom Questionnaire, were significantly improved at 1-, 2- and 3-year follow-up for all severity grades (mild, moderate and severe; $p<0.001$).

Bonavina et al 2008[22], Bonavina et al 2010[21], Lipham et al 2012[3]

This multicentre (four centres across the USA and Europe), prospective case series study enrolled patients with GORD between February 2007 and October 2008 for treatment with the LINX® device. The earliest study reported that 38 of 41 enrolled patients were implanted with the LINX® device (the remaining three were unable to undergo implantation for the reasons stated below under the Safety subheading); however, the latter two studies reported a total of 44 patients were implanted with the LINX® device. It is unclear why the patient number differs between the studies.

Patients were ineligible for inclusion in this study if they had any of the following: a hiatal hernia of at least 3 cm; a history of abdominal surgery or endoscopic anti-reflux procedures; erosive oesophagitis Grade B, C or D (Los Angeles Classification); a BMI greater than 35 $kg/m^2$; Barrett's oesophagus; motility disorders; gross oesophageal anatomic abnormalities; or known allergies to any of the materials that comprise the LINX® device. Baseline screening included a symptom questionnaire (Gastroesophageal Reflux Disease–Health Related QoL Questionnaire), endoscopy, Barium swallow, oesophageal manometry and pH monitoring. These, in addition to chest x-rays and a modified Barium swallow on postoperative day one, were repeated at 3-month, 1-year and 2-year follow-up. Oesophageal manometry and pH monitoring was performed at 3-month and 1-year follow-up only, with the exception of one European centre which performed pH monitoring at 2- and 3-year follow-up also. Symptom questionnaires and recording of adverse events were the only long-term (4-year) follow-up reported. Insertion of the LINX® device occurred via five laparoscopic ports, in a procedure similar to that described previously in this Technology Brief. Inclusion criteria and patient demographics at baseline are summarised in Table 5.

*Safety*

Three patients were unable to undergo implantation with the LINX® device. One was converted to Nissen fundoplication because of a hiatal hernia (>3 cm) and a leiomyoma at the oesophagogastric junction, another withdrew consent prior to surgery, and the third patient was found to have insufficient peristalsis (motility disorder). There were no intraoperative or device-related complications reported beyond one year.

At the 4-year follow-up, 95 per cent (42/44) of patients were free from major complications related to the LINX® device or the implantation procedure. The most common minor complication encountered was mild dysphagia, which occurred in 20 patients (43%) and resolved without the need for intervention within two months. In one case, persistent

dysphagia and oesophageal acid exposure resulted in device removal at eight months. Another patient was hospitalised for chest pain 22 days after implantation, which resolved completely by two months. It was not reported whether the chest pain was related to the LINX® device or implantation procedure. Two other patients underwent device removal: one at 18 months due to the need for magnetic resonance imaging (MRI) and the other elected to undergo Nissen fundoplication due to persistent GORD symptoms. All patients were able to belch and vomit following implantation with the LINX® device.

*Effectiveness*

The median operative time (measured from the time all laparoscopic ports were placed to when the first port was removed) was 40 minutes (range 19–104 minutes). Discharge from hospital occurred within 48-hours for 98 per cent (43/44) of patients.

The proportion of patients who remained off daily PPIs at the 3-month and 1- and 2-year follow-ups were as follows: 89, 90 and 86 per cent, respectively. The mean QoL score was significantly lower at three months (4.6, $p<0.005$), one year (3.8) and two years (2.4) after treatment ($p<0.0001$), compared with baseline (25.7). All patients (n=23) had a reduction in QoL scores of at least 50 per cent at the 4-year follow-up (Table 7).

**Table 7 Mean Gastroesophageal Reflux Disease–Health Related QoL Questionnaire score reported by Lipham et al[3]**

| | Follow-up time point (mean score) | | | | | |
|---|---|---|---|---|---|---|
| **QoL questionnaire** | **Baseline n=44** | **3-month n=37** | **1-year n=39** | **2-year n=35** | **3-year n=31** | **4-year n=23** |
| How bad is your heartburn? | 3.7 | 0.6 | 0.6 | 0.4 | 0.6 | 0.5 |
| Heartburn when lying down? | 3.1 | 0.3 | 0.4 | 0.3 | 0.4 | 0.2 |
| Heartburn when standing up? | 3.3 | 0.4 | 0.4 | 0.2 | 0.3 | 0.3 |
| Heartburn after meals? | 3.6 | 0.6 | 0.6 | 0.4 | 0.6 | 0.7 |
| Does heartburn change your diet? | 3.1 | 0.5 | 0.2 | 0.3 | 0.6 | 0.5 |
| Does heartburn wake you from sleep? | 2.5 | 0.0 | 0.3 | 0.1 | 0.3 | 0.0 |
| Do you have difficulty swallowing? | 1.2 | 0.7 | 0.6 | 0.3 | 0.3 | 0.4 |
| Do you have bloating and gassy feelings? | 2.9 | 0.8 | 0.5 | 0.5 | 0.4 | 0.4 |
| Do you have pain with swallowing? | 0.6 | 0.4 | 0.1 | 0.0 | 0.1 | 0.0 |
| If you take medication, does this affect your daily life? | 2.0 | 0.2 | 0.2 | 0.1 | 0.5 | 0.2 |
| **% of patients satisfied with their present condition?** | **0%** | **84%** | **87%** | **86%** | **88%** | **87%** |

There were no significant changes in manometric parameters (including LOS resting tone, LOS length, abdominal length, relaxation and swallowing effectiveness) at the 3-month and 1-year follow up, compared with baseline, with the exception of a significant increase in LOS resting pressure (6.5 to 14.6 mmHg) at one year in nine patients with hypertensive LOS pressure ($p<0.005$).

Oesophageal acid exposure returned to normal in 79 per cent (19/24) of patients at the 3-month follow-up and remained normalised at the 1-, 2- and 3-year follow-up in 77 per cent, 90 per cent and 80 per cent of patients respectively. Overall, all components of the DeMeester score/pH monitoring were significantly improved at the 3-month follow-up, compared with baseline, and remained significantly improved at the 1- and 2-year follow-up.

An additional 'article-in-press' was identified after the August HealthPACT committee meeting and is briefly summarised here.[23] This study was published by the same group of authors as Bonavina et al and reports the 6-year clinical outcomes of 100 consecutive patients with GORD implanted with the LINX® device in a single centre in Milan, Italy (some patient overlap is apparent). This article found median total acid exposure time was significantly reduced post-implant, as was GORD- related QoL. Independence from PPIs was achieved in 85% of patients and there were no long-term complications. Three patients required device removal due to consistent GORD symptoms. Overall, this study describes similar findings to those included in the Technology Brief and looks at a similar patient population (specifically those without significant hiatal hernia or esophagitis).

### Economic evaluation

There were no economic evaluations identified for the use of the LINX® Reflux Management System.

### Ongoing research

There were four ongoing trials identified from ClinicalTrials.gov and the Australian and New Zealand Clinical Trails Register, all of which had industry sponsorship and only one of which was comparative (Table 8).

**Table 8 Ongoing trials for LINX Reflux Management System**

| Trial Identifier | Country | Trial Status | N | Study Design | Interventions | Estimated completion date |
|---|---|---|---|---|---|---|
| NCT00776997 | United States, Netherlands | Ongoing but not recruiting | 100 | Case series | LINX | October 2014 |
| NCT01058070 | United States | Ongoing but not recruiting | 14 | Case series | LINX | October 2013 |
| NCT01057992 | Italy | Ongoing but not recruiting | 31 | Case series | LINX | October 2013 |
| NCT01624506 | Austria, Germany, Italy, United Kingdom | Recruiting | 800 | Non-randomised comparative | LINX versus laparoscopic fundoplication | January 2016 |

Like the current evidence base, these trials are being conducted in Europe and the USA and are examining similar treatment outcomes, including oesophageal acid exposure and the incidence of adverse events, in similar patient populations.

**Other issues**

- To date, all of the peer-reviewed literature looking at the safety and effectiveness of the LINX® Reflux Management System has been designed or sponsored by the manufacturer of the device. This is most likely a reflection of the stage of development of the device.
- The studies included in this Technology Brief had stringent inclusion and exclusion criteria, namely excluding those patients with significant oesophagitis and hiatal hernia, which makes it difficult to extrapolate the findings to the broader GORD population.
- Given the small number of patients implanted with the LINX® device in each of the included studies (i.e. Ganz et al enrolled 100 patients across 14 centres and Bonavina et al enrolled 44 patients across four centres) there is likely to have been a learning curve observed. It is possible that as the surgical team preforming LINX® implantation becomes more experienced in doing so it will impact the patient outcomes seen.
- The reversibility of the LINX® procedure must also be considered. Apart from reporting that patients who underwent device removal were able to undergo Nissan fundoplication, it is not clear from the included studies what complications, if any, were associated with device removal (for example, fibrosis).
- Device slippage/migration is also an issue. At this stage, there was no incidence of device migration in the included studies; however, as was the case for an earlier anti-reflux prosthesis (Angelchik™), migration is a potential problem that should continue to be monitored in long-term follow-up studies.
- It is important to note that patients implanted with the LINX® Reflux Management System will be unable to undergo MRI. Given the increased utilisation of MRI as a diagnostic tool, this is a significant consideration in regards to the suitability of this technology. Use of the device is also not recommended in patients with existing electrical implants (such as pacemakers and implantable defibrillators) or in those patients with metallic abdominal implants.[24]

**Summary of findings**

The findings of the two clinical trials reported in this Technology Brief illustrate promising results for the use of the LINX® Reflux Management System in treating patients with GORD. In particular, the device's ability to be removed if required and the lower rate of side effects, compared with conventional surgical intervention, make the device a favourable treatment alternative (provided its utility in patients with significant oesophagitis and hiatal hernia can

be determined). However, the evidence base for this technology is in its infancy and it is not currently possible to determine the safety and effectiveness of the LINX® device. Future studies should be comparative (ideally randomised), with broader patient populations and without industry sponsorship. Particular outcomes of interest for future studies should include the durability of the device (i.e. the lifespan of the magnets), its ability to reduce the likelihood of complications of GORD (i.e., Barrett's oesophagus and cancer) and patient QoL. In addition, regulatory approval of the LINX® Reflux Management System in Australia does not appear to be imminent, and the cost of the device is likely to be a barrier to its uptake in clinical practice at this time.

**HealthPACT assessment**

The LINX® Reflux Management System shows promising results. Given the unlikelihood of new evidence becoming available in the near future, it is recommended that the technology be monitored for a period of 36 months. In this time it is hoped that the device will be closer to implementation in Australia, its cost may no longer be preclusive and its evidence base will be more developed.

**Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies 4

Total number of Level IV intervention evidence studies 4

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**Search criteria to be used (MeSH terms)**

LINX reflux management system

Magnetic AND gastroesophageal reflux

Magnetic AND sphincter augmentation

Sphincter augmentation AND gastroesophageal reflux