RELIEF Study

A Prospective, Multicenter Study of **Re**flux Management
with the **LI**NX® System for Gastroesophageal
R**EF**lux Disease after Laparoscopic Sleeve Gastrectomy

PROTOCOL NUMBER	4600 Rev 5
SPONSOR	Torax Medical, Inc. 4188 Lexington Avenue North Shoreview, MN 55126 Phone: 651-361-8900 Fax: 651-361-8910
INVESTIGATOR'S SIGNATURE	I have received and reviewed the above mentioned protocol and revision. I agree to personally conduct or supervise the described clinical study in accordance with the protocol at my institution. _____ Principal Investigator's Printed Name _____ Principal Investigator's Signature _____ Date

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Protocol Synopsis Protocol ID 4600	
Sponsor	Torax Medical, Inc. 4188 Lexington Ave. North Shoreview, MN 55126 Tel: (651) 361-8900 Fax: (651)361-8910
Study Title	RELIEF Study: A Prospective, Multicenter Study of Reflux Management with the LINX® System for Gastroesophageal Reflux Disease after Laparoscopic Sleeve Gastrectomy
Study Device	The LINX® Reflux Management System (LINX)
Indication	The LINX® Reflux Management System is a laparoscopic, fundic-sparing anti-reflux procedure indicated for patients diagnosed with Gastroesophageal Reflux Disease (GERD) as defined by abnormal pH testing, and who are seeking an alternative to continuous acid suppression therapy (i.e. proton pump inhibitors or equivalent) in the management of their GERD.
FDA Approval	March 22, 2012
Study Design	An observational, multicenter, single-arm study with prospective enrollment.
Purpose	To evaluate the safety and efficacy of LINX for its approved indication in patients who have had prior gastric surgery, specifically, laparoscopic sleeve gastrectomy (LSG).
Objective	To confirm safety and efficacy after LSG in patients indicated for LINX is similar to the outcomes that formed the basis for Premarket Approval (PMA) to support modification of the current labeling with a statement that prior gastric surgery with LSG has been evaluated for safety and efficacy.
Number of Subjects	Up to 30 subjects
Study Centers	Up to 12 implanting sites in the U.S.
Study Duration	36 months (24-month enrollment period + 12-month follow-up period)
Evaluation of Safety	Rate of serious device and procedure related adverse events assessed by reporting all adverse events and by estimating the rate of serious device and procedure related adverse events through 12 months post implantation. Safety will also be evaluated by endoscopy to assess the mucosa and abdominal/chest X-ray evaluations to verify device location at 12 months post implantation.
Evaluation of Efficacy	Percentage of subjects reporting at the 12-month follow-up: • Normalization of total distal acid exposure (% total time pH<4) or at least 50% reduction in total distal acid exposure compared to baseline • At least 50% reduction in total GERD-HRQL score compared to baseline (off PPIs) • At least 50% reduction in average daily PPI dosage compared to baseline
Study Management	Torax Medical Inc. or Designate

Schedule of Data Collection

Screening/ Baseline	Implant /Discharge	2-week Post-Operative Visit (Day 7 – Day 21)	3 months (Day 76 – Day 104)	6 months (Day 150 – Day 210)	12-month Visit (Day 305 – Day 425)	Data Collected
X						Demographics (gender, race)
X					X	Height and Weight
X					X	Medical History
	X					Implant Procedure and Discharge Data
X					X	Endoscopy (LA Grade Classification)
X					X	Manometry/Motility
X	X[3]				X	Barium Esophagram
	X[3]				X	Upright Bi-Planar X-Rays (AP and Lateral)
X			X	X	X	GERD Medications
X[1]			X[2]	X[2]	X[2]	GERD-HRQL
X[2]			X[2]	X[2]	X[2]	Foregut Symptom Questionnaire
X[2]					X[2]	Esophageal pH Measurements (off PPIs)
	X	X	X	X	X	Device and/or Procedure Adverse Events

X=All study subjects

[1]Screening/baseline GERD-HRQL questionnaire is completed twice: once on GERD medication and once off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment.

[2] Completed/conducted off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment.

[3]Testing performed after implant and prior to discharge or within 7 days of implant, whichever occurs first.

1.0 BACKGROUND

There are several types of surgical weight loss procedures. The Laparoscopic Sleeve Gastrectomy (LSG) is a restrictive weight loss procedure that is performed by removing about 75% of stomach. It is estimated that as many as 84.1% of the subjects with pre-existing Gastroesophageal Reflux Disease (GERD) that undergo the LSG can continue to have chronic GERD symptoms[1] and as many as 8.4% of patients that did not have pre-existing GERD can develop new onset GERD symptoms. The traditional surgical method of using the patients' anatomy (fundus) to perform a fundoplication is no longer an option for these patients and the treatment alternatives for patients experiencing GERD symptoms after LSG are few. The Roux-en-Y Gastric bypass (RYGB) has been recommended as a conversion procedure for those who develop or continue to have reflux after LSG. However, the LINX Reflux Management System (LINX) has been considered as an alternative and less invasive option that may potentially have fewer complications compared to RYGB.

2.0 THE LINX REFLUX MANAGEMENT SYSTEM

2.1 DEVICE DESCRIPTION

The LINX® Reflux Management System is a laparoscopic, fundic-sparing anti-reflux procedure indicated for patients diagnosed with Gastroesophageal Reflux Disease (GERD) as defined by abnormal pH testing, and who are seeking an alternative to continuous acid suppression therapy (i.e. proton pump inhibitors or equivalent) in the management of their GERD. The LINX device is a permanent implant placed at the area of the lower esophageal sphincter (LES) and is designed to augment a weak LES and minimize or eliminate GERD-related symptoms.

2.2 REGULATORY HISTORY

The LINX System has been evaluated in two IDE studies under G060172. A feasibility study enrolled 44 study subjects at 4 study centers (2 US, 2 OUS), with the first implant performed in February 2007. The pivotal study enrolled 100 study subjects at 14 centers (13 US, 1 OUS), with the first implant in January 2009. A Post Approval-Study of the LINX System is ongoing to supplement existing safety and efficacy data. The LINX Reflux Management System received approval for U.S. marketing from the Food and Drug Administration (FDA) on March 22, 2012.

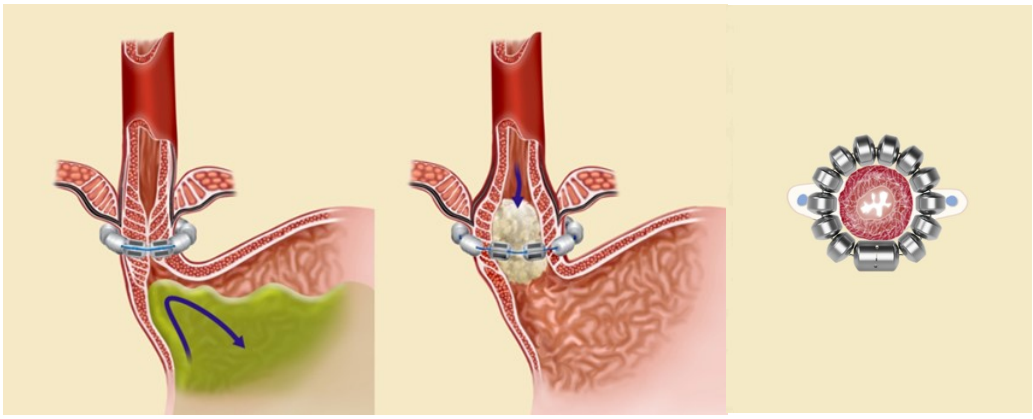
The LINX device consists of a series of titanium beads each with a magnetic core connected together with independent titanium wires to form an annular shape, when implanted **(Figure 1)**. The attractive force of the magnetic beads is designed to provide additional strength to keep a weak LES closed. During swallowing, the

[1] *DuPree et al JAMA Surg.* 2014;149(4):328-334. doi:10.1001/jamasurg.2013.4323.

magnetic beads slide away from each other on the independent titanium wire "links" to allow esophageal distention as the bolus passes by **(Figure 2)**.

	
Figure 1 – Illustration of Implant, Closed	**Figure 2 – Illustration of Implant, Open**

The LINX System allows a surgeon, using existing laparoscopic techniques and instruments, to augment a weak sphincter and restore the barrier function of the LES. The mechanism of action for the LINX device is to augment the sphincter's capacity to resist gastric pressure by using magnetic forces. For abnormal reflux to occur following implantation of the LINX device, gastric pressure must overcome both the native sphincter resistance and the magnetic bond between the LINX beads. Prior to implant, the esophagus is sized to select a device that fits the external diameter of the esophagus. At rest, the LINX device encircles the LES with each bead resting against an adjacent bead, which avoids compression of the esophagus and allows the patient to belch or vomit as necessary. Upon swallowing, the magnetic bond between the beads is overcome by the higher pressures of peristaltic swallowing forces, and the device expands to accommodate a normal swallow **(Figures 3-5)**.



LINX device creates resistance with magnetic forces to prevent the LES

Figure 3: Preventing Reflux

Higher pressures from swallowing overcome the magnetic forces,

Figure 4: During Swallow

LINX device does not compress the esophageal wall.

Figure 5: Non-Compressive

3.0 STUDY PURPOSE AND OBJECTIVE

The purpose of this study is to evaluate the safety and efficacy of LINX for its approved indication in patients who have had prior gastric surgery, specifically, LSG. The objective of the study is to confirm safety and efficacy after LSG is similar to the outcomes that formed the basis for Premarket Approval (PMA) in order to support modification of the current labeling with a statement that prior gastric surgery with LSG has been evaluated for safety and efficacy.

4.0 STUDY RATIONALE

The LSG procedure involves removal of the fundus. As a result, fundoplication is extremely difficult to perform with the limited amount of fundus tissue present in patients with prior LSG. Roux-en-Y Gastric bypass (RYGB) has been recommended as a conversion procedure for those who develop or continue to have reflux after LSG. However, LINX has been considered as an alternative and less invasive option that may potentially have fewer complications compared to RYGB. Additionally, patients may not be interested in RYGB due its associated malabsorption. The LINX device is implanted in the area of the gastroesophageal junction (GEJ), which is largely undisturbed with LSG. Patients with prior gastric surgery, such as LSG, have not to date been enrolled in clinical studies for the LINX device. This study is the first to prospectively enroll and evaluate under protocol the LINX device for GERD in post-LSG patients.

5.0 STUDY DESIGN

The study is an observational, multicenter, single-arm study with prospective enrollment. Based on the observational status of the study, No formal statistical hypothesis tests will be conducted. Up to 30 patients meeting the eligibility requirements will be implanted with LINX and followed through 12-months after implant. Up to twelve (12) clinical sites will enroll subjects. The study duration is expected to be about 36 months (24-month enrollment period and 12-month follow-up). Safety evaluations will be ongoing throughout the duration of the study, starting at the implant procedure. Efficacy endpoints will be evaluated at the 12-month visit.

5.1 ASSESSMENT OF SAFETY

Safety will be assessed by evaluating device and/or procedure related adverse events, perioperative complications, device malfunctions, device removals, and hospital readmissions experienced by subjects post-LINX implant out to 12 months. Esophageal anatomy and functionality will be monitored by performing manometry and barium esophagram at 12-months post-implant. This will allow for identification of any abnormal or atypical findings. Further, device migration will be assessed by confirming device position at the GEJ by obtaining upright, bi-plane X-rays and device erosion will be assessed by performing endoscopy at the 12 month visit.

5.2 ASSESSMENT OF EFFICACY

Efficacy will be assessed by evaluating the percentage of subjects reporting at the 12-month follow-up:

- Normalization of total distal acid exposure time or at least 50% reduction in total distal acid exposure time compared to baseline
- $\geq$50% reduction in total GERD-HRQL score compared to baseline (off PPIs)
- $\geq$50% reduction in average daily PPI dosage compared to baseline

6.0 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 INCLUSION CRITERIA

Subjects included in the study must meet all the following criteria:

1. Age >22 years
2. Laparoscopic sleeve gastrectomy (LSG) for obesity $\geq$12 months prior to proposed device implantation date.
3. Subject is a surgical candidate, i.e. is able to undergo general anesthesia and laparoscopic surgery.
4. Documented typical symptoms of GERD for longer than 6 months (regurgitation or heartburn which is defined as a burning epigastric or substernal pain which responds to acid neutralization or suppression).
5. Subject requires daily proton pump inhibitor or other anti-reflux drug therapy.

6. Total distal ambulatory esophageal pH must meet the following criteria: pH <4 for ≥4.5% of the time. Note: Subjects shall have discontinued any GERD medications for at least 7 days prior to testing, with the exception of antacids up to the morning of testing.
7. Subjects with symptomatic improvement on PPI therapy demonstrated by a GERD-HRQL score of ≤10 **on** PPI and ≥15 **off** PPI, or subjects with a >6 point improvement when comparing their **on** PPI and **off** PPI GERD-HRQL scores.
8. GERD symptoms, in absence of PPI therapy (minimum 7 days).
9. If the subject is of child bearing potential must have a negative pregnancy test within one week prior to implant and must agree to use effective means of birth control during the course of the study.
10. Subject is willing and able to cooperate with follow-up examinations
11. Subject has been informed of the study procedures and the treatment and has signed an informed consent form.

6.2 EXCLUSION CRITERIA

Subjects should be excluded from the study based on the following criteria:

1. The procedure is an emergency procedure.
2. Suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials.
3. Presence of >3 cm hiatal hernia as determined by endoscopy or barium esophagram.
4. Subject had any major complications related to the laparoscopic sleeve gastrectomy that may interfere with, or increase the risks of the LINX procedure (such as, but not limited to, leaks from the gastric remnant and infection at the sleeve gastrectomy)
5. Plans to surgically revise the gastric pouch (either known preoperatively or decided intraoperatively)
6. Currently being treated with another investigational drug or investigational device.
7. Suspected or confirmed esophageal or gastric cancer or prior gastric or esophageal surgery or endoscopic intervention for GERD (with the exception of sleeve gastrectomy).
8. Distal amplitude <35 mmHg or <70% peristaltic sequences (if using Conventional Manometry)

   -or-

   If using High Resolution Manometry (exclude for any of the following):
   - Distal Contractile Integral (DCI) ≤ 450 mmHg·s·cm or
   - ≥ 50% ineffective swallows or
   - ≥ 50% fragmented swallows

(Fragmented swallows are defined as those with a ≥ 5cm break [large] in peristaltic integrity)

9. Presence of esophagitis – Grade C or D (LA Classification).
10. BMI >35.
11. Symptoms of dysphagia more than once per week within the last 3 months.
12. Diagnosed with Scleroderma.
13. Diagnosed with an esophageal motility disorder such as but not limited to achalasia, nutcracker esophagus, or diffuse esophageal spasm or hypertensive LES.
14. Subject has a history of or known esophageal stricture or gross esophageal anatomic abnormalities (Schatzki's ring, obstructive lesions, etc.)
15. Subject has esophageal or gastric varices
16. History of/or known Barrett's esophagus.
    *Note: The diagnosis of Barrett's esophagus requires both **endoscopic** and **histologic** evidence of metaplastic columnar epithelium. Endoscopically, there must be columnar epithelium within the esophagus. Histologically, the epithelium must be metaplastic, as defined by the presence of goblet cells.*
17. Subject cannot understand trial requirements or is unable to comply with follow-up schedule
18. Pregnant or nursing, or plans to become pregnant during the course of the study.
19. Any reason which the Investigator believes may cause the subject to be non-compliant with or unable to meet the protocol requirements.
20. Subject has an electrical implant or metallic, abdominal implants.

7.0 STUDY SCHEDULE AND ASSSEMENTS

Table 1 provides a schedule of data collection and follow-up windows. It should be noted that certain data is collected while on and/or off GERD medications.

Standard of care practices for antireflux surgery will be the basis of the assessments performed to determine if a subject is a candidate for the LINX device. Investigators should refer to the LINX Instructions for Use (IFU) for prescribing information (see **Appendix A**). Further, the study center will obtain appropriate study informed consent prior to evaluating the subject study specific evaluations. Data will then be collected at the screening/baseline visit, the implant procedure and the hospitalization period following implant until discharge. The subject will be followed at 2-weeks, 3-months, 6-months, and 12-months post-implant, with data collection occurring at each time point. Follow-up assessments may be completed by telephone or visit, with the exception of the X-rays, manometry, barium swallow, endoscopy and esophageal pH testing which must be conducted during a visit.

Subjects will complete questionnaires to evaluate reflux-related symptoms (GERD-HRQL and Foregut Symptom Questionnaire). With the exception of the GERD-HRQL

at baseline, the questionnaires are completed off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment. At the screening/baseline visit, the questionnaires will be completed twice for the GERD-HRQL – once on GERD medications and once off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment (**Table 2)**.

Table 1: Schedule of Data Collection and Follow-Up Windows

Screening/ Baseline	Implant /Discharge	2-week Post-Operative Visit (Day 7 – Day 21)	3 months (Day 76 – Day 104)	6 months (Day 150 – Day 210)	12-month Visit (Day 305 – Day 425)	Data Collected
X						Demographics (gender, race)
X					X	Height and Weight
X					X	Medical History
	X					Implant Procedure and Discharge Data
X					X	Endoscopy (LA Grade Classification)
X					X	Manometry/Motility
X	X[3]				X	Barium Esophagram
	X[3]				X	Upright, Bi-Planar X-Rays (AP and Lateral)
X			X	X	X	GERD Medications
X[1]			X[2]	X[2]	X[2]	GERD-HRQL
X[2]			X[2]	X[2]	X[2]	Foregut Symptom Questionnaire
X[2]					X[2]	Esophageal pH Measurements (off PPIs)
	X	X	X	X	X	Device and/or Procedure Adverse Events

X=All study subjects

[1]Screening/baseline GERD-HRQL questionnaire is completed twice: once on GERD medication and once off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment.

[2] Completed/conducted off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment.

[3]Testing performed after implant and prior to discharge or within 7 days of implant, whichever occurs first.

Table 2: Completion of Questionnaires and GERD Medication

Visit	GERD-HRQL	Foregut
Baseline/Screening	On GERD medications Off GERD medications	Off GERD medications
3-Month	Off GERD medications	Off GERD medications
6-Month	Off GERD medications	Off GERD medications
12-Month	Off GERD medications	Off GERD medications

The data detailed in **Table 3** will be obtained at each of the identified time points. Use the following guidelines provide suggested methods and documentation for testing (**Appendix B**):

- 4663 Guidelines for Endoscopy testing
- 4664 Guidelines for X-rays testing
- 4665 Guidelines for Barium Esophagram testing
- 4666 Guidelines for Manometry/Motility testing

Table 3: Planned Assessments

Visit	Assessments/Data to be Collected
Screening/ Baseline	• Informed Consent • Demographics (Date of Birth, Gender, Race) • Height and weight • GERD History: Duration of PPI use, Years with GERD, GERD New Onset or Pre-existing after LSG • GERD-HRQL (on/off PPIs) and Foregut Symptoms Questionnaire (off PPIs) • Baseline GERD related medication use • Esophageal pH measurements (off PPIs) • Endoscopy • Manometry/Motility • Barium Esophagram • Motivation for surgery • Inclusion/Exclusion criteria evaluation
Implant/ Discharge	• Surgery Date • Surgery start and stop time • Implanted device size • Concomitant procedures (e.g. hiatal hernia repair, cholecystectomy) • Barium esophagram and upright Bi-Planar X-Rays (AP and Lateral) • Discharge Date • Perioperative and device and/or procedure related adverse events
2 Week	• Device and/or procedure related adverse events
3-Month	• GERD-related medication use within the last 30 days • GERD-HRQL (off PPIs) and Foregut Symptoms Questionnaire (off PPIs) • Device and/or procedure related adverse events
6-Month	• GERD-related medication use within the last 30 days • GERD-HRQL (off PPIs) and Foregut Symptoms Questionnaire (off PPIs) • Device and/or procedure related adverse events

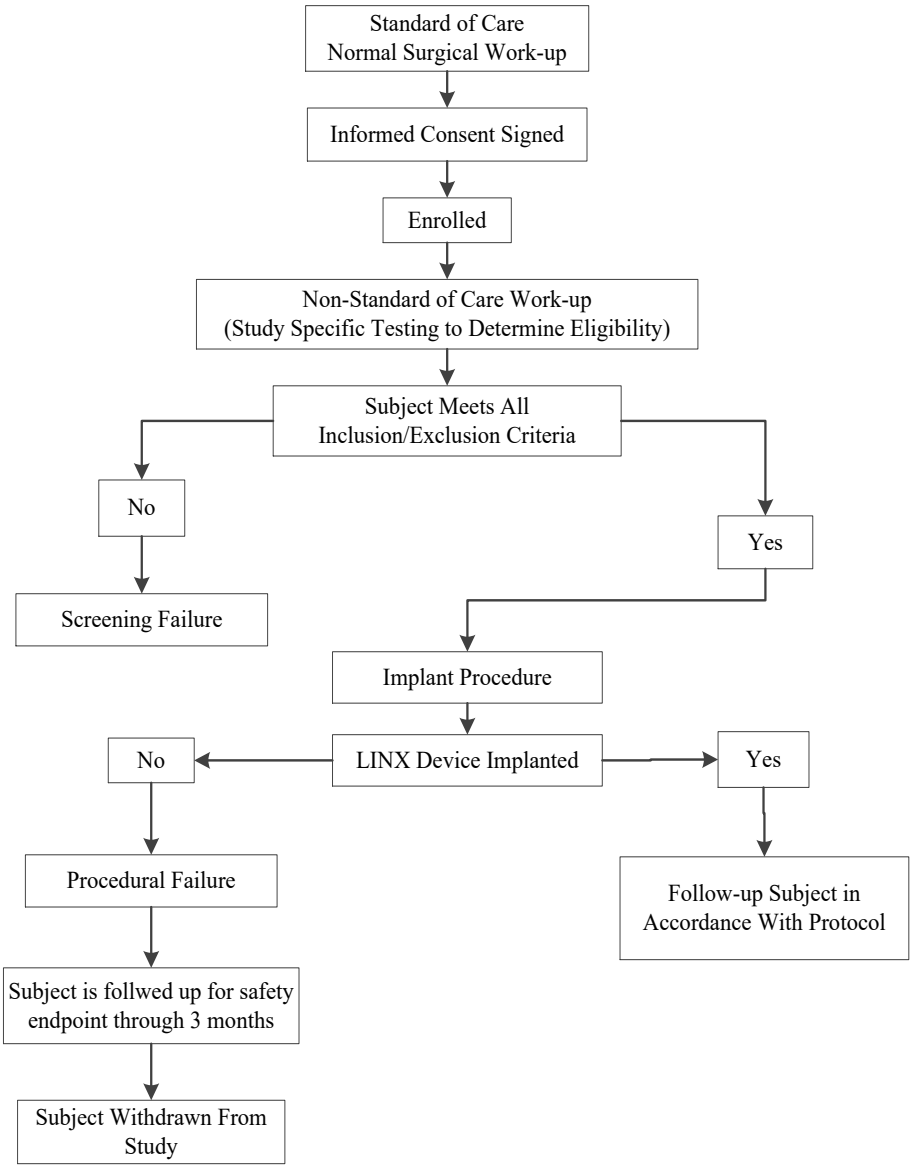
Visit	Assessments/Data to be Collected
12 Month Follow-up	• Height and weight • GERD-HRQL (off PPIs) and Foregut Symptoms Questionnaire (off PPIs) • GERD-related medication use within the last 30 days • Esophageal pH testing (off PPIs) • Manometry/motility • Endoscopy • Barium esophagram and upright Bi-Planar X-Rays • Device and/or procedure related adverse events

The data collection window for each visit is outlined in **Table 4**. The 2-week follow-up visit is +/- 7 days from the anniversary of the implant procedure. The 3-month follow-up visit is +/- 14 days from the anniversary of the implant procedure. The 6-month follow-up visit is +/- 30 days from the anniversary date of the implant procedure. The 12-month follow-up visit is +/- 60 days from the anniversary date of the implant procedure.

Table 4: Follow-up Windows

Visit	Follow-up Window
2-week (±7 days)	7—21 days
3 months (±14 days)	76–104 days
6 months (±30 days)	150-210 days
12 Months (±60 days)	305-425 days

8.0 SUBJECT FLOW CHART



9.0 RISK ANALYSIS

9.1 POTENTIAL RISKS

The LINX Reflux Management System has been previously studied and known risks associated with the surgical procedure and device implant can be found in the Instructions for Use (**Appendix A**). The proposed study will monitor the subjects through 12-months after implant for adverse events.

9.2 POTENTIAL BENEFITS

The potential benefits to subjects being implanted with the LINX device are the reduction or elimination of GERD-related symptoms and to reduce or eliminate dependence on GERD medications.

10.0 STATISTICAL PLAN

No formal statistical hypotheses were pre-defined for this study. Summary statistics are used to display results of effectiveness outcomes at each study time point. For categorical parameters, this includes the number and frequency; and for continuous parameters, the mean, median, standard deviation, range and 95% confidence limits are presented. For continuous efficacy parameters, the p-value for a one-sample, paired t-test to test if there is statistical evidence that the change from baseline is $\neq 0$ is also given.

10.1 EFFICACY

Efficacy will be measured by a comparison of GERD control before and after placement of the LINX Reflux Management System defined by esophageal pH measurements, GERD-HRQL score and PPI use. Subjects will serve as their own control. The change from baseline by follow-up will be calculated and summarized.

10.1.1 ESOPHAGEAL ACID EXPOSURE

Testing will be performed with subjects off PPIs. The subject's total distal esophageal acid exposure time will serve as the control and will be compared to results at the 12-month visit. Normalization for total distal ambulatory esophageal pH testing is defined as pH< 4 for < 4.5% of the time. If longer pH evaluations are received the total distal acid exposure time will be recorded as a 24 hour average (e.g. 48 hour Bravo testing). Note: The same testing equipment used at baseline should be used at subsequent follow-ups if possible.

10.1.2 QUALITY OF LIFE

Subjects GERD-HRQL (Health Related Quality of Life) scores will be assessed off all GERD medications. The subject's baseline GERD-HRQL score will serve as the control and be compared to the subject's GERD-HRQL 12 months post implantation.

10.1.3 USE OF PPIS

Subject's average daily dose of PPI will be evaluated. The subject's baseline average daily dosage will serve as the control and be compared to the subject's average daily dosage 12 months post-procedure.

10.2 SAFETY

Safety will be assessed by the rate of (number and percentage of subjects experiencing) device and/or procedure related adverse events after LINX

placement out to 12 months. Esophageal anatomy and functionality will be monitored by performing manometry and barium esophagram at 12-months post-implant. This will allow for identification of any abnormal or atypical findings. Further, device migration will be assessed by confirming device position at the GEJ by obtaining upright, bi-plane X-rays and device erosion will be assessed by performing endoscopy at the 12 month visit. Incidence of device migration and erosion will be compared to current incidence rates (i.e. zero documented incidents of device migration and a low but established occurrence of esophageal erosions) to assess concurrence of the safety profile of study subjects to that of patients without a prior LSG.

10.3 ADDITIONAL ANALYSES

- Summary statistics for components of the DeMeester score at 12 months
- Percentage of subjects who discontinue daily PPI use at 3, 6 and 12 months.
- Percentage of subjects who eliminate moderate or severe regurgitation as assessed by the Foregut Symptoms Questionnaire (FSQ) at 3, 6 and 12 months.
- Percentage of subjects with extra-esophageal symptoms as assessed by the FSQ at 3, 6 and 12 months.
- Percentage of subjects with esophagitis by endoscopy at 12 months.

Side effects will be assessed by subject questionnaires including the following:

- Percentage of subjects with ability to belch at 3, 6 and 12 months.
- Percentage of subjects with ability to vomit at 3, 6 and 12 months.

10.4 SUBJECT POPULATION FOR ANALYSIS

All subjects who meet the eligibility criteria, provide informed consent, complete baseline assessments and undergo the LINX procedure will represent the study population for analysis. Data analyses will be performed on available data at the follow-up visits.

11.0 STUDY PROCEDURES AND MANAGEMENT

11.1 CLINICAL STUDY REGISTRATION

The study will be registered by the Sponsor at www.clinicaltrials.gov.

11.2 STUDY CENTER SELECTION AND PARTICIPATION

Study centers interested in participating in this study will be assessed for their ability to fully and appropriately participate in the study. In general, study centers will be selected if patient volume is adequate to support enrollment of patients into the study and the participating physician(s) are qualified by education, training and surgical experience.

No site will enroll more than 6 subjects without prior written approval provided by the Sponsor.

11.3 INFORMED CONSENT

Prior to IRB submission, the Investigator or designee will prepare an Informed Consent Form (ICF) in accordance with this study protocol and all regulatory requirements (e.g. where applicable, 21 CFR Part 50 and in accordance with the Declaration of Helsinki) using the sample ICF provided **(Appendix C)**. A copy of the final IRB approved ICF must be submitted to Torax Medical and a site must be activated by Torax Medical prior to enrolling patients at that investigational center. All study patients (or their legal guardian) must document their consent by signing an IRB-approved ICF prior to completing any protocol-specific assessments that are not considered standard of care.

11.4 INSTITUTIONAL REVIEW BOARD

This protocol, informed consent form (ICF), and authorization for the use and disclosure of health information (as applicable) must be reviewed and approved by the study center's IRB before any study patient is enrolled. Changes to the protocol must be approved in writing by Torax Medical and the IRB (as applicable) before the change is implemented.

Prior to study patient enrollment, a signed copy of the IRB approval letter addressed to the Investigator and the final approved ICF must be submitted to Torax Medical. The letter should reference this protocol by title, date or number/revision number as well as the approved ICF and HIPAA Authorization (as applicable). Investigators are responsible for submitting and obtaining initial approval and continuing approval from the IRB and forwarding copies of the approval letters to Torax Medical. The original letters are to be kept in the study center's regulatory file designated for this study.

The Investigator will notify the Sponsor within five (5) working days of withdrawal of IRB approval.

11.5 SITE ACTIVATION

A study center may not begin enrolling subjects until the Sponsor provides notification that the site has provided all required study start-up documents and completed training. At minimum, the Principal Investigator at the study center will be notified in writing of "Site Activation" when start-up activities have been completed. Upon receipt of this notification, the study center may begin enrolling subjects.

11.6 STANDARD OF CARE

As part of screening/baseline, all patients will undergo the standard of care anti-reflux surgery work-up. The anti-reflux surgery work-up used for the study enrollment should be completed within the 1-year time period prior to signing of the study ICF. For purposes of the study, the questionnaires (GERD-HRQL,

Foregut Symptom Questionnaire, and RDQ) will be considered standard of care to facilitate pre-screening of patients. However, only questionnaires completed by a subject who has provided informed consent for the study will be accessible to the Sponsor.

11.7 SCREENING/ENROLLMENT

Potential study subjects will be identified from the Investigator's practice or by referral. During the screening/enrollment visit, informed consent will be obtained prior to any study specific assessments and eligibility against the inclusion and exclusion will be confirmed prior to implant.

11.8 DEVICE TRACKING

Devices used for the study will be tracked (by lot number and number of beads) and captured on the case report forms.

11.9 ADVERSE EVENT REPORTING

If an intraoperative decision is made to not implant the LINX device, the subject will be monitored for procedure related adverse events for a period of at least three months (90 days) or longer if needed until resolution before withdrawing the subject from the study.

If a decision is made to explant the LINX device during the study, the subject will be monitored for explant-related adverse events for a period of at least three months (90 days) or longer if needed until resolution before withdrawing the subject from the study. No other study testing and/or questionnaires would be required after the device is explanted.

For all other subjects starting at the time of implantation and proceeding throughout the duration of the follow-up period, the Investigator will closely monitor each subject for the development of device and/or procedure related adverse events. A subject presenting with new onset dysphagia, abdominal pain, nausea, or vomiting, may be assessed for device migration and/or erosion if symptoms persist and benign causes cannot be established, at the discretion of the Investigator. This may include additional, non-study visit, x-rays or endoscopic evaluation. Adverse events will continue to be monitored at each of the study follow ups until resolution and/or study completion.

For the purposes of this study, a reportable event will be defined as any untoward medical occurrence which has a strong relationship to the LINX device and/or implant procedure and another etiology is unlikely. The Investigator must decide whether each event meets the definition of a Serious Adverse Event (SAE). All device and/or procedure related serious adverse events (SAE) must be reported immediately (within 5 days of discovery) to Torax Medical. SAE reporting to the IRB is per institutional policy.

An AE is considered **serious** if it meets one or more of the following criteria:

- **Is life-threatening or results in death**
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does **not** refer to an event that hypothetically might have caused death if it were more severe.
- **Requires subject hospitalization > 24 hours**
- **Requires prolongation of an existing hospitalization**
- **Results in persistent or significant disability/incapacity**
- **Results in fetal distress, fetal death, or a congenital anomaly or birth defect**
- **Requires intervention to prevent permanent impairment or damage of body function or structure**
- **Other serious important medical events that do not fit in the other outcomes and may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes**

Unanticipated Adverse Device Effects

Unanticipated adverse device effects (UADEs) include any serious adverse effects on the health or safety of a study subject or any life-threatening problem or death caused by, or associated with, the LINX device that are not typically associated with the procedure or the device. All unanticipated adverse device effects must be reported to the IRB within 10 working days and to Torax Medical within 24 hours after the Investigator first learns of the adverse device effect.

The following definitions for rating the severity of adverse events will be used:

Mild	Awareness of signs of symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities.
Moderate	Discomfort intense enough to cause interference with usual activities.
Severe	Incapacitating with inability to do work or usual activities.

11.10 SUBJECT COMPLETION AND WITHDRAWAL

All study subjects have the right to withdraw their consent to participate at any time during the study. Whenever possible, the site staff should obtain written documentation from the subject of his/her request to withdraw consent. If the site staff is unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded in the subject's medical record.

On completion of the study (either by completion of protocol requirements or withdrawal), the Withdrawal/Completion CRF will be completed.

A subject may withdraw (or be withdrawn) from the study prematurely for the following reasons:

- Withdrawal of consent by subject
- Adverse event (Adverse Event Log or SAE CRF must be completed)
- Protocol deviation
- Lost to follow-up (In case of early withdrawal of a subject, at least three (3) documented attempts should be made to contact the subject and have them come into the clinic).
- Termination of study by the Sponsor
- Investigator believes it is in the best interest of the subject
- Other (must be specified)

12.0 ROLE AND RESPONSIBILITIES

Each investigational center will identify appropriate personnel to perform all study tasks.

12.1 INVESTIGATOR

- This clinician will have responsibility to treat all subjects.
- Documents all reportable adverse events that occur during the study.
- Be responsible for signing the CRFs.
- Be responsible for providing medical care to subjects during the study.
- Have responsibility for determining eligibility.
- Conduct baseline assessments of the subject's GERD.
- Interview subjects about their GERD symptoms.
- Be available for each subject follow-up visit.

12.2 STUDY COORDINATOR

In addition to the Investigator, a Study Coordinator will be identified at each investigational center to facilitate and manage the study.

13.0 STUDY CENTER DOCUMENTATION

A study center site will provide the following documentation to Torax Medical prior to a site being activated to enroll patients:

- Study training/initiation completed for the Investigators and study staff listed on the delegation log
- Signed clinical trial agreement (CTA)
- Current signed curriculum vitae and medical licenses for all Investigators listed on the CTA

- Financial disclosure for all Investigators listed on the CTA
- IRB approval letter and approved ICF

14.0 STUDY PATIENT RECRUITMENT AND RETENTION PLAN

As needed, the Sponsor will provide study centers with materials and financial support to recruit patients for the study. All recruitment activities will require prior approval by the IRB before implementation.

Efforts will be made to ensure the retention and compliance of study patients once enrolled. Examples of strategies for subject retention include:

- Instruct study centers to obtain multiple contact numbers and addresses from a subject to make it easier to reach the participant.
- Counsel patients about the importance of returning to follow-up during informed consent and follow-up visits.
- Accommodate a subject's schedule as much as possible to make the follow-up as convenient as possible.
- Encourage the study centers to continue open communication with enrolled subjects and to schedule follow-up visits early in the protocol-defined window.
- Provide database-generated follow-up schedules to study centers and discuss dates of upcoming visits.
- Monitor follow-up rates closely so that follow-up problems can be identified and addressed as soon as possible.
- Request that study centers thoroughly document all attempts to contact enrolled subjects.

15.0 DATA HANDLING AND RECORD KEEPING

15.1 CONFIDENTIALITY

Information about study subjects will be kept confidential and managed according to applicable laws, regulations and guidelines. All subject information documented on CRFs will be referenced by a subject's identification (ID) number and initials only. If supplemental laboratory or imaging reports are submitted into the study, the subject's name or other prohibited identifiers must be deleted and the subject initials and ID number added to each item. A subject's privacy and personal health information will be protected as required by law.

15.2 SOURCE DOCUMENTS

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, surgical notes, memoranda, subjects' diaries, questionnaires or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy and at the laboratories involved in the clinical trial.

15.3 CASE REPORT FORMS

The study case report form (CRF) is the primary data collection instrument for the study **(Appendix D)**. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE-OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

15.4 RECORDS RETENTION

The Investigator/institution will retain the study-related essential documents until two years after the final data analysis is complete.

16.0 QUALITY ASSURANCE AND QUALITY CONTROL

The Principal Investigator at each study site is responsible for assuring that accurate and complete data are collected and sent to the Sponsor. Data will be reviewed periodically by the Sponsor for missing data points, incomplete information, and discrepancies. When necessary, issues will be resolved by electronic mail, telephone, facsimile, or site visit. The Investigator will permit study-related monitoring, audits, and inspections by the IRB, the Sponsor, government regulatory bodies, and institutional compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

17.0 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the Sponsor for the purposes of performing the study, will be published or passed on to any third party without the written consent of Torax Medical. Any Investigator involved with this study is obligated to provide the Sponsor with complete test results and all data derived from the study.