The CALIBER Study

Randomized Controlled Trial of LINX versus Double-Dose Proton Pump Inhibitor Therapy for Reflux Disease

Protocol Number	4959
Protocol Date	June 8, 2015
Sponsor	Torax Medical, Inc. 4188 Lexington Avenue North Shoreview, MN 55126 Phone: 651-361-8900 Fax: 651-361-8910

PROTOCOL SUMMARY

Title	The CALIBER Study Randomized **C**ontrolled tri**AL** of L**I**NX versus dou**B**le-dos**E** p**R**oton-pump inhibitor therapy for reflux disease
Sponsor	Torax Medical, Inc.
Purpose	To compare mechanical sphincter augmentation (LINX Reflux Management System) to double-dose proton pump inhibitors (PPIs) for the management of reflux symptoms related to gastroesophageal reflux disease (GERD).
Study Premise	LINX may provide superior reflux control, as defined by control of reflux symptoms, and in particular regurgitation, when compared to double-dose PPIs in patients who were refractory to once daily PPI.
Study Design	Prospective, multicenter, 2:1 randomized, cross-over, two arms • Control arm: Double-dose PPI [Omeprazole 20 mg BID (twice a day)] • Treatment arm: LINX Reflux Management System
Study Centers	Up to 20 study centers throughout the U.S. will participate.
Enrollment	Approximately150 patients will be enrolled into the study. Subjects will be randomized 2:1 into the double-dose PPIs arm (100 subjects) and the LINX arm (50 subjects).
Primary Inclusion Criteria	• Patient seeks consultation for troublesome symptoms related to reflux despite use of once daily PPIs. • Dependent upon once daily PPIs for ≥ 8weeks • Moderate or severe regurgitation per the Foregut Symptom Questionnaire while taking PPI therapy • Abnormal distal esophageal pH while off GERD medications for at least 7 days by total % time or DeMeester Score
Primary Exclusion Criteria	• Patient is currently on double-dose PPIs (twice a day dosing) • Patient is unable to take double-dose PPIs due to contraindication to medication or known medical condition • Patient has contraindications, warnings or precautions related to LINX
Study Duration	The following estimates the randomization and visit schedule: • First subject randomized: Q3 2015 • Last subject randomized: Q1 2016 • Last 6-month visit: Q3 2016 • Last 12-month visit: Q2 2017
Schedule of Evaluations	See **Table 1**

Study Groups (after 6-month evaluations)	After completion of the 6-month follow-up visit, subjects assigned to the double-dose PPI arm will: 1.) Have their PPI dose stepped-down to single-dose (Omeprazole 20 mg daily) and continued until the 12 month visit, unless symptoms return and double-dose PPIs are restarted *OR* 2.) Have the option to cross-over to LINX if cross-over criteria are met See **Figure 1**
Cross-Over Criteria (after 6 month evaluations)	The following criteria must be met for cross-over to LINX: • Abnormal total number of distal reflux episodes as assessed by the 6-month impedance testing completed on double-dose PPIs • Presence of moderate or severe regurgitation reported on the 6-month Foregut Symptom Questionnaire completed on double-dose PPIs • Patient consents to LINX procedure
Primary Endpoint and Additional Effectiveness Measures	Primary Endpoint Percentage of subjects treated with LINX compared to percentage of subjects treated with double-dose PPIs who have elimination of moderate or severe regurgitation per the Foregut Symptom Questionnaire at 6-months Additional Effectiveness Measures • Impedance measurements at 6 months • Moderate or severe regurgitation at 12 months • Esophageal pH exposure at 12 months • GERD-Health Related Quality of Life (GERD-HRQL) total score at 6 and 12 months • Reflux Disease Questionnaire score at 6 and 12 months
Evaluation of Side Effects	The GERD-HRQL, Foregut Symptom Questionnaire and the Reflux Disease Questionnaire include questions to evaluate potential side effects (such as difficulty swallowing, gas/bloat, nausea, etc.). These data will be analyzed to evaluate for differences in side effect profiles between the LINX and double-dose PPI arms.
Evaluation of Safety	Rate of occurrence of serious adverse events (SAEs) related to LINX or double-dose PPIs will be evaluated throughout the duration of the study. No formal statistical hypothesis test will be conducted. Additionally, the number of related events, number of study subjects with events, and the percent of subjects with an event will be summarized.

Table 1. Schedule of Data Collection

Data Collected/Testing Completed	Visit Schedule			
	Screening/ Baseline	Randomization	6 Month	12 Month
Demographics	X			
Height/Weight	X		X	X
Medical History	X		X	X
GERD Medication	X		X	X
Foregut Symptom Questionnaire	X[1]		X[2]	X[3]
GERD-HRQL	X[1]		X[2]	X[3]
Reflux Disease Questionnaire	X[1]		X[2]	X[3]
Esophagogastroduodendoscopy (EGD)	X			X[3]
Manometry/Motility and/or Barium Esophagram per Standard of Care	X			
Esophageal pH Monitoring	X[1]			X[3]
Treatment Assignment/Implant		X		
Cross-Over/Step-Down Information			X (PPI arm)	
Impedance Monitoring			X[2]	
Adverse Events		X	X	X

[1]Screening/baseline questionnaires 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. Esophageal pH monitoring conducted off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment.

[2]At 6-month follows-up, testing/questionnaires completed per treatment assignment: PPI arm completed while on double dose PPIs with no other GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment; LINX arm completed off all GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment (in the event PPIs had been restarted).

[3]At 12-month follow-up: LINX or Cross-Over LINX complete testing/questionnaires off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment. Step-down PPI subjects complete testing/questionnaires while on single-dose PPI, with all other GERD medications stopped for at least 7 days (including a second dose of PPI), with the exception of antacids which can be taken up until the morning of assessment. *Exception to note: For those subjects crossing-over to LINX after the 6-month visit, the 12-month visit is 6 months ±30 days from the implant procedure date.*

Figure 1. Study Groups (after 6 month evaluation)

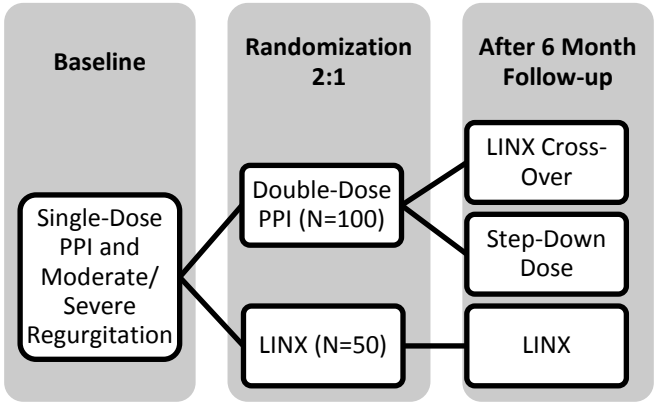


TABLE OF CONTENTS

APPENDICES

1.0 INTRODUCTION

1.1 Background

Gastroesophageal reflux disease (GERD) is a condition where gastric content refluxes into the esophagus and causes troublesome symptoms and/or complications.[1] Normally, food travels from the mouth, down through the esophagus, and into the stomach. In those who have GERD, the lower esophageal sphincter (LES) does not close properly, allowing acid and other contents of the digestive tract to move up (reflux) into the esophagus. GERD, which primarily manifests as heartburn, regurgitation, or both, is a chronic disorder associated with substantial morbidity, potential malignancy and a major adverse impact on quality of life.[2] In industrialized nations the disease has become increasingly common, with an estimated prevalence of 7% in the general population based on the presence of daily symptoms.[3]

The predominant medical therapy for GERD is acid suppression with proton-pump inhibitors (PPIs). PPIs are a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production. They are the most potent inhibitors of acid secretion available. Although PPIs remove most of the acid from the reflux, these medications do not eliminate reflux. As a result, PPIs are most effective for heartburn and progressively less effective for regurgitation, chest pain and extra-esophageal symptoms.[4] Approximately 10 to 40 percent of patients with GERD fail to respond symptomatically, either partially or completely, to a standard dose PPI.[5-7] Lack of satisfactory symptomatic response to PPI once a day is sufficient to consider it as a treatment failure.[8] Doubling the PPI dose has become a common practice in patients with GERD who have failed PPI once daily (single-dose) with confirmed abnormal esophageal acid exposure by pH monitoring.[4,8] Once symptoms are better managed, studies have shown patients who are prescribed a higher dose of PPI can decrease or "step down" the dose without return of symptoms or decrease in quality of life.[5]

In the case of persistent symptoms despite PPIs, anti-reflux surgery is an alternative. The LINX® Reflux Management System (LINX) is indicated for patients with abnormal esophageal pH testing who have persistent symptoms despite medical therapy. The device was approved by the FDA for commercial use March 22, 2012. In clinical studies, the LINX has demonstrated improved reflux control through reduction in esophageal acid exposure, elimination of regurgitation, improvement in GERD-related quality of life scores, and freedom from daily dependence on PPIs, while minimizing the side effects commonly associated with Nissen fundoplication.[9-14] LINX is the only anti-reflux surgical option to mechanically restore competency to the reflux barrier without using the gastric fundus.

1.2 Rationale

No randomized controlled trials have been conducted comparing LINX to double-dose PPIs for control of reflux symptoms in patients who continue to have symptoms while on single-dose PPIs. This study will provide clinical data to compare the clinical outcomes of two different approaches for managing persistent reflux symptoms: increased acid suppression therapy versus mechanical augmentation of the LES. Since acid suppression does not eliminate reflux but rather decreases the acidity of the refluxate, a mechanical approach may provide better reflux control and symptom improvement.[15-17] The scientific rationale for the design of the LINX device is based on the premise that an incompetent (weak) LES will remain susceptible to gastroesophageal reflux until the LES barrier function is restored. The LINX is designed to augment the LES function and is placed, via a laparoscopic approach, on the external aspect of the esophagus in the region of the LES. The device is comprised of a series of titanium beads with magnetic cores that are linked together with independent titanium wires. As a series, the device forms an annular shape (See **Section 4.1** for device description). Based on the premise that the origin of GERD is largely a mechanical issue of a weak or incompetent LES unable to prevent abnormal reflux, which may lead to troublesome symptoms, the LINX addresses the mechanical dysfunction of the LES with a mechanical approach. The commercial availability of PPIs and LINX is at least 25 years and 3 years, respectively. The use of PPIs is well-established as a treatment for GERD, whereas the role of LINX in the treatment continuum for GERD is still evolving. Clinical studies of the LINX have shown that mechanical augmentation of the LES with a magnetic ring can eliminate the symptom of moderate or severe regurgitation as well as heartburn. In comparison, acid suppression therapy is very effective at managing acid-related symptoms like heartburn, but less effective at regurgitation. This study is important to evaluate control of regurgitation in a randomized controlled trial comparing mechanical augmentation of the LES with LINX to acid suppression with double-dose PPIs, and how control of acid-related symptoms like heartburn symptoms compares between LINX and double-dose PPIs.

2.0 STUDY PURPOSE AND OBJECTIVES

2.1 Purpose

To compare mechanical sphincter augmentation with LINX to double-dose PPIs for the management of reflux symptoms related to GERD.

2.2 Primary Objective

The primary objective of this study is to assess if LINX in comparison to double-dose PPIs provides superior elimination of moderate and severe regurgitation at 6 months in patients who were refractory to single-dose PPIs at baseline.

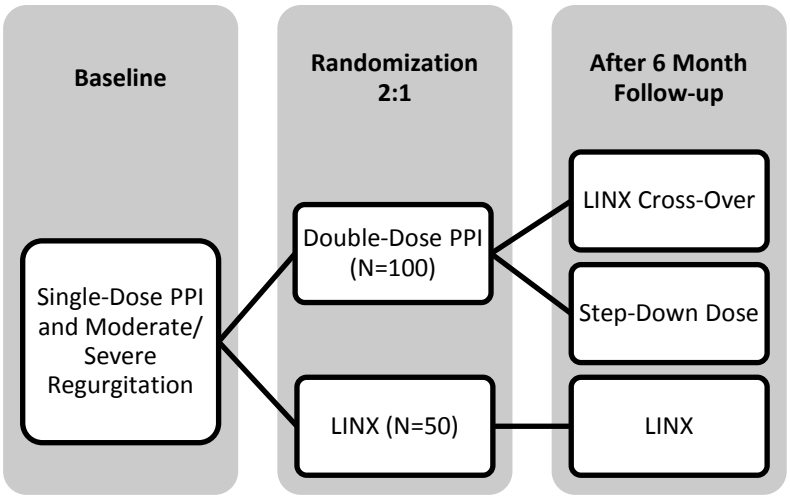
2.3 Secondary Objectives

Secondary objectives of this study are to compare the following between the randomized arms:

- Impedance measurements at 6 months
- Presence of moderate or severe regurgitation at 12 months
- Esophageal pH measurements at 12 months
- Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) scores at 6 and 12 months
- Reflux Disease Questionnaire (RDQ) scores at 6 and 12 months

3.0 STUDY DESIGN

- Prospective, multicenter, randomized controlled, cross-over trial conducted at up to 20 centers in the U.S.
- Subjects will be randomized to either LINX or double-dose PPIs (twice a day dosing)
- Randomization 2:1 and enrollment of approximately 150 subjects (100 double-dose PPI and 50 LINX)
- Subjects will complete follow-up at 6- and 12-months after randomization or LINX implant
- Primary endpoint evaluation will be based on 6-month data per the subject's randomization assignment
- After the 6-month follow-up, subjects in the PPI arm will either step-down PPI dose to once a day dosing, or be offered the LINX procedure if the cross-over criteria are met.



4.0 STUDY TREATMENTS

4.1 The LINX Reflux Management System

The LINX Reflux Management System is intended for use in those patients diagnosed with pathologic GERD as defined by abnormal pH testing and who continue to have chronic GERD symptoms despite maximum medical therapy. The device received FDA approval March 22, 2012. 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.

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 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

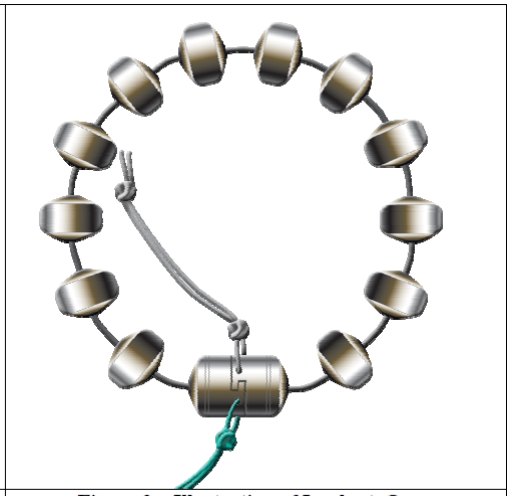
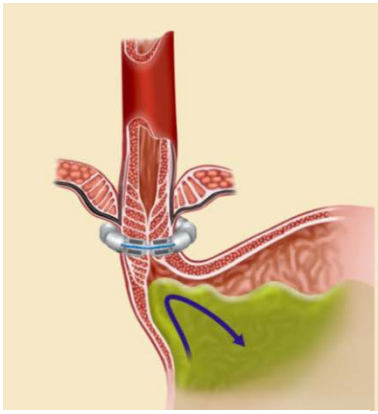


Figure 2 – Illustration of Implant, Open

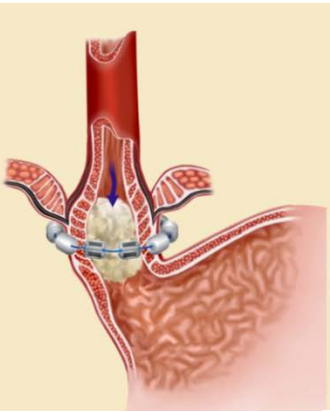
The LINX System allows a surgeon, using existing laparoscopic techniques and instruments, to augment a weak sphincter and restore the barrier function of the LES. The mechanism of action for the LINX device is to augment the sphincter's capacity to resist gastric pressure by using magnetic forces. For 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. 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)**. See **Appendix A** for *Instructions for Use*.

Figure 3:
Preventing Reflux



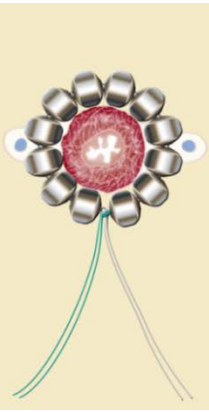
LINX device creates resistance with magnetic forces to prevent the LES from opening.

Figure 4:
During Swallow



Higher pressures from swallowing overcome the magnetic forces, causing the device to expand.

Figure 5:
Non-Compressive



LINX device does not compress the esophageal wall.

Acid suppression is the mainstay of medical therapy for GERD. The American Gastroenterological Association (AGA) and the American College of Gastroenterology (ACG) recommend PPIs as first-line therapy for the treatment of severe GERD-related symptoms or erosive esophagitis (EE).[18,19] In current clinical practice, seven PPIs are available and considered roughly equal in effectiveness and safety. For the purpose of standardization, all subjects in this study randomized to double-dose PPIs will be treated with omeprazole 20 mg BID (twice a day).

Omeprazole is a selective and irreversible proton pump inhibitor. It suppresses stomach acid secretion by specific inhibition of the H^+/K^+ ATPase system found at the secretory surface of gastric parietal cells. The inhibitory effect of omeprazole occurs within 1 hour after oral administration. The maximum effect occurs within 2 hours. The duration of inhibition is up to 72 hours. When omeprazole is stopped, baseline stomach acid secretory activity returns after 3 to 5 days. The inhibitory effect of omeprazole on acid secretion will plateau after 4 days of repeated daily dosing.[20] See A**ppendix B** for Drug Information for Omeprazole.

5.0 SELECTION OF SUBJECTS

5.1 Number of subjects planned

A total of approximately 150 subjects will be enrolled in the study, with approximately 100 subjects randomized to double-dose PPIs and approximately 50 subjects randomized to LINX.

5.2 Inclusion Criteria

Patients are eligible for the study if all of the following criteria are met:

1. Patient seeks consultation for troublesome symptoms related to reflux despite use of once daily PPIs.
2. PPI taken once a day at a standard dose for symptomatic GERD or healing of esophagitis for at least 8 weeks.
3. Age ≥21 years old.
4. Abnormal distal esophageal pH determined by total % time pH <4 or DeMeester Score. Testing to be completed off GERD medications for at least 7 days, with the exception of antacids, which may be taken up until the morning of assessment.
5. Moderate or severe regurgitation per the Foregut Symptom Questionnaire while taking once daily PPIs.
6. A total GERD-HRQL score of ≥11 while off GERD medications for at least 7 days, with the exception of antacids, which may be taken up until the morning of assessment.

7. Suitable surgical candidate (i.e. is able to undergo general anesthesia and laparoscopic surgery).
8. Patient has provided written informed consent for participation in the randomized study.
9. Patient is willing to be randomized to either LINX or double-dose PPIs and to follow the treatment plan and follow-up examinations per protocol to which he/she has been assigned.

5.3 Exclusion Criteria

Patients will not be included in the study if any of the following criteria apply:

1. Currently taking double-dose PPIs (twice daily dosing).
2. Currently being treated with an investigational drug or investigational device.
3. Patient is contraindicated for double-dose PPIs or has a medical history or condition where use of double-dose PPIs is not advised.
4. History of gastric surgery, gastroesophageal surgery, anti-reflux procedures, or gastroesophageal/gastric cancer.
5. Prior endoscopic anti-reflux intervention for GERD and/or previous endoscopic intervention for treatment of Barrett's esophagus.
6. Suspected or confirmed esophageal or gastric cancer.
7. Hiatal hernia >3cm as determined by endoscopy.
8. Distal esophageal motility (average of sensors 3 and 4) is less than 35 mmHg peristaltic amplitude on wet swallows or <70% (propulsive) peristaltic sequences.
9. Esophagitis Grade C or D (Los Angeles classification).
10. Body mass index >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. Esophageal stricture or gross esophageal anatomic abnormalities (Schatzki's ring, obstructive lesions, etc.).
15. 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. Pregnant or nursing, or plans to become pregnant during the course of the study.

18. Medical illness (i.e. congestive heart failure) that may cause the patient to be non-compliant with or able to meet the protocol requirements, or is associated with limited life expectancy (i.e. less than 3 years).
19. Uncontrolled major depression or diagnosis of DSM-5 psychiatric disorder (e.g. bipolar, schizophrenia, etc.).
20. Suspected or known allergies to titanium, stainless steel, nickel or ferrous materials.
21. Patient has an electrical implant or metallic, abdominal implants.

5.4 Methods of Assigning Subjects to Treatment Group

The study management team (Torax Medical) will allocate treatment based on a pre-specified randomization sequence of sealed envelopes or other method, generated by the biostatistics group, using the study center as a stratification parameter. Study centers will be blinded to the determinants for the randomization sequence (block size, stratification, etc.)

After eligibility is documented based on the inclusion/exclusion criteria, the study center will complete and submit the "Request for Randomization" form to the study management team (**Appendix C**). The study management team will review to confirm eligibility. The next sequentially assigned sealed envelope for the study center will be selected and opened to conduct the randomization. The treatment assignment will be documented on the Request for Randomization form and returned to site along with a copy of the randomization envelope.

All subjects randomized are irrevocably in the study, whether or not they are subsequently found to be eligible or actually receive the allocated treatment, and they should be followed until the end of the study.

The allocated treatment should take place as soon as possible after randomization (on the same day for double-dose PPIs and within 6 weeks for LINX).

6.0 MEASUREMENT OF CLINICAL OUTCOMES

6.1 Efficacy

6.1.1 Primary Efficacy Endpoint

Percentage of LINX subjects who have elimination of moderate or severe regurgitation per the Foregut Symptom Questionnaire at 6-months compared to subjects treated with double-dose PPIs.

6.1.2 Additional Efficacy Outcomes

- Elimination of moderate or severe regurgitation at 12 months.
- Esophageal pH at 12 months (% of subjects with normalization or 50% reduction in total % pH<4 compared to baseline; summary statistics of DeMeester components at follow-up compared to baseline).
- GERD-HRQL total score at 6 and 12 months (% of subjects with at least 50% reduction in total score compared to baseline off PPI score; summary statistics of GERD-HRQL score at follow-up compared to baseline on and off PPIs).
- RDQ score at 6 and 12 months (summary statistics of scores at follow-up compared to baseline on and off PPIs).
- Impedance at 6 months (summary statistics of number of reflux episodes; % of subjects with normal number of reflux episodes).

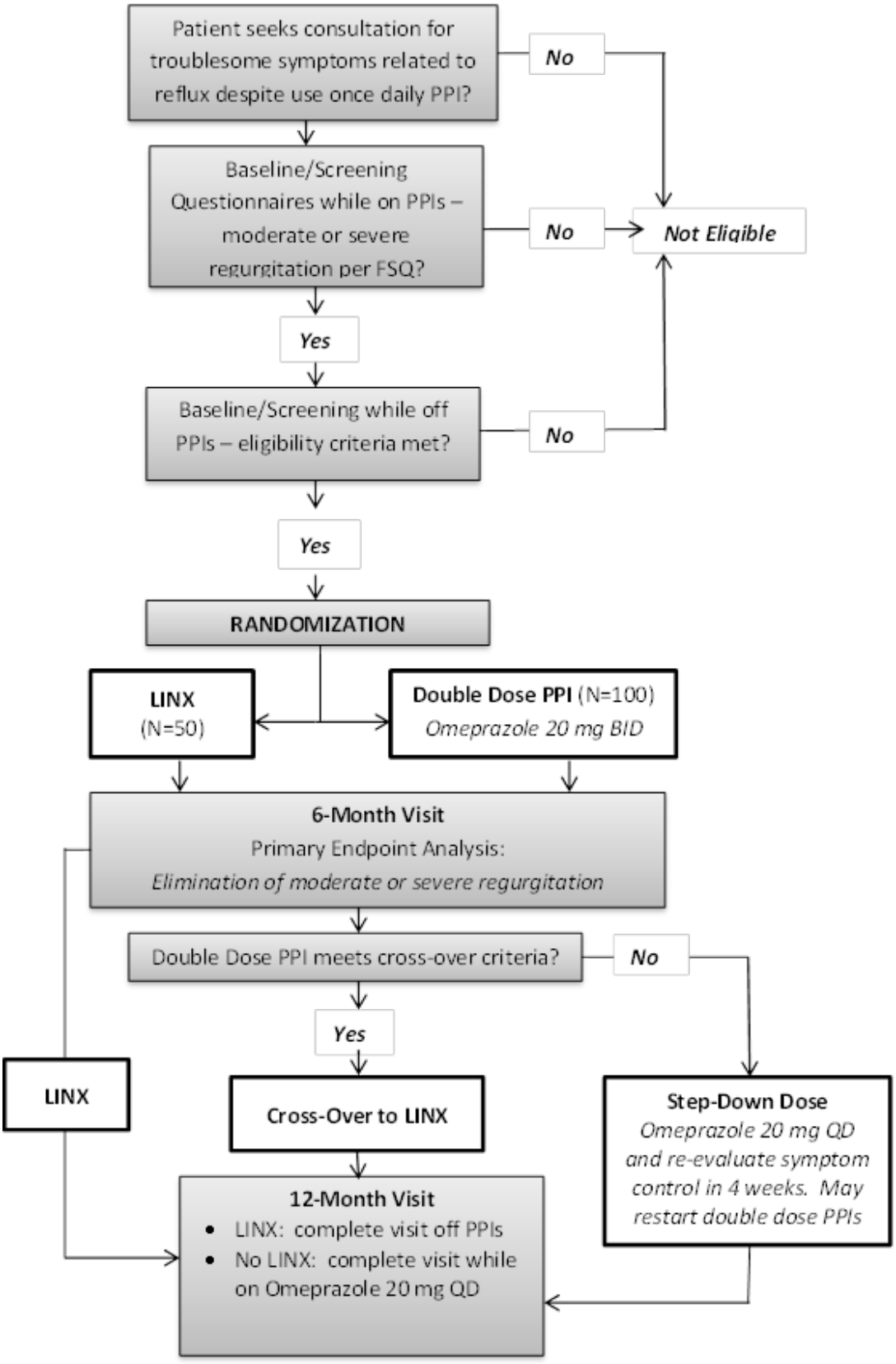
6.2 Side Effects

The GERD-HRQL, Foregut Symptom Questionnaire and RDQ include questions to track potential side effects (such as difficulty swallowing, gas/bloat, nausea, etc.). The data from these questionnaires will be analyzed to evaluate differences between the LINX and double-dose PPIs at 6 months as well as stepped-down dose of PPIs at 12 months.

6.3 Safety

Rate of occurrence of serious adverse events (SAEs) related to LINX or PPIs will be evaluated throughout the duration of the study. No formal statistical hypothesis test will be conducted. Number of related events, number of study subjects with events, and the percent of subjects with an event will be summarized. Because the LINX is a surgical procedure, there are inherent risks not applicable to medical therapy (PPIs). An acceptable level of risk has been documented for the LINX procedure. It is expected that re-hospitalization or device removals will not exceed 6% (upper confidence limit of 12.6%) at the 12-month visit based on the clinical experience from the LINX Pivotal Trial in support of FDA approval, which established this level of risk did not outweigh the benefit of treatment with the LINX device.

7.0 STUDY FLOWCHART



8.0 STUDY PROCEDURES

8.1 Clinical Study Registration

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

8.2 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 15 randomized subjects without prior written approval provided by the Sponsor.

8.3 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.

8.4 Informed Consent

Prior to IRB submission, the Investigator or designee will prepare an 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 D)**. 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.

8.5 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.

8.6 Standard of Care

As part of screening/baseline, all patients will undergo an anti-reflux surgery work-up in the event of randomization to LINX. This work-up can be used in the event of cross-over to LINX as well, provided subjects have not had significant changes to their health. 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. Subjects who cross-over to LINX after the 6 months visit are not required to repeat the anti-reflux surgical work-up, unless deemed necessary by the Investigator.

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.

8.7 Schedule of Data Collection

The Screening/Baseline visit will determine the eligibility of a subject to be randomized to either LINX or double-dose PPIs. After randomization, subjects will be followed at 6 months and 12 months. All follow-up assessments should be completed during an office visit, with the exception of the questionnaires, which may be completed by a phone call or electronically mailed as needed. Sample case report forms are provided in **Appendix E**. **Table 1** shows the schedule of data collection.

Table 1. Schedule of Data Collection

Data Collected/Testing Completed	Visit Schedule			
	Screening/ Baseline	Randomization	6 Month	12 Month
Demographics	X			
Height/Weight	X		X	X
Medical History	X		X	X
GERD Medication	X		X	X
Foregut Symptom Questionnaire	X[1]		X[2]	X[3]
GERD-HRQL	X[1]		X[2]	X[3]
Reflux Disease Questionnaire	X[1]		X[2]	X[3]
Esophagogastroduodendoscopy (EGD)	X			X[3]
Manometry/Motility and/or Barium Esophagram per Standard of Care	X			
Esophageal pH Monitoring	X[1]			X[3]

Treatment Assignment/Implant		X		
Cross-Over/Step-Down Information			X (PPI arm)	
Impedance Monitoring			X[2]	
Adverse Events		X	X	X

[1]Screening/baseline questionnaires 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. Esophageal pH monitoring conducted off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment.

[2]At 6-month follows-up, testing/questionnaires completed per treatment assignment: PPI arm completed while on double dose PPIs with no other GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment; LINX arm completed off all GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment (in the event PPIs had been restarted).

[3]At 12-month follow-up: LINX or Cross-Over LINX complete testing/questionnaires off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment. Step-down PPI subjects complete testing/questionnaires while on single-dose PPI, with all other GERD medications stopped for at least 7 days (including a second dose of PPI), with the exception of antacids which can be taken up until the morning of assessment. *Exception to note: For those subjects crossing-over to LINX after the 6-month visit, the 12-month visit is 6 months ±30 days from the implant procedure date.*

8.8 Data Collection Windows

The data collection window for each visit is outlined in Table 2. The 6-month follow-up visit is +/- 30 days from the anniversary date of the implant procedure or first dose of double-dose PPIs after randomization. The 12-month follow-up visit is +/- 60 days from the anniversary date of the implant procedure or first dose of double-dose PPIs after randomization. (*Exception to note: For those subjects crossing-over to LINX after the 6-month visit, the 12-month visit is 6 months ±30 days from the implant procedure date.)*

Table 2: Follow-up Windows

Visit	Follow-up Window
6 months (±30 days)	150-210 days
12 Months (±60 days)*	305-425 days

*12-month visit for cross-over subjects will be 6 months (±30 days) after the cross-over LINX implant procedure date.

8.9 PPI Dosing

At screening, a subject must be currently taking a once a day standard PPI dose for symptomatic GERD or healing of esophagitis for at least 8 weeks. If a subject is randomized to double-dose PPIs, the subject will take Omeprazole 20 mg BID (twice a day).

When doubling the PPI dose, one PPI dose should be given before breakfast and the other before dinner (ideally 30 minutes before the meal). Subjects should be counseled on the importance of compliance with medical therapy.

Subjects randomized to double-dose PPIs who do not cross-over to LINX after the 6-month follow-up will be stepped-down to a single-dose PPI (Omeprazole 20 mg QD). Four weeks after stepping-down the PPI dose, the subject will be contacted for symptom assessment. If symptoms are not controlled on single-dose, subject may resume double-dose PPI (Omeprazole 20 mg BID) if directed by the Investigator. Use of supplemental GERD medications, after LINX are discussed in **Section 8.19**.

8.10 Questionnaires

At each visit, subjects will complete the following questionnaires to evaluate reflux-related symptoms: GERD-HRQL, Foregut Symptom Questionnaire, and Reflux Disease Questionnaire (RDQ). Samples of these questionnaires are found in **Appendix E**.

At the screening/baseline visit, the questionnaires will be completed twice: 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

At the 6-month follow-up visit, the testing/questionnaires will be completed per treatment assignment:

- Double-dose PPI arm completed while on double-dose PPIs with no other GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment.
- LINX arm completed off all GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment.

At 12-month follow-up, LINX and Cross-Over LINX will complete the testing/questionnaires off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment. Step-down PPI subjects (all subjects without LINX) will complete testing/questionnaires while on single-dose PPI (Omeprazole 20mg QD), with all other GERD medications stopped for at least 7 days (including a second dose of PPI), with the exception of antacids which can be taken up until the morning of assessment.

8.11 Screening/Baseline/Enrollment Visit

Informed consent will be obtained prior to any study specific assessments. Data collected at baseline will include the following:

- Date of birth
- Demographics (gender and race)
- Height and weight
- Duration of PPI use
- Years with GERD
- Baseline GERD related medication use
- GERD-HRQL (on and off GERD medications)

- Foregut Symptoms Questionnaire (on and off GERD medications)
- Reflux Disease Questionnaire (on and off GERD medications)
- Esophageal pH measurements (off GERD medications)
- Esophagogastroduodendoscopy (EGD)
- Manometry/motility or barium esophagram

8.12 Randomization/Implant Visit

LINX

Subjects randomized to LINX should complete the implant procedure within 6 weeks of randomization. The following data will be collected:

- Surgery date
- Implanted device size
- Concomitant procedures (e.g. hiatal hernia repair, cholecystectomy)
- Discharge date and length of stay
- Perioperative and device and/or procedure related adverse events

Double-Dose PPI

Subjects randomized to double-dose PPIs will start the increased acid suppression regimen as soon as possible after randomization. All subjects randomized to double-dose PPIs will take Omeprazole 20 mg BID (twice a day). Subjects will be instructed to take one dose (20mg) 30 minutes prior to breakfast and the second dose (20mg) 30 minutes prior to the evening meal.

8.13 6-Month Visit

Testing/questionnaires will be completed per treatment assignment. The PPI arm will complete testing/questionnaires while on double-dose PPIs with no other GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of. The LINX arm will complete off all GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment (in the event PPIs have been re-started).

At the 6-month visit, the following assessments will be completed:

- Height and weight
- GERD-related medication use within the last 30 days
- Questionnaires: GERD-HRQL, Foregut Symptom Questionnaire and Reflux Disease Questionnaire
- Impedance monitoring
- Review of changes in health and medical history
- Adverse events

Impedance monitoring will be performed per the instructions provided by the Core Lab and the report **forwarded within one week of its completion to the Core Lab** for reading and interpretation.

8.14 12-Month Visit

Subjects without LINX (stepped-down PPI) will complete testing/questionnaires while on single-dose PPI, with all other GERD medications stopped for at least 7 days (including any second dose of PPI), with the exception of antacids which can be taken up until the morning of assessment.

At the 12-month follow-up visit, the LINX and Cross-Over LINX will complete testing/questionnaires off GERD medications for at least 7 days, with the exception of antacids which can be taken up until the morning of assessment.

The following assessment will be completed at the 12-month visit:

- Height and weight
- GERD-related medication use within the last 30 days
- Questionnaires: GERD-HRQL, Foregut Symptom Questionnaire and Reflux Disease Questionnaire
- Endoscopy
- Esophageal pH testing
- Review of changes in health and medical history
- Adverse events

8.15 LINX Implant Procedure

The LINX implant procedure will be performed by a surgeon who has successfully completed the company required training for certification. The subject should have routine post-operative visit about 2-4 weeks after the LINX implant procedure. Subjects will be provided a copy of the LINX post-operative care brochure **(see Appendix F).**

8.16 Cross-Over to LINX

The following criteria must be met for cross-over to LINX:

- Abnormal total number of distal reflux episodes as assessed by 6-month impedance testing completed on double-dose PPIs (abnormal defined in Core Lab's Manual of Operation by manufacturer)
- Presence of moderate or severe regurgitation reported on the 6-month Foregut Symptom Questionnaire completed on double-dose PPIs
- Patient consents to LINX procedure

If a subject crosses-over to LINX, the implant procedure must be completed within 6 weeks of notification that the subject has met the cross-over criteria. Timing of the 12-month visit for cross-over subjects will be 6 months ($\pm$30 days) after the cross-over LINX

implant procedure date. See **Section 8.15** for additional information about LINX implant procedure.

8.17 PPI Step-Down

If cross-over criteria are not met, double-dose PPI will be stepped-down to single-dose (Omeprazole 20 mg QD). Four weeks after stepping down the PPI dose, symptom assessment by either office visit or phone call will be conducted. Double-dose PPIs may be resumed or other GERD medications started at the discretion of the Investigator.

8.18 PPIs after LINX

Subjects in the LINX arm may resume PPIs or other GERD medications after the LINX implant procedure as directed by the Investigator to manage reflux symptoms. PPIs should be used at the lowest frequency and dose necessary for symptom relief.

8.19 Supplemental GERD Medication

As needed for symptom management, subjects may take other supplemental GERD medications. GERD medications other than PPIs, H_2 receptor antagonists (H2 blockers) or antacids are not allowed during the study.

8.20 Adverse Events

For all subjects starting at the time of randomization 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 or GERD-medication-related adverse events (AEs). 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 or PPI 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**

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.

Unanticipated Adverse Device or Drug Effects

Unanticipated adverse device or drug 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 or Omeprazole that are not typically associated with the procedure, device or drug. All unanticipated adverse 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 effect.

8.21 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)

9.0 RISK ANALYSIS

9.1 Potential Risks and Benefits

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**). Risks associated with Omeprazole can be found in the Drug Information **(Appendix B)**. The study will monitor the subjects through the duration of the subject's participation for adverse events.

The potential benefits to subjects are the reduction or elimination of GERD-related symptoms that were not effectively managed with once daily PPI.

10.0 STATISTICAL PLAN

10.1 Subject Population for Analysis

All randomized subjects who either start double-dose PPIs or undergo the implant procedure will represent the study population for the primary efficacy endpoint analysis at 6 months (Treatment Group). Analyses will also include intent-to-treat (ITT) at 6 months for elimination of moderate or severe regurgitation (all randomized subjects, whether treatment was started or not). All other analyses will be performed on available data at the follow-up visit.

10.2 Primary Efficacy Endpoint

The primary efficacy endpoint will be elimination of moderate or severe regurgitation assessed by the Foregut Symptom Questionnaire at 6 months. The primary efficacy endpoint will be analyzed for the Treatment Group. Subjects not evaluable at 6 months due to early withdrawal or missing data will be counted as failures of the primary efficacy endpoint. The randomized groups will be compared for the primary efficacy objective according to the following hypotheses:

H_0: $\Pi_L \leq \Pi_P$

H_A: $\Pi_L > \Pi_P$

where Π_L is the percent of study patients randomized to LINX with elimination of moderate or severe regurgitation and Π_P is the percent of subjects randomized to the PPI group with elimination of moderate or severe regurgitation. The percent of randomized

subjects with a successful elimination of moderate or severe regurgitation will be compared between groups using a Pearson's chi-square test. The required sample size was calculated using SAS v9.3 under the following assumptions:

- Type I error = 5%
- Assumed success rate in LINX group = 70%
- Assumed difference in success rates = 30%
- Power = 85%

Under these assumptions, a minimum of 108 subjects enrolled and followed to 6 months are required. The study will enroll approximately 150 subjects.

10.3 Additional Efficacy Outcomes

Summary statistics will be used to display results of other efficacy 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.

10.4 Safety

Safety will be assessed by the rate of (number and percentage of subjects experiencing) treatment-related adverse events after randomization and throughout the study to 12 months.

11.0 ROLE AND RESPONSIBILITIES

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

11.1 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.

11.2 Study Coordinator

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

12.0 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

13.0 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.

14.0 DATA HANDLING AND RECORD KEEPING

14.1 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.

14.2 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.

14.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. 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.

14.4 Records Retention

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

15.0 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.).

16.0 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.

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