*C*LINICAL INVESTIGATION PLAN (CIP)

The HEURISTIC Study

HErnia Red**U**ction P**RI**or to **S**cheduled **TI**F **C**ompletion

This document complies with requirements of the Declaration of Helsinki, International Harmonized Standards: EN ISO 14155-1 and ISO 14155-2:2003(E) and with 21 CFR Parts 50, 54, 56, and 812.

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Study Responsibility:	Investigator Initiated Each study investigator is responsible for institutional and protocol compliance
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Principal Investigator:	Michael J. Murray, M.D. Northern Nevada Medical Group 2385 E Prater Way Ste 205 Sparks, NV 89434
CO- Investigators:	Medhat Fanous, MD (Iron River Hospital, Iron River, MI) Mamoon Raza, MD (Indiana Medical Research, Elkhart, IN)

Date of Issue: December 19, 2017

Protocol Approval Page

STUDY TITLE:	**HE**rnia Red**U**ction P**RI**or to **S**cheduled **TI**F **C**ompletion **- The HEURISTIC Study**
PROTOCOL NUMBER:	D031517
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We, the undersigned, have read and approve the protocol specified above and agree on its content.

Adrian Lobontiu, MD

Date:

Michael A. Daniel
CRO

Date:

Investigator's Signature Page

STUDY TITLE: **HE**rnia Red**U**ction P**RI**or to **S**cheduled **TI**F **C**ompletion **- The HEURISTIC Study**

STUDY CENTER: _____

(Print name of study center)

We, the undersigned, have read and understand the protocol specified above and agree on its content. We agree to perform and conduct the study as described in the protocol.

Investigator	Date
Print name:	
Investigator	Date
Print name:	
Investigator	Date
Print name:	
Investigator	Date
Print name:	

Protocol Synopsis

The HEURISTIC Study

HErnia Red**U**ction P**RI**or to **S**cheduled **TI**F **C**ompletion

Primary Objective	Evaluation of the relative merits, safety and effectiveness of the EsophyX ZR transoral device in performing the standardized TIF 2.0 procedure preceded by laparoscopic Hiatal Hernia repair in PPI-prescribed patients with persistent "troublesome symptoms" per the Montreal consensus definition.
Test Device	EsophyX ZR System
Principal Investigator	Michael J. Murray, M.D. Northern Nevada Medical Group 2385 E Prater Way Ste 205 Sparks, NV 89434
Co-Investigators	, Medhat Fanous, MD (Iron River Hospital, MI) Mamoon Raza, MD (Elkhart Hospital, IN)
Type of Study	Prospective, investigator initiated, multicenter, non-randomized single arm, open label.
Study Duration	6 Months for primary endpoint. 1 and 2 year follow-up for QOL per SOC.
Number of Patients Number of Sites	50 patients from 3 sites
Follow-Up Schedule	Following TIF procedure, patients will be expected to complete follow-up visits at the 2-Week, 3-Month, and 6-Month time points. Additional follow-up to be completed at 12 and 24 months to assess long-term symptom relief. Consideration will be given to extending follow-up with questionnaires to 3, 4 and 5 years. The study will be considered complete (with regard to the primary effectiveness endpoint) after all patients have completed the 6-Month follow-up visit.

Inclusion Criteria	1. Age 18-80 years 2. Dependent upon daily PPIs for > 6 months. Daily use is defined as a double dose, or full dose or half dose taken daily for more than 80% of the total number of days during the proceeding evaluation period 3. Troublesome symptoms, specifically heartburn or regurgitation, while on optimized dose of PPI's Troublesome heartburn or regurgitation symptoms are those which occur a minimum of 2 days a week and are mild to severe in severity 4. Abnormal ambulatory (Bravo) pH study after off PPI therapy for 7 days, i.e. > 5.3% of the time with pH < 4 in a 48-hour monitoring period 5. Normal or near normal esophageal motility (by Upper GI/ esophagram or manometry as required) 6. Pre-enrollment Hiatal Hernia (axial height and transverse dimension) from > 2 cm up to 4 cm inclusive. 7. Patient willing to cooperate with post-operative dietary recommendations and assessment tests at the requisite follow-up visits 8. Signed informed consent
Pre-enrollment Exclusion Criteria	1. BMI > 35 2. Hiatal hernia ≤ 2 and > 4 cm 3. Esophagitis Los Angeles grade C or D 4. Esophageal ulcer 5. Esophageal stricture 6. Long-segment Barretts esophagus (Prague: C > 1, M > 3) 7. Esophageal motility disorder 8. Pregnancy or plans for pregnancy in the next 12 months (in females) 9. Immunosuppression 10. ASA > 2 11. Portal hypertension and/or varices 12. History of previous resective gastric or esophageal surgery, cervical spine fusion, Zenker's diverticulum, esophageal epiphrenic diverticulum, achalasia, scleroderma or dermatomyositis, eosinophilic esophagitis, or cirrhosis 13. Active gastro-duodenal ulcer disease 14. Gastric outlet obstruction or stenosis 15. Severe gastroparesis or delayed gastric emptying confirmed by solid-phase gastric emptying study if patient complains of postprandial satiety during assessment 16. Coagulation disorders 17. Atypical symptoms including gas bloat and dysphagia. 18. Any other presenting condition that in the opinion of the investigator would not make participation in this study in the patient's best interest.

Post Enrollment Exclusion	1. Inability to repair Hiatal hernia with at least 2cm of intra-abdominal esophagus length.
Intervention	**Treatment:** Standardized Transoral Incisionless Fundoplication (TIF 2.0) using EsophyX ZR system with SerosaFuse fasteners (EndoGastric Solutions, Inc., Redmond, WA, USA) preceded by Hiatal Hernia repair. **Control:** Each patient will serve as his/her own control (condition prior to HH repair and TIF 2.0)
Evaluation Criteria	**Primary Effectiveness Endpoint:** Normalization in esophageal acid exposure is defined by ≤ 5.3% of total time pH < 4 in a 48-hour monitoring period. **Secondary Effectiveness Endpoint 1:** Per Montreal Consensus definition, troublesome symptoms are mild symptoms occurring two (2) or more days per week, or moderate/severe symptoms occurring more than 1 day per week. **Secondary Effectiveness Endpoint 2:** Clinically significant PPI consumption reduction is defined as from daily use to occasional use or none at all. Daily use is defined as a double dose, or full dose or half dose taken daily for more than 80 % of the total number of days during the proceeding evaluation period.

Study Hypotheses	**Primary Effectiveness hypothesis** At 6-month follow-up, the proportion of TIF patients with normalized esophageal acid exposure will be statistically non-inferior to results from the EGS RESPECT study. **Secondary Effectiveness hypothesis 1** The proportion of TIF patients who are free of "troublesome" symptoms will be the same as or higher than the EGS RESPECT study. **Secondary Effectiveness hypothesis 2** At 6-month follow-up, ≥ 50% of the TIF patients will have a clinically significant reduction in PPI consumption as compared with their pre-TIF consumption. **Primary Safety hypothesis 1** At 6-month follow-up, no increase in medically significant AE's as compared with the RESPECT study **Secondary Safety hypothesis 1** At 6-month follow-up, no new onset symptoms and side effects frequently associated with Nissen fundoplication procedures including dysphagia and gas bloat.

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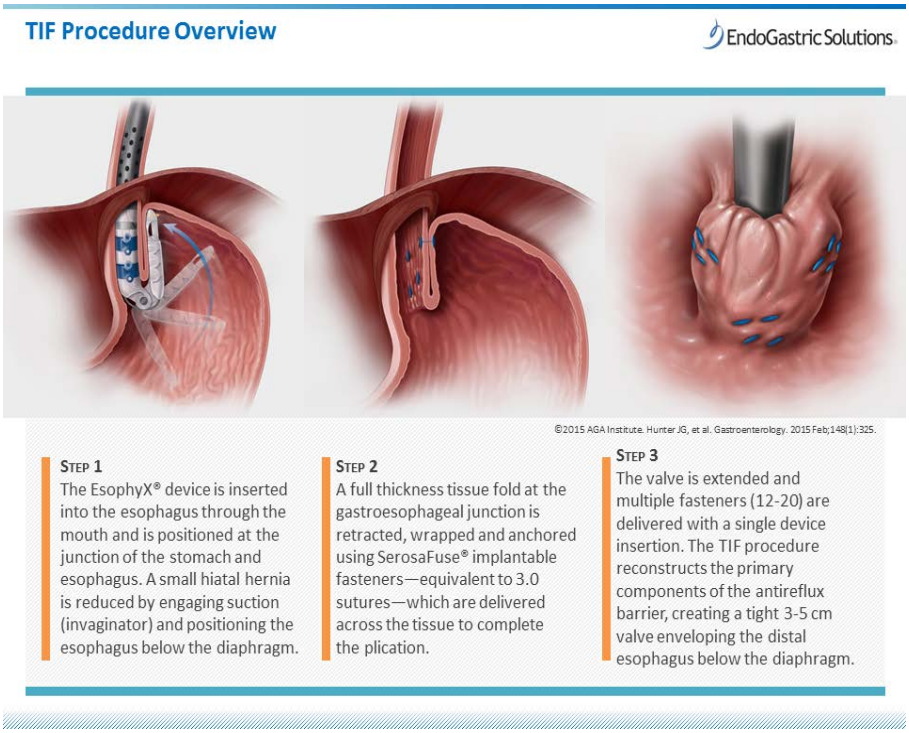
1. Introduction and History of Prior Investigations

The need for a safe, effective, and durable treatment of gastroesophageal reflux disease (GERD) has become increasingly apparent in the past 15 years as a result of a growing prevalence and incidence of this chronic disease.[1-6] The likelihood of developing GERD increases with the severity of anatomical change and dysfunction of the gastroesophageal (GE) junction, which represents the primary defense against reflux of gastric content into the esophagus. [7-12, 13] Restoration of the gastroesophageal junction competence at the anatomic, mechanic and physiologic levels is critical for an effective long-term treatment of GERD.[2] At the same time, complications and new onset symptoms associated with traditional laparoscopic Nissen fundoplication, including dysphagia and gas bloat must be avoided.

A novel transoral incisionless device was developed in an attempt to mimic well established and long term proven principles of antireflux surgery via constructing a fundoplication at the gastroesophageal junction, restoring the angle of His, increasing sphincter augmentation, recreating the high pressure zone and reducing small hiatal hernia, but with fewer side effects. The EsophyX™ system with SerosaFuse fasteners (EndoGastric Solutions, Redmond, WA, USA) has been cleared by the U.S. FDA for treatment of GERD and reduction of ≤2 cm hiatal hernia and has been successfully used to reconstruct the gastroesophageal junction through partial fundoplication with tailored delivery of multiple fasteners during a single-device insertion (**Figures 1,2,3**). [14]

The technique has been refined resulting in a significantly higher normalization rate of esophageal acid exposure and a significant increase of LES pressure and length, combined with long term symptom control.



The Esophyx device has been well-established for the indication of GERD treatment by the U.S. FDA through numerous Class II device 510(k) pre-market clearances dating back to 2009 (and most recently K160960). A summary of past clinical trials has been provided in **Table 2**. Based on the success of prior TIF surgeries, EndoGastric Solutions has recently fine-tuned the Esophyx device allowing for more user-friendly and automatic, stapler-like reliable fastener deployment, as stylet manipulation is no longer required (See "3. Device Description" section). Neither the initial Intended Use nor the Indications for Use have been altered as a result of this design refinement. The FDA cleared Indications for Use is provided below.

"The EndoGastric Solutions EsophyX Z System with SerosaFuse Fastener and Accessories is indicated for use in transoral tissue approximation, full thickness plication and ligation in the GI tract and is indicated for the treatment of symptomatic chronic gastroesophageal reflux disease in patients who require and respond to pharmacological therapy. It is also indicated to narrow the gastroesophageal junction and reduce hiatal hernia ≤ 2cm in size in patients with symptomatic chronic gastroesophageal reflux disease."

The current ≤ 2cm hiatal hernia size limitation presents a problem for treating patients with hiatal hernias >2 cm. Traditionally, these patients, with more advanced anatomical defects, have been surgically treated via a laparoscopic Nissen Fundoplication (NF). Although laparoscopic, the NF is a complex and relatively invasive procedure best performed by very experienced surgeons in order to increase the probability of achieving the desired repair of the hiatal hernia and completion of a total circumferential 360 degree "floppy" wrap without the complications of dysphagia and gas bloat.

A recent n=64, 10-year follow-up study showed a 10.9% defective fundic wrap in laparoscopic Nissen candidates.[1] Due to the fundamentally different approaches between TIF and Nissen procedures, the serious risks associated with Nissen that are inherently absent from the EsophyX TIF 2.0 technique include: excessive scarring, vagus nerve injury, dysphagia, gas bloat, and vomiting/ eructation inhibition from supra-physiological fundic overwrapping.[2]

Historically, clinical results, with patients presenting with ≤2cm hiatal hernias, have demonstrated that the TIF procedures using the EsophyX system with SerosaFuse fasteners is effective in eliminating symptoms, decreasing the need for daily PPIs, normalizing esophageal acid exposure, increasing LES resting pressure, and promoting healing of esophagitis in more than 80% of patients with chronic GERD. The obtained improvement in clinical and pathophysiological outcomes correlated significantly with the quality of the anatomic reconstruction. This clinical study is designed to explore use of the TIF procedure in patients who have had their hiatal hernias reduced from between >2cm and ≤4 cm to ≤2cm. Demonstration that TIF results with these patients are similar to TIF results from patients initially presenting with ≤2cm hiatal hernias while avoiding traditional NF complications could provide expanded patient choices in the minimally invasive treatment of GERD.

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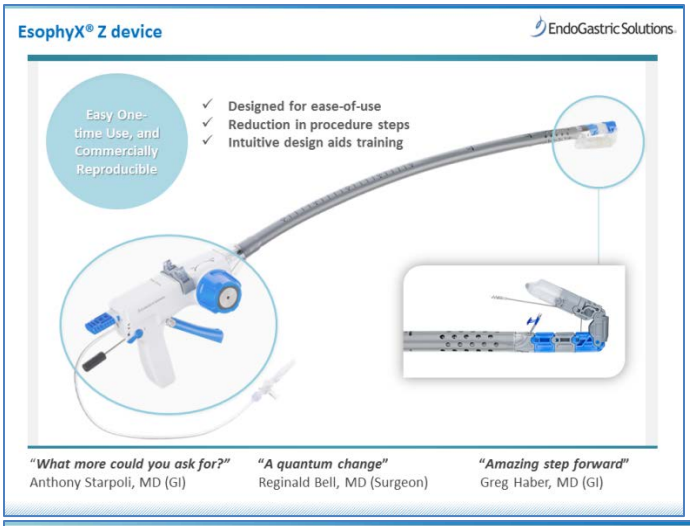
[1] Neuvonen, Perttu, Mauri Iivonen, and Tuomo Rantanen. "Endoscopic evaluation of laparoscopic nissen fundoplication: 89% success rate 10 years after surgery." *World journal of surgery* 38.4 (2014): 882-889.
[2] Waring JP (1999). "Postfundoplication complications. Prevention and management". Gastroenterol. Clin. North Am. 28 (4): 1007–19, viii–ix. doi:10.1016/S0889-8553(05)70102-3. PMID 10695014.

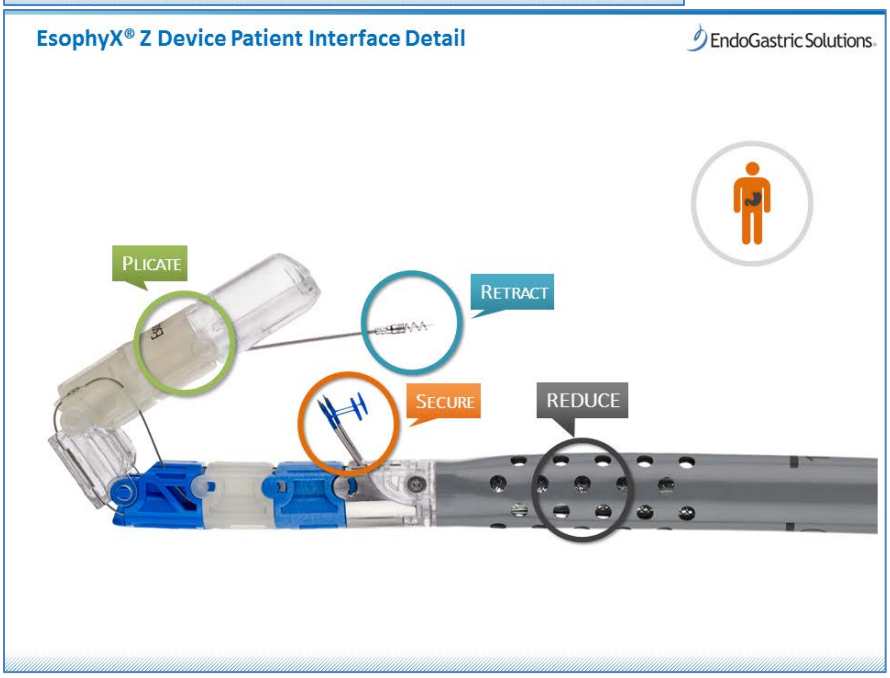
	RESPECT[16]	**TEMPO**[17,18,19]	**TIF vs. Sham**[20]	**TIF Registry**[21,22,23]	**STAR Registry**
Design	A multi-center, randomized, single-blind, controlled TIF/Placebo vs. Sham/PPIs trial	A multi-center, randomized, open-label, controlled TIF vs. PPI trial	A multi-center, double-blind, sham controlled randomized trial	A multi-center, prospective, open-label, post market registry	An AGA-sponsored, multi-center, prospective, open-label, post market registry
Objective	To compare safety and effectiveness of TIF vs. Sham/PPIs in patients with "troublesome symptoms" specifically regurgitation	To compare safety and efficacy of TIF vs. PPIs for the treatment of chronic medically refractory GERD	To gauge the time to 'treatment failure' during the first 6 months after intervention	To evaluate the safety and efficacy of TIF in a broad range of GERD patients treated in routine clinical practice	To compare the safety and efficacy of TIF procedure vs. Laparoscopic Nissen Fundoplication Surgery (LNF)
Patients	2:1 ratio TIF/Placebo group (n=80) vs. Sham/PPI group (n=40)	2:1 ratio TIF group (n=28) vs. PPIs group (n=14)	1:1 ratio TIF group (n=22) vs. sham group (n=22)	274 patients treated with TIF procedure	1:1 ratio TIF group (n=250) vs. LNF group (n=250)
Duration(s)	6 months, 1 year w/ crossover (abstract)	6 months, 1 year w/ crossover, 3 years	6 months	6 months, 1 year, 2 years	Ongoing
Key Outcomes	✓ Troublesome regurgitation was eliminated in 72% of TIF patients at > 1Y ✓ Median heartburn score decreased from 17 to 5 at 6 months and to 3, at > 1Y post-TIF ✓ Complete cessation of PPI therapy was achieved in 72% of TIF patients > 1Y	✓ All symptomatic outcome measures were stable between 1Y, 2Y and 3Y follow-up ✓ Esophagitis was healed in 86% of patients at 3Y follow-up ✓ 71% of patients completely off PPIs at 3Y follow-up ✓ Improvement in pH parameters remained stable at 3Y follow-up	✓ Average of 197 days "time in remission" post-TIF vs. 107 days post-sham ✓ Six months post-op 13/22 (59%) of TIF patients were in clinical remission with complete cessation of PPIs consumption. ✓ 69% of the TIF group normalized esophageal acid exposure vs. 20% of the sham group	At 2Y follow-up: ✓ 65% normalization in the Reflux Symptom Index score ✓ 74% normalization of Gastroesophageal Reflux Symptom Score ✓ A decrease from 91% to 29% in daily PPI use ✓ 75% of patients had esophagitis healed	In enrollment

Table 2. Summary of Level I and II Clinical Studies (TIF 2.0)

2. Device Description

The EsophyX® Z device is a single use, hand-held flexible instrument that is introduced transorally with a flexible endoscope in the center of the device, so the entire procedure can be done safely under direct visualization. The device is designed so the physician can manipulate esophageal and gastric tissue, creating a partial fundoplication, secured by and deploy strong, H-shaped fasteners in order to reconfigure lower esophageal anatomy to prevent GERD.





3. Study Design Rationale

In spite of the promising results described in the previous section, the TIF 2.0 procedure with EsophyX Z is not an ideal option for all GERD patients. Early GERD syndrome and disease is clearly best medically treated with antacids, H2 blockers and/or Proton Pump Inhibitors (PPIs). These pharmacological approaches may be palliative but are both highly effective and believed to be very safe at labeled dosages and durations, in early stage of the disease. The current general Gastroenterology consensus, as documented in the American Gastroenterological Association (AGA) Medical Position Statement on "The Management of Gastroesophageal Reflux Disease", is that only patients who are either intolerant of PPIs, or who have persistent troublesome symptoms while on properly adjusted doses of PPIs should be considered for antireflux surgery. "Troublesome" symptoms in this context are defined by

the "Montreal Consensus"[1] as mild symptoms occurring two (2) or more days per week, or moderate/severe symptoms occurring more than 1 day per week.

Frequently, patients exhibiting GERD symptoms and Hiatal Hernias are treated with Nissen fundoplications. However, the Nissen technique is complex, and requires significant training and expertise to perform. Many surgeons lack the requisite experience and resources to perform such a procedure safely and effectively. Demonstration of TIF effectiveness post hiatal hernia reduction from up to 4 cm, gastroenterologists would have an option as opposed to referring patients to select hospitals for a Nissen.

As in RESPECT RCT, patients are required to cease PPI intake 7 days prior to the procedure to ensure of accurate pH measurement via the BRAVO capsule.

In this context, an ideal study would consist of enrolling patients who suffered from persistent troublesome symptoms while on optimized dose of PPIs. The prospective study is open-label, non-randomized, and investigator initiated at multiple (3) sites (n=50). The primary endpoint is a clinically significant pH improvement, i.e. normalization, at the 6 month post-op mark. The proportion of patients with normalized esophageal acid exposure after 6 months will be compared to that of the previous EsophyX RESPECT trial to demonstrate equivalent (non-inferior) effectiveness. A sequence of follow-up visits will be required (2 week, 3 month, 6 month) to monitor symptom presence and PPI intake via Quality of Life surveys in addition to the primary endpoint. This follow-up and symptom monitoring will include evaluation of potentially new onset symptoms such as dysphagia and gas bloating commonly associated with the NF procedure.

4. Study Objective

Evaluation of the relative merits, safety and effectiveness of the EsophyX Z transoral device in performing an advanced TIF procedure preceded by laparoscopic Hiatal Hernia repair (hiatal hernias >2cm and ≤4 cm) in PPI- prescribed patients with "troublesome symptoms" per the Montreal consensus definition.

5. Study Hypotheses

5.1. *Primary Efficacy Hypothesis 1*

At 6-month follow-up, the proportion of TIF patients with normalized esophageal acid exposure will be statistically non-inferior to results from the EGS RESPECT study.

5.2. *Secondary Efficacy Hypothesis 1*

The proportion of TIF2 patients who are free of "troublesome" symptoms will be the same as or higher than the results from the EGS RESPECT study.

5.3. *Secondary Efficacy Hypothesis 2*

At 6-month follow-up, ≥ 50% of the TIF patients will have a clinically significant reduction in PPI consumption as compared with their pre-TIF consumption

5.4. *Primary Safety Hypothesis 1*

At 6-month follow-up, no increase in medically significant adverse events as compared with the RESPECT study

5.5. *Secondary Safety Hypotheses 1*

At 6-month follow-up, no new onset symptoms and side effects frequently associated with Nissen fundoplication procedures including dysphagia and gas bloat.

6. Study Design

6.1. *Study Population*

The study population will consist of patients with chronic "troublesome" GERD symptoms while on PPIs and proven anatomic deterioration of the gastroesophageal junction who prefer a laparoscopic Hiatal Hernia Repair followed by an endoscopic intervention (TIF 2.0) over the long term treatment of PPIs. These patients should have well documented GERD with or without endoscopic signs of esophagitis, hiatal hernia >2cm and up to 4 cm and a history of > 6 months of daily use of PPI to control major GERD symptoms.

6.2. *Study Schematic Design*

Please see next page.

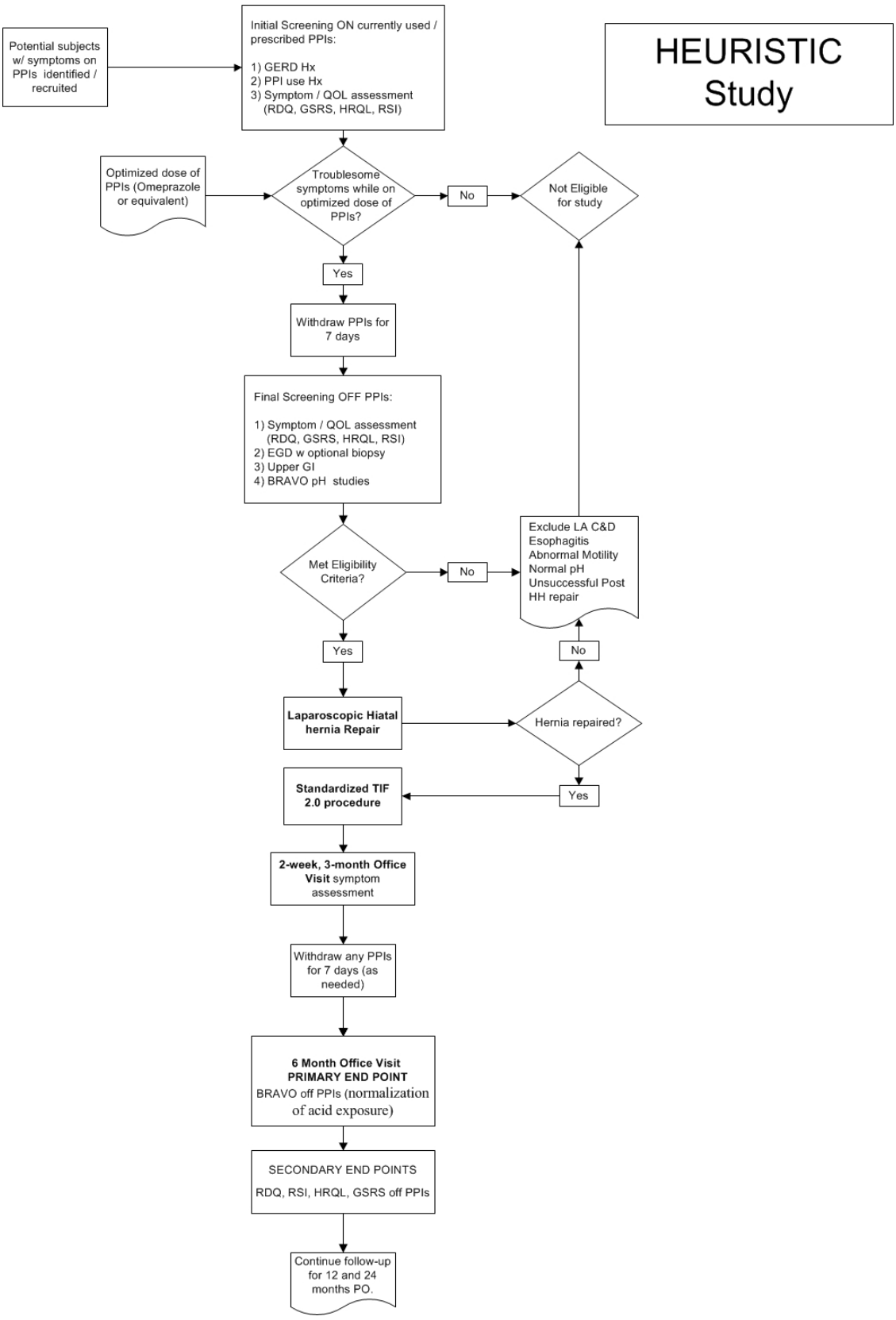


Figure 6. Schematic of Study Design

7. Study Population

7.1. *Selection Criteria*

The table on the following pages outlines the specific inclusion and exclusion criteria for the study. Before randomization in the study, a patient must meet all of the inclusion and exclusion criteria.

Inclusion Criteria:	
1.	Age 18-80years
2.	Dependent upon daily PPIs for > 6 months. Daily use is defined as a double dose, or full dose or half dose taken daily for more than 80 % of the total number of days during the proceeding evaluation period
3.	Troublesome symptoms, specifically heartburn or regurgitation, while on optimized dose of PPI's. Troublesome heartburn or regurgitation symptoms are those which occur a minimum of 2 days a week and are mild to severe in severity.
4.	Abnormal ambulatory (Bravo) pH study after off PPI therapy for 7 days, i.e. >5.3% of the time with pH < 4 in a 48-hour monitoring period
5.	Normal or near normal esophageal motility (by Upper GI/ esophagram or manometry as required)
6.	Pre-enrollment Hiatal Hernia (axial height and transverse dimension) from > 2cm and up to 4 cm inclusive
7.	Patient willing to cooperate with post-procedure dietary recommendations and assessment tests at the requisite follow-up visits
8.	Signed informed consent
Pre-enrollment Exclusion Criteria:	
1.	BMI > 35
2.	Hiatal hernia ≤ 2 and > 4 cm
3.	Esophagitis Los Angeles grade C or D
4.	Esophageal ulcer
5.	Esophageal stricture
6.	Long-segment Barretts esophagus (Prague: C > 1, M > 3)
7.	Esophageal motility disorder
8.	Pregnancy or plans for pregnancy in the next 12 months (in females)
9.	Immunosuppression
10.	ASA > 2
11.	Portal hypertension and/or varices
12.	History of previous resective gastric or esophageal surgery, cervical spine fusion, Zenker's diverticulum, esophageal epiphrenic diverticulum, achalasia, scleroderma or dermatomyositis, eosinophilic esophagitis, or cirrhosis
13.	Active gastro-duodenal ulcer disease
14.	Gastric outlet obstruction or stenosis
15.	Severe gastroparesis or delayed gastric emptying confirmed by solid-phase gastric emptying study if patient complains of postprandial satiety during assessment
16.	Coagulation disorders
17.	Symptoms including gas bloat and dysphagia.
18.	Any other presenting condition that in the opinion of the investigator would not make participation in this study in the patients best interest.
Post-enrollment Exclusion Criteria:	
1.	Inability to repair Hiatal hernia with at least 2cm of intra-abdominal esophagus length.

7.2. *Withdrawal*

While study withdrawal is discouraged, patients may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Withdrawn patients will not undergo any additional follow-up. In all cases of withdrawal, the reason(s) for withdrawal (if given) will be recorded upon study termination.

8. Study Methods and Techniques

8.1. *Clinical Symptom Assessments*

The following four GERD-specific questionnaires will be used to assess typical and atypical symptoms, their frequency and intensity, as well as their impact on daily life, relationships, quality of life, state of mind, worries and concerns, sleep and diet.

- Reflux Disease Questionnaire (RDQ)
- GERD HRQL Quality of life assessment
- GERD GSRS Quality of life assessment
- RSI Questionnaire for atypical symptoms

- The time needed for completion of all four questionnaires is estimated for 35 minutes maximum.
- A ≥ 50% improvement in the total GERD-HRQL and GERD-GSRS scores compared to the baseline off PPIs will be considered clinically significant.
- A reduction in severity from ≥ moderate to ≤ mild and/or a reduction in frequency from ≥ 2 days per week to ≤ 1 day per week is indicative of a clinically significant result as measured by the Reflux Disease Questionnaire (RDQ).

8.2. *PPI Usage*

The use of PPIs plus other GERD medication such as histamine receptor antagonists (H2RA) and antacids will be recorded in a medication diary using generic names **(Table 3)** and classified according to the daily dose and frequency. [18, 21]

Usage will be defined as “Daily” if a double dose, full dose or half dose is taken daily for more than 80% of the total number of days during the proceeding follow-up period.

Note: “Full Dose” is defined as the first number of mg listed for each PPI in the following table.

Table 3. Proton Pump Inhibitors (PPI)

Generic Name	Brand Names	Available Pill Sizes (mg)
Esomeprazole	Nexium	20, 40
Lansomeprazole	Prevacid, Dakar, Lanso, Lanzor, Prezal, Lanzol	15, 30
Omeprazole	Prilosec, Losec, Logastric	10, 20, 40
Pantoprazole	Protonix, Zurcal, Pantozol, Zurcale	20, 40
Rabeprazole	Aciphex, Pariet	20

8.3. *Upper GI Endoscopy*

- Diagnosis of esophagitis according to the Los Angeles classification confirmed by esophageal biopsy. [22]
- Hiatal hernia size will be diagnosed based on the distance from Z-line to diaphragmatic impression measured in cm at retraction of the endoscope without insufflation.
- Geometrical aspects of the TIF valves will be assessed by evaluating their:
  - **Length**, defined as the length in cm from the apex of the fundus to the valve lip as demonstrated in **Figure 7**;[23]
  - **Circumference**, defined as the distance in degrees between the two most distant fasteners as demonstrated in **Figure 4**;
  - **Adherence** to the endoscope defined as tight, moderate or loose;
  - Grade using **Hill classification** system,[24] defining grade I by the presence of a prominent tissue fold surrounding the endoscopic shaft; grade II by the presence of a moderately prominent tissue fold which rarely opens with respiration and closes promptly; grade III by a barely present fold which fails to close around the endoscope; and grade IV by the lack of a muscular fold with lumen of esophagus staying open all the time allowing the squamous epithelium to be viewed from below.

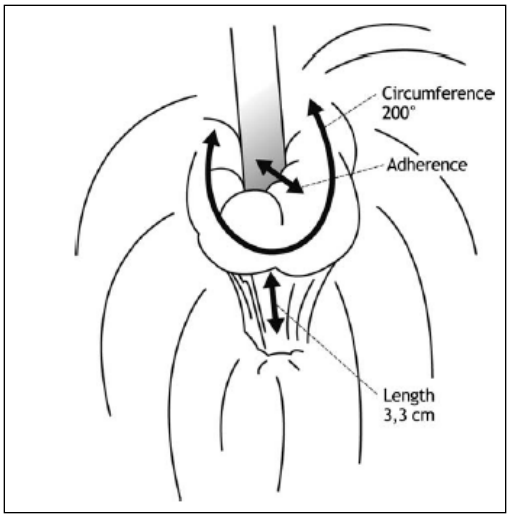


Figure 7. Schematic drawing of TIF valve and its geometric aspects (Illustration from Cadiere et al 2008 [16])

8.4. *BRAVO pH Studies*

Acid reflux (off all antisecretory compounds for a minimum of 7 days) will be documented using pH-metry techniques utilizing BRAVO system. The BRAVO system will be used both at baseline/screening and at 6 monts post procedure to document in a consistent way, across all sites for an ambulatory 48 hour pH.

Normal pH will be considered if pH < 4 lasts for ≤ 5.3% of the time in a 48-hour monitoring period.

8.5. *Esophageal Motility*

- Measures LES resting pressure following standard protocol
- > 50% peristalsis with > 30% distal amplitudes
- 10 consecutive water swallows allows the assessment of propulsive motor function of the esophagus
- High-resolution motility is optional

9. Study Procedures

The schedule of observations and assessments to take place during the study follows on the next page. **(Table 4)**

Table 4. Study Events Schedule

	Initial Screening	Final Screening	Procedure	Post-Procedure/ Hospital Discharge	2-Week ±3 days	3-Month ± 15days	6-Month ± 20 days	12 and 24 Months ± 20 days
Inclusion/Exclusion Criteria	X	X						
Sign Informed Consent Form		X						
Demographics and Medical History	X							
Physical examination	X			X				
Record concomitant medications	X	X	X	X	X	X	X	
Recording of GERD Medications	X				X	X	X	X
Recording of duration of GERD Symptoms	X				X	X	X	X
Recording of type of GERD Symptoms	X				X	X	X	X
Recording of PPI Use; except for 2-week and 3-month visits, discontinue PPI usage for 7 days to evaluate study endpoints	X			X	X	X	X	X
RDQ, atypical symptom RSI, Quality of Life questionnaires GSRS, HRQL after being off PPI for at least 7 days	X						X	X
Discontinuation of anticoagulants if applicable (at least 10 days before scheduled TIF)	X							
EGD with optional biopsy		X					X	
Motility studies (High resolution optional)		X						
BRAVO pH study (at least 7 days after stopping all antisecretory compounds)		X					X	
Study Enrollment		X						
Hiatal Hernia Repair			X					
TIF 2.0 Procedure (if Hiatal Hernia successfully repaired with at least 2 cm of intra-abdominal esophagus)			X					
Adverse Event Reporting			X	X	X	X	X	

9.1. *Determination of Patient Eligibility – Screening Process*

Initial Screening -
The following pre-procedure data must be collected in order to determine patient eligibility:

- Demographics and medical history, to include age, weight, gender, and race
- Usage of GERD medication (medication, dosage, frequency and duration)
- Duration of GERD symptoms
- Type of GERD symptoms
- Duration of PPI Use
- Clinical symptom assessments (RDQ) and Quality of Life questionnaires (GSRS, HRQL, Atypical Symptom RSI)
- All general inclusion/exclusion criteria have been met

Upon completion of the Initial Screening Process, if it is determined that the patient does not have "troublesome" symptoms while on PPIs, they are **NOT eligible** for the study

Final Screening -:
The following pre-procedure data must be collected in order to determine eligibility:

- Informed consent signing
- Physical Examination
- Days since last PPI intake (prior to BRAVO pH study)
- EGD with optional biopsy
- High resolution motility studies (optional)
- Upper GI endoscopy
- Bravo pH studies (48 hours)

Patients who have met all entry criteria are enrolled to the study.

9.2. *Prior to the Study Procedure*

- The usage of any anticoagulants will be discontinued before TIF for at least 10 days.
- 12-hours before the procedure, the patient is expected to be fasting.
- Immediately before the procedure, each patient will undergo an endoscopic examination of the stomach and esophagus.

9.3. *During the Study Procedure*

A Transoral Incisionless Fundoplication will be performed following the standard laparoscopic Hiatal Hernia Repair and closure of the diaphragmatic defect (crura closure will be made

posterior with 2-3 separate stitches). The patient will be terminated from the study if hiatal hernia cannot be repaired, with at least 2 cm intra-abdominal esophageal length.

TIF Procedure (Treatment)

The TIF procedure **(treatment)** will be conducted under continuous visualization following a standard TIF2.0 protocol (**Figures 8**).

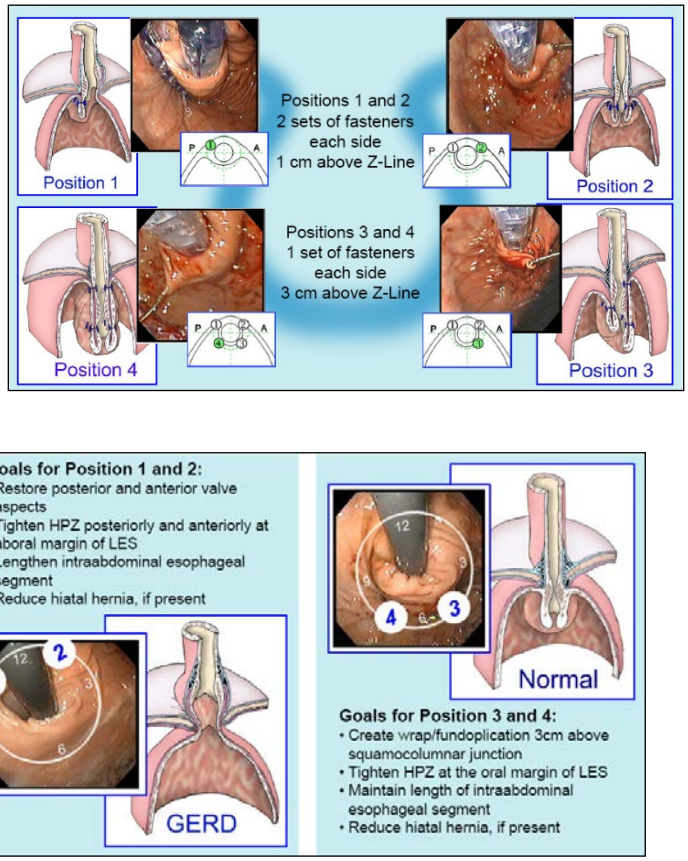


Figure 8. Standard TIF2 protocol

The usage of any anticoagulants will be discontinued before HHR and TIF 2.0 for at least 10 days. Patients are expected to fast for 12 hours before the procedure. Antibiotic prophylaxis will be administered during induction of general anesthesia (oro-tracheal intubation and anti-emetic protocol; dehydrobenzoperidol, dexamethasone, Zofran, Primperan).

As stated in Section 10.2, immediately before the procedure, each patient will undergo an endoscopic examination of the stomach and esophagus. The EsophyX ZR will be inserted transorally through a bite-block into the esophagus with the patient in either in supine, or 45 degrees or left lateral position.

During a single insertion of the device, a valve similar to that created through antireflux surgery will be reconstructed by retraction of full-thickness plications and tailored placement of multiple fasteners circumferentially 1-3 cm above the Z-line. The procedure is expected to last for 30-45 minutes. The quality of the

created valve will be evaluated by an endoscopic examination immediately after the procedure. Any complications related to the procedure will be recorded.

In the event of patient complaint of significant unmanaged GERD symptoms 14 days post procedure, the patient will be offered continued PPI therapy. (See below)

9.4. *Post-Procedure / Hospital Discharge*

Patients will be released the next day after a complete physical examination and instructed to consume a liquid diet during the first two weeks and a soft diet during the following four weeks. The liquid diet will consist of strained soups, pudding, milk, gelatin, yogurt, well-cooked and puréed vegetables, and chewable multivitamins. During weeks 3 to 6, patients will introduce a soft diet consisting of moist fish, canned fruits, bananas, berries, soft eggs, cooked vegetables, mashed potatoes, pasta, moist rice, and cereals (softened in milk). After the six-week healing time, patients can then incorporate fresh vegetables, meats, bread, citrus and alcohol back into their diet.

The usage of PPIs will be continued for 14 days following the procedure to allow healing of the gastric mucosa around the fasteners and to reduce patients' post procedure anxiety. In the event of the recurrence of troublesome symptoms, patients will be encouraged to contact the study coordinator. The nature, intensity and frequency of these symptoms will be assessed during in-office visits.

The designated staff at the clinical site will review the study requirements with the patient to maximize compliance with the follow-up schedule and the required medication regimen. Patients will be instructed to return for follow-up assessments according to the study event schedule in Section **8**. A date for the follow-up visit (office or phone as appropriate) should be established between the patient and Investigator, and if possible the visits scheduled at the time of hospital discharge.

9.5. *Follow-up*

All enrolled patients will be evaluated at 2-weeks, 3-, 6-, and 12-Months and 24 months post TIF- procedure.

The study will be considered complete (with regard to the primary endpoint) after all patients have completed the 6-Month follow-up period.

Consultations may become necessary if major reflux symptoms emerge. Before each follow up time point the patient will be contacted by telephone in order to enhance clinical assessments and data compliance. Refer to the Schedule of Events **(Table 4)** for a comprehensive outline of protocol requirements.

10. Statistical Considerations

10.1. *Analysis Populations and Missing Data Handling*

Effectiveness Population - Per the Intent-to-Treat principle, all enrolled patients who receive the protocol TIF 2.0 procedure will be included in the effectiveness analysis.

Safety Population - Safety analysis will include all enrolled patients who receive any portion of the protocol required Hiatal Hernia Repair or TIF 2.0 procedures.

Missing data: All analyses will be based on available data. Missing data will not be imputed by methods.

10.2. *Statistical Analysis Plan*

10.2.1 General Methodology

Patient demographics and key baseline and disease characteristics at screening will be summarized by descriptive statistics. Mean, standard deviation, median, minimum and maximum will be reported for continuous variables. Frequency counts and proportions will be presented for categorical variables. Effectiveness and Safety endpoints will be similarly summarized with 95% confidence intervals for means and proportions of interest.

10.2.2 Effectiveness Analysis

The primary analysis timepoint for effectiveness is 6 months post TIF procedure. Descriptive summaries as described in 10.2.1 General Methodology will be provided for the primary effectiveness endpoint of proportion of patients with normalized esophageal acid exposure, and secondary endpoints of proportion of patients free of "troublesome" symptoms and proportion of patients with a clinically significant reduction in PPI consumption from their pre-TIF screening consumption.

At each assessment time point, RDQ, atypical symptom RSI, Quality of Life questionnaires GSRS, HRQL will summarized as continuous measures. At 6 months, changes from baseline will be similarly summarized for each of these instruments. As defined in Section 8.1, portions of patients with clinically significant improvements will also be reported with 95% confidence intervals for GERD-HRQL, GERD-GSRS, RSI, and RDQ.

In addition, for the primary endpoint, proportion of patients with normalized esophageal acid exposure, 44% was observed in the EGS RESPECT study. Non-inferiority testing will be conducted for the same proportion observed in the HEURISTIC study vs. the RESPECT result. The hypotheses are as follows.

H_0: HEURISTIC 6-month normalization rate $\leq 44\% - 20\% = 24\%$

H_A: HEURISTIC 6-month normalization rate $> 44\% - 20\% = 24\%$

The HEURISTIC normalization rate will be considered non-inferior to the 44% RESPECT rate if H_0 can be rejected at a 1-sided $p<0.05$ level by exact binomial

probability calculation. To achieve this goal in 50 evaluable patients, the observed 6-month normalization rate in HEURISTIC must be 18/50 (36%) or higher.

10.2.3 Safety Analysis

Treatment emergent adverse events, i.e. adverse events occurring during or after the first protocol procedure (i.e. hiatal hernia reduction), will be summarized. The proportion of patients with medically significant adverse events will be compared to the same proportions observed in the RESPECT study.

In addition, the number and proportion of subjects reporting any given adverse event, including any clinically significant hiatal hernia repair complications and new onset symptoms (dysphagia, gas bloat) should they occur, will be tabulated. Separate tables will be constructed for (a) all reported treatment emergent adverse events, (b) protocol procedures (hiatal hernia reduction, TIF) related adverse events, and (c) serious adverse events.

10.1. *Sample Size and Power Estimation*

For the primary endpoint, proportion of patients with normalized esophageal acid exposure at 6 months post TIF procedure, 44% was observed in the EGS RESPECT study. It is assumed that the true underlying rate for HEURISTIC treatment would be the same, i.e. 44%. In order to reject an inferior normalization rate of 24% at a 1-sided $p < 0.05$ level, the observed 6-month normalization rate in HEURISTIC must be 18/50 (36%) or higher. With 50 evaluable subjects, the chance (power) for successfully reaching this goal is 0.90.

11. Clinical Effectiveness Endpoints and Evaluation Criteria

11.1. *Clinical effectiveness*

Primary effectiveness endpoint and evaluation criterion

The primary efficacy endpoint is normalization in esophageal acid exposure at 6 months post TIF procedure. Normalization in esophageal acid exposure is defined as ≤ 5.3% of time with pH < 4 in a 48-hour monitoring period.

Secondary effectiveness measures and evaluation criteria

Secondary effectiveness measures include free of "troublesome" heartburn and/or regurgitation symptoms and a clinically significant reduction in PPI use.

Per Montreal Consensus definition, troublesome symptoms are mild to severe symptoms which occur a minimum of 2 days a week.

A clinically significant PPI consumption reduction is defined as from daily use to occasional use or none at all. Daily use is defined as a double dose, or full dose or half dose taken daily for more than 80 % of the total number of days during the proceeding follow-up period.

Table 5. Study Effectiveness Endpoints and Success Criteria

Study Endpoints/Outcomes	Control	Pre-procedure Value	Post-procedure Value	Success Criteria
PRIMARY EFFECTIVENESS				
Normalized acid exposure	Self-Comparison	BRAVO Ph studies after off anti-secretory meds ≥7 days	BRAVO Ph studies at 6 months after off anti-secretory meds ≥7 days	Treatment success will be defined by a proportion of TIF patients with normalized acid exposure that is non-inferior to the RESPECT result as defined in 10.2.2.
SECONDARY EFFECTIVENESS				
GERD symptoms	Self-Comparison	Reflux Disease Questionnaire (RDQ) scores	Reflux Disease Questionnaire (RDQ) scores at and 6 months	Treatment success will be defined by a proportion of TIF patients free of troublesome symptoms at 6 months that is ≥ the same proportion in RESPECT Trial (67%)
PPI usage	Self-Comparison	PPI usage (must be "daily")	PPI usage at 6 months	Treatment success will be defined by ≥50% of TIF patients that has a clinically significant reduction, i.e. from "daily" PPI use to "none" or "occasional' use, at 6 months.

12. Risks

The following risks are anticipated and can result from the TIF procedure or general anesthesia:

Expected typical risks or discomfort:

- Pharyngolaryngeal pain (e.g., sore throat)
- Musculoskeletal pain (e.g., left shoulder pain)
- Temporary epigastric or abdominal pain, which can be treated with standard pain medication
- Temporary dysphagia (i.e., difficulty swallowing) due to swelling
- Nausea or vomiting

Unusual risks or discomfort:

- Oral or dental injury
- Bleeding
- Bloating sensation
- Hematoma

Rare risks:

- Esophageal perforation, laceration or tear
- Aspiration, hypoxia, achalasia

- Nerve damage
- Arrhythmia
- Pneumothorax, chest pain
- Pneumoabdomen
- Fistula
- Infection of the mediastinal space

Additional risks:

- Operation to remove a defective device or its parts
- Reoperation after a failed procedure (insufficient symptom relief)

13. Adverse Events

All adverse events will be monitored from the time of enrolling through the 6-month follow-up visit. Unanticipated adverse device effects (UADE) and SAEs will be monitored through the 12-month follow-up.

An AE is defined as any undesirable clinical occurrence in a patient whether or not it is considered to be device related. In addition, the definition of AE applies to any event with an onset post study treatment or to any underlying diseases, present at baseline, that exacerbate in severity post study treatment. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE. This definition includes events occurring during the follow-up period.

All AEs must be recorded in the electronic database. A description of the event, including the start date, resolution date, action taken, and the outcome should be provided, along with the Investigator's assessment of the relationship between the AE and the study treatment.

A serious adverse event (SAE) is defined as an event which leads to:

- Death due to any cause
- Life-threatening condition
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalization or prolonged hospitalization
- Necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure
- Results in congenital abnormality

13.1. *Causality and Seriousness Assessment*

The Investigator and Sponsor will bring all expertise to bear on determining adverse event relationship to investigational device or other study treatment. The Investigator and Sponsor will promptly review documented adverse events and abnormal test findings to determine if the:

- Abnormal test finding or experience should be classified as an adverse event
- Adverse event was definitely, probably, possibly, unlikely or not related to the, and
- Adverse event meets the criteria for a serious adverse event.

Causality/Relationship Definitions:

Definitely	Clear-cut temporal association and no other possible cause.
Probably	Clear-cut temporal association and a potential alternative etiology is not apparent.
Possibly	Less clear temporal association; other etiologies are also possible, but there is a reasonable possibility that the incident, experience, or outcome may have been caused by the drugs, devices or procedures involved in the research
Unlikely	Does not follow a reasonable temporal association; or causal relationship with the drugs, devices or procedures involved in the research is unlikely but cannot be completely ruled out
Not related	AE is completely independent of study product administration; and/or evidence exists that the event is definitely related to another etiology.

13.2. *Reporting Serious Adverse Events*

Study personnel must report to the **EndoGastric Solutions Clinical Affairs Team** any SAE by telephone, fax, or electronic data capture entry within **24 hours** of learning of the event. When telephoning in notification of an event, a telephone log or other source record should be retained at site as adequate documentation of timely event reporting. When faxing in notification of an event, a fax confirmation report must be retained at site as adequate documentation of timely event reporting.

Attention: Adrian Lobontiu, MD, FACS
Telephone Reporting: 650-474-9259
E-mail Reporting:
alobontiugsahyun@endogastricsolutions.com

Study personnel must forward follow-up information as the event continues and/or resolves.

It is the responsibility of the Site Principal Investigator to inform the IRB of SAE and events as required by local procedure. EndoGastric Solutions is responsible for relaying adequate information on SAEs/UADEs to all participating investigators and regulatory authorities.

13.3. *Withdrawal of Subjects Due to Adverse Events*

Patients who experience adverse events during or after the procedure will remain enrolled in the study. Once enrolled, all patients will be followed for safety and efficacy evaluations with the exception of consent withdrawals by patient.

13.4. *Device Failures and Malfunctions*

All failures and malfunctions of the study device will be documented in the electronic database, and the device will be returned to EndoGastric Solutions for analysis. Device failures and malfunctions should also be documented in the patient's medical record.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded in the usual way.

14. Data Management

14.1. *Data Collection*

Data will be collected via a standard paper-based system of CRFs. In addition to collecting data as required per this protocol, various cost and reimbursement information will be captured on a per-patient and per-site basis. All data will be treated confidentially and exported only in the aggregate non-identifiable form.

14.2. *Data Processing*

Data will be entered into a spreadsheet based database by the CRO. Visual and computer error checks will be carried out. The Investigator will be queried on errors concerning completeness and consistency.

Audits may be performed for quality assurance of the electronic database.

15. Monitoring Procedures

15.1. *Monitoring and Auditing*

Monitoring visits to the clinical sites will be made periodically during the study, to ensure that all aspects of the current, approved protocol/amendment(s) are followed. Original source documents will be reviewed for verification of data.. The Investigator/institution guarantees direct access to original source documents by EndoGastric Solutions personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a patient that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review.

The study may also be subject to a quality assurance audit by EndoGastric Solutions or its designees, as well as inspection by appropriate regulatory authorities.

It is important that the Investigator and relevant study personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

15.2. *Device Accountability*

Device accountability records must be maintained at the study site. Each site will purchase the devices from EGS.

16. Ethical Considerations

16.1. *Declaration of Helsinki*

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, and with the regulations and guidelines of FDA; whichever affords the greater protection to the patient.

16.2. *Institutional Review Board*

A copy of the protocol, proposed Informed Consent form, other written patient information and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written IRB approval of the protocol and Informed Consent form must be received by EndoGastric Solutions before recruitment of patients into the study.

The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the Informed Consent form. The Investigator should notify the IRB of deviations from the protocol or SAEs/UADEs occurring at the site and other SAE/UADE reports received from EndoGastric Solutions in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB continuance of approval must be sent to EndoGastric Solutions.

16.3. *Informed Consent Form*

A sample Informed Consent form is provided in Appendix A for the Investigator to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential patient population.

The reviewing IRB and the sponsor must first approve the Informed Consent forms that are used. The Informed Consent forms that are used should be in accordance with the current guidelines as outlined by the Good Clinical Practices (GCP) guidelines, Declaration of Helsinki and the International Conference on Harmonization (ICH).

Prior to participation in the clinical trial, each patient must give written Informed Consent after the context of the study has been fully explained to the patient in language that is easily understood by the patient. The patients must also be given the opportunity to ask questions and have those questions answered to their satisfaction.

Written Informed Consent must be recorded appropriately by means of the patient's, or their legal representative's dated signature. The patient will receive a copy of the Informed Consent form.

16.4. *Amending the Protocol*

This protocol is to be followed exactly, and will only be altered by written amendments. Administrative changes that do not affect the patient benefit/risk ratio (e.g., editorial changes for clarity) may be made without any further approvals. Any change that would require alteration of the Informed Consent form must receive approval from appropriate EndoGastric Solutions personnel and from the IRB prior to implementation. Following approval, the protocol amendment(s) will be distributed to all protocol recipients with instructions to append them to the protocol.

16.5. *Emergency Actions*

EndoGastric Solutions accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well being of a study patient. The Investigator must give notice of any emergency deviations and justification for the deviation to EndoGastric Solutions and the IRB as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

16.6. *Protocol Deviations*

Deviations from clinical protocol requirements, including ICH/GCP guidelines, will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective actions put into place.

17. Study Administration

EndoGastric Solutions will make necessary efforts to ensure that this study is conducted in compliance with GCPs and all applicable regulatory requirements.

17.1. *Pre-Study Documentation Requirements*

Prior to shipment of investigational product, the following documents must be provided to CRO / EGS:

- Signed and dated Investigator Agreement
- A copy of the written IRB approval of the protocol
- A copy of the written IRB approval of the Informed Consent Form
- A copy of the curriculum vitae of the Coordinating Investigator and Co-Coordinating Investigator (if applicable)

17.2. *Record Retention*

The Investigator will maintain all essential trial documents and source documentation, in original format, that support the data collected on the study patients in compliance with the ICH/GCP guidelines. Documents must be retained for at least 2 years after the

last approval of marketing application or until at least 2 years have elapsed after last enrolled patient. These documents will be retained for a longer period of time by agreement with EndoGastric Solutions or in compliance with other regulatory requirements. When these documents no longer need to be maintained, it is EndoGastric Solutions responsibility to inform the Investigator. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. EndoGastric Solutions must receive written notification of this custodial change.

17.3. *Criteria for Terminating Study*

EndoGastric Solutions reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. Investigators and associated IRB will be notified in writing in the event of termination.

Possible reasons for study termination include (but are not limited to):

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.

17.4. *Criteria for Suspending/Terminating a Study Center*

EndoGastric Solutions reserves the right to stop enrolling of patients at a study center at any time after the study initiation visit if no patients have been enrolled or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

Possible reasons for suspending/terminating a study center include:

- Repeated failure to complete case report forms prior to scheduled monitoring visits.
- Failure to obtain written Informed Consent.
- Failure to report SAE/UADE to EndoGastric Solutions within 24 hours of knowledge.

17.5. *Investigator Responsibilities*

- Agree to sign and adhere to the Investigator Agreement
- Agree to participate in Investigator meetings as scheduled by EndoGastric Solutions
- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol
- Comply with all required elements of this protocol Agree to obtain written Informed Consent before any study specific procedures are performed in accordance with GCP
- Complete all data modules prior to scheduled monitoring visits

- Be willing to change hospital routine if required by protocol (as long as patient safety and well-being is not compromised)

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APPENDIX

A Sample Informed Consent Form

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: **The HEURISTIC Study**

HErnia Red**U**ction P**RI**or to **S**cheduled **TI**F **C**ompletion

PROTOCOL NO.: D031517

WIRB® Protocol #xxxxxx

PRINCIPAL INVESTIGATOR:

Michael J. Murray, M.D.
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STUDY SITE(S):

Medhat Fanous, MD (Iron River Hospital, Iron River, MI)

Mamoon Raza, MD (Elkhart Hospital, Elkhart, IN)

SPONSOR:

EndoGastric Solutions, Inc.
Redmond, Washington
United States

STUDY-RELATED PHONE NUMBERS:

[Principal Investigator's name]
[Phone number]

CO- PRINCIPAL INVESTIGATOR(S):

Medhat Fanous, MD (Iron River Hospital, MI)

Mamoon Raza, MD (Elkhart Hospital, IN)

United States

STUDY-COORDINATOR:

Adrian Lobontiu, MD, FACS
Medical Director, EndoGastric Solutions
650 474 9259

This consent form may contain words that you do not understand. Please ask the study doctor or the study coordinator to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

SUMMARY

You are being asked to be in a research study. The purpose of this consent form is to help you decide if you want to be in the research study. Please read this form carefully. To be in a research study, you must give your informed consent. "Informed consent" includes:

- Reading this consent form,
- Having the study doctor or staff explain the research study to you,
- Asking questions about anything that is not clear, and
- Taking home an unsigned copy of this consent form. This gives you time to think about it and to talk to family or friends before you make your decision.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- Taking part in a research study is entirely voluntary. No one can make you take part.
- If you decide to take part, you can change your mind later on and withdraw from the research study.

- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study do involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your insurance provider may be billed for the costs of any of the procedures performed for the research study (for example, upper gastrointestinal (GI) endoscopy and radiography, or follow-up procedures).

After reading and discussing the information in this consent form, you should know:

- Why this research study is being done;
- What will happen during the research;
- What drug or device or procedures will be used;
- Any possible benefits to you;
- The possible risks to you;
- The other medical procedures, drugs, or devices that could be used instead of being in this research study; and
- How any problems you may have will be treated during the study and after the study is over.

If you take part in this research study, you will be given a copy of this signed and dated consent form.

PURPOSE OF THE STUDY

You are being asked to voluntarily be in a research study to evaluate the relative merits, safety and effectiveness of the EsophyX ZR transoral device in performing the standardized an advanced TIF 2.0 procedure preceded by laparoscopic Hiatal Hernia repair (≤4cm) in PPI-prescribed patients with persistent "troublesome symptoms" per the Montreal consensus definition will be evaluated. The EsophyX ZR device was cleared by the U.S. FDA in 2016 for treatment of symptomatic chronic GERD, after it was proven safe and effective.

Who is being asked to take part in this research study?

You are invited to participate in a research study of the EndoGastric Solutions Inc., EsophyX ZR System. You were selected as a possible subject because your diagnostic tests, endoscopy, manometry or pH-metry, have indicated you are suffering from Gastro-esophageal Reflux Disease (GERD) .You also have a hiatal hernia greater than 2 but less or equal to 4 cm., are intolerant onPPIs or have troublesome heartburn or regurgitation symptoms which occur at a minimum of 2-3 days a week and are having laparoscopic Hiatal Hernia repair. You have been recommended for antireflux surgery.

Currently your GERD is treated with medication, proton pump inhibitors (PPI's), but you have indicated that either you continue to experience symptoms despite taking PPI medication or you prefer an alternative treatment.

The study is being performed on 50 patients by several doctors across the U.S. and will last for 6 months.

PROCEDURES

Subjects will undergo the standardized laparoscopic Hiatal Hernia Repair and closure of the diaphragmatic defect (crural closure) followed by the TIF 2.0 procedure with EsophyX ZR device, which consists of inserting the EsophyX ZR device through your mouth, down the esophagus and into your stomach. The surgeon will use prolene fasteners to create an effective flap valve between your stomach and the esophagus to help prevent acid reflux. The device will be removed and the plastic fasteners will remain in the tissue of your esophagus to hold the flap valve.

If you decide to take part in this research study, you will undergo the following procedures that are not part of your standard medical care:

Screening Procedures:

Procedures to determine if you are eligible to take part in a research study are called "screening procedures." For this research study, the screening procedures include the following:

- You will have a physical exam.

- You must answer questions about your general medical history, symptoms and history of GERD, medication history, surgical history, the food you commonly eat and what activities you do. Additionally, you will be asked to fill out three short questionnaires to determine your frequency and intensity of your GERD symptoms and to evaluate their impact on your quality of life. Your name will not be associated with these questions, so no one outside of your study doctor's office will be able to connect you with your answers. This visit will require about 1 hour of your time.

- You will undergo an upper GI radiography (optional). Before the test, you will drink barium (a chalky liquid) and possibly some gas-making crystals. The doctor will watch the movement of the barium through your esophagus. Several x-rays will be taken at different times and from different views. This will allow the study doctor to look at your esophagus and make sure you are a good candidate for the EsophyX procedure.

- An upper gastrointestinal endoscopy is a procedure that allows your doctor to look at the interior lining of your esophagus, your stomach, and the first part of your small intestine through a thin, flexible viewing instrument called an endoscope. The tip of the

endoscope is inserted through your mouth and then gently moved down your throat into the esophagus, stomach, and duodenum (upper gastrointestinal tract).

- You will undergo an esophageal manometry test which is used to identify swallowing problems (optional, only if dismotility is suspected). It measures the strength and muscle coordination of your esophagus when you swallow. The esophagus is the "food pipe" leading from the mouth to the stomach. During the manometry test, a tube is passed through the nose, along the back of the throat, down the esophagus, and into the stomach.

- You will undergo pH studies to measure the level of acidity in your esophagus coming from the stomach. It will require placing a small capsule with pH sensor into your esophagus. The capsule placement will be performed under local sedation. The capsule attaches temporarily to the esophageal wall and transmits esophageal pH data wirelessly to a portable receiver. You will be instructed to eat and live normally during the pH monitoring and to record times where you eat, sleep and experience symptoms. You will be required to carry around the receiver for the data from this detector for two days and then return to the doctor's office for the removal of the device. The capsule will naturally detach within 3-4 days and will come out with the stool. This test may cause some discomfort in your esophagus and chest. It will allow the doctor to see how much acid moves from your stomach into your esophagus on a daily basis and how that correlates with your symptoms.

In the event that a clinically significant, unsuspected disease or condition is identified during this screening, the standard diagnostics and/or treatments will be applied.

The Proposed Procedure:

If you qualify to take part in this research study, you will undergo the standard of care procedures listed below.

- You are required to not eat anything for 12 hours before the procedure.

- Before the Laparoscopic Hiatal Hernia repair followed by the TIF 2.0 procedure and immediately after the procedure, you will undergo endoscopy. It will allow us to measure your gastroesophageal valve before and after the procedure.

The TIF 2.0 procedure is performed under general anesthesia. The EsophyX ZR device will be inserted through your mouth, down the esophagus and into your stomach. The surgeon will use prolene fasteners to create a small flap valve between your stomach and the esophagus to help prevent acid reflux. The device will be removed, while the plastic fasteners will remain in the tissue of your esophagus to hold the flap valve. This procedure was invented based upon other surgical treatments for GERD but does not include incisions in the abdomen and has

fewer side effects. The only small abdominal incisions you will have are from the standard of care laparoscopic Hiatal Hernia Repair (HHR).

- Before you are discharged from the hospital, you may have an upper GI radiography. This requires you to drink a liquid that will be tracked through your esophagus and stomach by X-ray to verify that there are no leaks from the procedure.

- After the procedure, you will be on a diet of liquid foods for two weeks and a diet of soft foods for an additional four weeks. This reduces the pressure on the new valve and allows for adequate healing time.

- The Laparoscopic Hiatal Hernia Repair followed by the TIF 2.0 procedure is a one time (two steps) procedure and will take place at the surgery department of the <NAME OF INSTITUTION>. Duration will approximately be 30-45 minutes and it will require a one night hospital stay.

Follow-up Procedures:

Procedures to evaluate the safety and effectiveness of the experimental TIF procedure are called "follow-up" procedures. For this research study, the follow-up procedures will include:

- The morning after the Laparoscopic Hiatal Hernia Repair and EsophyX ZR TIF 2.0 procedure, the nurse will give you after surgery instructions and a physical exam. You will meet with the study doctor or the study coordinator to discuss a new diet plan, and then you will be discharged from the hospital.

- 2-Weeks after your procedure, you will return to the study doctor's office. You will be asked a few questions about how you feel after the procedure and you will progressively stop taking GERD medication.

- 3 and 6 months after your procedure, you will return to the study doctor's office. You will be asked a few questions about how you are feeling after the procedure and you will then be asked to complete questionnaires to determine the frequency and intensity of your GERD symptoms and to evaluate their impact on your quality of life. 12 and 24 Month surveys will be sent but an office visit is not required.

- At the follow-up 6-Month visit, you will be asked how you are feeling and asked to complete questionnaires just as you have done at previous office visits. You will also undergo a pH study just as you did at your screening visit. The pH study measures the level of acidity in your esophagus coming from stomach, as described above.

In addition to the listed procedure, you may also undergo any of the following procedures during follow-up visits per your study doctor recommendation:

- *Endoscopy* - to determine the current status of your esophagus and the junction between your esophagus and stomach. This is performed under sedation. The doctor will put a camera through your mouth, down the esophagus, into the stomach and back out. A small esophageal biopsy will be taken for tissue evaluation.

- *Manometry* (optional) - to verify your swallowing pattern and identify important aspects of the valve between your stomach and esophagus. A tube will be inserted through your nose into your stomach and you will be asked to swallow some water.

- *Upper GI radiography* - to determine the current status of your esophagus and the junction between your esophagus and stomach. Before the test, you will drink barium (a chalky liquid) and possibly some gas-making crystals. The doctor will watch the movement of the barium through your esophagus and the junction on a video screen. Several x-rays will be taken at different times and from different view.
- *pH Studies* - You will undergo pH studies to measure the level of acidity in your esophagus coming from the stomach.

What are the possible risks, side effects, and discomforts of this research study?

The possible risks of this research study may be due to the surgical procedure, the anesthesia, the follow-up tests, and/or the use of proton pump inhibitors PPI (standard medical treatment for GERD).

Risks of the TIF procedure:

Previous human research studies using the Laparoscopic Hiatal hernia Repair procedure have shown that the nature and number of adverse events associated with its use are similar to other procedures that involve acid reflux surgery.

Previous human research studies using the TIF 2.0 procedure have shown that the nature and number of adverse events associated with its use are significantly lower than other procedures that involve acid reflux surgery.

Likely risks or discomforts (occur in greater than 10%, or more than 10 out of 100 people): Sore throat, left shoulder pain (from lying on your shoulder during surgery), temporary abdominal or esophageal pain that can be treated with standard pain medication or temporary difficulty swallowing due to swelling. These adverse events are usually mild in severity.

Infrequent adverse events (occur in 1-10%, or 1-10 out of 100 people): Oral or dental injury, bleeding, bloating sensation or bruising. These adverse events are usually mild in severity.

Rare adverse events (occur in less than 0.5% , or less than 1 out of 200 people): Nerve damage, perforation of the esophagus, chest pain, gastric ulcer, infection, long-term swallowing disorders, foreign material entering the lungs, or arrhythmia (abnormal heartbeat). Rarely, additional surgeries may be needed to repair an adverse event from the first procedure including: operation to repair an above-mentioned adverse event or operation to remove a defective device or its parts. These adverse events can be moderate to severe.

As with any new surgical procedure, there may be adverse events or side effects that are currently unknown and certain of these unknown risks could be permanent, severe, or life threatening.

A physician, emergency drugs and equipment will be readily available should you experience any adverse events from the surgical procedure.

If you are a woman of child-bearing potential, you will undergo a pregnancy test prior to your exposure to the TIF procedure. Tests have not been done to determine the risk of the TIF procedure to pregnant women. To avoid risks to the fetus, it is important that you not be pregnant when we conduct this study. We also advise that you not become pregnant for at least six months after the procedure, as it may impact the outcome of the procedure. Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you should use an appropriate "double barrier" method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed "birth control" pills, injections, or implants. If you choose to be sexually active during this study, pregnancy could still result even with the use of these birth control methods.

Risks of the Anesthesia:

Any time you undergo a procedure that requires general anesthesia, there are risks involved. Some of the mild to moderate risks include headache, vision problems, muscle pain, dizziness, drowsiness, mood changes, nausea or vomiting. Additionally serious and possibly life-threatening reactions can occur while under anesthesia. It is very important that your doctor is aware of any and all medications before undergoing this procedure to help prevent serious reactions.

Risks of the follow-up tests:

- -*pH-Metry* – can cause in some patients a discomfort felt in the upper chest.

- *Endoscopy* - A temporary, mild throat irritation sometimes occurs after the exam. Serious risks are very uncommon but include bleeding, fever, infection, breathing difficulty and heartbeat irregularity. In extremely rare instances, a perforation, or tear, in the esophagus or stomach wall can occur. This may require hospitalization and, rarely, surgery.

- *Manometry* - can sometimes cause coughing or vomiting during tube placement or removal.

- *Upper GI radiography* - participation will also involve radiation exposure. The amount of radiation exposure that you will receive from this procedure is about 0.245 rem (a unit of radiation exposure) to the chest with minimal exposure of other body areas. For comparison, radiation workers are permitted, by federal regulation, a maximum radiation exposure of 50 rems per year to any single body organ. There is no minimum amount of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that you will receive from taking part in this study is felt to be low and comparable to everyday risks.

Risks of the long-term use of PPIs:

If PPIs are used over a long period of time, the following risks have been shown to be a possibility: gastric polyps, gastroenteritis, osteoporosis, hip fracture, dementia, kidney failure, c. difficile infection.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

You will be promptly notified if any new information develops during the conduct of this research study which may cause you to change your mind about continuing to participate.

What are possible benefits from taking part in this study?

Your GERD symptoms may improve or even go away as a result of your participation in this study. However, there is no guarantee that you will receive such a benefit.

The information from this research study may lead to a better treatment in the future for people with GERD.

Who will pay for the surgery?

The costs of the study procedure and study-related tests will be billed to your insurance company. Ask your study doctor what costs will or will not be covered by the insurance. This discussion should include the costs of treating possible side effects. Otherwise, you might have unexpected expenses from being in this study.

Will I be paid if I take part in this research study?

You will receive a compensation of $200 for completing each 6-month and 12-month follow-up visit.

Who will pay if I am injured as a result of taking part in this study?

This research study involves the FDA- approved EsophyX ZR device, being evaluated for its FDA- approved use in the treatment of symptomatic chronic gastro- esophageal reflux disease (GERD). If you should suffer an injury related to the evaluation of this device in this research study, you should immediately contact the Principal Investigator listed on the first page of this consent form. Necessary medical care will be provided to you. The costs of this medical care will be billed to you or your insurance company in the usual manner (as per the costs of an injury that you may have suffered from any FDA- approved device). In the event that your insurance company does not pay for these costs or you do not have insurance, the costs of injury treatment will be billed directly to you. If you have concerns about this, you should discuss these concerns with the study doctor. The surgical device company, EndoGastric Solutions, Inc., that developed the EsophyX ZR device and the TIF 2.0 procedure, will not provide additional care for injuries related to this research. There is no plan to provide you with other payments for or related to your injury. However, you do not give up your legal right by signing this form.

Who will know about my participation in this research study?

Any information about you obtained from this research will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

Will this research study involve the use or disclosure of my identifiable medical information?

This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other (e.g., doctor's office) records. The information that will be recorded will be limited to information concerning your GERD symptoms and the effect on your life, the procedure itself, your medication history, the follow-up exams

previously listed in this document, and any adverse events that may have been associated with the TIF procedure.

The nature of the identifiable information resulting from your participation in this research study that will be recorded in your medical record includes the results of the additional follow-up tests performed for research purposes and information related to any adverse events you may suffer following the TIF surgical procedure.

Who will have access to identifiable information related to my participation in this research study?

In addition to your study doctor listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the WIRB may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law.

Authorized representatives of the sponsor of this research study, EndoGastric Solutions, Inc., will review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data. Authorized representatives of the study sponsor may also be present during your participation in the TIF procedure performed as part of this research study. While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical information.

The investigators involved in the conduct of this research study may receive funding from the sponsor to perform the research procedures and to provide the sponsor with identifiable research and medical information related to your participation in the study.

Authorized representatives of the U.S. Food and Drug Administration may review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy of the research data. While the U.S. Food and Drug Administration understands the importance of maintaining the confidentiality of your identifiable research and medical information.

Authorized representatives of <NAME OF INSTITUTION> or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders made by the investigators for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated wit-h research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e., quality assurance).

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of seven years after final reporting or publication of a project.

May I have access to my medical information that results from my participation in this research study?

In accordance with the Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider.

Is my participation in this research study voluntary?

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the provider. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at your provider or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your study doctor is involved as an investigator in this research study. As both your doctor and a research investigator, he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

May I withdraw, at a future date, my consent for participation in this research study?

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study, you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care institutions or your current or future relationship with a health care insurance provider.

If I agree to take part in this research study, can I be removed from the study without my consent?

It is possible that you may be removed from the research study by the researchers if you do not meet the criteria for entry into the study; for example, your pregnancy test proves to be positive, you do not follow the instructions of your doctor regarding this study or you will not be able to participate in all monitoring/follow up visits for any reason,

If you are withdrawn from participation in this research study, your doctor will continue providing you with the standard of medical care for your GERD and may discuss other options with you. The described monitoring/follow- up procedures for your safety and the effectiveness evaluation of your GERD treatment will also be available to you after withdraw from study participation.

Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

What are alternatives to participating in this study?

If you choose to not to take part in this research study, you may consult your doctor for standard alternatives to the medication you are currently on for GERD or remain on your current medication.

SOURCE OF FUNDING FOR THE STUDY

The sponsor, EndoGastric Solutions, Inc., will pay for this research study.

QUESTIONS

Contact:

Michael J. Murray, M.D.
Northern Nevada Medical Group
2385 E Prater Way Ste 205
Sparks, NV 89434
for any of the following reasons:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury, or
- if you have questions, concerns, or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
3535 Seventh Avenue, SW
Olympia, Washington 98502
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com.

WIRB is a group of people who independently review research.

WIRB will not be able to answer some types of questions, such as questions about appointment times. You may contact WIRB if you cannot reach the research team or if you want to talk to someone else.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

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VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact [Add name], Chairman of the WIRB office, at 360-252-2500 to discuss problems, concerns, and questions, obtain information, offer input, or discuss situations in the event that the research team is unavailable.

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____	_____	_____
Signature of Subject	Printed Name of Participant	Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions, concerns or complains as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study

_____	_____
Signature of Person Obtaining Consent	Date

B Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged

must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable

to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

C Appendix C – GSRS-Quality of Life Assessment

GSRS Questionnaire

Site :_____ Patient ID :_____ Date___/___/___

Please answer every question by circling ONLY ONE response that best describes how you have felt during the past 2 weeks.

1. **Heartburn.** Representing retrosternal discomfort or burning sensation.

   a. How much has heartburn bothered you on a daily basis?

Not at all	Mild	Moderate	Severe
1	2	3	4

   b. How often have you experienced heartburn?

Never	Once a month	Once a week	2-4 times a week	Daily
0	1	2	3	4

2. **Regurgitation.** Representing sudden regurgitation of acid gastric content.

   a. How much has regurgitation bothered you on a daily basis?

Not at all	Mild	Moderate	Severe
1	2	3	4

   b. How often have you experienced regurgitation?

Never	Once a month	Once a week	2-4 times a week	Daily
0	1	2	3	4

3. **Abdominal distention.** Representing bloating with abdominal gas.

   a. How much has epigastric fullness bothered you on a daily basis?

Not at all	Mild	Moderate	Severe
1	2	3	4

   b. How often have you experienced epigastric fullness?

Never	Once a month	Once a week	2-4 times a week	Daily
0	1	2	3	4

GSRS Questionnaire Page 1 of 2

4. **Dysphagia.** Representing painful swallowing or the sensation of a lump in the throat.

   a. How much has dysphagia bothered you on a daily basis?

Not at all	Mild	Moderate	Severe
1	2	3	4

   b. How often have you experienced dysphagia?

Never	Once a month	Once a week	2-4 times a week	Daily
0	1	2	3	4

5. **Coughing.** Representing the need to expel air from the lungs suddenly and noisily, often to keep the respiratory passages free of irritating material.

   a. How much has coughing bothered you on a daily basis?

Not at all	Mild	Moderate	Severe
1	2	3	4

   b. How often have you coughed?

Never	Once a month	Once a week	2-4 times a week	Daily
0	1	2	3	4

Administered by

Date (mm/dd/yy)

Monitored by

Date (mm/dd/yy)

Reference
Allen CJ, Parameswaran K, Belda J, Anvari M. "Reproducibility, validity, and responsiveness of a disease-specific symptom questionnaire for gastroesophageal reflux disease." *Diseases of the Esophagus* 2000; 13:265-270.

Appendix D – GERD- HRQL Quality of life assessment

Patient Name:_____ Date ___/___/___

Check the box to the right of each question that best describes your experience over the past ***<u>two weeks</u>****.*

0 = No symptom
1 = Symptoms noticeable but not bothersome
2 = Symptoms noticeable and bothersome but not every day
3 = Symptoms bothersome every day
4 = Symptoms affect daily activity
5 = Symptoms are incapacitating to do daily activities

1.	How bad is the heartburn?	□0 □1 □2 □ 3 □4 □5
2.	Heartburn when lying down?	□0 □1 □2 □ 3 □4 □5
3.	Heartburn when standing up?	□0 □1 □2 □ 3 □4 □5
4.	Heartburn after meals?	□0 □1 □2 □ 3 □4 □5
5.	Does heartburn change your diet?	□0 □1 □2 □ 3 □4 □5
6.	Does heartburn wake you from sleep?	□0 □1 □2 □ 3 □4 □5
7.	How bad is the regurgitation?	□0 □1 □2 □ 3 □4 □5
8.	Regurgitation when lying down?	□0 □1 □2 □ 3 □4 □5
9.	Regurgitation when standing up?	□0 □1 □2 □ 3 □4 □5
10.	Regurgitation after meals?	□0 □1 □2 □ 3 □4 □5
11.	Does regurgitation change your diet?	□0 □1 □2 □ 3 □4 □5
12.	Does regurgitation wake you from sleep?	□0 □1 □2 □ 3 □4 □5
13.	Do you have difficulty swallowing?	□0 □1 □2 □ 3 □4 □5
14.	Do you have pain with swallowing?	□0 □1 □2 □ 3 □4 □5
15.	If you take medication, does this affect your daily life?	□0 □1 □2 □ 3 □4 □5
16.	How satisfied are you with your present condition?	
	□ Satisfied □ Neutral □ Dissatisfied	

Appendix E – Reflux Disease Questionnaire

Reflux Disease Questionnaire

Please answer each question by ticking one box per row.

1. Thinking about your symptoms over the last seven days, how often did you have the following?

	Did not have	Less than one day a week	One day a week	2-3 days a week	4-6 days a week	Daily
a. A burning feeling behind your breastbone	☐	☐	☐	☐	☐	☐
b. Pain behind your breastbone	☐	☐	☐	☐	☐	☐
c. A burning feeling in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
d. A pain in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
e. An acid taste in your mouth	☐	☐	☐	☐	☐	☐
f. Unpleasant movement of material upwards from the stomach	☐	☐	☐	☐	☐	☐

2. Thinking about symptoms over the last seven days, how would you rate the following?

	Did not have	Very mild	Mild	Moderate	Moderately severe	Severe
a. A burning feeling behind your breastbone	☐	☐	☐	☐	☐	☐
b. Pain behind your breastbone	☐	☐	☐	☐	☐	☐
c. A burning feeling in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
d. A pain in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
e. An acid taste in your mouth	☐	☐	☐	☐	☐	☐
f. Unpleasant movement of material upwards from the stomach	☐	☐	☐	☐	☐	☐

RDQ (UK-English) 2002.

Appendix F. – RSI (Reflux Symptom Index

REFLUX SYMPTOM INDEX

Name: _____ Date: ___/___/___
Within the last **month,** how did the following problems affect you?
(0-5 rating scale with 0 = No problem and 5 = Severe)

1. Hoarseness or a problem with your voice 0 1 2 3 4 5

2. Clearing your throat 0 1 2 3 4 5

3. Excess throat mucous or postnasal drip 0 1 2 3 4 5

4. Difficulty swallowing food, liquids or pills 0 1 2 3 4 5

5. Coughing after you ate or after lying down 0 1 2 3 4 5

6. Breathing difficulties or choking episodes 0 1 2 3 4 5

7. Troublesome or annoying cough 0 1 2 3 4 5

8. Sensations or something sticking in your throat 0 1 2 3 4 5

9. Heart burn, chest pain, indigestion, or stomach 0 1 2 3 4 5

acid coming up

TOTAL: _____

Normative data suggests that a RSI of greater than or equal to 13 is clinically significant. Therefore a RSI > 13 may be indicative of significant reflux disease.