Clinical Study Protocol Title:

AN OBSERVATIONAL CLINICAL FEASIBILITY STUDY OF THE OMEGA-CUFF™ DEVICE FOR GERD

Study ID: 03-0001-000

Rev 10, 10 October 2023

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INVESTIGATOR AGREEMENT

All participating investigators will sign this agreement or its equivalent section in the Clinical Trial Agreement (CTA), and no investigator will be added until the agreement is signed.

- I have read this protocol, appendices, and amendment(s), if applicable, and agree to adhere to its requirements.
- I will provide copies of this protocol and all pertinent information to the study personnel under my supervision.
- I will discuss this material with study personnel and ensure they are fully informed regarding the device and the conduct of the study.
- I will conduct the study in accordance with the protocol and Good Clinical Practice guidelines, as well as local regulations, and I accept respective revisions to the protocol approved by authorized personnel of the Sponsor and by regulatory authorities.

Principal Investigator (print)

Principal Investigator (signature) Date

Institution Name/Location (print)

DOCUMENT HISTORY

Revision	Date	Change(s)
0-8	24 Feb 2022	• Initial versions modified • Changed the number of sites from two sites to up to 3 sites • Study Management contact updated • Grammar and administrative edits • Details and clarifications added regarding follow-up visits and assessments
9	23 May 2022	• Study management contact updated • Intent to treat principle section modified for clarity.
10	10 Oct 2023	• Sponsor name and logo updated to Aplos Medical • Sponsor email updated • Study management contact updated • Modifications made in conjunction with CEC and PIs to eliminate enrollment obstacles and reflect current standard of care practice: o **Screening/Baseline Visit** - Adjust the timeframe that the following assessments can be performed prior to implant procedure: barium esophagram, endoscopy, motility/manometry, 24hr pH profile, GERD-HRQL, health history, and physical exam. o **Hiatal hernia evaluation** - Clarify what methods will be used to perform the evaluation. o **Exclusion criteria** – Modify exclusion criteria related to hiatal hernia size. o **Discharge visit** – Remove the GERD-HRQL and concomitant medications assessment. o **24hr pH profile** – Clarify how the 24hr pH profile results will be documented and interpreted for inclusion criteria and performance endpoints. o **24Hr pH profile and GERD-HRQL** – Change from 10 to 7 days that participants must stop PPIs or other anti-reflux medications prior to these assessments. o **Additional follow-up visits –** Modification of parameters surrounding need for 18-24 month follow-up visits.

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INVESTIGATIONAL PLAN SUMMARY

Study Title:	An Observational Clinical Feasibility Study of the Omega-Cuff™ for GERD
Study ID:	03-0001-000
Study Device:	The implantable single-use Omega-Cuff (Ω-Cuff) device consists of a thin single-piece Ω-shaped nitinol device with open struts. The device is supplied sterile and is placed through an open incision or through a laparoscopic port with a minimum internal diameter of 15 mm using the Introducer.
Study Purpose:	The purpose of this feasibility study is to collect preliminary performance and safety information and develop procedural optimization for the Aplos Medical (formerly known as CT Resources, Inc.) Ω-Cuff device in augmenting Esophageal Sphincter function to treat Gastroesophageal Reflux Disease (GERD). The information from this study will be used to support the design and conduct of a pivotal clinical trial.
Target Indication for Use:	The Omega-Cuff device is indicated for patients diagnosed with Gastroesophageal Reflux Disease (GERD), as defined by abnormal pH testing, and who continue to have chronic GERD symptoms despite maximum medical therapy for the treatment of reflux.
Study Design:	The study is an observational, prospective, non-randomized, open label, early feasibility study in the United States of subjects with GERD. The primary performance measurements will be obtained by evaluation of the subject at Screening/Baseline, Implant/Procedure, and at various time points including discharge, 2-4 weeks, 2 months, 3 months, 6 months, 9 months, and 12 months post-procedure implant. It is currently undetermined when the shorter-term data will allow an assessment that provides enough information to justify a pivotal study (requested via an IDE supplement). Additional follow-up visits may occur between 18 and 24 months, as needed per the discretion of Aplos Medical. The primary safety parameter will be the rate of all adverse events at various time points, at minimum including discharge, 2-4 weeks, 2 months, 3 months, 6 months, 9 months, and 12 months post-procedure. It is currently undetermined when the shorter-term data will allow an assessment that provides enough information to justify a pivotal study (requested via an IDE supplement). Serious device and procedure-related adverse events will be summarized separately.

	Analyses will be performed continuously throughout the study period, and results of the analyses will be used to support the design and conduct of a pivotal clinical trial. This study will also provide the Investigator with the opportunity to optimize the implant procedure for the pivotal clinical trial and post-approval implants.
Study Duration:	Approximately 2 years (includes enrollment and continued follow-up).
Investigational Study Centers:	This clinical evaluation will be conducted at up to three investigational centers. Investigators will be selected among surgeons with experience performing the LINX® procedure and/or fundoplication procedures.
Subject Population:	Subjects seeking surgical intervention for Gastroesophageal Reflux Disease who meet the study inclusion/exclusion criteria are eligible for this study. The study subject limit is fifteen (15) subjects implanted with the device.
Study Objectives:	**Safety Objective:** To evaluate the incidence of all adverse events at various time points including discharge, 2-4 weeks, 2 months, 3 months, 6 months, 9 months, and 12 months post procedure implant. Subjects will be consented to allow for an additional follow-up as needed so that all implanted subjects' data are within six months of summary data analysis and approximately coinciding with study termination. **Performance Objectives:** • To monitor the improvement of GERD symptoms and LES function at various time points including discharge, 2-4 weeks, 2 months, 3 months, 6 months, 9 months, and 12 months post procedure implant. • To optimize the implant technique.

Study Endpoints:	There are no statistically derived endpoints for this feasibility study. The safety objective will be met via reporting all adverse events at various time points including discharge, 2-4 weeks, 2 months, 3 months, 6 months, 9 months, and 12 months post-procedure implant. It is currently undetermined when the shorter-term data will allow an assessment that provides enough information to justify and define a pivotal study. Serious device- and procedure-related adverse events will be summarized separately. Safety will be characterized by endoscopy and abdominal/chest x-ray evaluations. Performance will be characterized as the reduction of GERD symptoms by subjective measurements using GERD-Health-Related Quality of Life (GERD-HRQL) and GERD-specific medication used; LES function will be characterized by objective measurements, using 24hr pH profile, manometry/motility, and barium esophagram.
Manufacturer:	Aplos Medical 11304 Bluestem Lane Eden Prairie, Minnesota 55347 Telephone: (952) 944-3749
Study Management:	Clinical Research Strategies, LLC Email: jennifer@clinicalresearchstrategies.com Telephone: 949-232-6469

1 Introduction

1.1 Background – Gastroesophageal Reflux Disease (GERD)

Prevalence

It is well understood that Gastro-esophageal Reflux Disease (GERD) is a very serious health condition. While a certain amount of reflux is normal, GERD, which manifests as heartburn, regurgitation, or both, is an excessive reflux in frequency and amount and is a chronic disorder associated with substantial morbidity and a major adverse impact on patient quality of life. In industrialized nations the disease has become increasingly common, with an estimated prevalence in the general population of approximately 7% of the population experiencing symptoms on a daily basis, 15% to 20% complain of heartburn at least once per week, and 45% to 60% mention one or more symptoms of reflux on an annual basis.[1]

Aside from the very detrimental effect the condition has on a person's quality of life, the condition often leads to more serious adverse consequences. Lagergren et al. report that the risk of esophageal adenocarcinoma is almost eight times as high among persons in whom heartburn, regurgitation, or both occur at least once a week as opposed to persons without such symptoms.[2] In another study, Sampliner describes the incidence of adenocarcinoma in patients with Barrett's esophagus to be approximately 0.5% per year.[3]

1.2 Current Treatment Options Including Benefits and Limitations

The normal physiological barrier to GERD is comprised of a lower esophageal sphincter muscle or LES. The LES provides tone to create a high-pressure zone to close the junction between the esophagus and the stomach, keeping gastric contents from refluxing into the esophagus. A competent LES keeps the esophagus closed to gastric contents and opens during swallowing to allow food to pass into the stomach. A weak LES, however, will open and allow gastric contents to reflux into the esophagus. A weak LES is the result of a weak muscle that does not have enough tone to keep the esophagus closed. The muscle may be weak due to poor resting tone, insufficient length, or increased frequency of inappropriate transient relaxations.

This condition is now treated in one of two ways. First, drug therapy, which is the most common treatment for GERD, is directed at symptom relief. Drugs known as proton pump inhibitors (PPI's), such as Prevacid® and Nexium,® reduce the acid production in the stomach, but do not affect the function of the LES or treat the defective muscle tone, thereby treating the symptoms and not the disease. These drugs are taken daily but may fail to control the symptoms in 10% to 20% of patients who remain symptomatic even on PPI Therapy.[4] Even in those instances where the drugs control the symptoms, with or without Barrett's, the esophagus can continue to experience pathological effects, including low intra-gastric pH.[5] Though PPIs are generally well tolerated, the long-term reduced gastric acidity has raised adverse events concerns, including FDA safety communications.[6]

Most importantly, these drugs do not treat the failing LES or reduce reflux. The patient remains vulnerable to the higher risks of progression of the disease and developing adenocarcinoma,

described above. Frazzoni et al. discuss cases where GERD patients were rendered symptom free with PPIs, but the esophageal acid exposure was still abnormal in 44% of the patients.[7] Furthermore, Sontag, et al., describe the results of a PPI trial where at 1-year follow-up, only 55% to 67% of patients remained healed (no recurrence of erosive reflux esophagitis), and 62.5% to 73.7% of the relapses remained asymptomatic.[8]

The second available treatment is surgical intervention with either a procedure referred to as Nissen Fundoplication or a recently FDA-approved device known as the LINX® Magnetic Esophageal Sphincter.

In the Nissen procedure, the upper portion of the stomach or fundus is wrapped around the LES region of the esophagus and sutured in place. The fundus is intended to buttress or support a weak LES. A limitation of this procedure, besides the significant physiological perturbations, is that the fundus is difficult to control in terms of how tightly it is placed around the esophagus. If wrapped too tightly, dysphagia occurs and if too loosely, efficacy may be limited. After surgery, new symptoms occur in 5% to 8% of these patients and may include dysphagia, gas, bloating, increased flatus, and difficulty with belching or vomiting.[4] Catarci et al. report a recurrence of GERD in up to 10.5% of cases, dysphagia and bloating in up to 57.9% of cases; and re-operation as often as 7.7% of the time.[9] Additionally, the efficacy of the fundoplication may wane over time, with as many as 62% of patients requiring medications to control recurrent reflux symptoms 10 years after surgery.[10]

In the LINX procedure, a device containing a series of titanium beads with magnetic cores are linked together with independent titanium wires to form a "necklace" around the esophagus. The attractive force of the magnetic beads reinforces a weak LES to restore its barrier function. When swallowing, the food/water bolus forces esophageal distention causing the magnetic beads to move away from each other on the independent titanium wires. The magnetic beads rejoin after the bolus passes. Esophageal buttressing with the LINX device can be an effective means to control GERD symptoms with Bonavina et al. reporting 90% of patients having normalized esophageal acid exposure at 2 years.[11] However, after implantation, complications such as dysphagia (68% of patients) exist.[12] In some cases, dysphagia has remained persistent resulting in device removal.[12]

1.3 Rationale

The scientific rationale for the design of Ω-Cuff device is based on the premise that patients with an incompetent (weak) LES are susceptible to gastroesophageal reflux. The Ω-Cuff device is designed to augment the LES by placement on the external aspect of the esophagus in the region of the LES. The implant is a Ω-shaped nitinol scaffold structure, which is placed around the outside of the esophagus and provides additional strength to keep a weak LES closed to restore its barrier function. When swallowing, the Ω-Cuff device, along with the uncovered natural esophageal tissue, expands allowing esophageal distention. The Ω-Cuff device, mimicking partial fundoplication, provides a constant resistance to gastric pressure at rest but will permit esophageal distension for easy swallowing. Its open side will allow some normal physiological function.

The rationale for conducting this early feasibility study is to establish a basic safety profile and

further develop and refine the implant technique to support the design and conduct of a pivotal clinical trial (requested via an IDE supplement). We will also evaluate the performance characteristics that will allow us to better define the efficacy requirements for the larger clinical trial.

2 Investigational Device: Omega-Cuff Device

The implantable single-use Ω-Cuff device is a single piece scaffold structure that is Ω-shaped (reference **Figure 1** below). The device is supplied sterile and is placed through an open incision or through a laparoscopic port with a minimum internal diameter of 15mm.

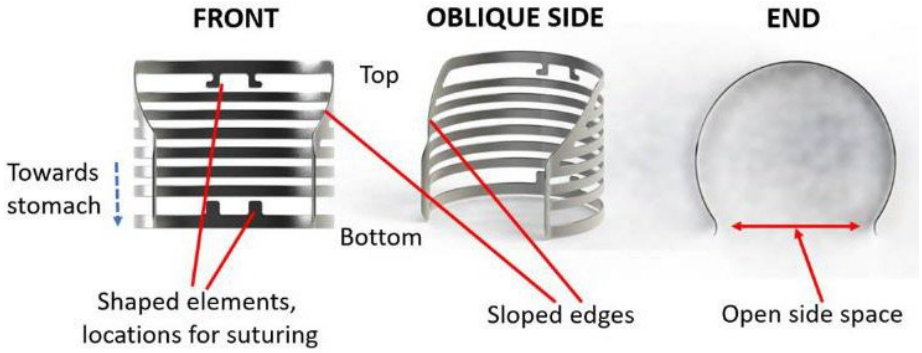

Figure 1: Illustration of the Ω-Cuff Device

The device is manufactured to different diameters to accommodate varying patient anatomy. For purposes of the proposed study, the smallest configuration will be 14mm diameter (nominal) and the largest will be 20mm diameter (nominal). The implant is provided with designated attachment sites for sutures to attach the top (cephalic) and bottom end of the Ω-Cuff device to the esophagus. The device is implanted around the outside of the esophagus at the region of the Lower Esophageal Sphincter (LES). The Ω-Cuff device on the LES provides support for the weak LES to maintain normal closure.

2.1 Esophagus-Sizing Technique

The Omega-Cuff device esophagus-sizing instructions are based on a measurement of the subject's empty esophagus circumference at the target implant location. **Figure 2** and Steps A through F below illustrate the recommended circumference measurement method.

The photographs below illustrate the steps to measure the esophagus circumference and convert that into the diameter using a suture.

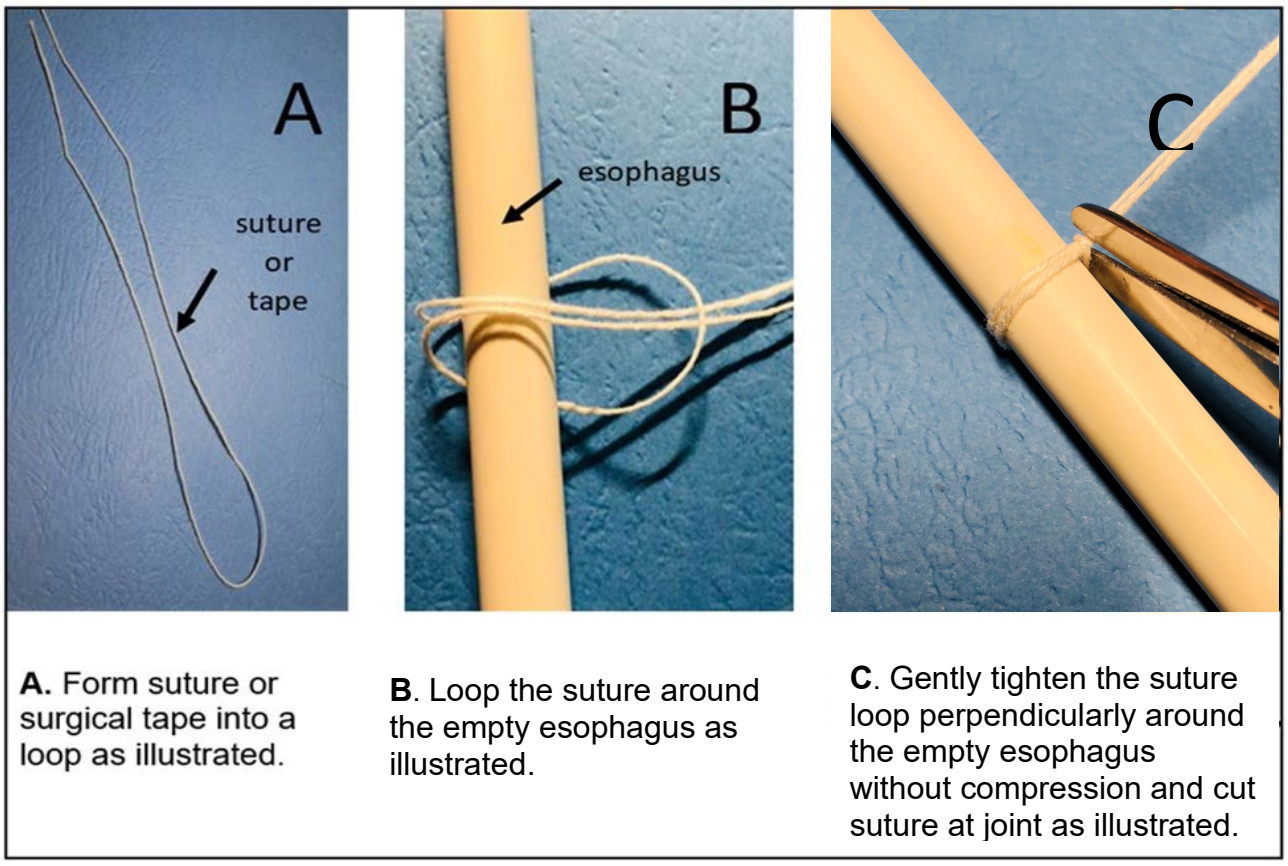

Figure 2: Esophagus Sizing - Circumference Suture Length Measurement Illustration Leading to Associated Device Diameter Selection.

D. Remove the cut suture or tape and measure its length against a ruler.

E. Divide that length by 2 to determine the circumference length of the esophagus.

F. Use the circumference length against the chart to determine the size of device to be used for implantation.

Use **Table 1** to select the appropriate Omega-Cuff device size, based on the esophagus circumference measurement as described above. When the measured length is between sizes, use the next smaller device size (e.g., measured circumference length is 53.4mm; the correct size selection is a 15.5mm device).

Table 1: Omega-Cuff Device Sizing Chart

Esophagus		Omega-Cuff Device Part Number Selection
Circumference Suture Length Measurement	**Diameter Range**	
43.9 -48.7 mm	14.0 - 15.5 mm	31-0000-014.0
>48.7 - 53.4 mm	15.5 - 17.0 mm	31-0000-015.5
>53.4 - 58.1 mm	17.0 - 18.5 mm	31-0000-017.0
>58.1 - 62.8 mm	18.5 - 20.0 mm	31-0000-018.5
>62.8 - 67.5 mm	20.0 - 21.5 mm	31-0000-020.0

If the Omega Cuff is unable to be placed for any reason, standard of care surgical treatment can be offered to the patient including either fundoplication or implantation of the LINX device, or the patient may elect to have the surgery aborted.

2.2 Target Indication for Use

The Omega-Cuff device is indicated for patients diagnosed with Gastroesophageal Reflux Disease (GERD), as defined by abnormal pH testing, and who continue to have chronic GERD symptoms despite maximum medical therapy for the treatment of reflux.

3 Study Design and Protocol Overview

The study is an observational, prospective, non-randomized, open label, feasibility study of patients receiving the Ω-Cuff device. The study is intended to evaluate the safety of the Ω-Cuff device and its ability to reduce the symptoms of GERD by augmenting the function of the LES. The study will be performed at up to three (3) investigational centers in the US with a maximum of 15 subjects who will be implanted with the device.

The **Screening/Baseline Visit** will determine eligibility of the subjects to receive treatment with the Ω-Cuff device.

Subjects will be followed at various time points, including discharge, 2-4 weeks, 2 months, 3 months, 6 months, 9 months, and 12 months post implant. If significant migration is observed in the timespan between discharge and 3-month follow-up as assessed by the clinician using the results of x-ray and measuring the distance between the device and the xiphoid; subjects will have additional assessments monthly including chest x-rays in order to monitor migration closely. In addition, they will be instructed to contact their study doctor between study visits if they experience adverse events. Subjects will be consented to allow additional follow-up as needed, per Sponsor discretion. It is currently undetermined when the shorter-term data will allow an assessment that provides enough information to justify a pivotal study. The study follow-up is outlined in **Figure 3** and the data collected during all visits are outlined in **Figure 4**.

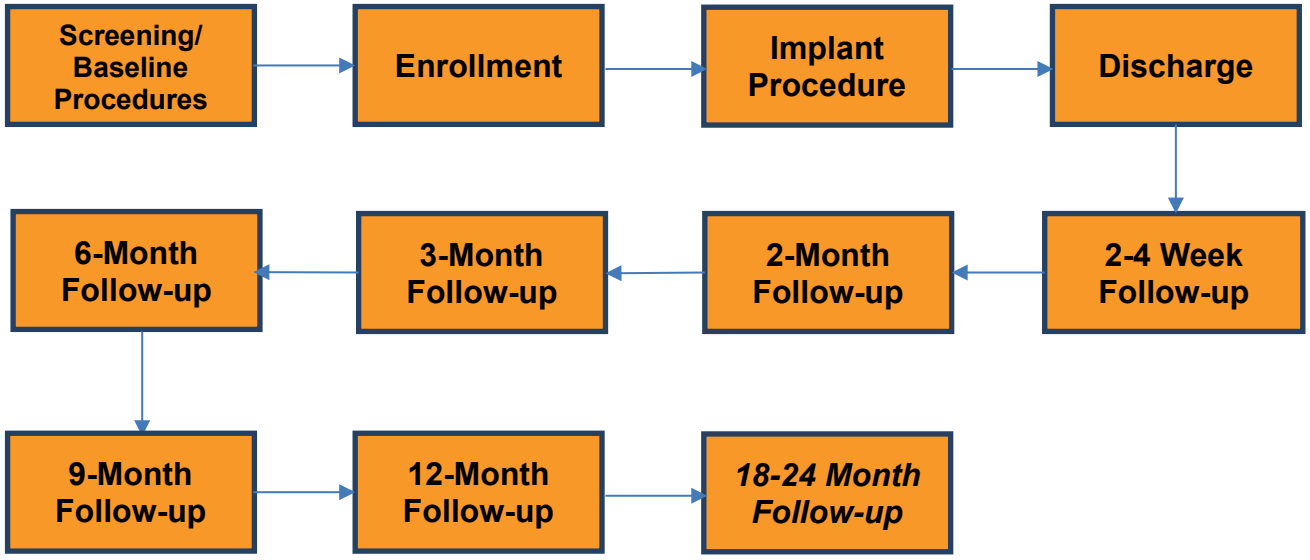

Figure 3: Schematic of Feasibility Study Design

Schedule of Assessments	Screening/Baseline	Implant Procedure	Discharge	2-4 weeks (21 days ± 7 days)	2 months (60 days ± 10 days)	3 months (90 days ± 15 days)	6 months (180 days ± 30 days)	9 months (270 days ± 30 days)	12 months (365 days ± 45 days)	18-24 months (630 days ± 90 days)
Informed Consent	X									
Confirmation of Eligibility	X									
Health History	X[3]								X	X
Physical Exam	X[3]									
Pregnancy Test	X[1]									
GERD-HRQL off PPIs	X[2, 3]			X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
GERD-HRQL on PPIs	X[4]									
PPI, H2RA, Antacid and other GERD Medication Use	X			X	X	X	X	X	X	X
24hr pH Profile	X[2, 4]					X[2]			X[2]	X[2]
Manometry/Motility	X[4]					X			X	
Endoscopy	X[4]					X			X	
Barium Esophagram (Fluoroscopy)	X[4]		X			X			X	
Abdominal/Chest X-ray			X	X	X	X			X	X
Adverse Events		X	X	X	X	X	X	X	X	X

1. For females of child-bearing potential only; a negative pregnancy test must be confirmed within one week prior to implant.
2. Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to the assessment.
3. Must be completed within 3 months (i.e. 90 days) prior to implant.
4. Must be completed within 12 months (i.e. 365 days) prior to implant.

Figure 4: Feasibility Study Evaluation Schedule

4 Study Purpose and Objectives

4.1 Study Purpose

The purpose of this feasibility study is to collect preliminary performance and safety information and develop procedural optimization for the Aplos Medical Ω-Cuff device in augmenting the Esophageal Sphincter function to treat Gastroesophageal Reflux Disease (GERD). The information from this study will be used to support the design and conduct of a pivotal clinical trial.

The implant technique will be optimized by obtaining evaluative statements and recommendations from the study Investigators. These statements will be used to provide a recommended implant procedure for use by surgeons involved in the pivotal clinical trial as well as to assist this study's Investigators with the development of a teaching methodology to be used with future implanters.

4.2 Study Objectives

Safety:

The safety-related objective of this study is to evaluate the incidence of all adverse events.

Performance:

The Ω-Cuff device performance objectives of this study are the following:

- To monitor the improvement of GERD symptoms during the study.
- To assess LES function during the study.
- To optimize the implant technique.

5 Study Endpoints

There are no statistically derived endpoints for this feasibility study.

5.1 Safety Endpoint

The primary safety parameter will be the rate of all adverse events at various time points, including discharge, 2-4 weeks, 2 months, 3 months, 6 months, 9 months, and 12 months post-implant procedure. It is currently undetermined when the shorter-term data will allow an assessment that provides enough information to justify a pivotal study. An additional follow-up visit may occur between 18 and 24 months, as needed per the discretion of Aplos Medical. Serious device and procedure-related adverse events will be summarized separately.

5.2 Performance Endpoint

The first co-primary effectiveness endpoint of this study will be based on normalization of pH (with normalization defined as pH <4 for no more than 4.5% of monitoring time) or reduction of at least 50% in total time that pH <4, relative to baseline.

The second co-primary endpoint will be at least a 50% improvement in the GERD-HRQL scores at 12 months.

A secondary endpoint will be the reduction of daily PPI use by subjective measurements using the GERD-HRQL, and LES function will be characterized by objective measurements using 24hr pH profile, manometry/motility, endoscopy, and barium esophagram.

5.3 Stopping Rules

The CEC will be charged to recommend study suspension if one or more of these complications or situations are observed:

- Concern about the subjects' safety or about lack of benefits for the subjects
- Considerable investigational plan failure from the Investigators
- Any erosion or migration of the device
- Subject's difficulty in swallowing due to stenosis caused by the device
- If more than 1 of the following events occur that persists in excess of 1-month even with medical treatment, and results in the surgical removal of the device.
  - Related severe dysphagia
  - Related severe pain
- Any UADE

If Aplos Medical suspends or prematurely terminates the study, Aplos Medical or its designee will notify the FDA and overseeing Institutional Review Board(s) with the date of the suspension/premature termination, the reason for the suspension/premature termination, and plans to restart the study, including the conditions to be fulfilled in order to restart the study.

If the study is suspended or terminated prematurely, follow-up will be performed to the extent possible of the subjects who have had the device implanted. A follow-up plan will be communicated to the appropriate regulatory authority and/or Institutional Review Board at the time of the suspension or the premature termination of the study. The clinical study will not restart until both the CEC and FDA review the details of the occurrence.

6 Investigational Study Centers

Up to three US investigational centers will be allowed to participate in this clinical study. Investigators will be selected according to appropriate experience performing Fundoplication procedures or similar experience in performing LINX implants. Investigators must perform a minimum five (5) Fundoplications or LINX procedures per year to qualify.

7 Study Population

The investigator(s) will be responsible for recruiting individuals to enroll in this trial (see Section 11.4 for definition of enrollment). Only those individuals satisfying the inclusion and exclusion criteria presented below may participate. Any questions regarding patient suitability will be referred to Aplos Medical for review.

7.1 Inclusion Criteria

- Subject must be at least 22 years of age and must be less than 75 years of age with a life expectancy > 3 years.
- Subject is a suitable surgical candidate, i.e., is able to undergo general anesthesia and laparoscopic surgery.
- Subject has documented typical symptoms of gastroesophageal reflux disease (GERD) for longer than 6 months (regurgitation or heartburn that is defined as a burning epigastric or substernal pain that responds to acid neutralization or suppression).
- Subject requires daily proton pump inhibitor or other anti-reflux drug therapy.
- Total Distal Ambulatory Esophageal pH must meet the following criteria: pH< 4 for ≥ 4.5% of the time Note: Subjects will have discontinued any GERD medications for at least 7 days prior to testing.
- Subject has symptomatic improvement on proton-pump inhibitor (PPI) therapy demonstrated by a GERD-Health-Related Quality of Life (GERD-HRQL) score of ≤ 10 on proton-pump inhibitors and ≥ 15 off PPIs, or subjects with a ≥ 6-point improvement when comparing his/her on-PPI and off-PPI GERD-HRQL score.
- Subject has GERD symptoms in absence of PPI therapy (minimum 7 days).
- If the subject is of child-bearing potential, she must have a negative pregnancy test within one week prior to implant and must agree to use effective means of birth control during the course of the study.
- Subject is willing and able to cooperate with follow-up examinations.
- Subject has been informed of the study procedures and the treatment and has signed an informed consent form.

7.2 Exclusion Criteria

- The procedure is an emergency procedure.

- Subject is currently being treated with another investigational drug or investigational device.
- Subject has a history of gastroesophageal surgery, anti-reflux procedures, or gastroesophageal/gastric cancer.
- Subject has undergone any previous endoscopic anti-reflux intervention for GERD.
- Subject has suspected or confirmed esophageal or gastric cancer.
- Subject has any size hiatal hernia >5cm as determined by endoscopy or barium esophagram.
- Distal esophageal motility (average of sensors 3 and 4) is less than 35 mmHg peristaltic amplitude on wet swallows or <70% (propulsive) peristaltic sequences.
- Subject has esophagitis – Grade C or D (LA Classification).
- Subject has a Body Mass Index (BMI)>35.
- Subject has symptoms of dysphagia more than once per week within the last 3 months.
- Subject is diagnosed with Scleroderma or an esophageal motility disorder such as but not limited to Achalasia, Nutcracker Esophagus, or Diffuse Esophageal Spasm or Hypertensive LES.
- Subject has a history of or known esophageal stricture or gross esophageal anatomic abnormalities (Schatzki's ring, obstructive lesions, etc.).
- Subject has esophageal or gastric varices.
- Subject has history of or known Barrett's esophagus.
- Subject cannot understand trial requirements or is unable to comply with the follow-up schedule.
- Subject is pregnant or nursing or plans to become pregnant during the course of the study.
- Subject has a medical illness (e.g., congestive heart failure) that may cause the subject to be non-compliant with or unable to meet the protocol requirements or is associated with limited life expectancy (i.e., less than 3 years).
- Subject is diagnosed with psychiatric disorder (e.g., bipolar, schizophrenia, etc.); however, subjects who exhibit depression but are on appropriate medication(s) may be included.
- Subject has suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials.
- Subject has an electrical implant or metallic abdominal implants.
- Subject is not a surgical candidate for open laparotomy.

7.3 Rationale for Including Subjects with BMIs of 30-35

Although subjects with BMIs in the range >30 and <35 kg/m^2 carry increased surgical and/or

anesthetic risks associated with their excess weight, this population is important to include in this study because, according to the prevalence data from the 2013–2014 NHANES survey of the National Center for Health Statistics (NCHS),[13] more than 1 in 3 adults (37.7 percent) were considered to have obesity and, thus, constitute a significant proportion of the US population. In addition, there is "a significant association between body mass and symptoms of gastroesophageal reflux."[14] To reject these individuals would result in the exclusion of a significant number of subjects who suffer from GERD.

But given that subjects with BMIs in the range of >30 and <35 kg/m^2 have increased surgical/anesthetic risks associated with their excess weight, the Principal Investigators will carefully screen potential subjects to ensure they are suitable surgical candidates able to undergo general anesthesia and laparoscopic surgery. No subject will be enrolled who does not meet this inclusion criterion.

8 Informed Consent

Prior to IRB submission, the investigator will prepare an informed consent form in accordance with this study protocol and all regulatory requirements (21 CFR Part 50), using the sample informed consent form provided for this investigational plan. A copy of the final IRB-approved informed consent form must be submitted to the Sponsor before initiating the study at that investigational site.

Prior to study enrollment, all subjects must document their consent for study participation and authorization for use and disclosure of health information by signing the appropriate IRB-approved Informed Consent Form. The subject will have the opportunity to ask questions of and receive answers from the personnel conducting the study.

The investigator will notify the Sponsor and the IRB within five (5) working days if device use occurs without subject informed consent.

9 Study Assessments and Data Management

9.1 Demographic and Baseline Assessments

The following variables will be collected at screening/baseline visit:

- Date of Birth
- Gender
- Ethnicity
- Race
- Medical History (If performed within 3 months (i.e. 90 days) prior to implant, the subject does not need to repeat the assessment. If performed more than 3 months prior to implant, then the medical history will be updated day of implant.)
- Physical exam (including measurements of height and weight. If performed within 3 months (i.e. 90 days) prior to implant, the subject does not need to repeat the test. If performed more

than 3 months prior to implant, then the physical exam will be performed day of implant.)

- Quality of Life (GERD-HRQL) (Subjects will discontinue any PPI therapy or other anti- reflux medication for at least 7 days prior to completing the GERD-HRQL. If performed within 3 months (i.e. 90 days) prior to implant, the subject does not need to repeat the test.)
- Subjects will also undergo a GERD-HRQL while taking PPIs or other anti-reflux medications to determine study eligibility. (If performed within 12 months (i.e. 365 days) prior to implant, subject does not need to repeat test).
- PPI, H2RA, and antacid history of use
- 24hr pH profile (Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the 24hr pH test. If performed within 12 months (i.e. 365 days) prior to implant, the subject does not need to repeat the test.)
- Manometry Test (If performed within 12 months (i.e. 365 days) prior to implant, the subject does not need to repeat the test.)
- Esophageal Motility Test (If performed within 12 months (i.e. 365 days) prior to implant, the subject does not need to repeat the test.)
- Endoscopy (If performed within 12 months (i.e. 365 days) prior to implant, the subject does not need to repeat the test.)
- Barium esophagram (If performed within 12 months (i.e. 365 days) prior to implant, the subject does not need to repeat the test.)
- Hiatal hernia evaluation by endoscopy or barium esophagram.

9.2 Safety

9.2.1 Safety Measurements: Endoscopy, Barium Esophagram, X-ray

To confirm that the device is in the correct position, the subject will undergo an abdominal/chest X-ray at discharge, 2-4 weeks, 2 months, and 3 months. The location of the subject device will be recorded in relationship to the xiphoid process for each image to enable later comparison. If notable migration is observed in the timespan between discharge and 3-month follow-up as assessed by the clinician; subjects will have additional assessments monthly including chest x-rays in order to monitor migration closely. Additionally, follow-up X-rays will also be taken if any subject develops dysphagia or experiences persistent or worsening GERD during the trial.

To ensure the device is functioning as intended, the patient will undergo esophageal endoscopy, barium esophagram, and abdominal/chest X-ray at 3 months and at 12 months.

9.2.2 Adverse Events

Subjects will be queried at each follow-up visit regarding adverse events.

The occurrence and device-relatedness of all adverse events will be documented each time the subject is seen or contacted: at the Implant/Procedure Visit, discharge, 2-4 weeks, 2 months, 3

months, 6 month, 9 months, and 12 months minimum post-procedure visits and any additional follow-up visit.

9.3 Performance Measurements

9.3.1 Esophageal pH Profile

Effectiveness measurements will be assessed by the treating investigators. These assessments will be performed at the baseline, 3-month, 12-month follow-up visits, and between 18-24 months as applicable. Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the 24hr Ph test. If investigators use the Bravo™ Wireless pH monitoring test, the results for each day of the monitoring time period will be documented. The investigator may choose the length of the Bravo test (e.g. 48 hours, 96 hours, etc.) as appropriate for each subject; however, the chosen length of the Bravo test must be maintained throughout all subsequent follow-up visits for that subject. The inclusion criteria regarding Total Distal Ambulatory Esophageal pH must be satisfied by the results of at least one of the days of the monitoring time period at the screening/baseline visit. The first co-primary effectiveness endpoint will be assessed based on the results of each day of the monitoring time period.

9.3.2 GERD Health-Related Quality of Life Scale

Subjects will undergo a GERD-HRQL (quality of life scale) while taking PPIs or other anti-reflux medications at screening/baseline visit to determine study eligibility. If performed within 12 months (i.e. 365 days) prior to implant, the subject does not need to repeat test. Post-implant performance will be evaluated by subject interview and clinical follow-up. The subject will report effectiveness of treatment using GERD-HRQL at baseline and all follow ups. Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the GERD-HRQL at baseline and all follow up visits.

The GERD-HRQL is a scale that asks subjects to rate their GERD symptoms on a scale from 0 to 5 (Scoring Scale: 0 = No symptoms 1 = Symptoms noticeable but not bothersome 2 = Symptoms noticeable and bothersome but not every day 3 = Symptoms bothersome every day 4 = Symptoms affect daily activities 5 = Symptoms are incapacitating – unable to do activities). The following questions are asked:

1. How bad is your heartburn?
2. Heartburn when lying down?
3. Heartburn when standing up?
4. Heartburn after meals?
5. Does heartburn change your diet?
6. Does heartburn wake you from sleep?
7. Do you have difficulty swallowing?
8. Do you have bloating or gassy feelings?

9. Do you have pain with swallowing?

10. If you take medication, does this affect your daily life?

11. How satisfied are you with your present condition? Satisfied Neutral Dissatisfied

9.3.3 GERD Medication Use

The subject will be asked to report current drug regimen at all follow-up visits. All medications, including those taken for GERD symptoms or that could impact the study, must be reported. This includes, but is not limited to, Proton Pump Inhibitors (PPIs), H2Ras, and antacids.

9.3.4 Manometry

The subject will undergo manometry at the baseline, 3-month, and 12-month follow-up visits. Manometry will measure the LES pressure and length.

9.3.5 Esophageal Endoscopy

The subject will undergo endoscopy at the baseline, 3-month, and 12-month follow-up visits to determine esophageal healing compared to baseline assessment. The Los Angeles Classification esophagitis grading scale will be used:

Los Angeles Classification[1]

Not present: No Breaks (erosions) in the esophageal mucosa (edema, erythema, or friability may be present.

Grade A: One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length.

Grade B: One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of two mucosal folds

Grade C: Mucosal breaks, those are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference

Grade D: Mucosal breaks, which involve at least 75% of the esophageal circumference. The presence or absence of strictures, ulcers, and/or Barrett's esophagus must be noted separately, e.g., "Grade B with stricture."

9.4 Data Management

All data will be entered into a 21 CFR Part 11 compliant database by trained personnel using good data management practices. The database may be used to modify, maintain, archive, retrieve, and transmit the data as necessary and in accordance with FDA's most recent guidance document "Computerized Systems Used in Clinical Investigations" (2007).

10 Study Procedures

10.1 Roles and Responsibilities

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

10.1.1 Principal Investigator

This clinician will have the following responsibilities:

- Treat all subjects enrolled in the trial.
- Record adverse events that occur during the procedure.
- Sign the CRFs.
- Provide medical care at the Implant/Procedure Visit and follow-up through the evaluation window after the treatment.
- Document training on experience performing Nissen Fundoplication and/or LINX implants.
- Conduct the initial diagnosis and subject enrollment consideration.
- Provide baseline assessments of the subject's GERD.
- Document adverse events other than those occurring during the procedure.
- Interview subjects about their GERD symptomology.
- Be available for each subject follow-up visit.

10.1.2 Study Coordinator

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

10.2 Assessments

10.2.1 Screening/Baseline Visit

Male or female subjects aged at least 22 years will be assessed as suitable candidates for this study against the screening inclusion and exclusion criteria. A log will be kept of all subjects screened for, but not entered in the study. The reason(s) for excluding these subjects will be recorded.

A signed and dated informed consent (including HIPAA authorization) will be obtained from all subjects before any study-specific procedures are performed.

The following assessments will be performed at the Screening/Baseline Visit and recorded on the CRF in order to determine eligibility for entry into the study:

- Record subject demographics.
- Record details of any prior/concomitant GERD medication (including PPI, H2RA, and antacids).
- Record medical/surgical history. (If performed within 3 months (i.e. 90 days) prior to implant, the subject does not need to repeat the assessment. If performed greater than 3 months prior, then the medical history will be updated day of implant.)
- Perform physical examination, including measurements of height and weight. (If performed within 3 months (i.e. 90 days) prior to implant, the subject does not need to repeat the test. If

performed greater than 3 months prior, then the physical exam will be performed day of implant.)

- Female subjects of child bearing age will be given a pregnancy test (within one week prior to implant).
- Review inclusion/exclusion criteria.
- GERD-HRQL off PPIs (Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the GERD-HRQL. If performed within 3 months (i.e. 90 days) prior to implant, the subject does not need to repeat the test.)
- GERD-HRQL on PPIs (Subjects will continue any PPI therapy or other anti-reflux medication. If performed within 12 months (i.e. 365 days) prior to implant, the subject does not need to repeat the test.)

Adequate patient records must be available and prerequisite tests must have been completed within one month of implant, unless otherwise noted.

The following assessments and procedures must be completed within 12 months prior (i.e. 365 days) to treatment:

- LES manometry/motility
- Endoscopy
- Barium Esophagram (Fluoroscopy)
- Esophageal pH profile (Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the 24hr pH test.)

Subjects are to discontinue the following medications prior to surgery as would be consistent with a Fundoplication or LINX procedure: non-steroidal anti-inflammatory medication (i.e., Motrin, Advil, Aleve, ibuprofen). Blood thinners such as aspirin, Coumadin, and Plavix should also be stopped prior to surgery.

10.2.2 Implant Procedure

The Investigator will perform the procedure according to the Ω-Cuff device Instructions for Use, implanting the Ω-Cuff device laparoscopically and recording any adverse events that may occur during the procedure. Subjects will not need to stay in the hospital overnight unless the principal investigator determines it is medically necessary.

10.2.3 Discharge

At this follow-up point, subjects will be queried for adverse events and will undergo a barium esophagram and chest/abdominal X-ray.

The subject will be reminded of 1.5 and 3.0 Tesla MRI conditional.

10.2.4 2-4 Week Follow-up (21 days ± 7 days)

At this follow-up point, subjects will be asked about their current drug regimens and asked the questions from the GERD-HRQL questionnaire. Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the GERD-HRQL, and they will undergo a chest/abdominal X-ray to ensure the device remains correctly placed. Subjects will also be queried for adverse events.

10.2.5 2-Month Follow-up (60 days ± 10 days)

At this follow-up point, subjects will be asked about their current drug regimens and asked the questions from the GERD-HRQL questionnaire. Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the GERD-HRQL, and they will undergo a chest/abdominal x-ray to ensure the device remains correctly placed. Subjects will also be queried for adverse events.

10.2.6 3-Month Follow-up (90 days ± 15 days)

At this follow-up visit, subjects will be asked about their current drug regimens and asked the questions from the GERD-HRQL questionnaire. (Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the GERD-HRQL.) Subjects will also be queried for adverse events. Other assessments to be performed at 3-month follow-up visit include those listed below:

- 24hr pH profile (Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the 24hr pH test.)
- Manometry/motility
- Endoscopy
- Barium Esophagram
- Chest/Abdominal x-ray

10.2.7 6-Month Follow-up (180 days ± 30 days)

At this follow-up visit, subjects will be asked about their current drug regimens and asked the questions from the GERD-HRQL questionnaire. Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the GERD-HRQL. Subjects will also be queried for adverse events.

10.2.8 9-Month Follow-up (270 days ± 30 days)

At this follow-up point, subjects will be asked about their current drug regimen and asked the questions from the GERD-HRQL questionnaire. Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the GERD-HRQL. Subjects will also be queried for adverse events.

10.2.9 12-Month Follow-up (365 days ± 45 days)

Three-hundred-sixty-five days (± 45 days) after the implant date, subjects will return to the clinic for the following assessments and procedures:

- Record details of drug regimen (PPI, H2RA, and antacid use)
- Complete GERD-HRQL (Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the GERD-HRQL.)
- Adverse events review
- 24hr pH profile (Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the 24hr pH test.)
- Manometry/Motility
- Endoscopy
- Abdominal/Chest X-ray
- Barium Esophagram (Fluoroscopy)
- Health history

10.2.10 18-24 Month Follow-up (630 days ± 90 days)

An additional follow-up visit may occur between 18 and 24 months, as needed per the discretion of Aplos Medical. At this follow-up visit, subjects will be asked about their current drug regimen and will complete the GERD-HRQL questionnaire. (Subjects will discontinue any PPI therapy or other anti-reflux medication for at least 7 days prior to completing the GERD-HRQL.) Subjects will also be queried for adverse events. The subject will also undergo a chest/abdominal x-ray, a health history reassessment, and 24hr pH profile.

11 Subject Completion and Withdrawal

11.1 Subject Completion

On completion of the study (either by legitimate completion or withdrawal), the investigator will complete the End of Study CRF.

11.2 Subject Withdrawal

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

- Withdrawal of consent by the subject
- Adverse event (Adverse Event CRF must be completed.)
- Lost to follow-up (In case of early withdrawal of a subject, every attempt should be made to have the subject come into the clinic.)
- Termination of study by the sponsor
- Other (must be specified)

The reason for termination will be recorded in the End of Study CRF.

11.3 Screen Failures

Screen failures are those subjects who are not eligible to start treatment following the screening assessment due to failure to meet inclusion and/or exclusion criteria.

A log of all subjects screened for, but not entered into the study will be maintained by each investigational center. The reason(s) for screening failure of these subjects will be recorded on this log.

11.4 Intent to Treat

The intent-to-treat principle will be applied to all subjects enrolled in the study who have signed the consent form to participate whether or not the patient receives the device. The enrollment goal for this study is a maximum of 15 subjects with the device implanted.

Information on all enrolled subjects screened for the study will be recorded. If the patient is not enrolled into the study, the reason for exclusion will be documented on the screening log. If the patient is enrolled in the study but the Ω-Cuff device is not implanted, the reason will be provided on the Procedure CRF. Each patient enrolled in the trial will receive an identification number.

This is a non-randomized clinical trial. All consecutively enrolled subjects will receive the Ω- Cuff device implant. This investigation is not blinded.

11.5 Device Explant Circumstances and Proposed Action(s)

The Ω-Cuff should be surgically removed if there are issues with the device, regardless of its migration status. Depending on the circumstances, the procedure could be laparoscopic, endoscopic or laparotomic.

If the device has migrated, the intervention will depend on the circumstances.

- If the device migrates with the esophagus above the diaphragm, such as during normal respiration, it should be removed if symptomatic (new symptoms like dysphagia or recurrent GERD).
- If the device migrates above hiatus slightly with esophagus and patient is asymptomatic and the device is still effective, it could be left alone unless it causes problems.
- If the device moves upward independent of the esophagus, it should be removed in the least arduous way.
- If the device erodes into the lumen of the esophagus, it should be removed in the least arduous way.
- If scarring is excessive or the plane is not clear, the device should be removed.

12 Adverse Events

12.1 Adverse Event Reporting

Beginning at enrollment and proceeding throughout the duration of the follow-up period, the investigator will closely monitor each subject for the development of clinical evidence of adverse events.

An adverse event (AE) is any undesirable/unusual experience that occurs to a subject during the clinical study, whether or not it is considered device related, including (but not limited to) those events that result from the use of the device as stipulated in the protocol. All adverse events that occur during the course of the follow-up period, whether observed by the investigator or by the subject and whether or not thought to be device- or procedure-related, will be reported in detail on the appropriate CRF and followed to their resolution.

Abnormal assessments that are judged by the investigator as clinically significant will be recorded as AEs if they meet the definition of an AE. Clinically significant abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal assessment is clinically significant.

12.2 Relationship to Study Devices/Procedures

The investigator will also evaluate the relationship to the study device and/or procedure according to the following definitions:

- ***Unrelated:*** AE is due to the underlying disease state or concomitant medication or therapy not related to the study-specific devices or procedures.
- ***Related:*** AE had a strong temporal relationship to the study-specific devices or procedures and another etiology is unlikely.
- ***Unknown:*** Relationship of the AE to the study-specific devices or procedures and alternative

etiology is unknown.

12.3 Serious Adverse Events

Adverse events that are defined as "serious," which is based on subject/event *outcome or action* criteria usually associated with events that pose a threat to a subject's life or functioning will serve as a guide for defining reporting obligations.

The investigator must decide whether each event meets the definition of a Serious Adverse Event (SAE). For the purposes of this study, a SAE will be defined as any untoward medical occurrence, whether related or unrelated to the study device or procedure, that meets one or more of the following criteria:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does **not** refer to an event that hypothetically might have caused death if it were more severe.

- Requires subject hospitalization > 24 hours
- Requires prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in fetal distress, fetal death, or a congenital anomaly or birth defect
- Requires intervention to prevent permanent impairment or damage

All serious adverse events (whether or not considered study-specific device- or procedural-related) must be reported immediately (within 24 hours of discovery) to the Sponsor by phone (Aplos Medical, 952-944-3749) or through submission of the Adverse Event CRF. Reporting instructions and contact information will be provided to the study teams.

12.4 Anticipated Adverse Events and Complications

Anticipated adverse events are those events that are reasonably expected to occur as a result of the subject's disease state, surgery, or use of the Ω-Cuff device.

The list of anticipated adverse events and reactions that may occur include, but may not be limited to, the following:

Potential Risks: General Surgery and Aesthesia

- Reaction to anesthesia including:
  - headache
  - muscle pain
  - nausea
- Anaphylaxis
- Cardiac arrest
- Death
- Diarrhea
- Fever
- Hypotension
- Hypoxemia
- Infection
- Myocardial infarction
- Perforation
- Pneumonia
- Pulmonary embolism
- Respiratory distress
- Thrombophlebitis

Potential Risks: After Anti-reflux Surgery Procedures & GERD Treatment Implants

- Achalasia
- Bleeding
- Death
- Decreased appetite
- Device erosion *(at least a portion of the device breaches the esophageal wall)*
- Device explant/re-operation
- Device failure
- Device migration *(device does not appear to be at implant site)*
- Diarrhea
- Dysphagia
- Early satiety
- Esophageal spasms
- Flatulence
- Food impaction
- Hiccups
- Inability to belch or vomit
- Increased belching
- Ineffective treatment
- Infection
- Impaired gastric motility
- Injury to the esophagus, spleen, or stomach
- Nausea
- Odynophagia
- Organ damage caused by device migration (abdominal and/or aorta)
- Pain
- Peritonitis
- Pneumothorax
- Regurgitation
- Retching
- Saliva/mucus build-up
- Stomach bloating
- Vomiting
- Weight loss
- Worsening of preoperative symptoms including but not limited to dysphagia and heartburn

12.5 Coding

AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

12.6 Adverse Events Requiring Intervention

Dysphagia after antireflux surgery (i.e., Nissen fundoplication surgery and magnetic sphincter augmentation surgery) is an expected event. For example, 100% of Nissen fundoplication procedures result in temporary dysphagia, presumably due to edema from the surgical procedure, which gradually improves with time. The LINX procedure has a known 40-60% short-term dysphagia rate post-operatively, which also gradually improves with time, although about 6% of patients will experience long-term dysphagia.[15]

When dysphagia occurs postoperatively, endoscopy and esophageal dilation is the standard and initial approach. It is well-reported that up to 20% of post-op Nissen and post-op LINX patients will require endoscopy and dilation. The Ω-Cuff patients will be treated similarly. Two to three weeks after surgery, if dysphagia is present, the patient would undergo endoscopy to make sure there are no other reasons for the dysphagia and, if appropriate, will be treated with esophageal dilation.

For persistent dysphagia, follow-up manometry and barium esophagography will be performed to observe device function and to verify if other reasons exist for the dysphagia. If the condition is not resolved in 3-4 months, the device may need to be removed. The device removal rate may be similar to that of LINX at 3-4%. However, due the partial surround design of the Ω-Cuff, dysphagia may be less prominent. If the patient develops severe dysphagia requiring esophageal dilation and medication, and the severe dysphagia fails to respond within 4 weeks, the device will be removed.

Odynophagia is rare and is often caused by post-op infection or reflux. Patients will be diagnosed with endoscopy, barium esophagram, manometry, and pH assessment as appropriate and treated with anti-secretory medications or anti-infectious agents.

For refractory reflux, patients will be assessed with endoscopy and pH monitoring to ascertain if the reflux condition is actually caused by device failure. Treat with acid suppression medication if needed.

If the patient develops severe odynophagia or medical refractory reflux, that do not resolve within 4 weeks of medication therapy, the device will be removed.

12.7 Unanticipated Adverse Device Effects

Unanticipated adverse device effects (UADEs) include any serious adverse effects on the health or safety of a subject or any life-threatening problem or death caused by, or associated with, the study device that are not typically associated with the procedure, investigational device, and the investigational device itself. All unanticipated adverse device effects must be reported to the IRB, per the IRB's reporting requirements, but no later than 10 working days and to the Sponsor within 24 hours after the investigator first learns of the unanticipated adverse device effect. The Sponsor will immediately conduct an evaluation of a UADE and report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the Sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

12.8 Data Safety Monitoring Board /Clinical Events Committee

An independent Data Safety Monitoring Board (DSMB) will not be required based upon FDA's DSMB guidance document; however, Aplos Medical will establish an independent Clinical Events Committee (CEC) that will serve as an adjudication committee to review all actual and potential serious adverse events experienced by study subjects during this trial. The CEC also has the responsibility to enforce the stopping rules. The committee will operate according to a standard operating procedure or charter that will be based upon FDA's guidance document and be approved by the CEC prior to performing formal deliberations.

Members of the CEC will not be employees of Aplos Medical, nor will they have a financial interest in the study device or manufacturer; however, they may receive a stipend for their participation. The CEC will be composed of 3 to 5 physicians with relevant clinical expertise. Meetings may occur via conference call or in-person and will be held at a frequency to be specified in the CEC procedure. Aplos Medical personnel may attend only the open sessions of these meetings.

The adjudication decision of the CEC will be used for the final classification of adverse events, including relatedness to the device and/or procedure, determination of safety endpoints, and all regulatory reports. Any decision unanimously rendered by the CEC will be considered binding.

13 Data Analysis Plan

13.1 Sample Size Determination

The goal of this study is to develop an information set that will assist the Sponsor with development of a pivotal clinical study plan. Since no hypotheses are being tested, no formal sample size calculations have been performed; however, adequate information regarding safety, device performance, and surgical technique can be obtained by enrolling a maximum of 15 subjects and following them for at least 12 months.

Experience implanting the study device in 15 subjects should be adequate for the investigator(s) to feel comfortable enough with the implant procedure to be able to teach it to other investigators in a pivotal clinical trial and to provide clear written direction in the Instructions for Use. Their experience and observations should also help elucidate any safety concerns that must be addressed before implementing a pivotal clinical trial.

13.2 Analysis Methods

13.2.1 Descriptive and Demographic Analyses

The demographic and baseline variables of interest will be summarized via standard descriptive statistics (e.g., mean, standard deviation, median, range). As this is a single-arm trial, hypothesis testing is not possible on these variables.

Objective 1: Safety Analysis

The rate of each type of distinct adverse event will be tracked. Events will also be summarized based upon seriousness, expectedness, and the relationship to both the device and the implant procedure. It is expected that rates of distinct events or categorical groupings of events can be combined with available literature on similar therapies to provide plausible sample size estimates for the safety portion of a pivotal clinical trial. Serious device- and procedure-related adverse events will be analyzed as a distinct group.

Objective 2: Performance Analysis

Summary statistics will be used to display results of all performance outcomes at each study time point. At a minimum, each summary will include the mean, median, range, standard deviation, and 90% confidence limits. Results from these summaries will be used in conjunction with available literature to provide sample size estimates for efficacy endpoints for a pivotal clinical trial.

13.2.2 Continuous Analysis of Study Results

The preliminary safety, performance data, and adverse events will be monitored continuously throughout this clinical trial. The analysis will be comprised of summary statistics and confidence intervals, as well as narratives for each subject. This summary will provide evidence of early esophageal healing and peri-procedural adverse events. The combination of these results with the

appropriate literature will provide a basis from which to elicit a meaningful pivotal clinical study design.

14 Risk Analysis

The Ω-Cuff device is manufactured from biocompatible materials and meets applicable principles of risk management, design control provisions of 21 CFR 820.3, and standards current at time of testing.

14.1 Risks

Complications associated with surgical procedures and device implants have been compiled from the scientific literature and were identified as anticipated adverse events. Aplos Medical has no evidence to suggest that the risk of complications associated with use of the Ω-Cuff device is greater than the risks posed by other existing marketed products or procedures. As with any investigational or approved device, a potential exists for the occurrence of adverse events.

The proposed study will monitor the subjects at discharge, 2-4 weeks, 2 months, 3 months, 6 months, 9 months, and 12 months. The subjects will be consented to allow additional follow-up in the 18 to 24-month interval, allowing for detection of adverse events. Furthermore, any risks associated with participation in this clinical study will be minimized and managed in accordance and full compliance with recognized Good Clinical Practices (GCP), CFR 50 Protection of Human Subjects, CFR 56 Institutional Review Boards, and CFR 812 Investigational Device Exemptions.

14.2 Potential Benefits

The potential benefits to subjects being implanted with the Ω-Cuff device include the following:

- Avoidance of a more invasive surgical procedure, such as the Nissen Fundoplication.
- Reduced or eliminated symptoms and/or the use of anti-reflux medications.
- A more precise therapy than currently offered. Unlike the current standard treatment with the Nissen Fundoplication, the Ω-Cuff device adds a specific pressure increase to the LES region. Similar to the Nissen Fundoplication, it provides the least resistance at rest and the most resistance when swallowing.
- Durability may be improved. Studies suggest the Nissen Fundoplication starts to lose efficacy over time. The strength of the Ω-Cuff device should not change over time.
- Implantation of the Ω-Cuff device may also be less invasive than the Nissen Fundoplication. By leaving the stomach anatomy alone and requiring less dissection, outcomes and side effects, such as pain, gas bloat, and diarrhea, may be improved.

14.3 Conclusion

Conduct of this study is not anticipated to pose new types of risks from those identified for similar products/procedures. To date, Aplos Medical has no evidence to suggest that the incidence of complications associated with use of its Ω-Cuff device will be greater than the risks posed by other existing marketed products. Therefore, the likely benefit of the Ω-Cuff device outweighs the

potential risks.

In conclusion, the need for the data from such a study together with the benefit of receiving GERD treatment in a controlled setting balances the risk related to the participation in this clinical study.

15 Protocol Modifications

Neither Aplos Medical, its designees (subcontractors), nor the study investigators may modify this protocol without obtaining written concurrence of each other and the IRB.

Any deviations from this protocol undertaken to protect the life or physical well-being of a subject in an emergency situation must be reported to the Sponsor within 48 hours of occurrence and the respective IRB(s), per the IRB's reporting requirements, but in no event later than five (5) calendar days after the emergency occurs.

16 Study Materials

16.1 Packaging and Labeling

The Ω-Cuff device packaging labels will include Part #, Lot #, Use-By-Date, and the following statement: "CAUTION—Investigational Device. Limited by Federal (United States) Law To Investigational Use." An additional sequentially assigned alpha/numeric designation, affixed to each package, will be used to ensure traceability of devices during the clinical study.

The Introducer is supplied as cleaned and contained in a pouch. It will need to be steam sterilized before use, per included instructions.

Labeling describing all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions are provided in the Instructions for Use.

16.2 Handling and Storage

The Investigator must ensure that the devices are stored according to the Instructions for Use.

The products are not to be used after the expiration date indicated on the label. If a package is damaged, sterility cannot be assured, and the contents must not be used. Investigators are not permitted to re-sterilize the product.

All supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any unused supply and is to return unused product to the sponsor.

16.3 Product Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or the head of the medical institution (where applicable) or designated center staff (e.g., storage manager, where applicable) must maintain investigational product accountability records throughout the course of the study.

16.4 Product Implant Technique

See Ω-Cuff device Instructions for Use.

17 Study Administration

17.1 Institutional Review Board (IRB) Approval

This protocol, the model consent form, and HIPAA Authorization for the Use and Disclosure of Health Information must be reviewed and approved by the overseeing IRB and the Sponsor before subject recruitment may begin. Changes to the protocol must be approved in writing by the Sponsor and the IRB (as applicable) before the change is implemented.

Prior to subject enrollment, a copy of the IRB approval letter, addressed to the Investigator, must be submitted to the Sponsor, certifying trial approval. Investigators are responsible for submitting and obtaining initial approval and continuing approval from their local IRBs and forwarding copies of the approval letters to the Sponsor. The original letters are to be kept in the investigational center Regulatory Binder designated for this study.

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

17.2 Investigator Agreement and Financial Disclosure

Each investigator will sign the Investigator's Agreement before beginning the study, as required by federal regulations. No investigator will be added until the agreement is signed.

The Investigator's signature signifies his/her willingness to follow the protocol and all regulations and reporting requirements. In accordance with federal regulations, all investigators will also be required to sign a Financial Disclosure form, which certifies the investigator's and his/her immediate family's financial interest in Aplos Medical and study outcomes. Investigators must inform the Sponsor of any changes to the information within the financial disclosure form during the study and for a period of one year after the device is approved by the FDA or the study is terminated, whichever is later.

17.3 Subject Confidentiality

All information and data sent to Aplos Medical and/or its designees concerning subjects and their participation in this study are considered confidential by Aplos Medical and its designees (subcontractors). Only authorized Aplos Medical personnel or approved contracted agents of Aplos Medical will have access to some portions of these confidential files and will act in accordance with applicable regulations as required by HIPAA. The IRBs and FDA also have the right to inspect and copy all records pertinent to this study. All data used in the reporting of this study will eliminate identifiable references to the subjects.

17.4 Study Management

The study will be managed and monitored in accordance with 21 CFR 812, 21 CFR 50, and 21 CFR 56. Aplos Medical (Minneapolis, MN), has contracted the services of a clinical research organization to manage the trial:

Study Management: Clinical Research Strategies, LLC
Email: jennifer@clinicalresearchstrategies.com

Telephone: 949-232-6469

A study team contact list will be provided to sites prior to initiation.

The monitors will follow standard operating procedures for clinical program management and monitoring, including monitoring report forms. These documents will be supplemented by a written monitoring plan that will specify the frequency and scope of investigational center inspections. This plan may be modified during the course of the study as needed to ensure study integrity.

Monitors will be restricted to qualified individuals trained in the aforementioned procedures as well as study-related documents. Copies of monitor training records will be maintained by the Sponsor.

17.4.1 Investigational Center Qualification

Investigational center qualification visits or phone calls will be conducted by the Sponsor prior to acceptance of the site into this study. The site qualification visit will be scheduled to include time with the Principal Investigator, co-investigators, study coordinator, and other study personnel. Areas of discussion include a review of personnel training, investigator qualifications, adequacy of potential subject pool, FDA-regulated study experience, protocol-specific requirements for procedures and equipment, and a review of staffing and equipment availability and appropriateness. Resolution of any concerns and/or completion of any appropriate study activities identified during the pre-study visit will be documented and submitted to the Principal Investigator.

17.4.2 Site Training

Study-specific training of trial personnel is the responsibility of the Sponsor and the Investigator. Study training will occur before the first device use. To ensure investigational plan and regulatory compliance as well as accurate data collection, site training will include a detailed review of this Investigational Plan, CRF completion, monitoring logistics, and regulatory requirements.

Investigational site study training personnel will ensure that study personnel do the following as required by their institutions:

- Submit this Investigational Plan to its IRB for appropriate review and obtain written approval for the conduct of the study prior to enrolling any subject for this study.
- Maintain all study correspondence, this Investigational Plan, and all related and required records on file at their facility.
- Assume full responsibility for the study investigation at their individual medical practices, clinics, and medical facilities.

17.4.3 Training of Investigators

Investigators will receive material illustrating the use of the Ω-Cuff device and any specific instructions to prepare the Ω-Cuff device for implantation as defined in the Instructions for Use. All training will be conducted and documented prior to subject enrollment.

17.4.4 Case Report Forms

Electronic case report forms (eCRFs) specifically created for this study will be used to collect all data for the study. The Principal Investigator or his/her designee at each site is responsible for recording all data onto the study eCRFs. FDA 21 CFR Part 11 will be followed as well as other applicable legislation on the handling of electronic data. Subject personal information will be pseudonymized. Site and subject numbers will be used to track subject information throughout the study.

The Investigator must review and electronically sign each eCRF; these responsibilities cannot be delegated to another person. The investigators are responsible for the accuracy and completeness of all data on the eCRFs.

Completed eCRFs will be reviewed at the investigational site by monitors at regular intervals throughout the study. Information on the eCRFs will be compared to information originally recorded on source documents related to the study (i.e., professional notes, laboratory reports, study-specific worksheets, etc.). Information on the eCRFs must match the source documents.

17.4.5 Monitoring Visits

This study will be conducted and monitored in accordance and full compliance with recognized Good Clinical Practices, 21§CFR 812, 21§CFR 50, 21§CFR 54, 21§CFR 56, HIPAA, this investigational plan, and the written monitoring plan. Study monitors will be assigned to each site and will be qualified, as stated above, on the basis of education, experience, and training.

All clinical sites will be monitored routinely for appropriate informed consent and HIPAA Authorization compliance, timeliness of data form completion, data accuracy compared to source documents, traceability of investigational devices, and investigational plan and regulatory compliance. CRFs will be reviewed for completeness, legibility, and clarity on site during regularly scheduled interim monitoring visits. Data clarification forms for missing or unclear data will be requested as necessary throughout the study. Aplos Medical or designee may request further documentation (e.g., clinic notes or lab reports) when AEs, complications, or malfunctions are observed and reported. Copies of monitoring reports will be submitted to Aplos Medical. Documented non-compliance will be subject to corrective action. If corrective actions are not undertaken or are not effective, the clinical site may be withdrawn from the study.

A final study close-out visit will be conducted to review final CRFs, verify disposition of investigational devices, resolve all data queries, and review regulatory documents. The Principal Investigator will be notified via a letter to document that all protocol-related activities have been completed and that the clinical study is completed and may be closed at the site.

17.4.6 Investigator Responsibilities

The investigator is responsible for ensuring that the study is conducted according to the Investigator Agreement, the investigational plan, and all applicable federal regulations for Investigational Device Exemption (IDE) studies and HIPAA. Specific responsibilities are listed in the Investigator Agreement and this Investigational Plan.

Records and reports must remain on file at the investigational site for a minimum of two years after the later of either the completion/termination of the investigational study or the date Ω-Cuff device receives market approval for the indication being studied. They may be confidentially disposed of only upon approval from Aplos Medical. The Investigator must contact Aplos Medical before destroying any records and reports pertaining to the study to ensure that they no longer need to be retained. In addition, Aplos Medical must be contacted if the investigator plans to leave the investigational site to ensure that arrangements for a new investigator or records transfer are made prior to investigator departure.

Records

Records to be maintained by the investigator in the designated study binder file include the following:

- Investigational plan and all amendments
- Signed Investigator Agreement(s)
- Signed Financial Disclosure form(s)
- IRB approval letter, including consent and HIPAA authorization form(s)
- IRB membership list or Letter of Assurance
- All correspondence relating to the study between the site and Aplos Medical
- CVs and professional licenses for all investigators
- Site personnel signature and responsibility list
- Clinical monitor sign-in log
- Blank set of each version of CRFs
- Subject Screening/Enrollment log
- Investigational device inventory log including date, quantity, serial numbers of all devices, identification of all persons the device was used on, and final disposition
- Reports (including annual reports and a final report from the investigator)

The following records must be maintained for each subject enrolled in the study:

- Signed consent form and HIPAA authorizations
- Completed CRFs
- Adverse event reports and any supporting documentation
- Protocol deviations
- Complete medical records, including procedure reports, lab reports, professional notes, etc.
- Records pertaining to subject death during the investigation (including death records, death certificate, and autopsy report, if performed)

Aplos Medical reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this study at any time.

Reports

Investigators are required to prepare and submit to the Sponsor and the IRB complete, accurate, and timely reports on this investigation when necessary, according to 21 CFR 812.150. Types of reports to be submitted include reports pertaining to unanticipated adverse device effects,

withdrawal of IRB approval, and deviations from the investigational plan.

The Investigator is required to submit an annual report to his/her IRB with a copy to the Sponsor and a final report upon completion or termination of this study. The final report must be submitted within 90 days of completion or study termination.

The final report must include the following:

- Device name
- Number of subjects screened, enrolled, withdrawn, and completed
- Number of devices received, used, and returned
- Summary of all adverse events (anticipated and unanticipated)
- Summary of all serious adverse events
- Summary of all protocol deviations
- Brief statement of results, outcomes, and conclusions

17.4.7 Investigational Site Termination

Aplos Medical reserves the right to terminate an investigational site for any of the following reasons:

- Failure to secure subject informed consent or Authorization for the Use and Disclosure of Health Information prior to study enrollment
- Failure to report unanticipated adverse device effects to the Sponsor within 24 hours of discovery and ten working days (to IRB) of learning of the event
- Failure to report serious adverse events within 24 hours of discovery
- Repeated investigational plan violations
- Repeated failure to appropriately complete CRFs
- Failure to enroll an adequate number of subjects
- Loss of or unaccounted for investigational product inventory
- Administrative decision by the company

18 Abbreviations and Definitions

Abbreviations:

AE	Adverse Event
CRF	Case Report Form
DSAE	Device and procedure-related serious adverse event
GERD	Gastroesophageal reflux disease
HIPAA	Health Insurance Portability and Accountability Act of 1996
H2RA	Histamine type 2 receptor antagonist
IDE	Investigational Device Exemption
IRB	Institutional Review Board
LES	Lower esophageal sphincter
PPI	Proton pump inhibitor
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect

Definitions: None

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