Latera RCT – Latera® Absorbable Nasal Implant vs. Sham Control for Lateral Nasal Valve Collapse

Device: Latera™
Protocol Number: CP04
Version: 3.0
23 March 2018

Sponsor
Spirox, Inc.
595 Penobscot Drive
Redwood City, CA 94063 USA

CONFIDENTIALITY STATEMENT

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SUMMARY OF CHANGES

Relevant Section(s)	Summary of Revisions	Rationale
Synopsis, Exclusion Criteria, p.12 and 4.1 Exclusion #13, p22.	Exclusion criteria for OSA and CPAP users changed from 4 weeks to approximately 2 weeks of post-procedure management of CPAP mask use.	Better reflects current practice and variety of masks in use throughout U.S.
Section 5.3, Page 29	Removal of "7 days".	Administrative change to remove inconsistency in study plan, no change to study version
Version 3.0	Add "X" to Table 2 – Schedule of Study Activities for consistency across all sections of protocol.	Administrative change to clarify data collected at 7 Day Visit. Administrative change to clarify pregnancy test requirements as part of screening for patient availability. Allows consistency with Eligibility and follow up and analysis plan.
	Widened windows from ±14 days to ± 30 days for 12Month, 18Month and 24 Month visits to support site scheduling needs.	Increase flexibility to assure likelihood of follow up. No impact on primary endpoint which uses 3Month assessments.
	NCT Identification number added	NCT Identification number now available.

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 812).

This Clinical Investigational Plan (CIP), informed consent forms (ICF), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of the CIP and the ICF must be obtained before any subject is enrolled. Any amendment to the CIP will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the ICF will be IRB-approved and a determination will be made regarding whether a new consent needs to be obtained from subjects who previously provided consent.

INVESTIGATOR SIGNATURE PAGE

Investigator Name	**Title**
Site Name	**Site Number**

I have read the protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined therein.

I agree to keep records on all subject information (e.g., source documents and informed consent forms), device shipments and return forms, and all other information collected during the study, in accordance with local and national regulations.

Investigator Signature	Date

SYNOPSIS

Study Title	Latera RCT – Latera® Absorbable Nasal Implant vs. Sham Control for Lateral Nasal Valve Collapse
Spirox Protocol Number	CP04
Investigational Device	Spirox Latera Absorbable Nasal Implant
ClinicalTrials.gov Identifier	NCT 03400787
Sponsor	Spirox, Inc. 595 Penobscot Drive Redwood City, CA 94063 USA
Study Purpose	To evaluate the Latera Absorbable Nasal Implant (Latera Implant) Implant versus Sham Control in subjects with nasal valve collapse due to or primarily due to insufficient cartilaginous support of the lateral nasal wall
Objective	The primary objective of the LATERA RCT is to demonstrate the superiority of the Latera Implant to improve nasal breathing, compared with a Sham Control treatment.
Phase of Study	Post-market
Study Design	Randomized (1:1), sham-controlled, single-blind, multicenter post-market trial using an adaptive trial design
Investigational Sites	Up to 15 investigational sites in the United States, in office-based locations with investigators experienced in standard nasal interventions for airway obstructions and the use of the Latera Implant
Study Population	The Adaptive Design allows for enrollment of up to 150 subjects with nasal airway obstruction due to or primarily due to nasal valve collapse.
Study Duration	Subjects will be followed for a total of 24 to 27 months after enrollment, Latera Implant and Sham Control, respectively. Overall study duration, enrollment and follow up, is expected to be approximately 4 years.
Treatment Arms	Latera Treatment Arm Subjects in the active treatment arm will receive the Latera Implant, a PLLA-PDLA copolymer, delivered to the region of the lateral nasal wall cartilages to provide support. It is placed using standard, minimally invasive techniques and is absorbed over a period of approximately 18 months.

	Sham Control Arm Subjects in the Sham Control arm will undergo the same preoperative assessments as those in the Latera Treatment arm up to and including anesthesia for the implant and cannula insertion into the nasal lateral wall, however, no implant will be placed. Randomization to the Sham Control Arm will be assessed by the independent Data Monitoring Committee (DMC) at each interim analysis time point. If the pre-determined efficacy, safety or operational criteria are met, randomization may be terminated. Crossover Subjects Subjects will be unblinded after the 3-month assessment is complete. For subjects in the Sham Control arm, the subject will be treated with the Latera Implant if they still meet all eligibility criteria. The subject's data will continue to be recorded thereafter through 24 months post-implant. If the subject does not meet the eligibility criteria, he/she will exit the study.
Primary Endpoint	The primary endpoint of the study is the Responder Rate, assessed 3 months post-procedure in the per protocol population of the Latera and Sham arms. Responder Rate is defined as the proportion of subjects with at least one (1) NOSE class improvement or at least 20% NOSE score reduction.
Secondary Endpoints	1. Responder Rate at 7 days, 30 days, and 6, 12, 18, and 24 months; 2. Frequency of procedure-related adverse events (non-serious and serious), assessed at the index procedure and through the 7-day, 30-day, 3-month, 6-month, 12-month, 18-month, and 24-month follow-up time points; 3. Frequency of device-related adverse events (non-serious and serious), assessed at the index procedure and through the 7-day, 30-day, 3-month, 6-month, 12-month, 18-month, and 24-month follow-up time points; 4. NOSE score, change from baseline, to the 7-day, 30-day, 3-month, 6-month, 12-month, 18-month, and 24-month follow-up time points; 5. Assessment of Nasal Breathing using a Visual Analogue Scale, change from baseline, to the 7-day, 30-day, 3-month, 6-month, 12-month, 18-month, and 24-month follow-up time points;

	6. Endoscopic lateral wall insufficiency (LWI) score as assessed by independent reviewers, change from baseline to the 3-month and 6-month time point; 7. Epworth Sleepiness Scale (ESS) score and Pittsburgh Sleep Quality Index (PSQI), change from baseline, to the 7-day, 30-day, 3-month, 6-month, 12-month, 18-month, and 24-month follow-up time points. All secondary endpoints will be assessed for the Sham Control Arm at two additional visits. The Sham arm will have follow up visits at 7 days, 30 days, and 3 months after randomization, and at 30 days, 3-months, 6, months, 12 months, 18 months, and 24 months after cross over.
Inclusion Criteria	*Subjects must meet the following criteria to be included in the study:* 1. Adults aged 18 and above; 2. Understands and provides written informed consent; 3. Stated willingness to comply with all study procedures, post-treatment care and availability for the duration of the study follow up of 2 years; 4. In good general health as evidenced by medical history; 5. NOSE score ≥55; 6. Dynamic bi-lateral nasal wall insufficiency as confirmed by Positive Modified Cottle Maneuver; 7. Nasal and facial anatomy appropriate to receive the Latera Implant; 8. Documented failure of benefit after at least 4 weeks of conservative medical management, including, for example, antihistamines or nasal steroids, evidenced by lack of efficacy or tolerability.
Exclusion Criteria:	*Subjects meeting any one of the following criteria will be excluded for the study:* 1. Unable to tolerate or not a candidate for procedures performed under local anesthesia; 2. Pathology other than lateral wall insufficiency (e.g. septal deviation, turbinate or adenoid hypertrophy, polyps, sinusitis, rhinitis) is the primary contributor to airway obstruction; 3. Requires or is anticipated to require any other concurrent nasal procedures (e.g. Functional Endoscopic Sinus Surgery (FESS), rhinoplasty, sinuplasty, septoplasty, or turbinate

	reduction) outside of the index procedure within 12 months after the index procedure; 4. FESS, sinuplasty, septoplasty, inferior turbinate reduction, or rhinoplasty within the past 6 months; 5. Any other rhinoplasty procedures are planned or planned usage of external dilators within 24 months after the index procedure; 6. Permanent nasal implant of any type (e.g. autologous, homologous, or synthetic graft) or dilator; 7. Presence of concomitant inflammatory or infectious conditions or unhealed wounds in the treatment area (e.g., vestibulitis, vasculitis, active acne), 8. Currently using chronic systemic steroids or recreational intra-nasal drugs; 9. Currently has cancerous or pre-cancerous nasal lesions, has had radiation in the treatment area, or is currently receiving chemotherapy; 10. History of a significant healing disorders including hypertrophic scarring, or keloid formation; 11. Poorly controlled diabetes mellitus; 12. Known or suspected allergy to PLA or other absorbable implant materials in the Latera Implant; 13. Severe obstructive sleep apnea (OSA) and cannot or is unwilling to refrain from continuous positive airway pressure (CPAP) for up to 2 weeks post-procedure based on expected healing needs and mask types, in agreement with the treating physician; 14. Female subjects, of child bearing potential, known or suspected to be pregnant or are lactating; 15. Any other presenting condition that, in the medical opinion of the investigator, would disqualify the subject from the study.
Independent Medical Monitor	An independent Medical Monitor (MM) will review all adverse events (AE). The MM will MedDRA code each AE and classify the events with respect to device and procedure relatedness, seriousness, and severity. When an AE is device-related (ADE), the MM will determine whether the ADE is anticipated or unanticipated and will confer with Sponsor for confirmation when deemed to be unanticipated.

Data Monitoring Committee	An independent DMC will review safety data, study execution and interim analyses per the statistical plan at predetermined time points and as requested by the Sponsor, the MM, or the DMC Chair. The DMC will make recommendations on protocol modifications and continuation of the study.
Principal Investigators	Pablo Stolovitzky, MD ENT of Georgia 5673 Peachtree Dunwoody Rd, Suite 150 Atlanta, GA 30342 404-297-4230 stol@entofga.com Doug Sidle, MD Northwestern University Feinberg School of Medicine NMH/Galter Room 15-200 675 N. Saint Clair Chicago, IL 60611 312-695-8182 dsidle@nmff.org

1. INTRODUCTION

1.1. Background on Nasal Valve Collapse

Nasal airway obstruction can be caused by several independent or concomitant factors including septal deviation, enlarged turbinates or a weakened nasal lateral wall, leading to nasal valve collapse (NVC). The nasal valve, first described in the early 20th century by Mink,[1] is a complex, three-dimensional, dynamically-alternating structure that controls nasal airflow resistance. A dysfunction of the nasal valve can lead to nasal obstruction with a significant drop in the quality of life for patients.[2]

Even a small decrease in the cross-sectional area of the nasal valve can contribute to airway obstruction. This is due to the Hagen–Poiseuille law which describes flow through a tube as proportional to the 4th power of the radius of the tube and inversely proportional to the pressure difference across the tube.

Common causes of NVC are prior rhinoplasty, aging, nasal trauma and congenital abnormalities that weaken the nasal cartilage, leading to a lateral wall weakness or insufficiency (LWI).[3,4]

Therapies to correct NVC range have been limited. These include invasive surgical procedures and non-surgical solutions to temporarily dilate the nasal valve, such as Breathe Rite® strips or nasal cones. Surgical strategies that involve septoplasty[5] or inferior turbinate reduction[6] may alleviate impaired nasal breathing, but do not directly address the weakened lateral wall. Procedures intended to stabilize the lateral wall include cartilaginous grafts typically harvested from the nasal septum,[7] ear,[8] or rib cartilage.[9] These grafts can be placed as lateral crural strut grafts,[10] alar batten grafts[11] or butterfly grafts.[12] Implants made from non-absorbable alloplastic materials have also been used for treatment of NVC including expanded polytetrafluoroethylene[13] and high-density porous polyethylene.[14] These materials have not gained wide utilization as they require invasive surgical procedures and are associated with increased risks of infection, extrusion, and the potential need for revision procedures.

Surgery to strengthen the lateral wall has been shown to significantly improve the quality of life for subjects suffering from nasal airway obstruction,[15] however current procedures are generally invasive and have the potential to permanently alter the patient's appearance.[16] This study utilizes a minimally invasive technique to address NVC by supporting the nasal lateral wall cartilage with an absorbable implant.

Spirox has developed the Latera Absorbable Nasal Implant and Delivery Device, to enable a less invasive alternative to current surgical approaches used to support weak lateral wall cartilage. This device has been cleared by the US Food and Drug Administration (FDA) and is currently in commercial distribution.

1.2. Prior Investigations

There have been three prior investigations of the Latera device, including an initial study performed in Germany, the LATERAL OR study, and the LATERAL Office study.

Initial German Study

The initial study sponsored by Spirox was a prospective, multicenter, non-randomized, single-arm trial (NCT#02188589), implanting the device in 30 subjects at three investigational sites in Germany.[a] Subjects with nasal valve collapse due to weakened lateral cartilage were included, and the device was used to support the upper and lower lateral nasal cartilage. Fifty-six devices were implanted in 30 subjects, who were then followed for 24 months.

Safety data was assessed at three (3) months as the primary safety endpoint, with 5 implant/device related events in 4 subjects. These events included 3 extrusions (device required retrieval), 1 hematoma, and 1 subject with inflammation, accounting for a per subject device-related adverse event (AE) rate of 13%. The device extrusions were internal nasal cavity extrusions related to the implantation technique or nasal manipulation by the subject. None of these events were associated with signs of tissue rejection for foreign body response and all occurred within the first postoperative month. The implanted devices were uneventfully removed with forceps at the time of the observation and no open surgical intervention was required. Each event resolved without further clinical sequelae.

Effectiveness of the device was assessed using the NOSE scores through follow-up time points at 1 month, 3 months, 6 months, 12 months, 18 months, and 24 months. The NOSE score is a validated scoring system for nasal obstruction.[17] The NOSE scores are assessed using a validated questionnaire using patient responses to a set of five (5) questions. A percent responder rate was calculated at each follow up time point to assess the proportion of subjects that noted a benefit. Responder Rate is defined as the proportion of subjects with at least one (1) NOSE class improvement or at least 20% NOSE score reduction. The NOSE Categories are as follows: mild 5-25 points, moderate 55-75 points, extreme 80-100 points. The responder rate was 86.7% at 1 month, 86.2% at 3 months, and continued improvement of 80% at 24 months. External and internal physical examination findings were normal, without evidence of implant migration. Results from an independent physician review of collected photographs demonstrated an adverse cosmetic effect at the 3-month follow-up time point in 1/30 subjects (3%). **Figure 1** (page 16, below) summarizes the study results. The 12-month results were reported in the medical literature in April 2017. The 24-month follow up was completed in July 2017.

In summary, the results of the first 30-subject clinical trial demonstrated safety and effectiveness of the device for the support of upper and lower lateral cartilage. The per subject ADE rate was comparable to the rates reported in published studies of other alloplastic materials used to provide lateral cartilage support in similar study populations.

[a] The INEX device was used in this study, a predecessor device of Latera. Latera is substantially equivalent to INEX, with modifications to device packaging and changes to enhance usability.

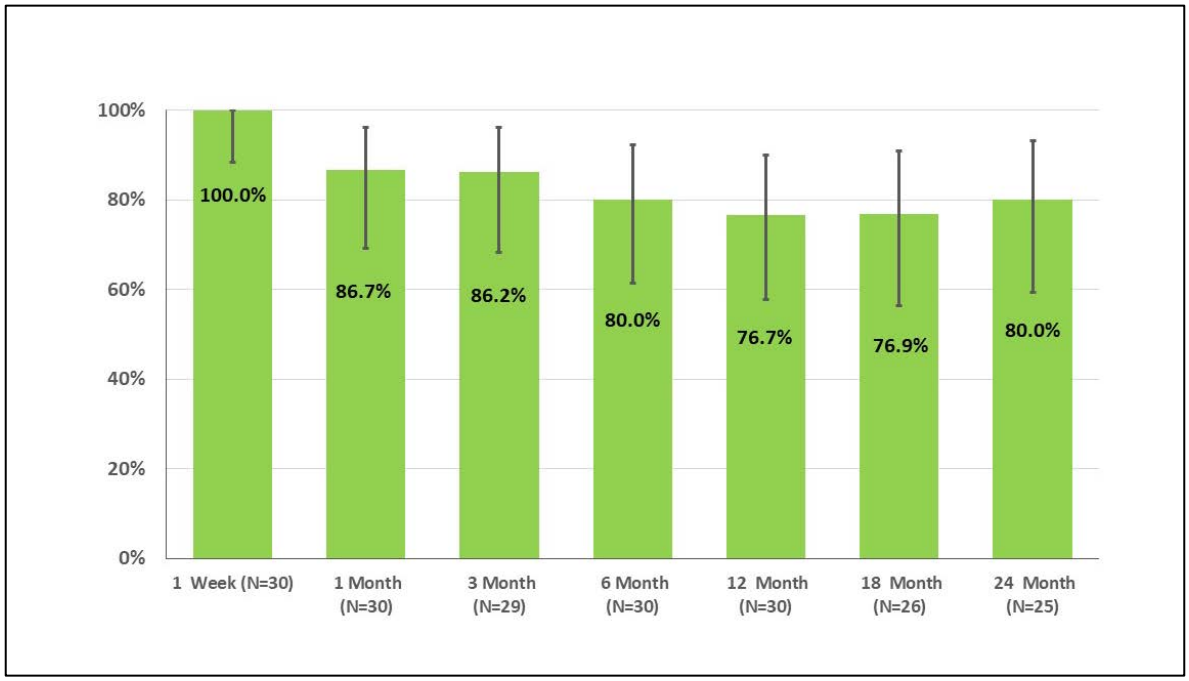

Figure 1. 24-Month Results from Spirox First Study; Percent Responders (NOSE Score)

Additional Studies

Spirox is currently sponsoring two additional studies on the Latera Implant, LATERAL OR and LATERAL Office studies (NCT#02952313 and NCT#02964312, respectively). While enrollment was very recently completed, some unmonitored, unpublished study results are available. Please note: these data are provided to share Latera experience in a broader patient population and based in the U.S. Current data is preliminary and is subject to change.

The LATERAL OR and Office clinical trials are designed for data collection and reporting on the Latera Nasal Implant. Three hundred and thirty (330) subjects with nasal valve collapse due to weakened lateral cartilage were enrolled, and the device was used to support the upper and lower lateral nasal cartilage. These studies do allow for concomitant procedures such as septoplasty and turbinate reduction, as additional interventions for NAO beyond the Latera NVC intervention. Table 1 (below) summarizes information available to date (n=278) and the completed study above. A comprehensive review of all available clinical data on the Latera Absorbable Nasal Implant shows consistent results in improvements in nasal breathing. Adverse device effects are few and are non-serious.

Table 1. Outcome in the three Latera studies

	LATERAL OR	LATERAL Office	Initial German Study
Subjects Treated	113	165	30
1-M Responder Rate	96/104 (92.3%)	135/152 (88.8%)	26/30 (86.7%)
3-M Responder Rate	79/83 (95.2%)	80/91 (87.9%)	25/29 (86.2%)
6-M Responder Rate	37/39 (94.9%)	28/35 (80.0%)	24/30 (80.0%)
24-Month Responder Rate	Follow up in progress	Follow up in progress	20/25 (80.0%)
Retrieval Rate*	5/223 (2.2%)	14/317 (4.4%)	3/56 (5.4%)
All ADE (all events)	6	15	5
ADE Rate†	5 / 223 (2.2%)	14 / 317 (4.4%)***	4/30 (13%)
Serious ADE Rate†	0 (0%)	0 (0%)	0 (0%)

Retrievals/Implants
†Events per Subjects Treated

1.3. Current Study: The Latera Randomized Controlled Trial

Spirox is sponsoring a clinical study to evaluate the performance of the device in comparison to no intervention, in this case, a "sham treatment". The study design and methods have been developed using input from previous and ongoing studies with the Latera Implant.

This randomized, single-blind, sham-controlled, multicenter study of the Latera Nasal Absorbable Implant will enroll subjects with nasal valve collapse due to or primarily due to insufficient cartilaginous support of the lateral nasal wall into one of two treatment arms, a) implantation with the Latera device or b) Sham Control.

2. STUDY DEVICE

This is a Non-Significant Risk ("NSR"), post-marketing study and will be conducted in accordance with the requirements prescribed in 21 CFR §812.2(b). Because it is a post-market evaluation of a 510(k) cleared medical device in commercial distribution, used according to FDA cleared indications for use, investigational device labeling described under §812.2(b) is not required. The choice of conducting this study under §812.2(b) represents a conservative approach as the study could otherwise have been categorized as Exempted per §812.2(c).

This evaluation of the Spirox Latera Absorbable Nasal Implant and Delivery Device is considered a NSR device study for the following reasons:

- While the device is an Implant, it does not present a potential for serious risk to the health, safety, or welfare of a subject;
- The device is not purported or represented to be used for supporting or sustaining human life;
- The device is not intended for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health; and,
- The device does not otherwise present a potential for serious risk to the health, safety or welfare of the subject.

2.1. Indication for Use

The Latera Absorbable Nasal Implant is indicated for supporting nasal upper and lower lateral cartilage. It is cleared for commercial use in the US.

2.2. Manufacturer and Study Sponsor

Spirox, Inc.
595 Penobscot Drive
Redwood City, CA 94063 USA

Study Contact: Elisa Hebb, VP
Clinical and Regulatory Affairs
ehebb@spiroxmed.com
650-249-6379 (O)

2.3. Clearance Status

Spirox received clearance from the US FDA to market the Latera Implant on June 23, 2016 (K161191). The device is Regulatory Class II, product code NHB. A predecessor of the device, the Spirox INEX Absorbable Nasal Implant System, was previously cleared on December 4, 2015 (K152958). The Latera device is similar to the original INEX Implant, with the exceptions of modifications to device packaging and changes to enhance usability.

2.4. Model Numbers

The Latera Implant is available in one size and model.

2.5. Device Description

The absorbable nasal Implant is comprised of a 70:30 blend of poly(L-lactide) and poly(D-lactide). The Implant is predominantly cylindrical in shape with a diameter of 1 mm and an overall length of 24 mm with a forked distal end for anchoring and features on the proximal end for increased flexibility. The copolymer is absorbed by the body over a period of approximately 18 months.[18] The Latera Implant is provided in a plastic tray with a sliding lid. The Implant and plastic tray are depicted in **Figure 2**, below.

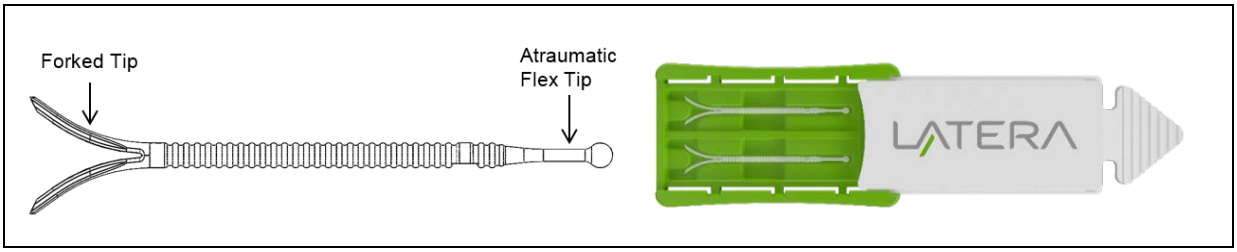

Figure 2: LATERA Absorbable Nasal Implant and Packaging

The Delivery Device is a single use device composed of an inner shaft, an outer handle with a push rod, a deploy button, an open button and a 16-gauge delivery cannula with a protective cover. The inner shaft includes an implant loading port which enables the loading of the Implant. The inner shaft transitions between the loading position and the cannula to collapse the implant forks within the cannula inner lumen and prepare the Implant for deployment. The outer handle includes deploy and open buttons that lock and release the handle from these respective positions. The outer handle also includes a push rod that shuttles the implant from the implant loading port to a ready position for deployment. The Implant Positioning Guide is packaged with the Delivery Device and is provided as an aid to the physician for planning the procedure and identifying the target Implant location. The Delivery Device and the Implant Positioning Guide are shown in **Figure 3** below.

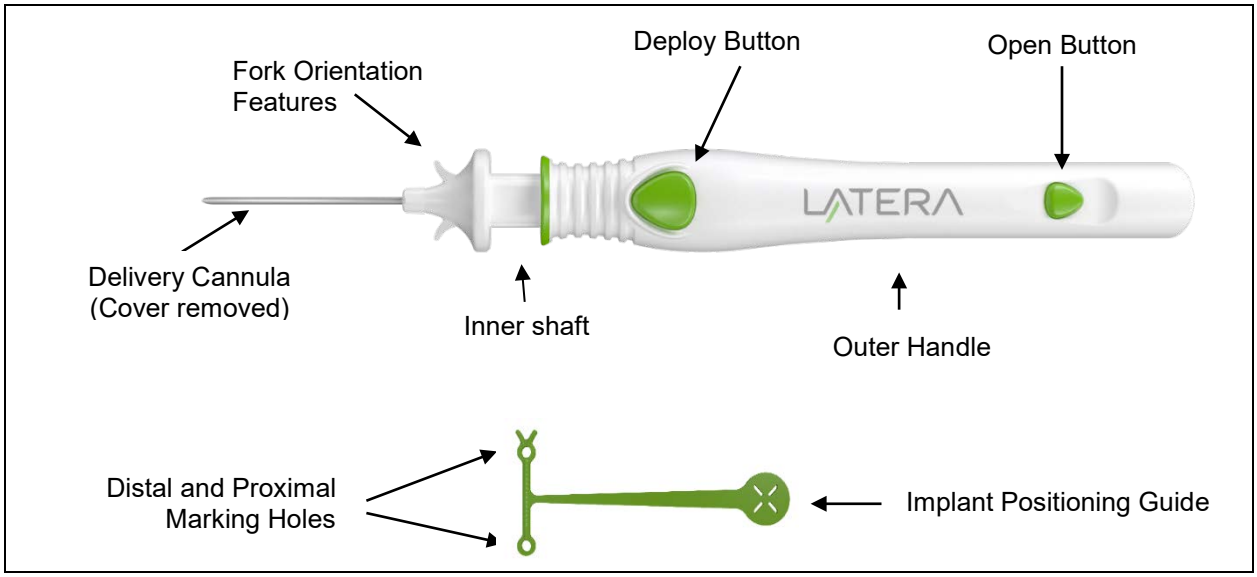

Figure 3. Delivery device and implant positioning guide.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

The primary objective of the LATERA RCT is to demonstrate the superiority of the Latera Implant to improve nasal breathing, compared with a Sham Control procedure.

3.2. Primary Endpoint

The primary endpoint of the study is the Responder Rate, assessed 3 months post-procedure in the per protocol population of the Latera and Sham arms. Responder Rate is defined as the proportion of subjects with at least one (1) NOSE class improvement or at least 20% NOSE score reduction.

3.3. Secondary Endpoints

The following endpoints comprise the secondary endpoints and the time points that each will be assessed:

- Responder Rate at 7 days, 30 days, and 6, 12, 18 and 24 months;
- Frequency of procedure-related adverse events (non-serious and serious), assessed at the index procedure and through the 7-day, 30-day, 3-month, 6-month, 12-month, 18-month, and 24-month follow-up time points;
- Frequency of device-related adverse events (non-serious and serious), assessed at the index procedure and through the 7-day, 30-day, 3-month, 6-month, 12-month, 18-month and 24-month follow-up time points;
- NOSE score, change from baseline, to the 7-day, 30-day, 3-month, 6-month, 12-month, 18-month, and 24-month follow-up time points;
- Visual Analogue Scale (VAS), change from baseline, to the 7-day, 30-day, 3-month, 6-month, 12-month, 18-month, and 24-month follow-up time points;
- Endoscopic lateral wall insufficiency (LWI) score as assessed by independent reviewers, change from baseline to the 3-month and 6-month time points;
- Epworth Sleepiness Scale (ESS) score and Pittsburg Sleepiness Quality Index, change from baseline, to the 7-day, 30-day, 3-month, 6-month, 12-month, 18-month, and 24-month follow-up time points.

All secondary endpoints will be assessed for the Sham Control Arm at two additional visits. The Sham arm will have follow-up visits at 7 days, 30 days, and 3 months after the initial treatment/randomization, and 30 days, 3 months, 6, months, 12 months, 18 months, and 24 months in subjects that cross over.

4. STUDY POPULATION

Subjects will be recruited from sites' existing patient populations that are seeking treatment for nasal airway obstruction including nasal valve collapse. Anatomical considerations may impact the race distribution (e.g. some races may be less prone to lateral wall collapse), but the intention is to enroll all eligible subjects.

Study brochures containing information on study participation and the Latera Implant may be provided to the sites, as well as posters that may be displayed either as hard copies or electronically on computer monitors in the office. All recruiting materials must be approved by the appropriate IRB (central or local).

4.1. Patient Eligibility

The trial will include up to 150 subjects at up to 15 investigational sites, male and female, aged 18 and above who are appropriate candidates for nasal intervention with the Latera Implant.

Inclusion Criteria

Subjects must meet the following criteria to be included in the study:

1. Adults aged 18 and above;
2. Understands and provides written informed consent;
3. Stated willingness to comply with all study procedures, post-treatment care and availability for the duration of the study follow up of 2 years;
4. In good general health as evidenced by medical history;
5. NOSE score ≥55;
6. Dynamic bi-lateral nasal wall insufficiency as confirmed by Positive Modified Cottle Maneuver;
7. Nasal and facial anatomy appropriate to receive the Latera Implant;
8. Documented failure of benefit after at least 4 weeks of conservative medical management, including, for example, antihistamines or nasal steroids, evidenced by lack of efficacy or tolerability.

Exclusion Criteria

Subjects meeting any one of the following criteria are ineligible for study participation:

1. Unable to tolerate or not a candidate for procedures performed under local anesthesia;
2. Pathology other than lateral wall insufficiency (e.g. septal deviation, turbinate or adenoid hypertrophy, polyps, sinusitis, rhinitis) is the primary contributor to airway obstruction;
3. Requires or is anticipated to require any other concurrent nasal procedures (e.g. Functional Endoscopic Sinus Surgery (FESS), rhinoplasty, sinuplasty, septoplasty, or turbinate reduction) outside of the index procedure within 12 months after the index procedure;
4. FESS, sinuplasty, septoplasty, inferior turbinate reduction, or rhinoplasty within the past 6 months;
5. Any other rhinoplasty procedures are planned or planned usage of external dilators within 24 months after the index procedure;
6. Permanent nasal implant of any type (e.g. autologous, homologous, or synthetic graft) or dilator;
7. Presence of concomitant inflammatory or infectious conditions or unhealed wounds in the treatment area (e.g., vestibulitis, vasculitis, active acne),

8. Currently use of chronic systemic steroids or recreational intra-nasal drugs;
9. Currently has cancerous or pre-cancerous nasal lesions, has had radiation in the treatment area, or is currently receiving chemotherapy;
10. History of a significant healing disorders including hypertrophic scarring, or keloid formation;
11. Poorly controlled diabetes mellitus;
12. Known or suspected allergy to PLA or other absorbable implant materials in the Latera Implant;
13. Severe obstructive sleep apnea (OSA) and cannot or is unwilling to refrain from continuous positive airway pressure (CPAP) for up to 2 weeks post-procedure based on expected healing needs and mask type, in agreement with the treating physician;
14. Female subjects, of child bearing potential, known or suspected to be pregnant or are lactating;
15. Any other presenting condition that, in the medical opinion of the investigator, would disqualify the subject from the study.

4.2. Patient Screening and Informed Consent

The investigator or designee, who is trained on the study protocol, will review and explain the study protocol and information, including the potential risks and benefits of participation. Time will be made available for the patient to read through the materials and ask questions. A study and protocol-specific Informed Consent Form (ICF), approved by a central or appropriate local Institutional Review Board (IRB) will be obtained from each subject prior to enrollment in the study. An electronic consent (eConsent) will be available on a web-based module of the study's electronic data capture (EDC) system. Alternatively, Investigators may utilize a standard written consent form. In either case, subjects will be provided with a hardcopy of the executed ICF. All subjects will be instructed that they are free to decline entry into the study or to withdraw from the study at any time without prejudice to future treatment. After completion of the consenting process and eligibility has been confirmed, subjects will be considered consented and enrolled for the study duration of up to 27 months of follow-up.

4.3. Subject Disposition and Flow Chart

The graphic below illustrates the flow of subjects in the study and potential points of study exit relative to analysis plan (**Figure 4**, page 23, below). Subjects are enrolled at the time of consent, and the ITT population is comprised of all consented subjects. Subjects are randomized after the anesthetic is administered. Subjects in the active treatment group receive the Latera implant, while those in the Sham Control group will undergo insertion of the cannula into the nasal lateral wall, but the Latera will not be implanted. The mITT population includes all subjects who were randomized, irrespective of whether they received the study device. The PP population includes those subjects who received the study device or the Sham Control and who are followed through 3 months.

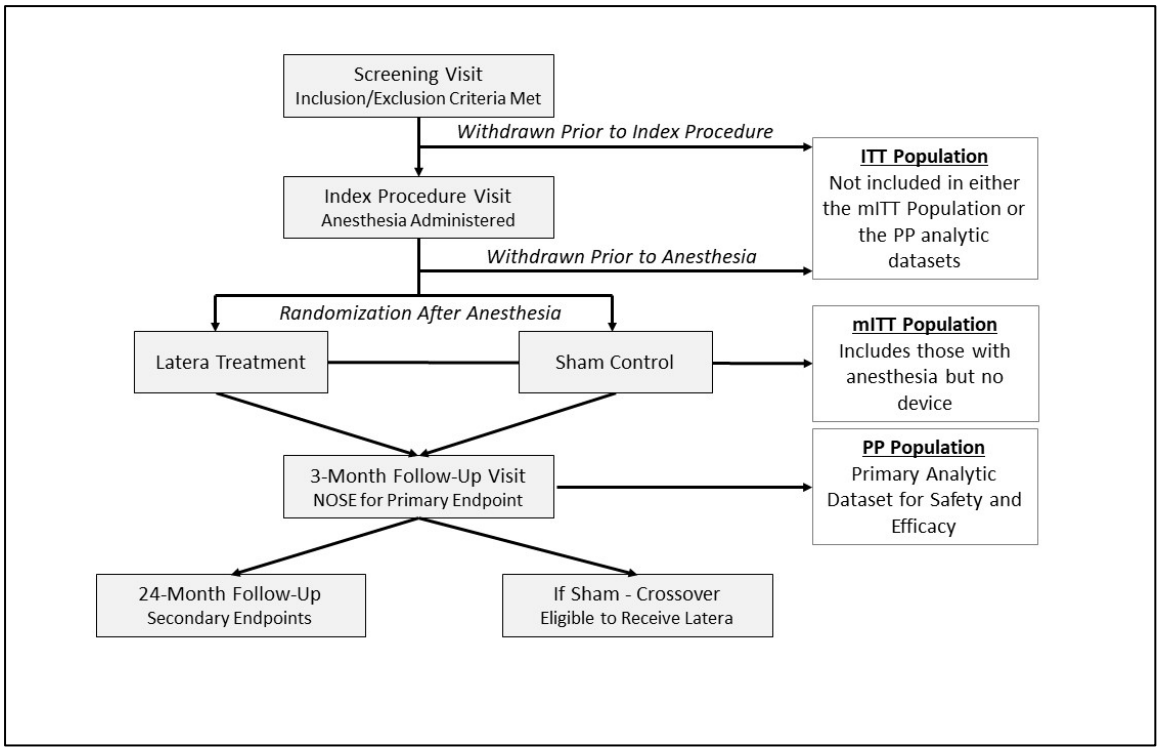

Figure 4. Flow of subjects in the trial and definitions of the ITT, mITT and PP populations.

4.4. Withdrawals and Loss to Follow-up

Participation is completely voluntary and each subject is free to withdraw from the study at any time. An investigator also has the right to withdraw the subject from the study in the event of reasons concerning the health or well-being of the subject, or in the case of lack of cooperation. Should a subject decide to withdraw for any reason, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal must be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal must be recorded on the subject's Study Exit Case Report Form (CRF). If the reason for the withdrawal is a device-related or procedure related AE, the event must be reported to the Sponsor and recorded in the AE CRF.

Withdrawal can occur at several time-points that would impact the follow up schedule for a study subject. If withdrawal occurs any time before the treatment procedure, anesthesia and randomization, the subject will be exited with no follow up assessment requirements. If withdrawal occurs after anesthesia,

regardless of whether randomization is complete, subjects will be followed through the 3 months follow up assessment and then exited from the study.

All efforts will be made to retain subjects in order to collect data at all the follow-up visits (7 days, 30 days, 3 months, 6 months, 12 months, 18 months, 24 months). Due diligence in reaching the subject must include:

- Two documented telephone contact attempts, emails, or regular postal mail letters, and
- A certified letter

After the above attempts are made, if no response is obtained, the Study Exit CRF page will need to be completed and communication attempts will need to be documented.

5. STUDY PROCEDURES AND FOLLOW-UP EVALUATIONS

5.1. Screening/Baseline Assessment

All patients seeking treatment for nasal obstruction will be screened for eligibility according to the inclusion/exclusion criteria. A member of the site's research team will review the patient's medical history for eligibility and potential inclusion into the study.

The Investigator or their designee will inform the patient about the purpose of the study and will explain the potential benefits and risks of both study arms, the Latera Implant and/or the Sham Control arm. Potential subjects will be counseled as to the nature of their condition. All subjects will have ample time to ask questions.

Patients indicating that they would like to proceed with study participation, and who are willing to comply with the requirements of the study protocol, will be asked to sign an Informed Consent Form (ICF) that has been approved by the governing IRB. Failure to provide written informed consent makes the patient ineligible for the study.

Female patients of childbearing potential will undergo a pregnancy test to verify eligibility. Women of childbearing potential are defined as any female who has experienced menarche and who is NOT permanently sterile or postmenopausal. Postmenopausal is defined as twelve (12) consecutive months with no menses without an alternative medical cause.

Patients will be considered enrolled as study subjects upon signing the ICF and meeting all study eligibility criteria. Once the subject has been enrolled into the study a baseline assessment will be completed.

The following baseline data will be collected at the Screening/Baseline visit prior to the procedure. All data must be recorded in the study specific EDC for Latera RCT within 5 business days.

- Nasal Obstruction Symptom Evaluation (NOSE) scale

- Epworth Sleepiness Scale (ESS)
- Pittsburg Sleep Quality Index (PSQI)
- NAO Breathing Assessment
- Demographic information
- Abbreviated Medical History
- Nasal medical history including risk factors
- Nasal Exam including assessment of the septum and turbinates
- Modified Cottle Maneuver
- Lateral Wall Motion Video
- Latera™ Implants may involve unknown risks to a pregnant woman, an embryo, fetus (unborn baby) or nursing infant. Any female that is pregnant, planning to become pregnant or is breastfeeding a child, cannot participate in this study. All women of childbearing potential will have a pregnancy test done prior to treatment.

Adverse events that occurred after the ICF was signed, should be entered in the EDC within 1 business day of completion of the visit.

Treatment must occur within 30 days of the date of consent. If the subject is not treated within 30 days, they will be exited from the study with no further follow-up.

5.2. Treatment Visit

The Schedule of Study Activities is located below in Table 2. Refer to the Instructions for Use (IFU) for device deployment techniques in Attachment C.

The treatment procedure must be completed in an office setting using standard aseptic techniques. Local anesthesia per the site's standard of care practice will be administered to the subjects in each study arm. Anesthesia techniques will be documented. Once the anesthesia has been administered the subject will be randomized into either the Sham Control Arm or the Latera Treatment Arm.

NOTE: Randomization will be facilitated using an electronically secure tablet computer that can be used in the exam room setting to access site-specific randomized treatment assignments in the EDC.

Optionally, an oral anxiolytic (e.g. Valium, Ativan or equivalent) and/or analgesic (e.g. Tylenol, or Tylenol with Hydrocodone or equivalent) may be offered to the subject prior to the procedure, per the investigator's discretion, consistent with local practice standards. Procedural medications will be recorded.

The below section includes a description of the activities occurring during the Latera Implant or Sham Control procedure:

1. Cephalexine or equivalent antibiotic may be administered to the subject before the procedure,

2. Clean the skin of the nose and the mucosal surface with an antiseptic solution (e.g. isopropyl alcohol, betadine or equivalent),
3. Examine nasal anatomy and mark the target trajectory for the Latera Implants with the aid of a sterile pen and sterile Latera Implant positioning guide per IFU **(Attachment C**).
4. Obtain photographs of planned implant target trajectory,
5. The following local anesthesia steps may be considered per site's standard of care procedures to ensure subject comfort during implant placement.
    a. SPRAY: Anesthetic (e.g. lidocaine or equivalent)
    b. TOPICAL: Few minutes after application of the spray, cotton balls or pledgets soaked in anesthetic (e.g. Tetracaine, 4% lidocaine or equivalent) may be placed in the nasal vestibule, ensuring contact with turbinate and floor of nose posteriorly, and to lateral nasal wall anteriorly).
    c. INFILTRATION:
        i. Anesthetic, such as Lidocaine with Epinephrine or mixture of Lidocaine/ Epinephrine mixed with Marcaine with Epinephrine, or the equivalent, may be injected locally.
        ii. The anesthesia may be injected to achieve an infraorbital block.
        iii. In addition, anesthesia may be injected along the proposed implantation track, starting at the alar rim and progressing to the supra-periosteal region of the maxilla. Additional injections into alar rim may also be considered.
    d. Wait approximately 10 minutes for anesthesia to be in full effect.
6. RANDOMIZATION: Subjects are randomized into the Sham Control Arm or the Latera Implant Treatment Arm, **after** anesthetic is delivered. Treatment assignment will remain blinded to the study subject.
7. In the event the subject is selected for the Latera Implant Arm, the implants (bilateral) will be delivered in a loaded delivery tool, using standard deployment technique per Spirox IFU (**Attachment C**). Only one Implant per side may be placed.
8. In the event the subject is selected for the Sham Control Arm, follow the exact same process for implant delivery per Spirox IFU (**Attachment C**), including pulling the alar rim back allowing insertion of the cannula of an unloaded (no implant) delivery tool. No implant is deployed in the Sham Control Arm.

The following data will be recorded on the subject's procedure CRF:

- Anesthesia regimen
- Photograph image with Trajectory Plan
- The Randomization Assignment
- All medication administered pre- and post-procedure.
- Implant placement or sham control logistical information
- Any adverse events or adverse device effects observed during this visit will be collected and documented.

Data collected for the Treatment Visit should be entered into the EDC no later than five (5) business days after the completion of procedure/visit.

IMPORTANT: Prior to discharge, provide the post-procedure reminder form and instructions for managing the post procedure recovery time. In addition, a course of antibiotics (e.g. Amoxicillin, Augmentin or equivalent) may be prescribed by the physician pursuant to local practice standards. Upon completion of the treatment visit, the subject will be scheduled for their next Follow-Up Visit.

Note: Space intentionally left blank.

Table 2. Schedule of Study Activities

Visits (± Windows)	**Screening/Baseline**	**Index Procedure - Day 0**	**Visit 3 - 7 ± 2 days**	**Visit 4 - 30 ± 7 days***	**Visit 5 - 90 ± 14 days***	**Cross-Over Screening** (for Sham Control Subjects only)	**Cross-Over Procedure** (for Sham Control Subjects only)	**Visit 6 – 6 month ± 14 days**	**Visit 7 – 12 months ± 30 days**	**Visit 8 – 18 months ± 30 days**	**Visit 9 – 24 months ± 30 days**	
Informed Consent	X					X						
Nasal Medical History & Exam	X											
Eligibility	X											
Lateral Wall Motion Video	X				X			X				
Turbinate Hypertrophy and Septum Assessment	X											
Nasal Obstruction Evaluation (NOSE)	X		X	X	X	X		X	X	X	X	
Sleep Assessments (ESS & PSQI)	X		X	X	X	X		X	X	X	X	
Photograph – Planning Images	X											
Pregnancy Test	X					X						
Nasal Breathing Assessment (VAS)	X		X	X	X	X		X	X	X	X	
Randomization		X										
Procedure Logistics		X					X					
Relevant Medications	X		X	X	X			X	X	X	X	
Adverse Events	X	X	X	X	X		X	X	X	X	X	
Note: *For Sham Control Subjects that cross-over after 90 day assessment for primary endpoint and meet stu eligibility for a Latera Implant, per the protocol, will have repeat 30 and 90 day visits, in addition to all the otl visits.												

5.3. Follow-Up Assessments

For subjects randomized to the Latera Implant arm, the follow-up evaluations will be at 7 days, 30 days, 3 months, 6 months, 12 months, 18 months, and 24 months post-procedure.

For subjects randomized to the Sham Control arm, the follow-up evaluation will be at 7 days, 30 days, and 3 months. After the 3-month follow-up evaluation, the subject will be eligible to cross over to the Latera Implant arm, if they continue to meet the study inclusion and exclusion criteria. If the subject is eligible to cross over to the Latera Treatment arm, an informed consent addendum will need to be presented to the subject and signed. If the Latera Implants are deployed, the follow-up schedule is restarted and occur at 30 days, 3 months, 6 months, 12 months, 18 months, and 24 months post-Latera Implant procedure. If the study subject does not meet the eligibility criteria or declined to continue participation, the subjects will be exited. See Section 6.2 for analysis implications.

The schedule of study activities (Table 2, page 28, above) specifies the assessments that will be completed at each follow up visit. Below are the descriptions of the PRO assessments and Lateral Wall Motion Video assessment:

Nasal Obstruction Symptom Evaluation (NOSE) scale

The Nasal Obstruction Symptom Evaluation (NOSE) Scale is a Patient-Reported Outcome (PRO) instrument that will be administered to capture subject perception of the degree of nasal airway patency.[17]

The NOSE scale is a validated instrument, developed by the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS), and has been used in several clinical trials. The scale is brief, easy to complete, and is an important tool for pre- and post-intervention evaluation of symptoms in subjects with nasal obstruction.

Subjects will be asked: "Since your last follow up visit, how much of a problem were the following conditions for you?" Specifically, subjects will be asked to rate their perceptions on the Likert scale with respect to the following characteristics:

- Nasal congestion or stuffiness
- Nasal blockage or obstruction
- Trouble breathing through my nose
- Trouble sleeping
- Unable to get enough air through my nose during exercise or exertion

Subjects will rate their responses using a Likert scale with response options 0, 1, 2, 3 or 4, as follows:

- Not a Problem
- Very Mild Problem
- Moderate problem
- Fairly Bad Problem
- Severe problem

The responses are rated along the continuum, with a rating of "0 – not a problem" indicating no problem breathing, with a completely free flow of air through the nasal airway; "1 – very mild problem", with

only slight obstruction in airflow; "2 – moderate problem", with mouth breathing considered easier; "3 – fairly bad problem," with considerable obstruction to airflow; and a rating of "4 – severe problem," with complete blockage and obstruction of the nasal passageway, where the subject cannot breathe through the nose and can only mouth breathe.

Nasal Breathing Assessment

A subject's perception of breathing cannot be quantitatively measured, but exists on a continuum from the subject perspective. The VAS is a PRO instrument that will be used to capture subjects' perception of their ability to breathe through the nose, allowing subjects to indicate the degree of breathing difficulty (or ease) they are currently experiencing.

Operationally, the VAS is a horizontal line, 100mm in length, anchored by word descriptors at each end, as illustrated in **Figure 3**. The subject will mark on the line the point that they feel represents their perception of their current state and the electronic PRO form will automatically calculate the score for VAS. The VAS score is determined by measuring in millimeters from the left end of the line to the point marked by the subject.

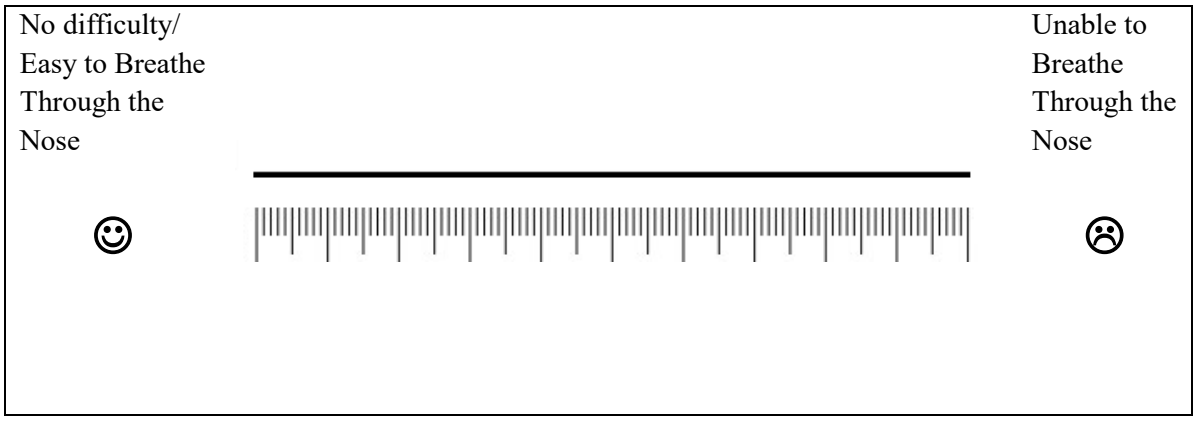

Figure 3: Visual Analog Scale. Left side represents 0 mm and right side represents 100 mm.

Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) is a widely-used PRO in the field of sleep medicine as a subjective measure of a patient's sleepiness.

The test is a list of eight situations that evaluate a subject's tendency to become sleepy on a scale of 0 (no chance of dozing), to 3 (high chance of dozing). The scale estimates whether the subject is experiencing excessive sleepiness that may possibly require medical attention.

Subjects will be asked: "How sleepy are you? How likely are you to doze off or fall asleep in the following situations?" They will be asked to rate their chances of dozing off, not just feeling tired and even if they have not done some of these things recently to try and determine how they would have affected them. For each situation, subjects will be asked to decide if they would have:

- No chance of dozing 0
- Slight chance of dozing 1
- Moderate change of dozing 2
- High chance of dozing 3

Using the above scale, subjects will write down the corresponding choice to the following situations:

- Sitting and reading
- Watching TV
- Sitting inactive in a public place (e.g. a theater or a meeting)
- As a passenger in a car for an hour without a break
- Lying down to rest in the afternoon when circumstances permit
- Sitting and talking to someone
- Sitting quietly after lunch without alcohol
- In a car, while stopped for a few minutes in traffic

The responses to the above situations is totaled for a final composite score.

Pittsburg Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a questionnaire used to assess sleep quality over the previous 1-month. The measure consists of 19 individual items (see CRF), creating 7 components that produce one total score. Component scores consist of subjective sleep quality, sleep latency (i.e., how long it takes to fall asleep), sleep duration, habitual sleep efficiency (i.e., the percentage of time in bed that one is asleep), sleep disturbances, use of sleeping medication, and daytime dysfunction.

Lateral Wall Motion Video Assessment

Video results from Endoscopy assessments will be captured and transferred to Spirox. The videos will be de-identified prior to transfer to an independent reviewer. The independent reviewer will make assessment of endoscopic lateral wall insufficiency score (1, 2 or 3).[19]

5.4. Retrievals and Re-Implantation

There is a low incidence of where the Latera Implant is removed, post-implant nasal manipulation by a patient. If this occurs, the Latera Implant may be re-implanted, within 30 days, of the removal at the discretion of the investigator, continuing the follow up schedule from the Index Procedure. An addendum to the Informed Consent is required to be reviewed and signed by subject. See Section 6.2 for analysis implications.

6. STATISTICS AND DATA ANALYSIS

This is a prospective, randomized, sham-controlled, single-blind, multi-center, post-market trial of the Latera Implant vs. Sham Control in subjects with nasal valve collapse due to or primarily due to insufficient cartilaginous support of the lateral nasal wall. The trial will enroll up to 150 subjects at up to 15 investigational sites in the US.

6.1. Hypothesis

The primary endpoint of the study is defined as the proportion of responders at 3 months following the index procedure. Responder is defined as a subject that has at least one (1) NOSE class improvement or at least 20% NOSE score reduction from baseline to 3 months post treatment.

The treatment (p_T) and control (p_C) will be compared using a 1-sided test for superiority of the following hypothesis:

$$H_0: \ p_T \leq p_C \text{ versus } H_A: \ p_T > p_C$$

6.2. Study Populations

Adult male and female patients presenting with symptomatic nasal valve collapse due to or primarily due to insufficient cartilaginous support of the lateral nasal wall will be enrolled, if they meet all eligibility criteria. The study will include up to 150 subjects enrolled at up to 15 investigational sites in the US. The maximum enrollment per site will be 20% of the total enrollment number therefore a 30-subject maximum per site. Initial site enrollment will be limited to 20-subjects and written permission from Sponsor will be required to enroll up to 30 subjects maximum.

The following populations will be analyzed in the study:

Intention-to-Treat (ITT) Population: The ITT analysis will be performed on all enrolled subjects in the study, irrespective of adherence with the entry criteria, treatment actually received, subsequent withdrawal, or deviation from the Clinical Investigational Plan.[20] Subjects who are enrolled but not randomized will not be included in the analytic datasets.

Modified Intention-to-Treat (mITT) Population: The mITT Population will comprise of ITT subjects who received anesthetic, regardless of whether they received the Latera Implant or underwent the Sham procedure. Subjects who are in the mITT population assigned to the Latera Implant Arm but who do not receive the device are followed for 3 months for safety-related endpoints and will be exited after 3-month follow-up assessments.

Per Protocol Population: The PP analysis will be performed on randomized subjects a) in the Sham Control Arm, and b) in the Latera Implant Arm who were treated and who had NOSE score assessments within the 3-month follow-up clinic visit window. The primary endpoint will be

evaluated on this population. Subjects will be analyzed according to the procedure actually received in the event of mis-randomization.

The point of enrollment into the study occurs when the subject signs the ICF and meets all eligibility criteria.

6.3. Unblinding and Crossover Subjects

All subjects will be un-blinded after the assessment is complete at the 3-month time point. If the subject is in the Sham Control group, a Latera implant may be implanted if they meet the eligibility criteria. Subjects who are un-blinded (within either treatment arm) prior to the 3-month time point will be excluded from the per protocol analysis dataset for primary and secondary analysis endpoints. However, data will continue to be recorded through the 24-month follow-up time point for these subjects.

Sham Control subjects may not receive a nasal implant prior to the 3-month primary endpoint assessment.

Cross-over subjects will have 2 additional visits as they will begin follow-up time points again once they have received the Latera Implant.

6.4. Sample Size

The primary analysis will be based on a 1-sided binomial test of proportions. Assuming a Sham Control response rate of 40% and a Latera Treatment response rate of 70% at month 3, a maximum sample size of 124 evaluable subjects is required for 90% power and preserving a 2.5% (one-sided) type I error rate. This study is designed as a group-sequential trial with 2 interim analyses and a final analysis. The stopping boundaries are derived using the Triangular Method [1], which is a special case of Unified Family (Power) boundaries. A shape parameter of 0.65 will be used, and both boundaries will be non-binding.

Interim analyses will occur when approximately 20 and 60 total subjects have been enrolled. The Latera response rate has been observed at approximately 85% in single-arm trials, and is likely to be slightly lower in a single blind setting. Thus, 70% is likely a conservative estimate. The placebo response rate observed in pain trials is approximately 30%, and may be even higher in a procedural setting, so 40% was selected for the control response rate used in the study design calculations.

Assuming up to a 10% drop out rate and a 10% potential retrieval rate, the sample size is adjusted up to 150 subjects will be enrolled to assure adequate sample size with 3 months follow up will be enrolled.

6.5. Missing Data

Every effort will be made to minimize the amount of missing data. Recognizing the difficulty of avoiding some missing data, however, data imputation methods with sensitivity imputation analyses will be pre-specified in the Statistical Analysis Plan. The robustness of the multiple imputation based sensitivity analyses for the primary outcome will be tested with a tipping point analysis encompassing all possible imputation outcomes.

6.6. Demographics and Baseline Characteristics

The baseline demographics and anatomic characteristics of the treatment groups will be presented with descriptive statistics.

6.7. Changes to Planned Analyses

All analyses will be detailed in the Statistical Analysis Plan (SAP). Any changes to the planned analyses will be documented as amendments to the SAP and in the study report.

6.8. Interim Analyses

There will be two planned interim analyses for this study (**Table 3**, below). The stopping boundaries are moderately aggressive for both effectiveness and futility to reduce the number of subjects enrolled if clear evidence of effectiveness or futility becomes apparent during the trial. When the design assumptions are correct (40% versus 70%), the chance that the trial will stop for effectiveness at the second interim analysis is about 1 in 3. However, if the Latera rate is 85% as seen in the single arm studies, the chance of stopping for effectiveness at the second interim analysis is better than 8 in 10. While all evaluable subjects enrolled at the time of the interim analysis would be followed through 3 months and included in the primary endpoint, an early termination at the second interim analysis could save 20-30% of the total sample size, depending on the enrollment rate.

Interim analyses will be carried out by an independent statistician and reviewed by the independent DMC. Details of the interim analysis plan and additional operational details will be found in the Statistical Analysis Plan and the DMC Charter.

Table 3. Planned analyses

Analysis	Evaluable (n)	Boundaries (p-value)		Cumulative Error Spending	
		Futility	Efficacy	Type II	Type I
Interim 1	22	0.7921	0.0005	0.0106	0.0005
Interim 2	60	0.2139	0.0090	0.0548	0.0093
Final	124	0.0194	0.0194	0.1000	0.0250

7. STUDY MANAGEMENT CONSIDERATIONS

7.1. Data Management: Collection of Clinical Data

The Sponsor and/or assigned designee will be responsible for the processing and quality control of the data. All other source data, source documents, CRFs, copies of protocols and protocol amendments, device accountability forms, correspondence, subject identification lists, informed consent forms, and other essential documents must also be retained for a period of at least 2 years.

No study document or image will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the Sponsor.

7.2. Protocol Amendments

Protocol amendments are the sole responsibility of the Sponsor. No changes from the final approved (signed) protocol will be initiated without the IRB's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The Principal Investigator will acknowledge the amendment by signing the Protocol Agreement.

7.3. Protocol Deviations

A protocol deviation is the non-adherence to or divergence from the protocol-specific study procedures. The following are all considered protocol deviations: inclusion of subjects outside the eligibility, visits outside the scheduled visit windows, missed data collection at visits, improper or lack of consent, lack of IRB approval, lack of adherence to randomization and procedural methods. A protocol deviation undertaken to protect the life or physical well-being of the patient in an emergency is a special circumstance that must be reported to the Sponsor and the reviewing IRB within 5 working days. No other type of prospective protocol deviation is permitted without prior written approval from the study Sponsor. A record of all protocol deviations will be maintained and reviewed throughout the conduct of the study. The Sponsor will address deviations and take appropriate corresponding and corrective action. Continued non-compliance with the study protocol may lead to termination of the Investigator's participation in the study.

7.4. Information to Study Personnel

The Investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting the study procedures and during the study (e.g., when new staff become involved). The Investigator must ensure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities.

The Sponsor or its designee is responsible for explaining the CIP to all study staff, including the Investigator, and for ensuring their compliance with the protocol throughout the study. Additional information will be made available during the study when new staff become involved in the study, and as otherwise agreed upon with either the Investigator or the monitor.

8. RISK-BENEFIT ANALYSIS

8.1. Risks to the Subjects

The list below described the general types of potential risks to the study subjects.

Adverse Events
Infection
Inflammation
Pain or discomfort
Serous wound drainage
Hematoma
Ecchymosis
Extrusion
Retrieval
Foreign body reaction
Foreign body sensation
Device Fracture
Device Malposition or Migration
Device Palpable
Skin Irritation
Allergic reaction to device
Allergic reaction to medications from procedure or follow up
Allergic reaction to any study related medications
Hematoma*, general (such as cannula insertion, delivery of anesthetics, manipulation of nose during procedure, etc.)
Perceptible cosmetic changes
Respiratory / sinus infection or rhinorrhea
Continued or worsened breathing symptoms
Scarring
Firmness, swelling, redness
Decreased sense of smell

**Includes hematoma from cannula insertion, delivery of anesthetics, manipulation of nose during procedure)*

There are other health risks and discomforts associated with the testing that the subjects will undergo before and after their procedure, including but not limited to pain and bruising at the implant pierce point site or areas of anesthetic injections.

For subjects in the Sham Control Group, the use of anesthetic and insertion of the cannula imparts the same risks except for those directly attributable to an implant, without the potential benefit of the treatment.

8.2. Risk Mitigation

The subject risks for participation in the Lateral RCT Study are mitigated through device design, protocol development, and study conduct methods.

The Latera Implant is designed and indicated for use to support of the lateral nasal cartilages. The device will be used as directed in the FDA Cleared Indications for Use. The device has been commercially available in the US for over a year and used in three (3) clinical studies with consistent high efficacy and low complication rates, as described previously.

The Latera RCT is a Group Sequential Study. This is an adaptive study design that allows for interim data review for potentially halting enrollment for early demonstration of success or for futility (inability to reach the primary objectives). Additionally, although the treatment assignment is blinded to the study subjects, an independent Data Monitoring Committee will be reviewing the data at pre-determined interim analyses to determine if the study is operationally sound or meets pre-determined success criteria, limiting randomization to no more subjects than are required to meet the primary objectives.

Risk mitigation through study operations include the selection of experienced investigators with the appropriate research infrastructure, providing training and data monitoring to limit protocol deviations and operational execution. The study includes IRB review and approval of the study protocol, informed consents for appropriate risk disclosure, and the patient brochure and study poster to assure the study meets clinical research standards and regulatory requirements.

The measures listed above will be implemented in this study to mitigate potential risks to the study subjects.

8.3. Benefit to Subjects

The Latera implant has been successfully deployed in over 7,000 patients in the past year, including over 300 in a research setting. This has enabled a high proportion to have a reduction in nasal obstruction symptoms with a low complication rate. This benefit may be afforded to the subjects that participate in this study. Subjects may also benefit from the additional monitoring and follow-up evaluations mandated by this study protocol. The Sham Control subjects have the opportunity to cross-over, if these symptoms persist and they remain eligible for the Latera Implant in this study. Those subjects will have the same potential benefit at that point as those randomized to the Latera Implant arm.

8.4. Study Justification

Nasal valve collapse (NVC) due to lateral wall weakness is significant contributor to NAO. The Latera Implant offers a minimally invasive treatment to support the lateral cartilages. The Latera RCT provides the opportunity to rigorously assess the impact of the implant itself in alleviating the symptoms of NVC due to lateral nasal wall weakness. Patients with other primary contributors to NAO will not be included such as septal conditions or turbinate hypertrophy since these potentially mask the full impact of the Latera Implant. Three (3) prospective, single-arm studies have continued to show the high rate of

reduction in nasal obstruction and low complications rates as well as support the study design for superiority.

9. ASSESSMENTS OF SAFETY

9.1. Defining Adverse Events

An adverse event is an untoward medical occurrence or exacerbation of an existing medical condition subsequent to the experimental therapy. Adverse events are rated in several ways:

- Severity (mild, moderate, severe)
  - *Mild*: No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
  - *Moderate:* Some limitation of usual activities or specific therapy is required.
  - *Severe*: Inability to carry out usual activities, hospitalization, emergency treatment, life threatening events, or death.
- Anticipated (anticipated, unanticipated)
- Device and procedure relationships (unrelated, possibly related, definitely related, or relationship unknown)
  - *Unrelated:* The clinical event is completely independent of study procedure/study device and/or evidence exists that the event is definitely related to another etiology.
  - *Possibly related:* The clinical event occurs within a reasonable time sequence to study procedure/study device and there is some evidence to "possibly" suggest a causal relationship. However, the influence of other factors such as underlying disease, concomitant medications, or concurrent treatment may have contributed to the event.
  - *Definitely related:* The clinical event occurs in a plausible time relationship to study procedure/study device and cannot be explained by any concurrent disease or other devices, drugs or chemicals.
  - *Relationship unknown:* The relationship to the study procedure/study device is not known.

Adverse events will be categorized as either serious or non-serious. A Serious Adverse Event (SAE) is an event that meets at least one of the following:

- Is fatal
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Results in permanent impairment of a body function or permanent damage to a body structure
- Results in hospitalization or prolongs a hospitalization
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

An adverse device effect (ADE) is any unwanted and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device and any event that is a result of user error. A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of the consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. An unanticipated adverse device effect (UADE) is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects."

Section 8.1 includes a list of possible adverse events associated with nasal interventions. These events are considered reportable at all time points throughout the trial and require submission to the Sponsor within 1 business day of receipt of information. It is recognized that adverse events may not be reported by the study subject until their follow up visits due to the low risk nature of the potential events.

9.2. Reporting of Adverse Events

In addition to events considered in the primary efficacy and primary safety analyses, all device- and/or procedure-related adverse events must be captured on the Adverse Event Case Report Form. The report should include, wherever possible, severity, duration, outcome, and the Investigator's written medical judgment as to the relationship of the adverse event to the study device, procedure, or underlying disease (i.e., not related, possibly related, definitely related, or relationship unknown).

All SAEs must be reported to the Sponsor or its Contract Research Organization (CRO) within 1 business day of the Investigator's knowledge of the event. The event is reported in the electronic data capture system. IRB notification of the adverse event may also be required, depending on the conditions of approval or requirements of the respective committee. Any unanticipated adverse device effects must be reported to the Sponsor/CRO within 1 business day from when the Investigator first learns of it.

Non-serious reportable adverse events are to be submitted via the electronic data capture system, also, within 1 business day of learning about the event. Certain reportable events may require adjudication; therefore, supporting documentation must be sent to the Sponsor/CRO.

9.3. Medical Monitor

An independent Medical Monitor, a member of the Contract Research Organization, will be charged with evaluating all adverse events, device deficiencies (including user errors), device malfunctions, and other events that arise during the trial. Each event will be assessed for its relatedness to the procedure or to the device, classified as to its seriousness and whether it is an unanticipated adverse device effect. All adverse events will be MedDRA coded to the most recent MedDRA version at the time of the start of the trial. In the event of a conflict between the site and the Medical Monitor classifications, those of the Medical Monitor will prevail.

9.4. Data Monitoring Committee

The Data Monitoring Committee (DMC) will be used in this study. It is the responsibility of the DMC to assess safety-related issues by reviewing data in aggregate and to assess the results of the interim analyses for operational study execution and early assessment of superiority or futility. The DMC for this trial will also assess efficacy with respect to the group-sequential design (§6.8, page 34, above). The DMC membership is represented from the key medical disciplines involved with nasal interventions, and may include an external biostatistician. None of the members is directly involved in other aspects of the clinical trial. The Sponsor has contracted a Clinical Research Organization to organize, facilitate, and document meetings for the DMC for this trial. The DMC will meet regularly and as necessary, guided by a DMC Charter.

10. STUDY ADMINISTRATION

10.1. Site Initiation and Study Monitoring

A Site Initiation Visit (SIV) will be conducted by the Sponsor or a designee, for example, its CRO, to ensure that all study supplies are present, to ensure proper training of the Investigator and study staff members in study-specific procedures, to ensure site readiness is complete prior to enrollment of the first study subject at each site.

Interim monitoring visits will be conducted by Spirox Inc. personnel or a designee to ensure compliance with the protocol, source data verification and other written instructions and regulatory guidelines.

10.2. Study Termination

Spirox Inc. and applicable regulatory authorities have the right to terminate the study or a particular study site at any time. Situations that could warrant study termination include, but are not limited to:

a) Increased incidence of adverse experiences and/or the severity of such, suggestive of a potential, device-related health hazard
b) Insufficient subject enrollment
c) Recurrent protocol non-compliance, violations or deviations
d) Inaccurate, incomplete, and/or untimely data recording (>5 business days) on a recurrent basis
e) Lack of cooperation with monitoring visits (e.g., failure to adequately prepare for visits, address action items from one visit to the next, or provide access to medical records)

10.3. Data Handling and Recordkeeping

Completing, Signing and Archiving Case Report Forms

The Investigator must keep a separate subject identification list showing enrollment numbers, names, and dates of birth to allow unambiguous identification of each subject included in the study. It is

recommended a note be made in the medical record that the subject is participating in a clinical research study.

The required data will be recorded on the Case Report Forms (CRFs). Clinical study data will be collected using electronic data capture (EDC). A web-based EDC database will be used to record and manage study data. CRF completion guidelines, the instructions for electronic data-entry, will be developed in conjunction with the sponsor, the CRO, and/or the EDC vendor. An embedded audit trail will capture the date, time and user making updates and changes to the electronic data.

A mechanism in the EDC will allow the Investigator to approve the data electronically. Additionally, study worksheets that become source documentation will require Investigator review and approval as indicated by signatures and dates.

Because it is important to have proper data collection in a timely manner, within 5 business days, the Investigator/Study Coordinator shall complete the CRFs. When the monitor requests additional data or clarification of data for the CRF, the request should be answered satisfactorily before the next monitoring visit.

Data Management and Archiving

The Sponsor will be responsible for the processing and quality control of the data. Source data for safety will be retained for at least 2 years after the termination/completion of the study. All other source data, eCRFs, copies of protocols and protocol amendments, device accountability forms, correspondence, subject identification lists, informed consent forms, and other essential documents must be retained for a period of at least 2 years after the final data lock.

No study document or image will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the Sponsor.

11. ETHICS

11.1. Informed Consent

Written informed consent must be obtained for each subject before any study-specific procedures or assessments are done and, specifically, prior to the subject being treated with the Latera implant. The methods used in the Latera RCT will include an electronic informed consent (eIC) and traditional paper. The Investigator or designee, trained on the protocol, will explain the nature, scope, anticipated benefits, and potential risks involved in the study. Written informed consent will be obtained after the aims, methods, anticipated benefits, and potential risks are explained.

All subjects may receive a stipend for their time and to cover travel costs for participation in the Latera RCT. The stipend and schedule must be approved by the investigational site's recognized IRB (central

IRB or local). The plans for the study is as follows: After completion the following study visits, subjects will receive a $50.00 prepaid debit card at end of the following visits: Baseline visit, Treatment, one (1) week, one (1), three (3), and six (6) month; and they will receive a $100.00 prepaid debit card for twelve (12), eighteen (18) and twenty-four (24) month study visits. The total compensation to each subject will be $600.00 for completion of all of the study visits for the Latera Implant group of the study or it will be $750.00 for completion of all the study visits for the Sham treatment group of the study.

If required by institutional policy, informed consent will be obtained prior to review of Baseline and Screening data. A Screening Consent Form may also be available to secure permission from the subject for reviewing prospective subject information (if requested/required by site or IRB policy) prior to the subject agreeing to participate in the trial and signing the study-specific Informed Consent Form.

Consenting addendums will be used to confirm continuing patient consent in the cases of re-implanting procedures and the cross-over implant procedures.

The subject's willingness to participate in the study will be documented in writing in a study-specific Informed Consent Form, which will be signed and dated by the subject or Legally Authorized Representative. The Investigator will keep the original consent form and a copy will be given to the subject. It will be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

11.2. Institutional Review Board (IRB)

This study must be approved by an appropriate IRB at each study site in accordance with 21 CFR Part 56.

The Sponsor must receive a copy of the IRB approval letter (or equivalent documentation) for the study protocol and Informed Consent Form before the study can be started at that site or devices shipped to that Investigator. The Sponsor will provide confirmation that sites may initiate consenting and enrollment after review of the approved IRB documents.

The IRB and Sponsor must approve any significant changes or amendments to the protocol as well as a change of Principal Investigator. Documentation of the IRB approval must be provided to the Sponsor. Records of all study review and approval documents must be maintained by the Investigator in the Regulatory Binder and are subject to inspection by the Sponsor or regulatory authority during or after completion of the study. Serious Adverse Events must also be reported to the IRB, as per their reporting requirements, and Sponsor (reference Section 10 for reporting instructions).

The Investigator must notify the IRB, as per their reporting guidelines, and the Sponsor when he or she deviates from the protocol. The Sponsor must be notified of all relevant action taken by the IRB and must receive a copy of all study-related correspondence between the Investigator and the IRB.

The IRB must receive notification of the completion of the study and final report within 3 months of study completion or termination. A copy of these reports must be provided to the Sponsor. The Investigator must maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

12. INVESTIGATORS AND RESPONSIBILITIES

12.1. Participating Institutions and Investigators

Study sites and Investigators will be selected based on a variety of factors including, but not limited to, experience with clinical research trials, proficiency with nasal interventional techniques including Latera Implant experience, access to required facilities and equipment, sufficient and adequately trained clinical and research personnel, and availability of potential subjects.

12.2. Agreements

All Principal Investigators and their Sub-Investigators or Co-Investigators must sign an Investigator Agreement. Spirox must receive a copy of the signed Investigator Agreements before the study may be started at that institution. Any Investigators joining the study after the site has been initiated may not receive devices or participate until study training occurs and is documented and an agreement is signed and received by the Sponsor.

12.3. Investigator Responsibilities

Investigator responsibilities include, but are not limited to, the following:

a.) Conducting the study in accordance with this investigational plan, signed agreement, and applicable regulations protecting the rights and safety of study subjects
b.) Informing all subjects that the study design includes randomization and has a sham control arm, and ensuring that the requirements relating to obtaining informed consent and IRB approval are met
c.) Ensuring that informed consent is obtained for each study subject in accordance with applicable regulations (e.g., ISO 14155-1, 21 CFR Part 50)
d.) Ensuring that IRB approval is secured prior to starting the study and ensuring continuing review and approval as required throughout the investigation
e.) Ensuring all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments
f.) Maintaining adequate and accurate records and ensuring those records are available for inspection at any time
g.) Ensuring that conducting the study does not give rise to conflict of interest (financial disclosure is required)
h.) Controlling of any study devices at their institution

13. DATA SECURITY AND SCIENTIFIC INTEGRITY

13.1. Access to Data

The Sponsor, auditors, and health authority inspectors (or their agents) will be given access to source data and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

The Investigator must maintain, at all times, the primary records (source documentations) of each subject's data. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, device inventory, device label records, and CRFs that are used as the source (source worksheets).

The Investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject. All study-related documents must be kept until notification by Spirox, Inc. at the study closeout visit.

13.2. Security and Confidentiality

Each Investigator must ensure that the privacy of all subjects, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the Sponsor, subjects will not be identified by their names, but by an identification code (i.e., subject number). If identifying information is transferred to the Sponsor, the Sponsor will de-identify or anonymize the information to the extent possible. Information will be maintained in a secure manner.

Personal medical information may be reviewed to verifying data recorded in the CRFs. The monitor may perform source data verification on behalf of the Sponsor or regulatory authorities. Personal medical information will always be treated as confidential.

Electronic data will only be accessible to authorized personnel using a unique user identifier and password. Access to electronic study data will be provided to research personnel upon completion of training. Read and write access will be provided to investigational sites but only for information and subject data at their own site. The CRO will have read-only access and can post queries for potential data-related discrepancies.

14. PUBLICATIONS

Latera RCT will be registered in the ClinicalTrials.gov website by Spirox, as the study sponsor. Spirox is committed to complying with applicable regulatory requirements for study registration and is committed to supporting dissemination of study results, as described in the protocol (protocol derived outcomes), in peer-reviewed medical journals, regardless of outcome.

At the completion of the primary analyses, it is anticipated that the Principal Investigators will prepare and submit a multi-center manuscript for publication in a reputable scientific journal. Additional authorship will be based on contribution to the conduct of the study and the target journal requirements. Further analyses, beyond those presented in the initial multi-center publication may be proposed to the Sponsor for secondary manuscripts and abstracts. Investigators are encouraged to submit requests to the sponsor for data sets to support further investigations. The Sponsor will respond in a timely manner for the data sets and reviews for publications.

Before submission for publication or presentation of data from the Latera RCT, the author(s) will provide them to Spirox at least 30 days in ahead of submission or deadline. Spirox reserves the right to review and comment on draft abstracts, manuscripts, presentations and other communications by investigators regarding Spirox-sponsored clinical studies, prior to their submission or public disclosure, to protect intellectual property and confidential information.

15. ABBREVIATIONS

Abbreviations contained throughout this document are listed in **Table 4**, below.

Table 4. Abbreviations

AE	Adverse Event
ADE	Adverse Device Effect
ASC	Ambulatory Surgery Center
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRF	Case Report Form – Paper or electronic
CRO	Contract Research Organization
EDC	Electronic Data Capture
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice, including ICH E6
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICF	Informed Consent Form
IFU	Instructions for Use

IRB	Investigational Review Board
ISO	International Organization for Standardization
LWI	Lateral Wall Insufficiency
MedDRA	Medical Dictionary for Regulatory Activities
NAO	Nasal Airway Obstruction
NSR	Non-significant Risk
NOSE	Nasal Obstruction Symptom Evaluation Instrument
NVC	Nasal Valve Collapse
OSA	Obstructive Sleep Apnea
PRO	Patient Reported Outcome
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
QSR	21CFR Part 820, Quality System Regulation
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
US	United States
VAS	Visual Analog Scale

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ATTACHMENT A. PROTOCOL APPROVAL PAGE

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Signed: _____ Date: 17 April 2018

Elisa Hebb
Vice President, Clinical and Regulatory Affairs, Spirox Inc.

Signed: _____ Date: April 17, 2018

Don Gonzales MD
Chief Medical Office, Spirox Inc.

ATTACHMENT B. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; 35th World Medical Assembly, Venice, Italy, October 1983; and the 41st World Medical Assembly, Hong Kong, September 1989.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Assembly 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."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures, and the understanding of the aetiology and pathogenesis of disease.

In current medical practice, most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research, a fundamental distinction must be recognized between medical research, in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special 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.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that, the standards, as drafted, are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles, and should be based on adequately performed laboratory and animal experimentation, and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol, which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country, in which the research experiment is performed.

3. Biomedical 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 his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out, unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks, in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, and to minimize the impact of the study on the subject's physical and mental integrity, and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects, unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation, if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation, not in accordance with the principles laid down in this Declaration, should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study, and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study, and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious, if the subject is in a dependent relationship to him or her, or may consent under duress. In that case, the informed consent should be obtained by a physician, who is not engaged in the investigation, and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject, in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved, and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Clinical Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if, in his or her judgment, it offers hope of saving life, reestablishing health, or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient --including those of a control group, if any-- should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I.2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person, on whom biomedical research is being carried out.

2. The subjects should be volunteers --either healthy persons, or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research, if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

ATTACHMENT C. INFORMED CONSENT FORM

ATTACHMENT D. LATERA INSTRUCTIONS FOR USE

ATTACHMENT E. FINANCIAL DISCLOSURE FORM

ATTACHMENT F. CASE REPORT FORMS AND PATIENT REPORTED OUTCOMES

ATTACHMENT G. PATIENT AND SITE BROCHURE