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SPI-CP-302

Protocol Title:
Spirox Latera™ Implant support of lateral nasal wall cartilage (LATERAL-OFFICE) study

Version Number: v 3 . 0

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Sponsor:

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LIST OF 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
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
IRB	Investigational Review Board
ISO	International Organization for Standardization
LWI	Lateral Wall Insufficiency
MAC	Managed Anesthesia Care
NAO	Nasal Airway Obstruction
NSR	Non-significant Risk
NOSE	Nasal Obstruction Symptom Evaluation
NVC	Nasal Valve Collapse
OHRP	Office for Human Research Protections
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
UP	Unanticipated Problem
US	United States
VAS	Visual Analog Scales

STATEMENT OF COMPLIANCE

I have received and reviewed this protocol. The trial will be carried out in accordance with this protocol and Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, and 21 CFR Part 56, and 21 CFR Part 812.2 (b)
- International Conference on Harmonisation (ICH) Good Clinical Practice E6
- ISO 14155:2011 Clinical investigation of medical devices for human subjects - GCP

All key personnel (all individuals responsible in the conduct of this trial) have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

_____

Investigator's Printed/Typed Name

_____

Investigator's Signature Date

PROTOCOL SUMMARY

Title: Spirox Latera™ Implant support of lateral nasal wall cartilage (LATERAL-OFFICE) study

Design: A prospective, multi-center, non-randomized, single arm, controlled study

Objectives: To obtain outcomes data in subjects with severe to extreme class NOSE scores undergoing placement of the Spirox Latera Implant with or without concurrent turbinate reduction procedures in an office setting.

Eligibility Criteria Reference Sections 5.1 and 5.2

Primary Endpoints: *Primary Efficacy Endpoint:* Proportion of treatment responders at 6 months post procedure.

Responder is defined as a subject that has at least one (1) NOSE class improvement or at least 20% NOSE score reduction

Primary Safety Endpoint: Nasal procedure and Latera™ device-related adverse events through 6 months

Secondary Endpoints:

1. Proportion of treatment responders at 1, 3, 12, 18 and 24 months post procedure.
2. Change in nasal airway obstruction from baseline to 1, 3, 6, 12, 18 and 24 months as reported by subjects on the VAS scale.
3. Subject satisfaction questionnaire at 6 months.
4. Procedure and device-related adverse events though 24 months.

Exploratory endpoints: Reference Section 4.2.3.

Population: Up to 250 subjects will be enrolled (includes up to 80 training subjects). At least 50 subjects will have stand-alone Latera Implant procedure.

Number of Sites: Approximately 25 sites in the U.S.

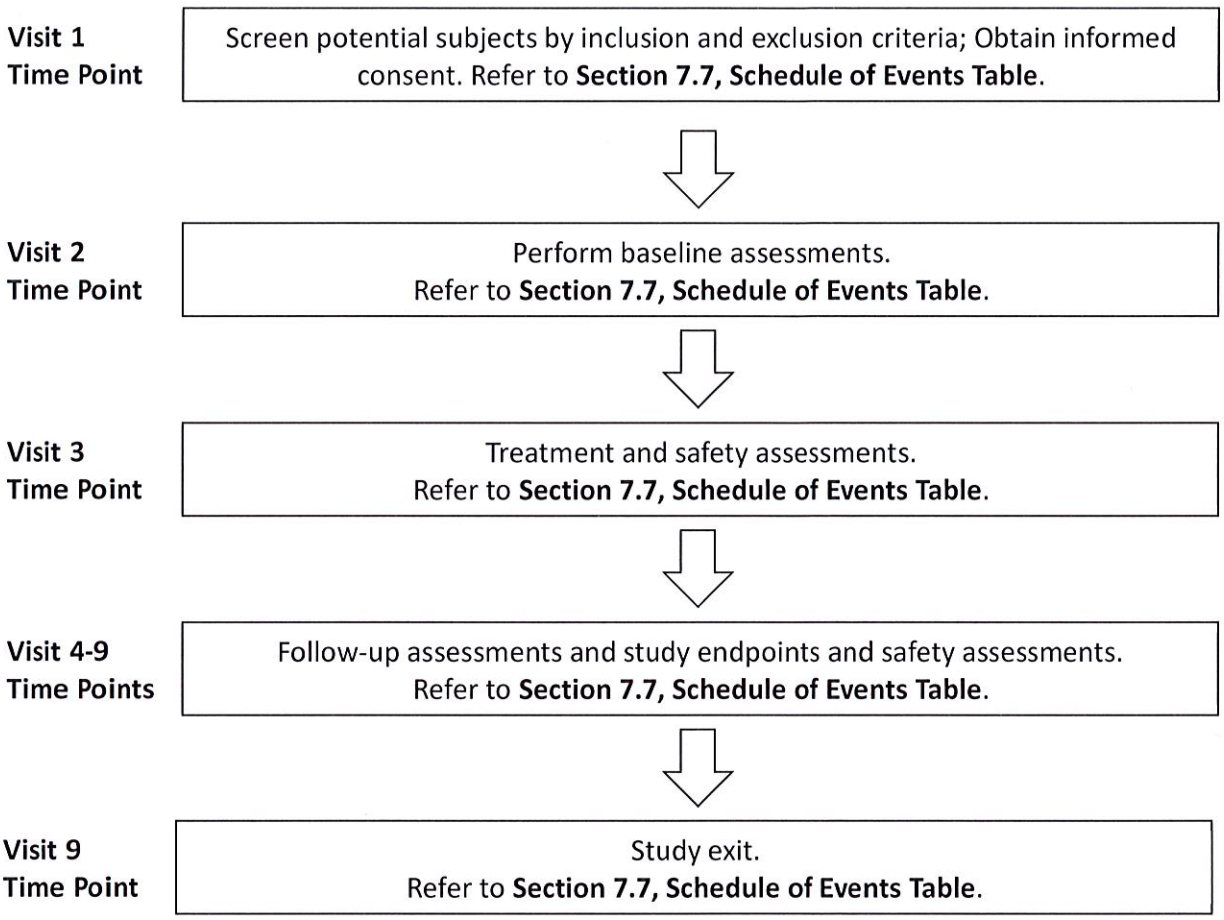
Description of Device: The Latera™ Absorbable Nasal Implant and Delivery Device includes an absorbable implant designed to provide internal support of the upper and lower lateral nasal cartilages. The Implant absorbs over a period of approximately 18 months. The absorbable Implant is comprised of a 70:30 blend of poly(L-lactide) and poly(D-lactide). The Implant is introduced through a trans-mucosal insertion technique using a delivery device. The Implant consists of a ribbed cylindrical structure which employs a forked end to facilitate anchoring within the target tissue. The geometry of the forked end is flexible, and collapses to fit within the 16-gauge cannula portion of the delivery tool.

Study Duration: Approximately 36 months from when enrollment begins to completion of data analyses.

Participant Duration: Enrolled subjects will be followed for 24 months post-procedure

Regulatory Status: This study is a post-market evaluation of a 510(k) cleared, non-significant risk, medical device in commercial distribution, used according to FDA cleared indications for use.

SCHEMATIC OF STUDY DESIGN



STUDY PROTOCOL

1. KEY ROLES

The following list of persons, companies, and/or groups serve in key roles in the conduct or oversight of the trial:

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2. INTRODUCTION: BACKGROUND INFORMATION AND STUDY RATIONALE

2.1. BACKGROUND INFORMATION

Nasal airway obstruction can be caused by several independent or concomitant factors including septal deviation, enlarged turbinates and 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]. As defined by the Hagen–Poiseuille law, the flow through a tube is proportional to the 4th power of the radius of the tube and inversely proportional to the pressure difference across the tube. Although more complex models would be required to account for turbulence and other factors, it is clear that even a small decrease in the valve area can contribute to nasal obstruction. Common causes of NVC are prior rhinoplasty, aging, nasal trauma and congenital abnormalities that weaken the nasal cartilage, leading to a lateral wall insufficiency (LWI)[3,4].

Therapies to correct NVC include invasive surgical procedures and non-surgical solutions to temporarily dilate the nasal valve, such as Breathe Right® 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 U.S. FDA and is currently in commercial distribution. The device will be used according to the cleared indications for use in this study. This non-significant risk, post-market study seeks to obtain outcomes data in subjects with severe to extreme[17] severity class NOSE scores (≥ 55), undergoing placement of Spirox Latera Absorbable Nasal Implant with or without concurrent turbinate reduction procedures in an office setting.

2.2. PRIOR INVESTIGATIONS

A prior study of this device was performed in the setting of an EC approved protocol in Germany. The study was conducted at three institutions under the oversight of Co-Principal Investigators, Professor Alexander Berghaus, MD and Marion San Nicolo, MD in Munchen, Germany. This prior first in man investigation evaluated the safety and performance of the Spirox device and its ability to support upper and lower lateral cartilage in subjects with nasal valve collapse as primary contributor to nasal airway obstruction (NAO) under general or local anesthesia. A brief summary of this prior investigation follows.

Fourteen (14) cases were performed in an operating suite under general anesthesia and sixteen (16) cases were performed in a clinic-based setting under local anesthesia. A total of fifty-six Implants were placed in thirty subjects. Subjects with a Nasal Obstruction Symptom Evaluation (NOSE) scale score ≥ 55 and Nasal Valve Collapse as primary contributor to NAO were eligible. Follow-up visits occurred at week 1 and months 1, 3, 6, 12 and 18 post procedure. These visits included documentation of medical history, physical exam, NOSE score and digital photography. The NOSE scale is a validated as a Quality of Life (QOL) instrument[18]. It uses a 20-point scale to capture severity of breathing symptoms, with higher scores indicating more severe symptoms than lower scores. The results are converted to 100-point scale by multiplying the total score by five.

There was a total of five (5) device-related adverse events reported in four (4) subjects. These events included 1 case of hematoma, 1 case of inflammation, and 3 Implant retrievals. All events resolved with no clinical sequelae. Investigators concluded that the 3 Implant retrievals were the result of suboptimal implantation methods or possible significant patient lateral wall manipulation during the first post-operative week and were not caused by adverse physiologic tissue rejection or infection. The Implant placement procedure was revised during the course of the study to address suboptimal implantation techniques and no further retrieval events occurred.

To date, all follow up visits through 18 months have been completed; 15 out of 30 subjects completed 18 months of follow up. Three subjects have had other nasal surgery procedures and consequently exited the study; two subjects after the 12 month visit and one subject after the 18 month visit.

A longitudinal summary of NOSE score is provided in the table below and these results demonstrate significant improvements over baseline for all time points measured.

		Score	Change from baseline			% Change from baseline		
Visit	N	Mean (SD)	Mean (SD)	LS Mean (95% CI)	p-value	Mean (SD)	LS Mean (95% CI)	p-value
1 Week	30	24.2 (16.14)	-52.5 (22.77)	-52.7 (-58.83, -46.55)	<.001	-67.2 (21.34)	-67.2 (-74.98, -59.51)	<.001
1 Month	30	27.0 (23.95)	-49.7 (25.56)	-49.9 (-58.79, -40.93)	<.001	-64.8 (29.09)	-64.9 (-75.92, -53.86)	<.001
3 Months	29	28.4 (26.90)	-48.4 (27.84)	-47.9 (-57.85, -37.96)	<.001	-63.4 (34.45)	-62.7 (-75.70, -49.66)	<.001
6 Months	30	33.3 (29.69)	-43.3 (31.28)	-43.5 (-54.61, -32.44)	<.001	-56.2 (37.85)	-56.3 (-70.46, -42.07)	<.001
12 Months	29	35.2 (29.17)	-40.9 (31.23)	-39.7 (-51.22, -28.11)	<.001	-53.1 (40.64)	-51.6 (-67.07, -36.12)	<.001
18 Months	15	38.0 (33.32)	-41.7 (36.24)	-40.7 (-55.01, -26.30)	<.001	-51.3 (41.76)	-52.2 (-70.59, -33.87)	<.001

This first in man study demonstrated the safety and effectiveness of the absorbable Implant to provide lateral cartilage support in patients with NVC as primary contributor to NAO.

2.3. POTENTIAL RISKS AND BENEFITS

2.3.1. NON-SIGNIFICANT RISK RATIONALE

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.

See Appendix II for additional information supporting the rationale for a Non-Significant Risk determination.

2.3.2. KNOWN POTENTIAL RISKS

In patients with nasal airway obstruction, three factors may influence a decrease in the cross-sectional area of the nasal passage: (1) deviated septum, (2) enlarged turbinates, and (3) collapsed lateral wall. If all three etiologies are present, the surgeon would offer a treatment that would address all three. Thus, the subjects may undergo Implant placement in conjunction with septoplasty and/or inferior turbinate reduction procedures.

Both septoplasty and turbinectomy procedures are standards of care for the treatment of nasal airway obstruction. In the US alone, there are at least 340,000 of these procedures completed each year[19]. The frequency of peri-operative adverse events is low, with an overall admittance rate of hospitalization of 0.85%.

While septoplasty in combination with turbinate reduction procedures are most commonly performed in the operating room setting under general anesthesia, turbinate procedures can be conducted in an in-office setting. In this study, subjects may receive the Latera implant(s) in a stand-alone procedure or in combination with a turbinate reduction procedure. Possible risks related to these procedures are described below.

Turbinate reduction procedure risks may include:

- Mild-to-moderate edema with subsequent nasal obstruction and thick mucus formation
- If mucosal erosion is present, the risk of postoperative bleeding and adherent crust formation increases
- Scar tissue (synechiae) may form between the turbinate and the septum
- Bleeding requiring further intervention
- Empty nose syndrome

The following complication rates have been reported after turbinate reduction:

- Synechiae rates up to 36%[20].

Latera™ implant procedure risks may include:

- Inflammatory foreign body reaction, foreign body sensation, pain or discomfort, infection, and extrusion
- Excessive activity, trauma, or loading may lead to bending, fracture, loosening, and/or migration of the Implant

- Implants placed near the skin surface may be palpable or cause skin irritation
- Temporary hematoma from cannula insertion
- Implant retrieval, defined as surgeon or subject initiated removal of implant not associated with body rejection of implant
- Unintended perforation of the skin

Risks related to the Latera Implant will be mitigated throughout the course of the study by investigator training, study monitoring and follow up evaluations. The training related to device placement will be provided to the investigators by the sponsor in a clinically relevant model prior to device use in clinic. In addition, prior to initiation of enrollment, investigators will have completed a number of commercial cases.

Monitoring and follow up will ensure that adverse events are being reported in a timely manner and shared with the investigators and members of the research team. Corrective action will be immediately taken if untoward trends are observed with a particular investigator.

2.3.3. KNOWN POTENTIAL BENEFITS

The Latera™ Absorbable Nasal Implant is indicated to support upper and lower lateral nasal cartilage. The prior investigation described in Section 2.2, demonstrated that the device reduced nasal obstruction symptoms by 53.1 % at 12 months in patients with nasal valve collapse as a primary contributor to NAO (no septal or turbinate treatment). For subjects requiring lateral cartilage support that also have enlarged turbinates, it is expected that the Latera Implant may provide additional benefit as part of the overall treatment to alleviate NAO. In addition, subjects may benefit from the additional clinical monitoring and follow-up evaluations required by this study protocol.

3. OBJECTIVES AND PURPOSE

The objective of the LATERAL-OFFICE study is to obtain outcomes data in subjects with severe to extreme[17] class NOSE scores undergoing placement of the Spirox Latera Implant with or without concurrent turbinate reduction procedures in an office setting.

4. STUDY DESIGN AND ENDPOINTS

4.1. DESCRIPTION OF THE STUDY DESIGN

This is a prospective, multi-center, non-randomized, single arm, controlled study. It is a post-market evaluation of a 510(k) cleared, non-significant risk medical device in commercial distribution, used according to FDA cleared indications for use. Each subject will serve as their own control.

4.2. STUDY ENDPOINTS

4.2.1. PRIMARY ENDPOINTS

Primary Efficacy Endpoint: Proportion of treatment responders at 6 months post procedure.

- *A responder is defined as a subject that has at least 1 NOSE class improvement or at least 20% NOSE score reduction.*

Primary Safety Endpoint: Nasal procedure and Latera device-related adverse events through 6 months.

4.2.2. SECONDARY ENDPOINTS

1. Proportion of treatment responders at 1, 3 12, 18 and 24 months post procedure.
2. Change in nasal airway obstruction from baseline to 1, 3, 6, 12, 18 and 24 months as reported by subjects on the VAS scale.
3. Subject satisfaction questionnaire at 6 months.
4. Procedure and device-related adverse events through 24 months.

4.2.3. EXPLORATORY ENDPOINTS

Exploratory endpoints for informational purposes only:

1. Index procedure resource utilization: Anesthesia, procedure time and time to discharge.
2. Follow up resource utilization: Nasal airway obstruction related return visits and medication utilization.
3. Subject satisfaction questionnaire at 1, 3, and 12 months.
4. Degree of nasal airway obstruction as reported by subjects on the VAS scale at baseline with decongestant use.
5. Endoscopic lateral wall insufficiency score per side[21] at baseline 1, 3, 6 and 12 months.
6. 3-D camera lateral wall motion assessment per side at baseline and 3, 6, and 12 months (at select sites).
7. Cosmesis changes from baseline evaluated by Independent Photo Review at 3 and 6 months (at select sites).
8. Change in subject sleepiness scale from baseline to 1, 3, 6, and 12 months as reported by subjects on the Epworth Sleepiness Scale (ESS).
9. Allergic rhinitis status at 1, 3, 6, and 12 months.
10. Nasal geometry: length of nose, height and width of nose, skin thickness of lateral wall at baseline.
11. Type of turbinate procedure.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. PARTICIPANT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following inclusion criteria:

1. The subject has NOSE Score ≥55.
2. The subject has dynamic lateral nasal wall insufficiency as confirmed by Positive Modified Cottle Maneuver.
3. The subject is ≥18 years of age.
4. The subject is willing and able to provide informed consent and comply with the study protocol.
5. The subject is seeking treatment for nasal airway obstruction due to Nasal Valve Collapse (NVC) and is willing to undergo an in-office nasal implant procedure alone or with a turbinate reduction procedure.
6. The subject has appropriate nasal and facial anatomy to receive the Latera Implant.
7. The subject agrees to follow-up examinations through twelve (12) months post operatively.
8. The subject has failed to benefit from appropriate maximal medical management [e.g., nasal steroids (at least 4 weeks); antihistamines; oral decongestants; nasal strips, stents, or cones]. Failure of maximal medical management may be from lack of effectiveness or tolerability.

5.2. PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. The subject is having a concurrent Functional Endoscopic Sinus Surgery (FESS) or sinuplasty.
2. The subject has had rhinoplasty within the past twelve (12) months.
3. The subject is planning to have other concurrent rhinoplasty procedure.
4. The subject is planning to have other rhinoplasty procedures or will use external dilators within twelve (12) months after the index procedure.
5. The subject has had septoplasty and/or inferior turbinate reduction within the past six (6) months.
6. The subject has, in the view of the clinician, inappropriate fixation on their nasal airway.
7. The subject plans to have any surgical or non-surgical treatment of their nasal valve, other than the index procedure, within twelve (12) months of the study.
8. The subject has a permanent implant or dilator in the nasal area.
9. The subject has concomitant inflammatory or infectious skin conditions or unhealed wounds in the treatment area.
10. The subject currently has active nasal vestibulitis.
11. The subject has a history of nasal vasculitis.
12. The subject is a chronic systemic steroid or recreational intra-nasal drug user.
13. The subject has had a cancerous or pre-cancerous lesion and/or has had radiation exposure in the treatment area or chemotherapy.
14. The subject has polyps or pathology (i.e., septal deviation) other than turbinate hypertrophy and/or lateral wall insufficiency that would contribute to airway obstruction.
15. The subject has a history of a significant bleeding disorder(s) that would prevent healing of the treatment area post procedure.
16. The subject has a known or suspected allergy to PLA or other absorbable materials.
17. The subject has a significant systemic disease such as poorly controlled diabetes which, in the investigator's opinion, could pre-dispose the subject to poor wound healing.
18. The subject is currently using nasal oxygen or CPAP.
19. The subject is not a candidate for procedures conducted under local anesthesia, and/or managed anesthesia care (MAC) or conscious sedation.
20. Female subjects, subject is of child bearing potential, known or suspected to be pregnant or is lactating.
21. Any other presenting condition that, in the medical opinion of the investigator, would disqualify the subject.

5.3. STRATEGIES FOR RECRUITMENT AND RETENTION

A maximum of 250 subjects will be enrolled in the study. Up to 170 of these will be enrolled to reach target of 150 subjects completing the 24 months follow up. Up to 80 additional subjects will be enrolled as training cases. It is anticipated that this enrollment will take place in the initial 8 months of the study after study start-up. Subjects will be enrolled at approximately 25 individual sites within the United States.

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. Based on an earlier study with the device, both genders are expected to be well represented in the study.

Study brochures containing information on study participation and the 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.

The following tools will be utilized to encourage subjects' compliance to the study visit schedule:

- Subjects enrolled as training cases may receive a stipend for their time and to cover travel costs. Subjects must complete the study through the 1 month visit and will receive $100 prepaid debit card at the end of the 1 month visit.

- All other subjects may receive a stipend for their time and to cover travel costs as outlined below.
    - Subjects who complete the study full 24 month follow up are eligible for a total stipend of $700.00 to be paid over a two year period. Upon completion of the Baseline, 1 Month, 3 Month, 6 Month, 12 Month, 18 Month and 24 Month visits, subjects will receive a $100.00 prepaid debit card at each visit or follow up. The 18 Month and 24 Month follow up evaluations will be conducted in one of the following manners: office visit, telephone interview, completion of form by subject and mailed to office for data entry, depending on subject availability.

- Additionally, subjects will be contacted by phone, and where available automated texting and email, for both reminders to schedule or confirm upcoming study visits and as reminders for visits that have already been scheduled.

5.4. TRAINING CASES

Each Investigator will complete 1-5 training cases (see section 7.7.1 Training Cases Schedule of Events Table).

Training cases will be attended by a Spirox-authorized Latera trainer. Trainers may be Spirox Clinical personnel or ENT Consultant.

The following criteria will be used to determine the satisfactory completion of the training case requirement to proceed with enrollment into main study population as assessed during the Treatment Visit (Visit 3) as the:

- Successful procedure completion, and
- No device-related and/or procedure-related Adverse Events.

Upon successful completion of implant procedure based on criteria outlined above, Spirox will issue written notification of having satisfactorily completed the train case requirement. Upon receipt of the notification the individual Investigator may begin enrollment in the main study population.

Subjects enrolled as training cases will only be followed through 1 month post procedure. An investigator will not be allowed to conduct additional training cases once he/she has begun enrollment for study subjects.

5.5. PARTICIPANT WITHDRAWAL OR EARLY TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. Investigators may withdraw or early terminate a subject from the study as deemed appropriate per safety measures and/or if the subject develops a medical condition that prohibits further study participation.

In the event of an early subject termination, the clinical investigational site will, at a minimum, document Adverse Events and Concomitant Medications changes, as appropriate, and all available data in the eCRFs. The clinical site will also complete the Study Exit eCRF.

5.6. PREMATURE TERMINATION OR SUSPENSION OF STUDY

The study enrollment may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for enrollment suspension or study termination, will be provided by the Sponsor to the investigator and regulatory authorities. If the study is prematurely terminated or enrollment suspended, the site PI will promptly inform the IRB(s) and will provide the reason(s) for the termination or suspension.

Both the sponsor and the investigator reserve the right to terminate the study at any time. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

If the sponsor, investigator, study monitor, or appropriate regulatory officials discover any conditions arising during the study that indicate that the study enrollment should be suspended or that the study site should be terminated, this action may be taken after appropriate consultation among the sponsor, investigator, and study monitor. Conditions that may warrant enrollment suspension or termination of the study site or of the study itself, may include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study;
- A decision on the part of the sponsor to discontinue the study;
- A decision on the part of the sponsor to suspend enrollment or discontinue evaluation of the device;
- A request from a regulatory authority;
- Failure of the investigator to enroll subjects into the study at an acceptable rate;
- Failure of the investigator to comply with pertinent regulations of appropriate regulatory authorities;
- Submission of knowingly false information from the research facility to the sponsor, study monitor, or appropriate regulatory authority;
- Insufficient adherence to protocol requirements.
- Determination that it is unlikely that the study null hypothesis can be rejected

In the event of enrollment suspension, the study may resume once concerns about safety, protocol compliance, or data quality are addressed to the satisfaction of the sponsor, IRB and/or FDA.

Subjects that have been enrolled and have undergone the index procedure at the time of study enrollment suspension will be followed per the study schedule through the 24-Month closeout visit. Subjects that have been consented, but not yet undergone index procedure, will be delayed until a decision about whether to restart enrollment has been made. These later subjects will be re-consented if the enrollment suspension lasts longer than thirty (30) days.

6. STUDY DEVICE

6.1. STUDY DEVICE ACQUISITION

The Latera™ System (Absorbable Nasal Implant and Delivery Device) is a commercially available device that has received FDA clearance (K161191). The device will be used under this study protocol in accordance with the cleared indications for use and instructions for use and provided to the investigators at no charge by Spirox, Inc.

6.2. STUDY DEVICE DESCRIPTION AND INDICATIONS FOR USE

The Latera Absorbable Nasal Implant is indicated for supporting nasal upper and lower lateral cartilage. 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[22]. The Implant is provided in a plastic tray with a sliding lid. The Implant and plastic tray are depicted in **Figure 1** below.

Figure 1: Latera Absorbable Nasal Implant and Packaging

The Delivery Device is a single use device composed of a handle body, deployment plunger and pushrod, and a 16-gauge delivery cannula with a depth marker and protective cover. The handle includes an Implant loading port which enables the loading of the Implant. The handle uses an internal transition between the loading position and the cannula to collapse the Implant forks within the cannula inner lumen and prepare the Implant for deployment. The Implant Positioning Guide is packaged with the Delivery Device to aid the physician in preparing for the procedure and identifying the target Implant location. The Delivery Device and the Implant Positioning Guide are shown in **Figure 2** below.

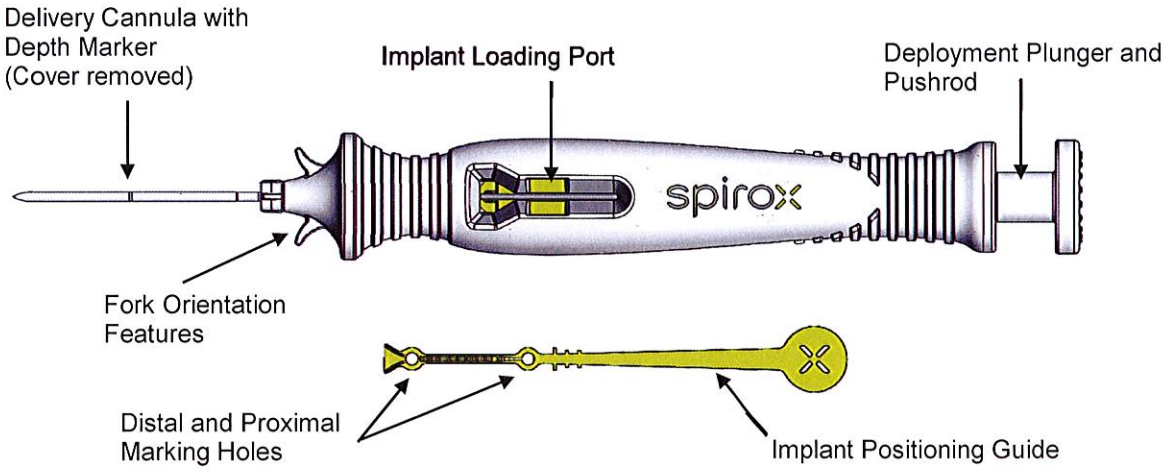

Figure 2: Delivery Device and Implant Positioning Guide

6.3. STUDY DEVICE STORAGE AND STABILITY

Follow Instructions for Use. The Implants are shipped in insulated containers containing frozen ice packs to protect the product from reaching high temperature. The Implants must be stored in a cool, dry location at or below 30°C. The Delivery Devices are shipped in cardboard boxes and are not subject to special shipping, storage or temperature requirements.

6.4. STUDY DEVICE PREPARATION AND IMPLANTATION

Instructions regarding the device preparation are provided in the Instructions for Use (IFU) (see Appendix III Latera IFU).

6.5. STUDY DEVICE ACCOUNTABILITY PROCEDURES

Accurate records of all study devices received and used to treat subjects, returned to the Sponsor, or designee, or destroyed at the study site, shall be maintained by the site. No Implants or Accessory Devices (Latera System) are to be destroyed or returned without authorization from the Sponsor. The lot number of each unit used will be tracked on the subject's eCRF and on each site's device accountability log.

Latera study devices will be provided by Spirox for use under this study protocol only. The investigators will not provide these devices to a third party, nor will he/she allow use of these devices outside of this study protocol.

7. STUDY PROCEDURES AND SCHEDULE

The procedures and schedule detailed in this section are applicable as noted, to both training case and non-training case subjects. Training cases are followed through 1 month, whereas non-training cases are followed up through 24 months. Refer to section 7.2 for schedule of events.

7.1. STUDY VISIT SPECIFIC PROCEDURES

7.1.1. Subject Screening and Enrollment Visit (Visit 1) (All Subjects)

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

The subject will be asked to fill out a NOSE score questionnaire and a NOSE score will be calculated. If all inclusion criteria (including NOSE score ≥55) are met and no exclusion criteria are present, the Investigator will inform the subject about the purpose of the study. The background of the proposed study along with the potential benefits and risks will be explained to the subject and questions will be answered. Potential subjects will be counseled as to the nature of their condition. All subjects will have ample time to ask questions.

Subjects 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 renders the subject ineligible for the study.

Female subjects 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.

Subjects that have signed the ICF and met eligibility criteria will be scheduled for Visit 2. Subjects will be considered enrolled upon signing the ICF, meeting study eligibility criteria, at the completion of the screening visit.

Study data including any adverse events that occurred after the ICF was signed, should be entered into the EDC within 24 hours of completion of the visit.

Subjects that have provided written informed consent and met the eligibility criteria may also be invited to participate in "Latera™ Patient Experience and Testimonials" (see Section 7.2.16 below).

7.1.2. Baseline Evaluation Visit (Visit 2) (All Subjects)

Baseline visit may occur up to one (1) month prior to procedure visit (Visit 3). This visit may be completed in conjunction with Visits 1 and 3. This visit is completed by all subjects.

The Investigator will view medical history and concomitant medications. Such history will also include information about previous treatments to further ensure compliance with the inclusion and exclusion parameters.

A detailed description of the visit assessments and evaluation methods are located in Section 7.2. The pre-intervention data collection will include the following:

1. Nasal Obstruction Symptom Evaluation (NOSE) Scale (See Section 7.2.1)
2. Epworth Sleepiness Scale* (See Section 7.2.3)
3. Baseline Health Economics Questionnaire* (See Section 7.2.4)
4. Demographics & Nasal Medical History (See Section 7.2.6)
5. Concomitant Medications (See Section 7.5)
6. Baseline Nasal Exam (See Section 7.2.7)
7. Modified Cottle Maneuver (See Section 7.2.9)
8. Lateral Wall Motion Video* (See Section 7.2.10)
9. Photography- Cosmetic* (selected sites only, See Section 7.2.11)
10. Photography- 3D* (selected sites only, See Section 7.2.12)
11. NAO Breathing Assessment (See Section 7.2.2)*
12. Assessment of Turbinate Hypertrophy Contribution to NAO (See Section 7.2.13)*

Note: Completion of assessments or evaluations noted with (*) is not required for training case subjects.

Adverse events related to head and neck and/or respiratory conditions observed during the baseline visit and through visit 2 will be collected and documented. Spirox will be notified as necessary pursuant to the description provided in Section 8.

All data collected during baseline visits should be entered into the EDC no later than seven (7) days after completion of the study visit. Upon completion of the baseline visit, the subject will be scheduled for Treatment Visit (Visit 3).

7.1.3. Treatment Visit (Visit 3) (All Subjects)

This visit may be completed in conjunction with Visits 1 and 2, and should take place within 1 month after Visit 1 (Screening & Enrollment Visit). This visit is completed by all subjects.

If treatment occurs more than 1 month after Visit 1, inclusion and exclusion criteria must be re-confirmed and the subject will be asked to re-review, initial and date the ICF to continue participation. Subjects will also complete a NOSE scale.

Procedures conducted under this study protocol must be completed in an office setting using sterile technique. In addition to local anesthesia, subjects may receive monitored anesthesia care (MAC) or conscious sedation per the site's standard of care practice. Only procedure-trained investigators that are authorized by the sponsor will be allowed to place the devices during this study.

Optionally, an oral anxiolytics (e.g. Valium, Ativan or equivalent) and/or analgesic (e.g. Tylenol, or Tylenol with Hydrocodone) may be offered to the subject prior to the procedure, per the investigator's discretion.

If the subject has agreed to provide a testimonial (see Section 7.2.16), video may be captured during the procedure visit.

The below section includes a description of the activities occurring during the Index procedure visit and placement of the Latera™ Implants:

1. Amoxicillin or equivalent antibiotic may be administered to the subject before the procedure.
2. If planned treatment includes turbinate reduction, it must be completed prior to implant placement per site's standard of care procedure.
3. The skin of the nose and the mucosal surface should be cleaned with an antiseptic solution (e.g. isopropyl alcohol or betadine ophthalmic) prior to Latera Implant(s) placement.
4. The nasal anatomy will be examined and target trajectory for the Implant(s) should be established and marked with the aid of a sterile pen and sterile implant positioning guide per IFU **(Appendix III)**.
5. Images of planned placements will be captured.
6. 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) or decongestant (e.g. Afrin or equivalent) may be sprayed into the nose.
    b. TOPICAL: Few minutes after application of the spray, cotton balls or pledgets soaked in anesthetic (e.g. Tetracaine, 4% lidocaine/mixed with Afrin, or equivalent) may be placed in the nasal vestibule, ensuring contact with turbinate and floor of nose posteriorly, and to lateral nasal wall anteriorly) for approximately 10 minutes.
    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 and 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.

7. The treatment area should also be pre-treated with an antibiotic ointment (e.g. Muciprocin or equivalent) to minimize potential risk of infection.
8. The Implant(s) (unilateral or bilateral) will be delivered per Spirox IFU20680 (**Appendix III**).
   Note: Only one Implant per side may be placed.
9. Step 8 will be repeated if the subject requires bilateral implant placement.

All medications used during the procedure and resource utilization will be recorded. Adverse events observed during this visit will be collected and documented. Spirox will be notified as necessary pursuant to the description provided in Section 8. Data collected for the Treatment Visit should be entered into the EDC no later than even (7) days after the completion of visit.

IMPORTANT: Prior to discharge, subjects will be provided with the post procedure reminder form (**Appendix IV).** In addition, a course of antibiotics (e.g. Amoxicillin, Augmentin or equivalent) may be prescribed by the physician pursuant to standard medical practice guidelines.

Planning images captured during procedure will be transferred to sponsor via BrickFTP.com (See Section 7.2.10 for information on BrickFTP).

Upon completion of the treatment visit, the subject will be scheduled for the Follow-Up Visit.

7.1.4. 1 Month Follow-Up Evaluation Visits (Visit 4) (All Subjects)

Safety and performance data will be collected at 1 month (+/- 7 days) post procedure. This visit is completed by all subjects. A detailed description of the visit assessments and evaluations are located in Section 7.2. The following data will be collected:

1. NOSE scale (See Section 7.2.1)
2. NAO Breathing Assessment* (See Section 7.2.2)
3. Epworth Sleepiness Scale* (See Section 7.2.3)
4. Subject Satisfaction Questionnaire* (See Section 7.2.14)*
5. Post Procedure Health Economics Questionnaire* (See Section 7.2.5)
6. Concomitant Medications, if changed (See Section 7.5)
7. Adverse Events since last visit (See Section 8)
8. Post Procedure Nasal Exam (See section 7.2.8)
9. Lateral Wall Motion Video* (See Section 7.2.10)

Completion of assessments or evaluations noted with (*) is not required for training case subjects

All data collected for these visits should be entered into the EDC no later than seven (7) days after the completion of each visit. For adverse events observed during these follow-up visits, Spirox will be notified as necessary pursuant to the description provided in Section 8.

Training subject participation will be complete at the 1 month follow-up time point and subjects will exit the study.

All non-training case subjects, upon completion of the follow-up visit activities, will be scheduled for the 3 Month Follow-up Evaluation Visit (Visit 5).

7.1.5. 3 – 24 Month Follow-Up Evaluation Visits (Visits 5-9) (All Subjects excluding training cases)

Safety and performance data will be collected at 3 months (+/-15 days), 6 months (+/- 15 days),12 months (+/- 30 days), 18 months (+/- 30 days), and 24 months (+/- 30 days) post procedure. These visits are completed by all non-training case subjects.

A detailed description of the visit assessments and evaluations are located in Section 7.2. The following data will be collected:

1. NOSE scale (See Section 7.2.1)
2. NAO Breathing Assessment (See Section 7.2.2)
3. Epworth Sleepiness Scale (See Section 7.2.3)*
4. Subject Satisfaction Questionnaire (See Section 7.2.14)*
5. Post Procedure Health Economics Questionnaire (See Section 7.2.5) *
6. Concomitant Medications, if changed (See Section 7.5)
7. Adverse Events since last visit (See Section 8)
8. Post Procedure Nasal Exam (See section 7.2.8)*
9. Lateral Wall Motion Video (See Section 7.2.10) *
10. Photography – Cosmetic (select sites only) – 3 and 6 Month Visits only (See Section 7.2.11) *
11. Photography – 3D (select sites only) – 3, 6 and 12 Month Visits only (See Section 7.2.12)*

*This assessment/evaluation will not be collected at the 18 and 24 month follow ups.

All data collected for these visits should be entered into the EDC no later than seven (7) days after the completion of each visit. Adverse events observed through the 12 month visit will be collected and documented. Only adverse device effects will be collected beyond the 12 month visit. Spirox will be notified as necessary pursuant to the description provided in Section 8. Data collected for these visits should be entered into the EDC no later than seven (7) days after the completion of each visit.

Upon completion of the follow-up visit activities, the subject will be scheduled for the next Follow-up Evaluation Visit.

Subject participation will be complete at the 24 month follow-up time point anddocumented in the Study Exit eCRF.

7.1.6. Implant Replacement Procedure (All Subjects excluding training cases)

In the event a subject experienced an implant(s) retrieval prior to their scheduled 3 month visit, which was not due to a physiologic rejection or an allergic reaction to the material, a subject may voluntarily undergo an in-office procedure to have a new Latera Implant(s) placed.

The 3 Month Follow Up visit should be completed prior to re-implantation. Replacement of the implant (i.e., re-implantation) should occur at least thirty (30) days after the device has been retrieved and within three (3) to five (5) months from the initial index procedure. One re-implantation procedure per side may be completed during the study period.

Subjects indicating that they would like to proceed with the re-implantation procedure will be asked to sign an Informed Consent Form (ICF) Addendum that has been approved by the governing IRB. The implant procedure should be followed as described in Section 7.1.3, without any concomitant procedures. Procedure must be completed in an office setting, using sterile technique. In addition to local anesthesia, subjects may receive monitored anesthesia care (MAC) or conscious sedation per the site's standard of care practice.

The subject will continue study participation at the 6,12, 18 and 24 Month Follow-up Visits (Visits 6, 7, 8 and 9), as outlined in section 7.1.5.

No additional compensation will be provided to the subject for this procedure/visit.

Training case subjects may not have an implant replaced during study participation.

7.2. STUDY EVALUATIONS METHODS

7.2.1. Nasal Obstruction Symptom Evaluation (NOSE) Scale

The Nasal Obstruction Symptom Evaluation (NOSE) Scale[18] is a Patient-Reported Outcome (PRO) instrument that will be administered to capture subject perception of the degree of nasal airway patency.

The NOSE scale will be completed at the Screening, Baseline, 1 Month, 3 Month, 6 Month, 12 Month, 18 Month and 24 Month visits. In the event that the Screening & Baseline Visits occur on the same day, only one NOSE score is required. The NOSE scale may additionally be completed at the Treatment Visit if more than one (1) month from Screening Visit.

The NOSE scale is a validated instrument, which was 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. NOSE Scale allows subjects to quantify their symptoms based on the severity of 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:

(0) Not a Problem
(1) Very Mild Problem
(2) Moderate problem
(3) Fairly Bad Problem
(4) 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. A copy of the Nasal Obstruction Symptom Evaluation Scale questionnaire is attached (See **Appendix V**).

7.2.2. NAO Breathing Assessment

A subject's perception of breathing cannot be quantitatively measured, but exists on a continuum from the subject perspective. A Visual Analog Scale (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. The NAO Breathing Assessment will be completed at the Baseline, 1 Month, 3 Month, 6 Month, 12 Month, 18 Month and 24 Month visits for non-training subjects.

Operationally a VAS is a horizontal line, 100mm in length, anchored by word descriptors at each end, as illustrated in **Figure 3**.

The subject will either mark on the line the point that they feel represents their perception of their current state or will communicate the information to the Study Coordinator verbally, who will, in turn, mark the form as indicated by the subject. The VAS score is determined by measuring in millimeters from the left end of the line to the point marked by the subject.

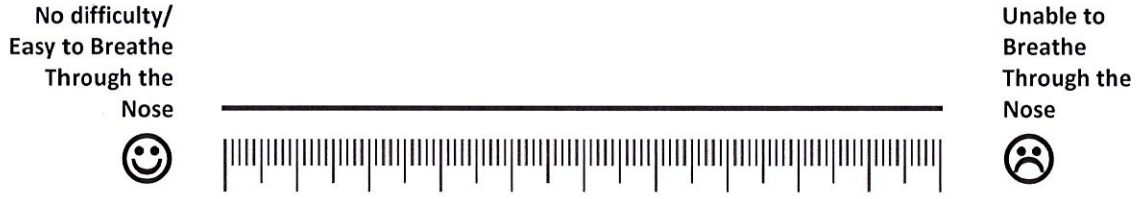

Figure 3: Visual Analog Scale. Left side represents 0mm and right side represents 100mm.

7.2.3. 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. Non-training case subjects will complete the ESS Assessment at the Baseline, 1 Month, 3 Month, 6 Month, 12 Month, 18 Month and 24 Month visits.

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? You should rate your chances of dozing off, not just feeling tired. Even if you have not done some of these things recently try to determine how they would have affected you. For each situation, decide whether or not you 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 score.

A copy of the ESS questionnaire is provided in **Appendix VI**. In order to avoid bias, the version of the ESS provided as a PRO to the subjects will not include the "Analyze Your Score" section of the questionnaire.

7.2.4. Baseline Health Economics Questionnaire

The Baseline Health Economics Questionnaire is a non-validated, Spirox-developed PRO used to document the frequency and type of doctor visits related to the Nasal Airway Obstruction condition over the one year prior to study enrollment. Non-training case subjects will complete the questionnaire at the Baseline Visit.

7.2.5. Post Procedure Health Economics Questionnaire

The Post Procedure Health Economics Questionnaire is a non-validated, Spirox-developed PRO completed at follow-up visits. The Post-Procedure Questionnaire differs from the Baseline version with regards to the timeframes that are referenced. The post-procedure health economics survey will document frequency and type of doctor visits related to the Nasal Airway Obstruction condition since the index procedure, excluding study visits. Non-training case subjects will complete the Questionnaire at the 1 Month, 3 Month, 6 Month and 12 Month visits.

7.2.6. Demographics & Nasal Medical History

Demographic information, such as age, gender, ethnicity, race and date of onset of nasal obstruction will be ascertained for all subjects at the Baseline Visit.

The past five years of relevant nasal medical history will include a complete review of nasal systems and evaluation of symptoms, including an assessment of nasal airway obstruction signs and symptoms. A history of prior nasal trauma or nasal surgery will be noted, as well as other medical conditions related to head and neck and respiratory conditions. Questions will be asked about the medications used by the subjects,

including the types and doses of medications that are used to control nasal obstruction symptoms and the performance of those medications in controlling their symptoms (i.e., OTC medications, nasal sprays, decongestants, nasal airway devices, etc.).

7.2.7. Baseline Nasal Exam

A Baseline Nasal Exams will be conducted for all subjects at the Baseline Visit. The exam will include collection of nasal anatomy parameters such as nose length, nose height, nose width and skin thickness.

In addition, each side of the nose will be examined with an endoscope to assess each subject's degree of inferior turbinate hypertrophy and septal deviation (superior and inferior). Each of these will be graded as Normal, Mild, Moderate, or Severe.

7.2.8. Post Procedure Nasal Exam

An internal and external nasal visual physical exam will be conducted at each follow-up visit to document any changes in nasal appearance. A nasal exam will be conducted for training case-subjects at the 1 Month follow-up visit, and for non-training case subjects at the 1, 3, 6 and 12 Month follow-up visits.

Any observation during the exam regarding the Implant, such as a bent or fractured Implant, or any evidence that the Implant has moved or migrated from its intended target location (without resulting in retrieval) shall be recorded.

Additionally, non-training case subjects, at all Follow-Up Visits, will have each side of the nose examined with an endoscope to re-assess each subject's remaining degree of inferior turbinate hypertrophy and septal deviation (superior and inferior). Each of these will be graded as Normal, Mild, Moderate, or Severe.

7.2.9. Modified Cottle Maneuver

In order to confirm that the subject has dynamic lateral wall insufficiency (LWI), the Modified Cottle Maneuver should be performed. The assessment will be done at the Screening and Baseline visits.

To test for LWI, the curette, cerumen loop, or similar instrument should be inserted into the nasal cavity and used to gently support the lateral nasal sidewall while the patient is asked to breathe in. The Subject will be asked to verbally report their relative improvement per side using the scale below (See **Figure 4**).

Figure 4: Verbally reported improvement in breathing with supported lateral wall.

7.2.10. Lateral Wall Motion Video

Videos will be captured at the Baseline, 1, 3, 6, and 12 Month follow-up Visits for all non-training case Subjects. Videos will be transferred to Spirox and will be blinded prior to transfer to independent reviewer. The independent reviewer will make assessment of endoscopic lateral wall insufficiency score (1, 2 or 3). Some sites may also capture additional endoscopic videos in conjunction with a mask designed to facilitate the collection of the subject's nasal airflow rate. Use of the nasal airflow rate mask will be limited to approximately three sites and subject participation is optional.

Spirox will utilize the HIPPA compliant file transfer protocol website (BrickFTP.com) BrickFTP site for the transfer of all images and videos from the site to Spirox for processing and analysis. Each site will only have access to upload and view images in their assigned folder(s) and will not have access to other site's folders on the BrickFTP.

See **Appendix VII** "Lateral Wall Motion Capture Instructions".

Lateral Wall Motion Videos will not be captured for Training Case Subjects.

7.2.11. Photography - Cosmetic

At select sites, photographs will be captured at the Baseline, 3 and 6 Month follow-up Visits for non-training case subjects to evaluate potential cosmetic changes.

Review of the nasal appearance changes attributed to the overall procedure as well as those attributed to the Latera Implant will be assessed by an independent physician reviewer.

Photographs will be taken to record baseline nose appearance to evaluate aesthetic changes. Six (6) photographs will be taken: five (5) static photographic views (straight, left side, right side, chin-up and chin-down) will be taken and two (2) at a full inhale photographic views (chin-up view and top-down).

Images will be blinded (e.g. black boxes placed over the eyes) by the sponsor prior to being sent to the independent reviewer. Images will be transferred using BrickFTP site.

See **Appendix VIII** "Cosmetic Photo Capture Instructions".

Cosmetic Photography will not be captured for Training Case Subjects.

7.2.12. Photography – 3D

At select sites, 3D Images will be captured at the Baseline, 3, 6 and 12 Month follow-up Visits for non-training case Subjects.

3D Image capture will be used to evaluate baseline and post-procedure changes regarding the depth and volume of nasal collapse at approximately two sites. 3-D photography review will be limited to approximately 3 sites, and subject participation is optional. Site selection for participation will be based on adequate facility space and staff to support this additional component. Subject participation in 3D photography is optional.

The Canfield Vectra H1 handheld imaging system allows for the capture and analysis of 3D images. The system is comprised of the Vectra H1 camera, Mirror® software and VECTRA Analysis Module. The Vectra H1 camera has an integrated flash to simultaneous capture photographs from dual-angles to build 3-D images. Photographs are either captured to the camera's SD card or tethered to a workstation. Photographs are captured and managed using Canfield Mirror® software and is analyzed with Canfield VECTRA Analysis Module. Images will be saved with the camera-generated sequence number (e.g. photo "38"), and then transferred for analysis using the subject ID and study visit for identification.

Images will be transferred using BrickFTP site.

See **Appendix IX** "3D Camera Image Capture & Transfer Instructions".

3D Images will not be captured for Training Case Subjects.

7.2.13. Assessment of Turbinate Hypertrophy Contribution to NAO

After completion of all other assessments at the Baseline Visit, non-training case subjects will be asked to assess their ability to breath after a decongestant (e.g. Afrin) has been administered. Administration of a decongestant is frequently used to diagnose significance of inferior turbinate contribution to NAO. After decongestant administration, subjects will be asked to rate their degree of nasal airway obstruction using the VAS scale (See Section 7.2.2).

7.2.14. Subject Satisfaction Questionnaire

The subject satisfaction questionnaire is a non-validated, Spirox-developed PRO form that will contain the questions related to subject satisfaction with the procedure and their nose appearance. Non-training Case Subjects will complete the Questionnaire at the 1 Month, 3 Month, 6 Month and 12 Month visits.

7.2.15. Discretionary Imaging

In addition to the protocol specific imaging outlined above, the Investigator may wish to share, or Spirox may request, additional images (digital photos) or videos of subject for the purposes of, but not limited to, consultation (e.g. placement of device ahead of procedure, etc.), documentation of changes (e.g. cosmetic change, lateral wall motion, etc.) or adverse event reporting (e.g. image of hematoma). Images may include endoscopic nasal video, digital video or photography. Images or videos may be taken at any time point during the study.

Digital images will be blinded (e.g. black boxes placed over the eyes). Images may be used for educational and/or research purposes only. Images or videos will be transferred to Spirox using BrickFTP.

7.2.16. Latera™ Patient Experience and Testimonials

Subjects that have enrolled in the study may also be invited to participate in "Latera™ Patient Experience and Testimonials". This invitation may occur at time of Screening or at any time point through study exit.

Spirox may choose to capture Latera™ patient experience and/or testimonials through film, videotape, photographs and/or quotes. Spirox may choose to capture the testimonials prior to, during and after the LATERA procedure is performed, at varying intervals (i.e., day of procedure, 1 week post-procedure, 1 month post-procedure, etc.). Spirox and the investigational sites may use these photographs, videos, personal images and quotes in whatever medium deemed appropriate by Spirox for any of the following purposes: (i) educational and research purposes, (ii) medical or audiological consultations, (iii) publication in professional journals, (iv) collateral and promotional materials, (v) web-based marketing materials including website content, (vi) public and media relations, or any other advertising methodology.

For these subjects, written consent in the form of an IRB approved addendum to the study ICF will be required. Participation is optional and will not impact their participation in the study. Consent to participate does not guarantee that they will be selected as a participant. No additional reimbursement beyond what is outlined in Section 5.3 will be provided.

7.3. LOST TO FOLLOW-UP

Site personnel should make reasonable efforts to ensure that all subjects complete the requisite follow up visits. Training cases subjects should complete 1 month follow up and rest of the subjects should complete 24 months follow up. A subject will be considered lost to follow-up if the site has:

1. Attempted to contact the subject with a minimum of two phone calls; and
2. Has mailed a certified letter to the subject with return receipt.

Before a subject is considered lost to follow up, the above described attempts to contact the subject must be documented in the subject's medical records and in the study CRFs.

7.4. STANDARD OF CARE STUDY PROCEDURE

Per an Investigator's decision, subjects may receive concomitant turbinate reduction procedure(s) in addition to placement of the Implants to address other potential causes for the nasal airway obstruction.

There are two commonly used approaches to reduce turbinate size: radiofrequency reduction, and microdebrider-aided resection using a submucosal approach. With this procedure, the lining of the turbinate is left intact, but the tissue from the inside of the turbinate is removed. As the turbinate heals, it becomes smaller than before surgery.

The decision to perform turbinate reductions should be made based on the judgment of the investigator, but should consider the findings of the nasal exam as well as Assessment of Turbinate Hypertrophy Contribution to NAO (see sections 7.2.13 and 7.2.7). Investigators will be instructed to consider concomitant turbinate reductions for any subject for whom the results of these evaluations suggest that turbinate enlargement is contributing to nasal obstruction.

Turbinate reductions procedures are well established and considered standard of care to address respective etiologies. Treatment of the lateral wall with Latera alone or in conjunction with these procedures is being evaluated in this study.

7.5. CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Implant procedure may be completed in conjunction with Turbinate reduction procedure(s).

Current medications related to the treatment of NAO, NVC, and the management of nasal allergies will be documented in the eCRFs.

7.6. PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Concomitant medications or therapies preventing subjects from being eligible to participate in this study are current use of nasal oxygen, CPAP, chronic use of systemic steroids and/or recreational intra-nasal drugs. Additionally, concomitant radiation exposure in the treatment area or chemotherapy will deem a subject ineligible to participate.

In addition, the following treatments will not be permitted concurrent with index procedure or within 24 months after index procedure:

- Functional Endoscopic Sinus Surgery (FESS)
- Sinuplasty procedure
- Rhinoplasty procedure
- Any surgical or non-surgical treatment of the nasal valve, other than the index procedure, within 12 months of the study
- Use of a dilator and/or an external device in the nasal area (e.g. nasal strips).

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7.7. SCHEDULE OF STUDY EVENTS

7.7.1. Training Cases - Schedule of Events Table

Study Events	Screening & Enrollment (Visit 1)	Baseline Evaluation (Visit 2)[1]	Treatment (Visit 3)[2]	Follow Up 1 Mo/Final Study Visit (Visit 4)	Early Exit
Secure Informed Consent	X				
Inclusion/Exclusion	X		X		
Pregnancy Test[3]	X				
NOSE Scale (PRO)[4]	X	X	X	X	
Modified Cottle Maneuver	X	X			
Demographics & Nasal Medical History		X			
Nasal Exam		X		X	
Photography – Planning Images			X		
NAO Treatment			X		
Concomitant Medications		X	X	X	X
Adverse Event Assessment		X	X	X	X
Complete Study Exit Form					X

[1]Visit 2 activities may be done in conjunction with Study Visit 1. In this instance, the Screening NOSE Scale is not required.
[2] If Visit 3 (Treatment Visit) is more than 1 month after Visit 1, inclusion/exclusion criteria need to be re-confirmed. Additionally, subjects should be asked to review IC form, initial and date the IC document to confirm continued consent for participation, and complete NOSE scale.
[3] Female subjects of childbearing potential
[4] If Visits 1, 2 and 3 are completed on the same day, the Screening and Treatment NOSE Scales are not required.

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7.7.2. Non-Training Cases - Schedule of Events Table

Study Events	Screening & Enrollment (Visit 1)	Baseline Evaluation (Visit 2)[1]	Treatment (Visit 3)[2]	Follow Up 1 mo (Visit 4)	Follow Up 3 mo (Visit 5)	Follow Up 6 mo (Visit 6)	Follow Up 12 mo/Final Study Visit (Visit 7)	Follow Up 18 & 24 mo/Final Study Visit (Visits 8 & 9)	Early Exit
Secure Informed Consent	X								
Secure Re-Consent for 18M and 24M Follow Up							X		
Inclusion/Exclusion	X		X						
Pregnancy Test[3]	X								
NOSE Scale (PRO)	X	X	X	X	X	X	X	X	
Modified Cottle Maneuver	X	X							
Epworth Sleepiness Scale (PRO)		X		X	X	X	X	X	
Subject Satisfaction Questionnaire (PRO)				X	X	X	X		
Health Economics Questionnaire (PRO)		X		X	X	X	X		
Demographics & Nasal Medical History		X							
Nasal Exam		X		X	X	X	X		
Lateral Wall Motion Video		X		X	X	X	X		
Photography- 3D Camera (select sites)		X			X	X	X		
Photography –Cosmetic (select sites)		X			X	X			
NAO Breathing Assessment (PRO)		X		X	X	X	X	X	
Assessment of Turbinate Contribution to NAO		X							
Photography – Planning Images			X						
NAO Treatment			X						
Concomitant Medications		X	X	X	X	X	X		X
Adverse Event Assessment		X	X	X	X	X	X		X
Adverse Device Effects Assessment								X	
Complete Study Exit Form								X[5]	X

[1] Visit 2 activities may be done in conjunction with Study Visit 1. In this instance, the Screening NOSE Scale is not required.
[2] If Visit 3 (Treatment Visit) is more than 1 month after Visit 1, inclusion/exclusion criteria need to be re-confirmed. Additionally, subjects should be asked to review IC form, initial and date the IC document to confirm continued consent for participation, and complete NOSE scale.
[3] Female subjects of childbearing potential
[4] If Visits 1, 2 and 3 are completed on the same day, the Screening and Treatment NOSE Scales are not required.
[5] To be completed at 24M follow up.

7.8. EARLY TERMINATION VISIT

In the event of an early subject termination, the clinical site should, at a minimum, document Adverse Events and Concomitant Medications changes. Refer to **Section 7.7** Schedule of Events.

8. ASSESSMENT OF SAFETY

8.1. SPECIFICATION OF SAFETY PARAMETERS

All Serious Adverse Events (SAE), Adverse Device Effect (ADE) and Serious Adverse Device Effects (SADE) will be collected and documented through the end of subject participation in the study. In addition, all non-serious device and procedure-related Adverse Events (AE) and all non-serious head and neck, and/or respiratory related AEs will also be collected and documented.

The primary safety endpoint evaluation will consider nasal procedure related and Latera related adverse events through 6 months post-procedure.

The following information for each AE, ADE, SAE and SADE will be collected:

- Date of onset
- Status and/or Outcome
- Date of resolution
- Adverse Event/Effect type (See Section 8.1.1)

  In the event of Implant loss or removal, the following information will be documented:
  - Implant exposed intranasal at pierce point or exposed on the external skin surface
  - Implant retrieved by surgeon or subject
  - Whether Implant loss or removal was complete or partial

- SAE or SADE (See Section 8.1.2 and 8.1.3)
- Severity of event (See Section 8.2.1)
- Relation to Study Device and/or procedure (See Section 8.2.2)
- Action taken
- Descriptive narration of Event/Effect

8.1.1. DEFINITION OF ADVERSE EVENTS TYPES

An adverse event (AE) or effect type will be determined by the Investigator. The AE/ADE type should be the categorized by the cause of the AE/ADE and not the action taken to resolve AE/ADE (i.e. foreign body rejection vs implant retrieval).

For consistency of reporting the following list provides guidance as to how AEs are categorized by Spirox. This list does not represent a full list of all possible AE types that could be reported, and is for reference only for consideration in the recording of AE/ADE types in the eCRFs:

- Excessive inflammation
- Significant foreign body sensation
- Excessive pain or discomfort
- Infection

- Foreign body rejection of implants (Extrusion)
- Skin irritation
- Hematoma
- Unintended perforation of the skin
- Intranasal retrieval
- External retrieval

8.1.2. DEFINITION OF ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or effect is defined as any untoward and unintended medical occurrence experienced by a clinical study subject. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product, whether or not related to the product.

The following events will be considered to be serious adverse events (SAE) and must immediately and without delay (within 24 hours) be reported to the study Sponsor by fax and/or email. These events must be reported whether or not the Investigator believes they are related to study procedures, activities or device:

- Death (the investigator will provide a copy of any post-mortem findings, including histopathology reports if available).
- Life-threatening event or injury
- Disability – significant, persistent, or permanent change, impairment, or damage or disruption in the subject's body function/structure, physical activities or quality of life
- Necessitate immediate medical or surgical intervention to:
    - Preclude permanent impairment of a body function or permanent damage to a body structure; or
    - Relieve unanticipated temporary impairment or damage.
- Prolongation of a hospitalization
- Require new hospitalization

8.1.3. DEFINITION OF ADVERSE DEVICE EFFECT (ADE) AND SERIOUS ADVERSE DEVICE EFFECT (SADE)

An Adverse Device Effect (ADE) is defined as any untoward or 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. This definition also includes 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 these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. All SADEs must immediately and without delay (within 24 hours) be reported to the study Sponsor by fax and/or email.

8.1.4. DEFINITION OF UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

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 plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)). All UADEs must immediately and without delay (within 24 hours) be reported to the study Sponsor by fax and/or email.

8.2. CLASSIFICATION OF AN ADVERSE EVENT

8.2.1. SEVERITY OF EVENT

The following guidelines will be used to describe the severity of an event:

- **Mild** – Awareness of the event, may cause no or minimal interference with the subject's daily life.
- **Moderate** – Discomfort enough to cause a noticeable impact on the subject's daily life.
- **Severe** – Incapacitation or significant impact on the subject's daily life.

8.2.2. RELATIONSHIP TO STUDY DEVICE/PROCEDURES

Two types of relationships will be assessed:

1. Related to the Latera device or Latera device-specific procedure, including Implant delivery
2. Related to turbinate reduction procedure

The procedure-trained Investigator's assessment of an AE's relationship to the study device or implant procedure and/or the concomitant procedure is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event must be reported. All AEs must have their relationship to the Latera study device or Latera device procedure assessed.

For all collected AEs, the Investigator who examines and evaluates the subject will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – The event is definitely related to the study device/procedure or concomitant procedure
- **Probably Related** – The event is probably related to the study device/procedure or concomitant procedure; or the event cannot be explained by other condition or illness.
- **Possibly Related** – The event is possibly related to the study device/procedure or concomitant procedure, but not likely.
- **Unlikely Related** – The event is unlikely related to the study device/procedure or concomitant procedure.
- **Not Related** – The event is definitely not related to the study device/procedure or concomitant procedure.

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8.2.3. EXPECTEDNESS

The Medical Monitor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the device as well as the concomitant turbinate reduction procedure.

Refer to section 2.3.2 for list of expected risks.

8.3. TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a subject presenting for medical care, or upon review by a study monitor.

All SAEs and all device and procedure-related AEs, including local and systemic reactions not meeting the criteria for SAEs, as well as all AEs related to head/neck and respiratory conditions occurring during the course of the study will be captured on the appropriate CRF.

Information to be collected includes event description, time of onset, Investigator's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis) or concomitant procedures, and time of resolution/stabilization of the event.

All SAEs and AEs will be followed to adequate resolution, or through the twenty-four month follow up visit.

Any medical condition that is present at the time of the participant's procedure will be considered as a baseline condition or comorbidity, and will not reported as an AE. However, if the subject's condition deteriorates at any time during the study, and the condition is procedure/device related, it will be recorded as an AE. AEs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4. REPORTING PROCEDURES

8.4.1. ADVERSE EVENT REPORTING

The investigator must document all AEs, ADEs, SADEs, UAE, UADEs and SAEs (see Section 8.1 for Definitions) on the AE Source Documents and subsequently enter this information into the electronic case report form, which will be reviewed by the study monitor and provided to the study sponsor. AE source documentation must be approved by the procedure-trained investigator.

8.4.2. SERIOUS ADVERSE EVENT REPORTING

The study investigator must report all SAEs and SADEs to the study sponsor immediately and without delay within 24 hours of site awareness and complete a AE CRF. See Section 1, Clinical Monitoring, for primary contact information.

All SAEs and SADEs will be followed until satisfactory resolution or until the site PI deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying FDA of SAEs pursuant to the MDR reporting requirements (21 CFR 803.19(a)(2)).

8.4.3. UNANTICIPATED PROBLEM REPORTING

An investigator shall submit to the sponsor and to the reviewing IRB a report of any Unanticipated Adverse Device Effect (UADE) occurring during an investigation as soon as possible, but no later than ten (10) working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)).

A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA pursuant to the MDR regulations and to all reviewing IRB's and participating investigators within ten (10) working days after the sponsor first receives notice of the effect.

8.5. STUDY HALTING RULES

Circumstances that may warrant termination or suspension include, but are not limited to the following unlikely events:

- Determination of unexpected, significant, or unacceptable risk to participants; or
- Insufficient compliance to protocol; or
- Determination that it is unlikely that the study null hypothesis can be rejected.

8.6. SAFETY OVERSIGHT

Adverse events will be reviewed periodically by the Medical Monitor. For any reported SAE, the Medical Monitor and Scientific Advisory Board members will review the relevant materials and may issue a recommendation to terminate the study as described above.

If this recommendation is reached, then the PI, study sites and IRBs will be notified. In addition, Spirox will follow the MDR reporting requirements pursuant to (21 CFR 803.19(a)(2)).

9. CLINICAL MONITORING

Clinical monitoring and oversight of the study will be conducted by the study sponsor, Spirox, to ensure that the safety, rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

The clinical site monitoring plan for this study will utilize both on-site and centralized (remote) monitoring, with on-site visits occurring early in site enrollment and continuing throughout the study as deemed necessary. Data verification will consist of 100% Source Document Verification of primary and secondary endpoint data and adverse device effects through 6 months, verification of correct ICF execution, subject eligibility, and compliance with the protocol. Clinical monitoring for the remainder of the data collected includes CRF reviews for timing, completeness and consistency of the CRF data for each subject through study exit. Onsite visits are documented including letters to the site principal investigator for visit planning and for a summary of any visit observations.

An independent audit of Clinical Study File at Sponsor's site may be conducted during the course of the study.

10. STATISTICAL CONSIDERATIONS

10.1. STATISTICAL AND ANALYTICAL PLANS

A Statistical Analysis Plan (SAP) will be finalized prior to database lock, which will contain further analysis details and statistical methods.

All efficacy endpoints will be analyzed using data collected after the training cases are completed. The training cases will not be included in the efficacy endpoint analyses. The training cases will be summarized with descriptive statistics for information purposes only and will include a summary of adverse events.

The subjects that receive a replacement implant will be included in the modified Intention-to-Treat population but excluded from the per-protocol population. A separate sensitivity analysis will be conducted in which the subjects that received a replacement implant are considered non-responders.

10.2. STATISTICAL HYPOTHESES

Primary Efficacy Endpoint:

- The primary efficacy endpoint is the proportion of treatment responders at 6 months post procedure. Since there is no direct comparison group in this study, the primary efficacy hypothesis is a superiority comparison to a target proportion:

  Null Hypothesis H_0: the proportion of responders at 6 months is = 0.50, versus
  Alternative Hypothesis H_A: the proportion of responders at 6 months is $\neq$ 0.50

- There are no other formal statistical hypotheses.

10.3. ANALYSES DATASETS

Four analysis populations will be considered: The analysis datasets described in the following section apply to the subjects enrolled in the main study (excluding training cases). The training subjects will not be included in the formal analyses for this protocol.

- Intention-to-Treat (ITT) Population: all enrolled subjects who began a nasal Implant procedure, regardless of concomitant turbinate treatment (i.e., Latera alone or in conjunction with turbinate treatment) or re-implant according to this protocol.
- Modified Intention-to-Treat (mITT) Population: all subjects enrolled who received at least one nasal Implant, regardless of concomitant turbinate treatment. Subjects that received a replacement implant will be included in this analysis dataset.
- Per-Protocol (PP) 6 Month Evaluable Population: subjects with 6 month post-Implant NOSE score assessments in clinic or by telephone, regardless of concomitant turbinate treatment. Subjects that received a replacement implant will not be included in this analysis dataset.
- Latera Stand-Alone Population: subjects who receive at least 1 Latera implant without concomitant turbinate treatment.

10.4. DESCRIPTION OF STATISTICAL METHODS

10.4.1. GENERAL APPROACH

This is a prospective, single arm, open label, controlled study to evaluate the impact of Spirox Latera™ alone or in conjunction with other procedures over 24 months of follow-up. Each subject will serve as their own control, and changes from baseline are of primary interest.

The study reference day (Day 1) is the day of Visit 3 (Treatment).

"Baseline" NOSE score refers to the measurement taken prior to the start of the procedure during the baseline visit.

Continuous variables will be summarized with descriptive statistics (N, mean, SD, median, quartiles), and categorical variables will be summarized as N (%).

Unless otherwise indicated, all p-values and confidence intervals will be 2-sided.

10.4.2. ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint will be the proportion of treatment responders at 6 months post procedure. The mITT analysis dataset will be used to analyze the primary endpoint.

Responder is defined as a subject that has at least one (1) NOSE class improvement or at least 20% NOSE score reduction compared to baseline.

Subjects will be classified as non-responders if neither of these criteria is met.

NOSE score is a PRO instrument which measures the impact of nasal obstruction on quality of life. It is scored in increments of 5 points, and the total score is calculated as the sum of all 5 questions multiplied by 5, where the range is 0 (asymptomatic) to 100 (most extreme deleterious impact on quality of life). The NOSE score classes[17] are based on the total calculated score:

Mild: 5 – 25 points
Moderate: 30 – 50 points
Severe: 55 – 75 points
Extreme: 80 – 100 points

This primary hypothesis will be evaluated for the mITT using a -2-sided exact test[23], and the corresponding exact (Clopper-Pearson) 2-sided 95% confidence interval will be calculated. The null hypothesis that the proportion of responders is $\neq 0.5$ will be rejected if the p-value is < 0.05.

Sensitivity analyses will be conducted to determine the impact of missing data on these results. These analyses will depend on the extent of missing data, and will be detailed in the SAP, but may include:

1. Last observation carried forward (LOCF)
2. Subjects with missing data classified as non-responders
3. Re-implanted subjects classified as non-responders

This analysis will be repeated for the Latera stand-alone Population alone. While this study is not sufficiently powered to reject the null hypothesis for this subgroup, the response rate, 95% confidence interval and p-value will be calculated. See section 10.5 for further details.

10.4.3. ANALYSIS OF THE SECONDARY ENDPOINT(S)

Response proportion as defined in section 10.4.2 will be evaluated for the 1, 3, 12, 18 and 24 month follow-up visits using the same technique as described for the primary endpoint.

Change in nasal airway obstruction from baseline at 1, 3, 6, 12, 18 and 24 months post-procedure as reported by subjects on a VAS 0-100 mm scale (0= no difficulty breathing through nose; 100mm=not-able to breathe through nose) will be analyzed using a mixed model for repeated measures (MMRM). Least-square mean change from baseline and corresponding 95% confidence intervals will be reported.

Baseline VAS score will be analyzed in a separate model, including decongestant use as a covariate. Decongestant use will be considered at baseline only to visualize the turbinate contribution to overall obstruction, thus no decongestant VAS will be assessed at the follow-up visits.

Results from the subject satisfaction questionnaire will be tabulated at 6 months. Sensitivity analyses for missing data will be described in the SAP.

10.4.4. SAFETY ANALYSES

Two analysis sets will be used to summarize adverse events. The ITT analysis set will be used to summarize acute adverse events (through 1 month post procedure), and the mITT analysis set will be used to summarize adverse events over the entire duration of follow-up. The primary safety reporting time-point is 6 months post-implant.

The overall incidence (i.e., number and percent of subjects with 1 or more adverse event) of adverse events, serious adverse device events, serious adverse events, fatal adverse events, and device related events (e.g., possibly, probably or definitely related) will be calculated for the acute phase, through 6 months post-procedure and for the entire duration of follow-up. The overall incidence of mild, moderate and severe events will be calculated by considering the most severe event for each subject.

In addition, the overall incidence for each adverse event type will be calculated. The adverse event types will be classified as defined in section 8.1.1

The implant retrieval rate will be calculated based on the number of implants retrievals per the total number of implants placed.

10.4.5. ADHERENCE AND RETENTION ANALYSES

Protocol deviations will be tabulated. Baseline demographic and medical history will be tabulated by whether the 6 month NOSE score data are available or missing to identify potential systematic differences between subjects with and without 6 month follow-up scores.

10.4.6. BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics, including demographic characteristics, medical history, patient-reported outcomes and physical measurements will be summarized using descriptive statistics.

10.4.7. PLANNED INTERIM ANALYSES

No interim analyses with formal stopping implications will be performed, though changes in NOSE score may be aggregated to facilitate sample size calculations for future studies.

10.4.7.1. INTERIM ANALYSES

No interim analyses with formal stopping implications will be performed, though changes in NOSE score may be aggregated prior to database lock to facilitate sample size calculations for future studies. As there is no opportunity to stop early for efficacy or to alter the study design based on this calculation, there will be no type 1 error adjustment for this analysis.

10.4.8. ADDITIONAL SUB-GROUP ANALYSES

Response percentage, change in NOSE scores and other variables including satisfaction will also be evaluated in the following subgroups:

- Turbinate reduction method - radiofrequency versus mechanical
- Time-dependent presence or absence of allergic rhinitis
- Nasal geometry factors
  - Nose length (above or below median)
  - Nose width (above or below median)
  - Categorical skin thickness

10.4.9. MULTIPLE COMPARISON/MULTIPLICITY

No formal type 1 error adjustment will be made for the analysis of secondary and exploratory endpoints. All endpoints except for the primary endpoint should be considered supportive, and inference should be drawn with caution.

10.4.10. TABULATION OF INDIVIDUAL RESPONSE DATA

Listings of adverse events may be produced.

10.4.11. EXPLORATORY ANALYSES

Cosmesis changes from baseline to 3 month and 6 months, evaluated by Independent Photo Review at select sites only, will also be tabulated.

Endoscopic lateral wall insufficiency score is a 3-level, categorical variable, which will be evaluated for each side separately. Baseline, 1, 3, 6 and 12 month post-baseline scores will be cross-tabulated, and the proportion with improvement will be calculated.

Response percentage, change in NOSE scores, ESS and other variables for procedures including turbinate reductions will be evaluated. Resource use will also be summarized.

10.5. SAMPLE SIZE

The primary study hypothesis is a superiority comparison to a target proportion:

Null Hypothesis H_0: the proportion of responders at 6 months is =0.50, versus
Alternative Hypothesis H_A: the proportion of responders at 6 months is ≠ 0.50

See section 10.4.2 for the definition of response. This hypothesis will be evaluated using an exact test.

In order to have > 90% power to rule out a response rate ≤ 50% at a 5% (2-sided) significance level, assuming a true response rate of 66%, 150 subjects with 6 month follow-up are needed. Assuming about 10% drop-out rate, up to 170 subjects will be enrolled. All mITT subjects will be used for this comparison, regardless of protocol deviations.

The assumed response rate is the minimum value is expected to be consistent with previous trials, where an 80% response rate at 6 months was observed.

The anticipated size of the Latera stand-alone Population is 50 subjects. With only 50 subjects in this cohort, the power to reject the primary null hypothesis is approximately 63%, given a true response rate of 66%. Although this cohort is not sufficiently powered to show significance for a true response rate of 66%, the p-value and exact binomial 95% confidence interval will be calculated for this population. Retrospective power for the actual response rate will also be calculated for this comparison in order to contextualize the results.

Sample size calculations were performed using the package RCT Design for R version 3.2.3.

10.6. MEASURES TO MINIMIZE BIAS

This is a single arm, open label study. Randomization and blinding are not used.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the study sponsor and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.
Source data includes all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aids or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Sponsor will provide Source Documents to the sites.

For each subject consented, the inclusion/exclusion source documentation must be signed by the investigator or authorized delegate from the trial staff. If a subject withdraws from the study, the reason must be noted on the Study Exit eCRF. If a Subject is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

All forms shall be filled out using indelible ink and must be legible. Errors shall be crossed out but not obliterated and correction inserted and the change initialed and dated by the investigator or authorized delegate. The investigator shall ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the eCRF and in all required reports.

Each investigator/institution agrees that they will permit trial-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data and/or documents.

12. QUALITY ASSURANCE AND QUALITY CONTROL

Regular monitoring will be performed according to ICH-GCP. See also **Section 9, Clinical Monitoring**.

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Manufacturing Practices (GMP).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1. ETHICAL STANDARD

The site PI will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6 and the Declaration of Helsinki.

13.2. INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3. INFORMED CONSENT PROCESS

13.3.1. CONSENT AND OTHER INFORMATIONAL DOCUMENTATION PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study device, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting study-related procedures. Site-specific Informed Consent Form will be submitted with this protocol for IRB review and approval.

13.3.2. CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Potential risks and benefits of participation will be discussed with the participants. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A Subject Research Participation Note will be filed in the subject's medical record, documenting that the informed consent process occurred and the subject voluntarily provided written informed consent to participate in the study.

13.4. PARTICIPANT AND DATA CONFIDENTIALITY

All information concerning subjects or their participation in this trial will be considered confidential and maintained in compliance with the HIPAA Rules. Only authorized study sponsor personnel and designated consultants will have access to these confidential files. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this trial. Enrolled subjects will be assigned a unique identifier that will be used to maintain confidentiality of subjects' medical information. Subject names and other protected health information will not be captured on the case report forms.

The sponsor, its designee, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at MedNet Solutions, the EDC system provider utilized for this study. This will not include the participant's contact or any identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites, Spirox, and any third party vendor contacted by Spirox to perform data management activities and/or statistical analysis will be secured and password protected. The identity of a subject will never be disclosed in the event that the study data are published.

13.5. COMPENSATION FOR INJURY

In the event that a subjects is injured as a result of the Latera™ Implant procedure done for the purpose of this study, the sponsor will pay for those medical expenses that are necessary to treat injuries that are not covered by subject's medical insurance or any other third party coverage provided that the Latera Absorbable Nasal Implant was implanted following this study protocol, the instructions for use and the cleared indications for use (i.e., for supporting the upper and/or lower lateral nasal wall cartilage). There are no plans to provide other compensation beyond that which is described herein or in the informed consent document.

14. DATA HANDLING AND RECORD KEEPING

14.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Data reported in the eCRF should be consistent with the source documents or the discrepancies should be explained and captured in the eCRF comments section and maintained in the participant's official study record.

Clinical data (including concomitant medications, and adverse events data) will be entered into iMedNet, a 21 CFR Part 11-compliant data capture system provided by MedNet Solutions.

The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2. STUDY RECORDS RETENTION

Study documents should be maintained in a professional manner and in compliance with the HIPAA Rules as applicable, so as to permit review the Study records, documents, information, data, and materials in full without disclosing to Sponsor any third party confidential or proprietary information. Site shall maintain all such records for the Study for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained. Spirox will maintain records according to the company's record retention policy.

14.3. PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirement. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report significant deviations of identification of the protocol deviation to the study Sponsor. All deviations must be documented on a protocol deviation eCRF. Protocol deviations must be sent to the local IRB per the IRB's reporting requirements. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

14.4. PUBLICATION AND DATA SHARING POLICY

Authorship and manuscript composition will reflect joint cooperation between the investigator, the study sites, and the study Sponsor. No individual publications will be allowed prior to completion of the final report of the study except as agreed with the study Sponsor. Additional details of data sharing policy can be found in each site's Clinical Trial Agreement.

The sponsor request that all publications are reviewed and approved prior to submission to publication.

The study Sponsor will register and report the results of the study on ClinicalTrials.gov.

15. STUDY ADMINISTRATION

15.1. STUDY LEADERSHIP

The Study Team will oversee the conduct of the study. The Study team will be composed of representatives of the Sponsor including the Medical Monitor, and the study Principal Investigators. The Study Team will meet periodically to review study progress and any available results.

16. CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. Spirox has established policies and procedures, including those pertaining to the Sunshine Act, to disclose conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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Appendix I – PROTOCOL REVISION HISTORY

Version	Date	Significant Revisions
1.0	11Oct2016	Initial Protocol Release
1.1	24Oct2016	• Clarification of pregnancy testing population and procedure. • Defining Training Case completion criteria. • Minor administrative corrections. • Administrative corrections and clarifications.
2.0	February 15, 2017	• Revised to improve content organization, provide clarity and enable better referencing. All addendums have been renamed as appendices and incorporated into this document • Added allowance to replace implants. • Added exclusion criteria #21 to allow for investigator's discretion to exclude a subject for unanticipated reasons. • Number of sites increased to 25 to ensure timely trial completion. • Added option to obtain discretionary images or videos such as documentation of implantation technique or adverse events (e.g. hematoma). • Increased frequency of Lateral Wall Motion Video collection from baseline and 6 months to also include 1, 3, and 12 moths follow up. • Added endoscopic assessment of turbinate hypertrophy and septal deviation at 1, 3, 6 and 12 months to evaluate if there is any residual contribution of these post-surgery at all time points • Added optional procedure to collect endoscopic videos in conjunction with air flow measurements
2.1	07Sept2017	• Addition of 18 month and 24 month follow up evaluations

Appendix II – RATIONALE FOR NONSIGNIFICANT RISK STUDY

Background

1. The Latera™ System (Absorbable Nasal Implant and Delivery Device) is a commercially available device that received FDA clearance on June 23, 2016 (K161191). The device is indicated for "supporting nasal upper and lower lateral cartilage." Clinical performance data was submitted in support of the initial Implant clearance (K152958). The Implant and Delivery Device were evaluated in a German clinical study that evaluated device safety and performance in 30 subjects.
2. Since clearance was obtained in June 2016, the device has been used in accordance with its cleared indications for use and instructions for use in approximately 300 US commercial cases (with over 500 implants placed, approximately 90% bilateral placement). These cases have included device usage across a spectrum of patients that include both stand alone cases (11%) and cases conducted in conjunction with standard of care procedures (89%) for addressing other types of nasal obstruction (i.e., septoplasty and/or turbinate reduction procedures). To date, no clinically significant complaints or MDR reportable events have been received.
3. Spirox developed the subject clinical protocol to evaluate device usage in a controlled manner in the US and to collect data to support potential regulatory applications and publications regarding device usage.
    a. In the proposed study protocol, the Latera Implant is being used according to its cleared indications for use and instructions for use (i.e., to support nasal lateral cartilage).
    b. While the Sponsor believes that this study meets the requirements of an exempt study (i.e., device is being used in accordance with its cleared indications for use and instructions for use), Spirox has opted to comply with a higher regulatory standard and as such respectfully requests IRB approval to conduct this study under the abbreviated IDE requirements. The decision to conduct this protocol as an NSR study as opposed to an exempt study affords Spirox with the opportunity to use this data to support potential regulatory applications and publications. For these reasons and those articulated below, Spirox does not believe that device usage under the subject study protocol meets the requirements of a significant risk study.

Non-Significant Risk Rationale for Latera Device

1. 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 Latera Implant is being used according to its cleared indications for use and instructions for use. The device was evaluated in a 30 patient clinical study in Germany. Thirty subjects have reached their 12 month follow up period and 18 subjects have reached the 18 month follow up period; no serious risks to the health, safety or welfare of the subjects have been reported. The device has been used in approximately 300 commercial cases since June 2016, and no clinically significant complaints or MDR reportable events have been received.*
2. The device is not purported or represented to be used for supporting or sustaining human life;
    - *The Latera Implant is used for supporting nasal lateral cartilage and is not used to support or sustain human life. Device usage is optional / elective and may be used to help reduce quality of life symptoms associated with nasal obstruction. Nasal obstruction associated with weak lateral cartilage or otherwise is not a life threatening disease or condition.*

3. 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 is used to support the nasal lateral cartilage and reduce quality of life symptoms associated with nasal obstruction, a condition that is not considered life-threatening. Therefore, device usage is optional / elective and is not of a substantial importance in treating disease. Several other elective options exist for supporting the lateral cartilage. These options range from the use of external nasal strips (e.g., over the counter Breathe Right strips) to surgical procedures employing the use of autologous and synthetic grafts. Latera is simply one option for supporting the lateral cartilage and is not for a use of substantial importance in treating disease (i.e., Latera cartilage support is used to reduce quality of life symptoms associated with nasal obstruction, not for a use of substantial importance in treating disease or otherwise preventing impairment of human health).*

4. The device does not otherwise present a potential for serious risk to the health, safety or welfare of the subject.

    - *The device has been used in a 30 patient clinical evaluation with up to 18 months of follow up and in over approximately 300 commercial cases since June 2016. No reports of a potential for serious risk to the health, safety or welfare of any subjects have been noted.*

Appendix III - IFU

Appendix IV – POST PROCEDURE INSTRUCTIONS

Appendix V - NOSE SCALE

Appendix VI - EPWORTH SLEEPINESS SCALE (ESS)

Appendix VII - LATERAL WALL MOTION CAPTURE INSTRUCTIONS

Appendix IX - 3D CAMERA IMAGE CAPTURE & TRANSFER INSTRUCTIONS