spirox

SPI-CP-301

Protocol Title:

Spirox Latera™ Implant support of lateral nasal wall cartilage (LATERAL-OR) study

Version Number: v 2 . 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
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	Monitored 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

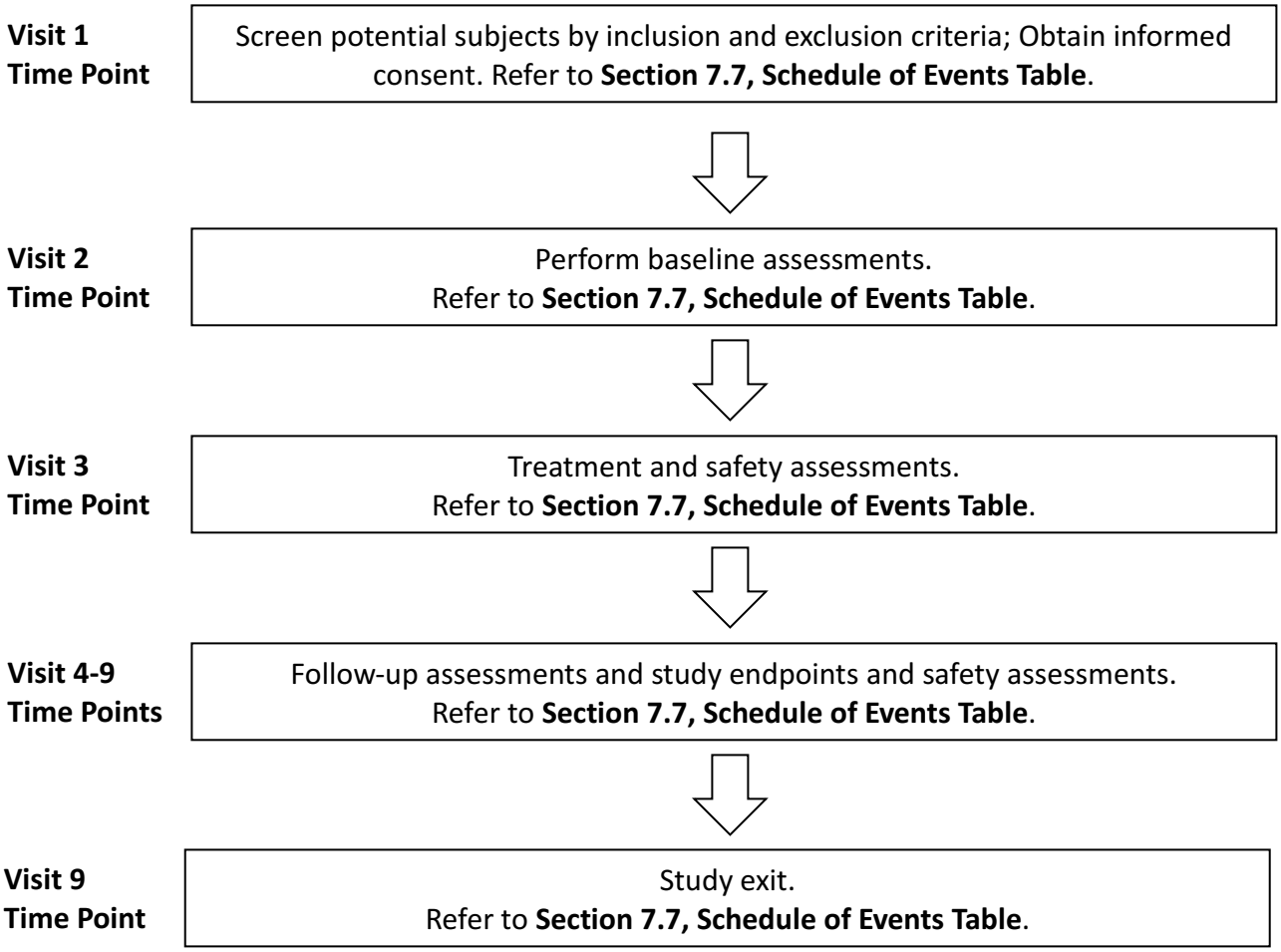
_____

Investigator's Signature Date

PROTOCOL SUMMARY

Title:	Spirox Latera™ Implant support of lateral nasal wall cartilage (LATERAL-OR) 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 septoplasty and/or turbinate reduction procedures in an operating room setting.
Eligibility Criteria	Reference Sections 5.1 and 5.2 below.
Primary Endpoints:	*Primary Efficacy Endpoint:* Proportion of treatment responders at 6 months post procedure. Responder is defined as 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 below.
Population:	Up to 170 subjects will be enrolled
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



CLINICIAL 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 SCIENTIFIC 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 utilized.

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 via 510(k) submissions 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 septoplasty and/or turbinate reduction procedures in an operating room 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 treated. 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.

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. The frequency of peri-operative adverse events is low, with an overall admittance rate of hospitalization of 0.85%. The most common reason for readmissions is hemorrhage[19]. Possible risks and complications for each procedure are described below.

Septoplasty procedure risks may include:

- Infections
- Nasal bleeding that may require surgical intervention or nasal packing
- Numbness of the nose, cheeks, and upper lip
- Bruising and swelling of the nose, eyelids, and upper lip
- Scarring, septal perforations, nose shape change including “saddle nose” deformity and nostril asymmetry
- A decreased sense of smell
- General anesthesia effect
- Pain and discomfort in the nose, particularly at the front
- Continued nasal obstruction
- Nasal crusting
- Cerebrospinal fluid leak
- Death

The following complication rates have been reported after septoplasty[20]:

- Infections – 3%
- Hematomas – 2-7%
- Septum perforations – 3-25%
- Changes in nose shape -5-60%
- Smelling disorders – less than 1%

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 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. Only procedure-trained investigators that are authorized by the sponsor will be allowed to place the devices during the study. In addition, prior to initiation of enrollment, procedure-trained 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 principal 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 primary contributor to NAO (no septal or turbinate treatment). For subjects requiring lateral cartilage support that also have deviated septum and enlarged turbinates, it is expected that the Latera Implant may provide additional benefit to the subjects who are also undergoing concurrent septoplasty and/or turbinate procedures. 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-OR 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 septoplasty and/or turbinate reduction procedures in an operating room 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 serves as his or her own control.

4.2. STUDY ENDPOINTS

4.2.1. PRIMARY ENDPOINTS

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

- *Responder is defined as 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 though 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 way 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 and 6 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 3 and 6 months (at select sites).
8. Allergic rhinitis status at 1, 3, 6 and 12 months.
9. Nasal geometry: length of nose, height and width of nose, skin thickness of lateral wall at baseline.
10. 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 nasal Implant procedure alone or with septoplasty and/or a turbinate reduction procedure in an operating room setting.
6. The subject has appropriate nasal and facial anatomy to receive 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 inability of subject to tolerate.

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 other than septal deviation and/or 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 general anesthesia, managed anesthesia care (MAC) or conscious sedation.
20. For female subjects, subject is 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 170 subjects will be enrolled in the study to reach target of 150 subjects completing the 24 Month follow-up post-procedure. 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 will receive a stipend for their time and to cover travel costs as follows: Subjects who complete the study are eligible for a total stipend of up to $700 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 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, or 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. PARTICIPANT WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. Investigators may withdraw 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 site will document Adverse Events, Concomitant Medications changes, as appropriate, and all available data in the eCRFs. The clinical site will also complete the Study Exit eCRF.

5.5. 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 study suspension or termination, will be provided by the suspending or terminating party to the investigator and regulatory authorities. If the study is prematurely terminated or 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 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 only be followed per the study schedule through the 24-Month close-out visit in the event the study is re-started. Subjects that have been consented, but not yet undergone index procedure, will be delayed until a determination to restart enrollment has been made. These latter 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. The devices used in this study will be purchased through standard channels for obtaining commercial product from 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.

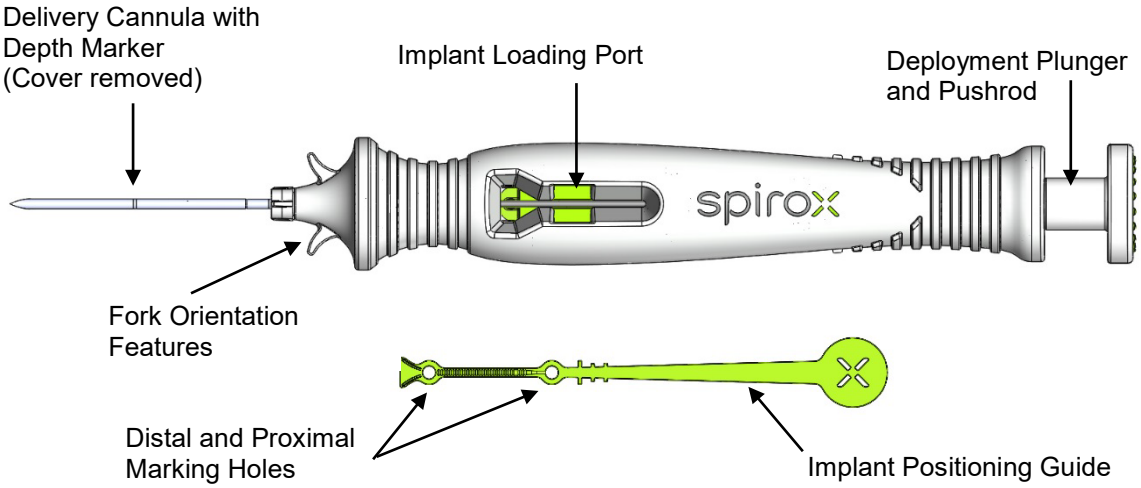

Figure 2: Delivery Device and Implant Positioning Guide

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 tools 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 Addendum A Latera IFU).

6.5. STUDY DEVICE ACCOUNTABILITY PROCEDURES

The investigator will maintain records for all devices received and used. The lot number of each unit used will be tracked on the subject's eCRF.

7. STUDY PROCEDURES AND SCHEDULE

7.1. STUDY VISIT SPECIFIC PROCEDURES

7.1.1. Subject Screening and Enrollment Visit (Visit 1)

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

Female subjects that may be pregnant will undergo a pregnancy test per the individual study sites' standard operating procedures.

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 who indicate 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.

Subjects that have signed the ICF and meet the eligibility criteria will be scheduled for Visit 2. Subjects will be considered enrolled upon signing the ICF and meeting the study eligibility criteria.

Study data should be entered into the EDC within 24 hours of completion of visit.

Subjects that have provided written informed consent and meet the eligibility criteria may also be invited to participate in "Latera™ Patient Experience and Testimonials" (see Section 7.2.15).

7.1.2. Baseline Evaluation Visit (Visit 2)

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.

The Investigator will record medical history and concomitant medications on the provided source worksheets. 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) (See Section 7.2.1)
2. Baseline Health Economics Questionnaire (See Section 7.2.3)
3. Demographics & Nasal Medical History (See Section 7.2.5)
4. Document Concomitant Medications (See Section 8.9)
5. Baseline Nasal Exam (See Section 7.2.6)
6. Modified Cottle Maneuver (See Section 7.2.8)
7. Lateral Wall Motion Video (See Section 7.2.9)
8. Photography- Cosmetic (selected sites only, See Section 7.2.10)
9. Photography- 3D (selected sites only, See Section 7.2.11)
10. NAO Breathing Assessment (See Section 7.2.2)
11. Assessment of Turbinate Hypertrophy Contribution to NAO (See Section 7.2.12)

Adverse events observed during the baseline visit will be collected and documented. Spirox will be notified as necessary pursuant to the description provided in Section 8. Data collected for baseline visits should be entered into the EDC no later than seven (7) days after the completion of visit. Upon completion of the baseline visit, the subject will be scheduled for Treatment Visit (Visit 3).

7.1.3. Treatment Visit (Visit 3)

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). 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 form.

During this visit, the subject will be treated with the study device according to the Instructions for Use. The procedure will be completed in either a hospital or ASC operating room setting. Only procedure-trained investigators that are authorized by the sponsor will be allowed to place the devices during this study.

The following procedures will be completed for the Index procedure visit and placement of the Latera™ Implants:

1. Subject will receive general anesthesia, monitored anesthesia care (MAC), or conscious sedation per standard operating room procedures.
2. Amoxicillin or equivalent antibiotic should be administered via either P.O. or IV to the subject before the Implant(s) is placed.
3. Subject will undergo all other planned procedures (e.g., septoplasty and/or turbinate reduction) first, with delivery of the Implant(s) being the last step.
4. The skin of the nose and the nasal mucosal surface should be cleaned and prepped with an antiseptic solution (e.g. isopropyl alcohol or betadine ophthalmic).
5. The nasal anatomy will be examined and target trajectory for the Implant(s) will be established and marked with the aid of the implant positioning guide per IFU (Addendum A).

6. Images of planned placements should be captured.
7. Prior to placement of the Implant(s), appropriate topical and local anesthesia should be administered to the injection site, depending upon the physician's judgement; for example a solution of 2% Lidocaine with Epinephrine injected locally (1:100,000) may be used. The anesthesia may be injected along the proposed implantation track, starting at the alar rim and progressing to the supra-periosteal region of the maxilla and along the alar rim at the area of targeted insertion. In addition, an infraorbital nerve block may be administered with the same anesthetic solution.
8. The treatment area should also be pre-treated with an antibiotic ointment (e.g. Mupirocin or equivalent) to minimize potential infection risk is recommended.
9. The implant(s) (unilateral or bilateral) will be delivered per the Spirox IFU20680 (Addendum A).

    Note: Only one Implant per side may be placed.

All medication used during the procedure visit (pre-, during and post-procedure medications) and resource utilization will be recorded.

IMPORTANT: Prior to discharge, subjects will be provided with the post procedure reminder form (**Addendum F**). 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 7.2.11 for information on BrickFTP).

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.

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

7.1.4. Follow-Up Evaluation Visits (Visit 4-9)

Safety and performance data will be collected at 1 month (+/- 7 days), 3 months (+/-15 days), 6 months (+/- 15 days) 12 months (+/- 30 days), 18 months (+/- 30 days) and 24 months (+/- 30 days) post procedure.

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. Subject Satisfaction Questionnaire (See Section 7.2.13)*
4. Post Procedure Health Economics Questionnaire (See Section 7.2.4)*
5. Update Concomitant Medications, if changed (See Section 8.9)
6. Adverse Events since last visit (See Section 8)
7. Post Procedure Nasal Exam (see section 7.2.7)*
8. Lateral Wall Motion Video – 6 Month Visit only (See Section 7.2.9)*
9. Photography – Cosmetic (select sites only) – 3 and 6 Month Visits only (See Section 7.2.10)*
10. Photography – 3D (select sites only) – 3, 6 and 12Month Visits only (See Section 7.2.11)*

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

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 and documented in the Study Exit eCRF.

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. The NOSE scale may additionally be completed at the Treatment Visit if more than 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

Participants 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 Addendum B).

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 patient-reported outcome 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, 18 Month and 24 Month visits.

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 that the patient marks.

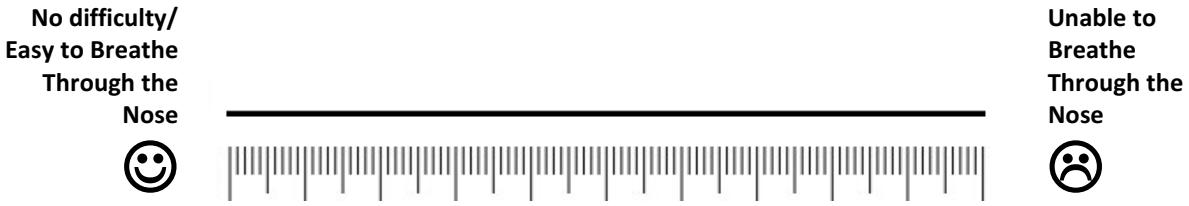

Figure 3: Visual Analog Scale. Left side represents 0mm and right side represents 100mm.

7.2.3. Baseline Health Economics Questionnaire

The baseline health economics questionnaire administered during the baseline visit is a PRO used to assess the frequency and type of doctor visits related to the Nasal Airway Obstruction condition over one year prior to procedure.

7.2.4. Post Procedure Health Economics Questionnaire

The post procedure health economics questionnaire administered post-procedure is different from the version completed at baseline in the timeframes being referenced. The post-procedure health economics survey will assess frequency and type of doctor visits related to the Nasal Airway Obstruction condition since the index procedure. Do not include visits related to the study when recording the frequency. Subjects will complete the Questionnaire at the 1 Month, 3 Month, 6 Month and 12 Month visits.

7.2.5. Demographics & Nasal Medical History

Demographic information, such as age, gender, ethnicity, race and date of onset of nasal obstruction will be ascertained at the baseline visit.

Relevant nasal medical history will also be captured at the baseline visit and will include a complete review of nasal system and evaluation of symptoms, including an assessment of nasal airway obstruction signs and symptoms. A history of prior trauma or surgery, including nasal trauma or surgery, will be noted, as well as other medical 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.).

7.2.6. Baseline Nasal Exam

Nasal exams will be conducted during the baseline visit and will include collection of nasal anatomy parameters such as nose length, nose height, 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.

7.2.7. Post Procedure Nasal Exam

An internal and external nasal physical exam will be conducted at each follow-up visit to document any changes in nasal appearance. In addition, during 6 months visit, each side of the nose will be examined with an endoscope to 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.

7.2.8. 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**).

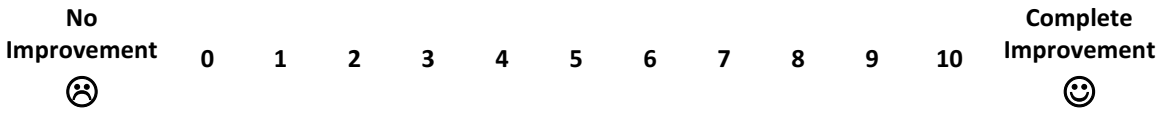

Figure 4: Verbally reported improvement in breathing with supported lateral wall.

7.2.9. Lateral Wall Motion Video

Using an endoscope, the investigator will record lateral wall motion at rest and at inspiration for each side of the nasal vestibule. Videos will be collected at the Baseline and 6 Month follow-up Visits. 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).

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 **Addendum C** "Lateral Wall Motion Capture Instructions".

7.2.10. Photography - Cosmetic

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 at baseline, 3, and 6 month time points four (4) static photographic views (straight, left side, right side and chin-up) will be taken and two (2) at a full inhale photographic views (chin-up view and top-down).

Cosmetic photography review will be limited to approximately 3 sites and subject participation is optional.. Images will be blinded (e.g. black boxes placed over the eyes) by the sponsor prior to being sent to the independent reviewer. Sites selected for cosmetic review will also be sites participating in 3D Photography (see Section 7.2.11). Images will be transferred using BrickFTP site.

See **Addendum D** "Cosmetic Photo Capture Instructions".

7.2.11. Photography – 3D

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.

3D Images will be taken to record baseline NVC of both the left and right side of the nose under static conditions and at inhale. Static and inhales images for both sides will be taken at 3, 6 and 12 month time points, to evaluate the change in the nasal collapse depth from baseline.

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. See Addendum D "3D Imaging Procedure" for comprehensive image capture and analysis procedures.

Images will be transferred using BrickFTP site.

See **Addendum E** "3D Camera Imaging Procedure".

7.2.12. Assessment of Turbinate Hypertrophy Contribution to NAO

After completion of all other assessments at the Baseline Visit, 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).

7.2.13. Subject Satisfaction Questionnaire

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

7.2.14. 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. Images or videos will be transferred to Spirox using BrickFTP.

7.2.15. 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. 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.

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 septoplasty and/or turbinate reductions in addition to placement of the Implants to address other potential causes for the nasal airway obstruction.

Septoplasty is a common surgical procedure to correct a deviated septum — a displacement of the bone and cartilage that divides the nasal passages. During the procedure, the lining (the mucosa) is first lifted off the cartilage and bone. The cartilage and bone can then be reshaped. Sometimes, portions of the cartilage and bone need to be removed. The lining is then laid back down.

Turbinate reduction or turbinate resection is a common procedure that is performed alone or in conjunction with septoplasty. 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.

Septoplasty and/or 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 Septoplasty and/or 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, according to the study protocol, the following treatments are not 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).

7.7. STUDY SCHEDULE OF EVENTS TABLE

Study Events	Screening & Enrollment (Visit 1)	Baseline Evaluation (Visit 2)[1]	Treatment (Visit 3)	Follow Up 1 mo (Visit 4)	Follow Up 3 mo (Visit 5)	Follow Up 6 mo (Visit 6)	Follow Up 12 moStudy 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[2]						
NOSE Scale (PRO) [3]	X	X	X[2]	X	X	X	X	X	
NAO Breathing Assessment (PRO)		X		X	X	X	X	X	
Subject Satisfaction Questionnaire (PRO)				X	X	X	X		
Health Economics Questionnaire (PRO)		X		X	X	X	X		
Nasal Medical History/Nasal Geometry		X							
Nasal Exam		X		X	X	X	X		
Lateral Wall Motion Video		X				X			
Photography- 3D Camera (select sites)		X			X	X	X		
Photography –Cosmetic (select sites)		X			X	X			
Turbinate Hypertrophy Contribution to NAO assessment (Nasal Decongestant)		X							
Photography – Planning Images			X						
NAO Treatment			X						
Concomitant Medications		X	X	X	X	X	X		
Adverse Event Assessment			X	X	X	X	X		X
Adverse Device Effects Assessment								X	
Complete Study Exit Form								X[4]	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] If Visits 1, 2 and 3 are done on the same day, the Screening and Treatment NOSE Scales are not required.
[4] 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. The clinical site will additionally complete the Study Exit eCRF. 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
- SAE or SADE
- Severity of event
- Relation to Study Device and/or procedure
- Action taken
- Descriptive narration of Event/Effect

8.1.1. 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
- New hospitalization

8.1.2. 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.

8.1.3. 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)).

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 concomitant procedures, such as septoplasty and turbinate reduction

The clinician's assessment of an AE's relationship to the study device, implant procedure and/or the concomitant procedure(s) 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 should be reported. All AEs must have their relationship to the Latera study device or Latera device procedure assessed.

For all collected AEs, the clinician 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.

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 concomitant procedures (septoplasty and/or turbinate reduction).

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 device or procedure-related AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician'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 AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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 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 signed off 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 tent (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
- Insufficient compliance to protocol
- 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 MONTIORING

Clinical monitoring and oversight of the study will be conducted by 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.

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 ≠ 0.50

- There are no other formal statistical hypotheses.

10.3. ANALYSES DATASETS

Three analysis populations will be considered:

- Intention-to-Treat (ITT) Population: all enrolled subjects who began a nasal Implant procedure
- Modified Intention-to-Treat (mITT) Population: all subjects enrolled who received at least one nasal Implant
- Per-Protocol (PP) 6 Month Evaluable Population: subjects with 6 month post-Implant NOSE score assessments in clinic or by telephone

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 patient will serve as his or her own control.

The study reference day (Day 1) is the day of the Implant procedure.

"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.

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

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

NOSE score is a patient-reported outcome 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[16] 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 6 Month Evaluable Population 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

10.4.3. ANALYSIS OF THE SECONDARY ENDPOINT(S)

Response proportion as defined in section 10.4.2 will be evaluated for the 1, 3,6, 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 in each class) 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 according to the following categories:

- Excessive Inflammation
- Significant Foreign body sensation
- Excessive Pain or discomfort
- Infection
- Implant Extrusion, defined as body rejection of implants
- Implant Retrievals, defined as surgeon or subject initiated removal of implants not associated with body rejection of implant
- Implant bent or fractured
- Implant loose
- Implant migration
- Skin irritation
- Hematoma
- Unintended perforation of the skin
- Other

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. SAFETY REVIEW

All adverse events will be reviewed by the Medical Monitor. For any reported SAE, the Medical Monitor and Scientific Advisory Board members will review the event and issue a recommendation.

The study sponsor will be responsible for notifying FDA of SAEs pursuant to the applicable MDR reporting requirements 21 CFR 803.

10.4.7.2. EFFICACY REVIEW

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 2 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 and 6 month post-baseline scores will be cross-tabulated, and the proportion with improvement will be calculated.

Response percentage, change in NOSE scores and other variables including satisfaction will also be evaluated by type of procedure (implant alone versus combinations with septoplasty and/or turbinate reductions).

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 expected to be consistent with previous trials, where an 80% response rate at 6 months was observed.

Sample size calculations were performed using the package RCTDesign 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 electronic 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
0.1	22July2016	Initial Protocol Release
0.2	27Jul2016	Addition of Inclusion Criteria 8: Previous medical management.
0.3	22Aug2016	Amendment applies to all subjects/sites, consented on or after approval date. • 2.2 Prior Investigation data updated. • 2.3.2 Potential Risks & Benefits updated/clarified. • 4.2 Study Endpoints - VAS scale corrected. • 5.1 Inclusion Criteria #8 refined. • 6. Study Device section updated. • 7. Study Procedures and Schedule clarified. • 8.1 Specification of Safety Parameters clarified. • 13.5 Compensation for Injury - Section added. • Administrative corrections/updates.
1.0	13Dec2016	Amendment applies to all subjects/sites, consented on or after approval date. Subjects consent prior to amendment will be re-consented. • Appendix II – Nonsignificant Risk Rationale added. • 4.2.1 Clarification of Primary endpoint. • MAC/Conscious sedation • Consent for patient experience and additional imaging • Discharge instructions • Increased number of sites • Inclusion criteria 8 clarified • Exclusion criteria 4 updated • Exclusion criteria 21 added • Schedule of events clarified to allow screening, baseline and treatment in one day • Schedule of events clarified to only need 1 NOSE score if screening, baseline and treatment are less than 30 days apart • Study procedures re-organized into section on visits and evaluation methods for clarity • Administrative corrections/updates
1.1	16Dec2016	• Limited frequency of evaluation of degree of inferior turbinate hypertrophy and septal deviation to baseline and 6 months nasal exams
1.2	07Sept2017	• Addition of 18 month and 24 month follow up evaluations

APPENDIX II – NONSIGNIFICANT RISK RATIONALE

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.*