The **V**ivaer® Procedure for Treatment of Nasal **A**irway Obstruction – A Prospec**T**ive, Multicenter **R**andomized Controlled Tri**A**l **C**omparing Vivaer to Sham Control **(VATRAC)**

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Sponsor Representative:	*<If the sponsor is not a resident in the country(ies) in which the clinical investigation is to be carried out, the name and address of a representative in that country (those countries) can be required according to national or regional regulations>*	

INVESTIGATOR

I, the undersigned, certify that I have reviewed this Clinical Investigational Plan (CIP) and agree to abide by the terms of the study described herein and within the Investigator Agreement, Clinical Trial Agreement and according to the Declaration of Helsinki and The Belmont Report as well as any conditions imposed by the reviewing Institutional Review Board, Ethics Committee, U.S. FDA or other regulatory agency.

Site Name: _____

Print Name: _____

Signature: _____ Date: _____

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Protocol Summary

Title of Study:	The **V**ivaer® Procedure for Treatment of Nasal **A**irway Obstruction - A Prospec**T**ive, Multicenter **R**andomized Controlled Tri**A**l **C**omparing Vivaer to Sham Control **(VATRAC)**
Purpose:	The purpose of this study is to compare the Vivaer procedure for treatment of nasal airway obstruction (NAO) with a sham procedure that simulates the actual procedure as closely as possible absent the delivery of radiofrequency (RF) energy to the nasal tissue.
Study Device:	Vivaer® ARC Stylus
Indications for Use (U.S.):	The Vivaer ARC Stylus is indicated for use in otorhinolaryngology (ENT) surgery for the coagulation of soft tissue in the nasal airway, to treat nasal airway obstruction by shrinking submucosal tissue, including cartilage in the internal nasal valve area. The Aerin Console is an electrosurgical system intended to generate radiofrequency (RF) electrical current for the use of an Aerin Medical Stylus. The Aerin Console is indicated for use in small clinic, office or hospital environments.
Intended and Indications for Use (European Union):	The Vivaer ARC Stylus is intended to improve nasal breathing by modifying the soft tissues of the nasal airway. It is indicated for use in patients who experience poor nasal breathing or chronic nasal obstruction. The Aerin Console is an electrosurgical system intended to generate radiofrequency (RF) electrical current for modification of soft tissues during ear, nose and throat procedures, when used with an Aerin Medical Stylus. It is indicated for use in delivering radio-frequency energy to tissues as part of ear, nose and throat procedures in small clinic, office or hospital environments.
Study Objective:	The primary objective is to assess the performance of the Vivaer procedure compared to a sham procedure with respect to individual participant success rates when used as a treatment for nasal airway obstruction. Individual participant success (“responder”) is defined as at least 1 Nasal Obstruction Symptom Evaluation (NOSE) Scale class improvement or an improvement (decrease) in NOSE Scale score of 20% or more from baseline at the 3-month evaluation.

Study Design:	The study is designed as a multicenter (up to 20 sites), prospective, randomized, controlled superiority trial with a one-way crossover component available to participants randomized to the control arm. A 2:1 site-stratified randomization will be used to allocate participants with NAO to either the active treatment arm (Vivaer procedure) or the control arm (sham procedure) to provide up to 120 total participants in the following groups: o 80 active treatment (Vivaer procedure) o 40 inactive treatment (sham procedure) All participants will be evaluated in-office prior to treatment and following treatment at week 4 (1 month) and week 13 (3 months). The 3-month evaluation will be used for the primary endpoint analysis. Active treatment participants (Vivaer procedure) will have an extended follow-up with evaluations conducted in-office at 6 months (26 weeks) and remotely at 12 months (52 weeks) and 24 months (104 weeks). Participants receiving the sham procedure may elect to crossover to the active treatment arm (Vivaer procedure) within 30 days after the 3-month follow-up evaluation provided they still meet all eligibility criteria. Continued follow-up will be conducted at 1, 3, 6, 12, and 24 months after the Vivaer procedure to provide additional information on longer-term efficacy and duration of treatment effect. Participants that received the sham procedure and do not elect to crossover or no longer meet all eligibility criteria will be exited from the study following the 3-month evaluation.
Active Treatment Arm (Vivaer procedure):	The Vivaer procedure will be performed in the study clinic using the Vivaer ARC Stylus and Aerin Console. The Vivaer ARC Stylus is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue when connected to the Aerin Console radiofrequency generating device. Participants in this study will undergo bilateral treatment of the nasal valves in a single study session. Each side of the nose will be treated with up to four (4) non-overlapping applications of RF energy at the junction of the upper and lower lateral cartilage on the lateral nasal wall. The default treatment settings will be used for the study: temperature 60° C, power 4 watts, treatment time 18 seconds, and cooling time 12 seconds. No repeat (“touch up”) procedures will be permitted after the initial procedure through the end of the study (24 months).
Control Arm (Sham procedure):	The sham procedure will be performed in the study clinic using the Vivaer ARC Stylus while audible sounds that accurately simulate the Aerin Console’s active treatment are produced even though RF energy is not being generated or delivered. All other aspects of the procedure will be the same as used for the active treatment, including administration of anesthetic agent(s).

Primary Study Hypothesis:	The proportion of participants in the active treatment arm (Vivaer procedure) with a successful outcome (responders) will exceed the proportion of participants in the control arm (sham procedure) with a successful outcome (responders) at 3 months postprocedure.
Primary Endpoint:	The primary endpoint is the responder rate at 3 months after the procedure for the randomized participants.
Secondary Endpoints:	• Mean change in NOSE Scale scores from baseline to 3 months after procedure. • Frequency of device-related and procedure-related serious adverse events through the 3-month evaluation.
Other Effectiveness and Safety Measures:	Adverse events - Incidence (type and category) of adverse events overall and by follow-up interval. Nasal Assessment - The target nasal valve area within each nostril will be visually assessed at baseline, just prior to treatment (if screening and procedure occur on different days), immediately after treatment, at 1 month, 3 months, and 6 months after the procedure. The use of an endoscope for visual assessment is required. Representative video of each nasal passage will be captured for each assessment. NOSE Scale score: • Mean and mean change from baseline at the 3-, 6-, 12-, and 24-month follow-up evaluations. • Distribution of NOSE Scale score severity categories (mild, moderate, severe, extreme) at the 3-, 6-, 12-, and 24-month follow-up evaluations. • Mean, change from baseline in mean, and response distribution of the 5 components of the NOSE Scale score (nasal congestion, nasal blockage, trouble breathing, trouble sleeping, and getting enough air during exercise) at the 3-, 6-, 12-, and 24-month follow-up evaluations. • Proportion of responders based on improvement in NOSE Scale score at the 3-, 6-, 12-, and 24-month follow-up evaluations. Visual analog scale (VAS) for pain - perception of pain associated with the procedure on a 0 to 100 mm scale with 0 indicating no pain and 100 indicating the worst pain imaginable assessed immediately after treatment, and at 1-month and 3-month follow-up evaluations. Visual analog scale (VAS) for ease of breathing - perception of the ability to breathe through the nose on a 0 to 100 mm scale with 0 indicating no difficulty and 100 indicating extreme difficulty assessed at baseline, 1-month, 3-month, and 6-month follow-up evaluations.

	Epworth Sleepiness Scale (ESS) - mean and change from baseline in the ESS score at each evaluation. The ESS evaluates the self-reported likelihood of dozing or falling asleep in 8 daytime situations with likelihood rated No Chance (0), Slight (1), Moderate (2), or High Chance (3) administered at baseline and the 1-, 3-, 6-, 12-, and 24-month follow-up evaluations. Participant Satisfaction Assessment - Five question self-reported survey of satisfaction with the procedure and recommendation to others administered at the 3-, 6-, 12-, and 24-month follow-up evaluations. Change in amount of "as needed" (PRN) medication/device use for nasal obstruction symptoms - Self-reported assessment of an increase, no change, or decrease in as needed medications and/or devices being used for treatment of nasal symptoms at each evaluation compared to use prior to the procedure administered at the 1- 3-, 6-, 12-, and 24-month follow-up evaluations. Medications - Medications associated with relief or treatment of nasal airway obstruction symptoms will be documented at baseline and updated as necessary at each evaluation. In addition, medications associated with treatment of adverse events will be documented.
Duration of Study:	The primary endpoint will be evaluated at 3 months. In addition, evaluations at 6, 12, and 24 months after treatment will extend follow-up to 2 years for evaluation of longer-term efficacy. Participants receiving the sham procedure and meeting all eligibility requirements may elect to crossover and receive the active Vivaer procedure within 30 days after the 3-month evaluation with continued follow-up for 24 more months for a total of 28 months of follow-up. Study enrollment is anticipated to be completed within 12 months. Therefore, total study duration is anticipated to be approximately 40 months.
Study Centers:	Up to 20 sites in the United States (U.S.) and Europe
Participants:	120
Inclusion Criteria:	1. Age 18 to 85 years (inclusively). 2. Willing and able to provide informed consent. 3. Willing and able to comply with the subject-specific requirements outlined in the Study Protocol. 4. Seeking treatment for nasal obstruction and willing to undergo an office-based procedure. 5. Baseline Nasal Obstruction Symptom Evaluation (NOSE) Scale score $\geq$55.

6. Nasal valve is a primary or significant contributor to the patient's nasal obstruction as determined by the study investigator (based on clinical presentation, physical examination, nasal endoscopy, etc.) and the patient has a positive response to any of the following temporary measures (based on patient history or office exam):
   - Use of external nasal dilator strips (eg, Breathe Right Strips)
   - Use of internal nasal dilator cones
   - Modified Cottle Maneuver (manual elevation of the lateral nasal wall using a small instrument or cotton-tipped applicator to open the nasal valve)
   - Cottle Maneuver (manual lateral retraction of the cheek to open the nasal valve)
7. Dissatisfaction with medical management as judged by the patient. Defined as failed medical therapy (eg, decongestants, antihistamines, and/or nasal sprays for an appropriate period of time), but a positive response to internal or external nasal dilators.

Exclusion Criteria:

1. Prior surgery of the lateral nasal wall, including cephalic resection of the lower lateral cartilage, dome division or suture plication, alar graft or spreader graft placement.
2. Rhinoplasty, septoplasty, inferior turbinate reduction or functional endoscopic sinus surgery (FESS) within the preceding 3 months.
3. Severe case of any of the following: septal deviation, turbinate hypertrophy, polyps, or ptotic nose tip believed to be the primary contributor to the patient's nasal obstruction symptoms and warranting surgical intervention.
4. Any adjunctive surgical nasal procedure planned on the same day or within 6 months after the Vivaer procedure.
5. Known or suspected to be pregnant or is lactating.
6. Participating in another clinical research study.
7. Other medical conditions which in the opinion of the investigator would predispose the patient to poor wound healing or increased surgical risk, or poor compliance with the requirements of the study.

Schedule of Events

	Screening	Treatment		Follow-up (office)			Extended Follow-up (remote)	
		Procedure	Immediate Postprocedure	1 Month (4 weeks)	3 Months[1,2] (13 weeks)	6 Months (26 weeks)	12 Months (52 weeks)	24 Months (104 weeks)
Window (days)	**(-30)**	**(0)**	**(0)**	**(± 7)**	**(± 14)**	**(± 30)**	**(± 30)**	**(± 30)**
Activity / Assessment								
Eligibility	X							
Consent	X							
Demographics / Medical History	X							
Physician Evaluations								
Nasal Assessment (physical, endoscopic)	X	X[3]	X	X	X	X		
Current medication use (study relevant)	X	X[3]	X	X	X	X	X	X
Participant Evaluations								
NOSE Scale	X			X	X	X	X	X
VAS nasal pain			X	X	X			
VAS ease of breathing	X			X	X	X		
Epworth Sleepiness Scale	X			X	X	X	X	X
Participant Satisfaction Survey					X	X	X	X
Adverse Events	X	X[3]	X	X	X	X	X	X

[1]Primary analysis endpoint.

[2] Control participants eligible to crossover and receive Vivaer procedure.

[3]Repeat on day of treatment if screening and procedure occur on different days.

List of Abbreviations

ADE – Adverse Device Effect

AE – Adverse Event

ANOVA – analysis of variance

BMI – Body Mass Index

CPAP – Continuous Positive Airway Pressure

CRF (eCRF) – Case Report Form (electronic Case Report Form)

CTA – Clinical Trial Agreement

EC – Ethics Committee

EDC – Electronic Data Capture

ENT – Ear, Nose, Throat; medical field of otorhinolaryngology (otolaryngology)

FDA – Food and Drug Administration

FESS – Functional Endoscopic Sinus Surgery

FWA – Federalwide Assurance for the Protection of Human Subjects

GCP – Good Clinical Practice

HIPAA – Health Insurance Portability and Accountability Act

ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICMJE – International Committee of Medical Journal Editors

IFU – Instructions for Use

IRB – Institutional Review Board

ISO – International Organization for Standardization

ITT – Intent-To-Treat

MDD – Medical Device Directive

NAO – Nasal Airway Obstruction

NOSE – Nasal Obstruction Symptom Evaluation Scale

OTC – Over-The-Counter (nonprescription)

PRN – Pro Re Nata (as needed or as required)

QOL – Quality of Life

RF – Radiofrequency

RFTR – Radiofrequency turbinate reduction

SAE – Serious Adverse Event

SADE – Serious Adverse Device Effect

SD – standard deviation

UADE – Unanticipated Adverse Device Effect

VAS – Visual Analog Scale

1.0 Introduction and Background

Nasal airway obstruction (NAO) is a highly prevalent disorder that affects the upper airway system causing restriction in normal airflow into the nasal cavity. Chronic nasal obstruction can elicit many symptoms, including congestion, stuffiness, headache, fatigue, sleep disturbance, daytime sleepiness, snoring and impairment of various daily and social activities leading to an overall decline in health-related quality of life (QoL).[1-3] Given its high prevalence, treatment of NAO can be costly, with expenditures for prescriptions, over-the-counter medications, and doctor's visits.

NAO can be mediated by a diversity of mucosal and structural disorders in the nasal cavity, including acute or chronic mucosal inflammation from infection, allergenic or non-allergenic irritants, or structural factors such as nasal masses or polyps, turbinate hypertrophy, nasal septal deviation, and nasal valve angle changes, narrowing or collapse.[1,4-7]

Treatment strategies have included both noninvasive management and surgical treatment with recent focus on treatment of the nasal valve region. The nasal valve is defined by the caudal cartilaginous nasal septum, the anterior head of the inferior turbinate, and the caudal end of the upper lateral cartilage. This region is critical in the development of nasal obstruction and represents the narrowest part of the nasal airway.[3,8-10] As described by Poiseuille's law, minute changes in the diameter of a tube will result in exponential changes in airflow[11].

Multiple devices designed to increase the size of the nasal passage at the nasal valve area are available over-the-counter (OTC) for noninvasive management of NAO. These products are marketed to people with poor nasal breathing, snoring difficulties, and those with increased breathing demands, such as athletes. These devices include adhesive external nasal dilator strips and internal nasal dilators. Both internal and external dilators have been found to effectively dilate the nasal airway and reduce airway resistance.[12-15] However, nasal dilating devices require significant patient involvement and compliance to be effective.

Surgical treatment most commonly consists of repair of a deviated nasal septum and reduction of the inferior turbinates. Surgical treatments may involve various suturing techniques used alone or in conjunction with grafting techniques using autologous cartilage typically harvested from the nasal septum or ear or synthetic biomaterials.[8,16-19] A new minimally invasive surgical procedure has also been introduced that uses an absorbable polymer blend nasal implant to support the upper and lower cartilage inside the lateral nasal wall similar to more traditional cartilage and nonabsorbable polymer grafts.[20] Surgical treatments are efficacious, but may require significant recovery periods with complication risks such as bleeding, intranasal adhesions, scarring, infection, and graft migration, resorption or extrusion.[16,19-23]

Radiofrequency (RF) energy has been used for decades in the fields of otorhinolaryngology (ENT), neurosurgery, cardiology, urology and general surgery.

The ability of radiofrequency, electrical current, or laser-mediated heating to reshape cartilage has been shown in ex-vivo studies on rib and septal cartilage.[24-26] ENT surgeons currently use radiofrequency energy in several nasal therapies. Numerous studies have demonstrated that radiofrequency therapy applied to tissue of the nasal passage can be safe and effective in improving nasal obstruction while preserving nasal function.[27] Radiofrequency turbinate reduction (RFTR), for instance, is a minimally invasive surgical option that can reduce tissue volume in a precise, targeted manner. This technique uses radiofrequency to create heat within the submucosal tissue of the turbinate, reducing tissue volume with minimal impact on surrounding tissues. Radiofrequency turbinate reduction differs fundamentally from traditional surgical methods by using low-power radiofrequency energy to provide a relatively quick and painless treatment for tissue coagulation and/or ablation.[28] There have been multiple studies analyzing the safety and outcomes of RFTR treatment. A systematic literature review of the RF ablation technique concluded that the technique is well tolerated and effective.[29]

Targeted radiofrequency heating of the lateral cartilaginous nasal wall has also been used in patients with inspiratory nasal valve collapse; however, an incisional approach was required.[30] In this investigation, 3 treatments were applied per side with intent to produce tissue retraction and volume reduction. Participants (n=28) were asked to evaluate their nasal blockage on a visual analog scale (VAS) from 0 to 10, with 10 indicating total blockage and 0, no sensation of blockage. At 16 weeks the mean VAS for the left nostril had decreased from 8.2 to 3.4 and decreased for the right nostril from 8.9 to 4.1. There were no major complications during or after the procedure.

The Vivaer procedure has previously been investigated in a prospective, nonrandomized multicenter study with 50 participants that supported regulatory clearance of the Vivaer ARC Stylus.[31] Participants exhibited significant symptoms of nasal obstruction attributed to internal nasal valve dysfunction with Nasal Obstruction Symptom Evaluation (NOSE) Scale score ≥60. Temperature-controlled radiofrequency treatment was applied intranasally using a bipolar stylus to the internal nasal valve region. Under local anesthesia, radiofrequency energy along with outward pressure was applied to the mucosa at the region of the caudal end of the weakened upper lateral cartilage to induce mechanical deformation and potentially change the shape of the lateral nasal wall. Contraction of the treated area during the healing process would serve to curve the treated portion of the upper lateral cartridge, creating a wider nasal airway and a stiffer nasal valve wall. Forty-nine participants were available for the primary analysis at the 6-month evaluation. No device or procedure-related serious adverse events occurred. There were 36 adverse events reported from 20 participants. None of the events were considered related to the device, although 13 were considered related to the procedure. Most events occurred in the period from the procedure to 4 weeks. Soreness, edema, and crusting resolved by 4 weeks. The mean baseline NOSE Scale score was 79.9 (SD 10.8, range 60-100), and all participants had severe or extreme nasal obstruction. At 6 months, mean NOSE Scale score improved to 24.7 (SD 20.4, range 0-90) with an average decrease

of 54.5 (68.6%). The severe and extreme nasal obstruction categories were reduced to 10%. At 12 weeks, all participants (100%) were treatment responders, defined as participants with at least a 15-point decrease in the NOSE Scale score, and at 6 months there were 3 nonresponders for a 94% responder rate. The decrease in NOSE Scale score did not differ significantly between patients who did or did not have prior nasal surgery.

Thirty-nine of this study's participants enrolled in a long-term follow-up study to assess NOSE score and quality of life through 2 years with evaluations at 12, 18, and 24 months. The mean NOSE Scale score at baseline was 80.8 (SD 10.7) for participants in the follow-up study. The mean NOSE Scale score for participants in this study improved to 24.9 (SD 21.3) at the 26-week endpoint of the pivotal study with a mean change from baseline of 55.9 (SD 23.6). Improvement in mean NOSE Scale score was maintained through the 12-, 18-, and 24-month evaluations (27.5, 32.7, and 26.5, respectively). At 6 months, severe and extreme nasal obstruction rates had decreased from 100% to 10% (4 of 39) of participants, and at 12-, 18-, and 24-months, 17%, 26% and 17% of participants had severe or extreme nasal obstruction, respectively. Using the definition of responder of at least a 15-point improvement in NOSE Scale score, 92% of participants in this study were classified as responders at 6 months and at 12 months 94% were classified as responders (3 participants were not evaluated at 12 months). All 39 participants were evaluated at 18 months with a responder rate of 87% and at 24 months, 36 of 39 participants were evaluated and had a responder rate of 97%. Participants in the study also responded favorably to the Aerin Medical Quality of Life survey showing improvement in areas such as sleep quality, energy and productivity, wellbeing and emotions, less sickness, and less frequent use of medication compared to prior to having the procedure. Treatment for symptoms of nasal obstruction attributed to internal nasal valve dysfunction with the Vivaer procedure was demonstrated to provide durable relief through 24 months. Response to the Aerin Medical Quality of Life survey provided additional support for the durability and benefits of the treatment.

2.0 Purpose

The purpose of this study is to compare the Vivaer procedure for treatment of nasal airway obstruction with a sham procedure that simulates the actual procedure as closely as possible absent the delivery of radiofrequency energy to the nasal tissue.

2.1 Device and Regulatory Status

The Vivaer procedure will be performed in the study clinic using the Vivaer ARC Stylus and Aerin Console. The Vivaer ARC Stylus is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue when connected to the Aerin Console radiofrequency generating device.

The Vivaer ARC Stylus was cleared for use in the United States (U.S.) by the Food and Drug Administration (FDA) under 510(k) K172529 and the Aerin Console was cleared under 510(k) K162810. Both devices are also CE-marked in the European Union.

2.2 Indications for Use (applicable to U.S. only)

The Vivaer ARC Stylus is indicated for use in otorhinolaryngology (ENT) surgery for the coagulation of soft tissue in the nasal airway, to treat nasal airway obstruction by shrinking submucosal tissue, including cartilage in the internal nasal valve area.

The Aerin Console is an electrosurgical system intended to generate radiofrequency electrical current for the use of an Aerin Medical Stylus. The Aerin Console is indicated for use in small clinic, office or hospital environments.

2.3 Intended and Indications for Use (applicable to European Union only)

The Vivaer ARC Stylus is intended to improve nasal breathing by modifying the soft tissues of the nasal airway. It is indicated for use in patients who experience poor nasal breathing or chronic nasal obstruction.

The Aerin Console is an electrosurgical system intended to generate radiofrequency (RF) electrical current for modification of soft tissues during ear, nose and throat procedures, when used with an Aerin Medical Stylus. It is indicated for use in delivering radio-frequency energy to tissues as part of ear, nose and throat procedures in small clinic, office or hospital environments.

2.4 Rationale

Patients suffering from symptoms attributed to nasal airway obstruction primarily due to internal nasal valve dysfunction, rather than hypertrophied turbinates, have treatment options ranging from OTC devices and medications to surgical procedures that have varying degrees of effectiveness, discomfort, and potential complications. There remains a significant need for a simple, safe, nonsurgical, minimally invasive treatment that can provide sustained relief for patients suffering with symptoms of nasal airway obstruction. The Vivaer procedure using RF technology has been shown to be safe, effective and durable in a single-arm trial comparing pretreatment condition with posttreatment condition. This study is being undertaken to provide additional evidence of the effectiveness of the procedure using the randomized, controlled trial, “gold standard” study design.

3.0 Study Objectives

3.1 Primary Objective

The primary objective is to assess the performance of the Vivaer procedure compared to a sham procedure with respect to individual participant success rates when used as a treatment for nasal airway obstruction.

Individual participant success ("responder") is defined as at least 1 Nasal Obstruction Symptom Evaluation (NOSE) Scale class improvement or an improvement (decrease) in NOSE Scale score of 20% or more from baseline at the 3-month evaluation.

The primary objective will be assessed through evaluation of the primary endpoint defined as the responder rate at 3 months after the procedure for the randomized participants.

3.2 Secondary Objectives

Additional objectives include assessment and comparison of secondary and informational outcome measures between the groups receiving the Vivaer procedure and the sham procedure.

Secondary endpoints are:

- Mean change in NOSE Scale scores from baseline to 3 months after procedure.
- Frequency of device-related and procedure-related serious adverse events through the 3-month evaluation.

Other Effectiveness and Safety Measures include:

- Adverse events - Incidence (type and category) of adverse events overall and by follow-up interval.
- Nasal Assessment - The target nasal valve area within each nostril will be visually assessed at baseline, just prior to procedure (if screening and procedure occur on different days), immediately after procedure, at 1 month, 3 months and 6 months after procedure. The use of an endoscope for visual assessment is required. Representative video of each nasal passage will be captured for each assessment. Endoscopic video of subject holding breath and during maximal inhalation to capture dynamic changes.
- NOSE Scale score:
    - Mean and mean change from baseline at the 3-, 6-, 12-, and 24-month follow-up evaluations.
    - Distribution of NOSE Scale score severity categories (mild, moderate, severe, extreme) at the 3-, 6-, 12-, and 24-month follow-up evaluations.
    - Mean, change from baseline in mean, and response distribution of the 5 components of the NOSE Scale score (nasal congestion, nasal blockage, trouble breathing, trouble sleeping, and getting enough air during exercise) at the 3-, 6-, 12-, and 24-month follow-up evaluations.
    - Proportion of responders based on improvement in NOSE Scale score at the 3-, 6-, 12-, and 24-month follow-up evaluations.

- Visual analog scale (VAS) for pain - perception of pain associated with the procedure on a 0 to 100 mm scale with 0 indicating no pain and 100 indicating the worst pain imaginable assessed immediately after procedure, and at 1-month and 3-month follow-up evaluations.
- Visual analog scale (VAS) for ease of breathing - perception of the ability to breathe through the nose on a 0 to 100 mm scale with 0 indicating no difficulty and 100 indicating extreme difficulty assessed at baseline, 1-month, 3-month and 6-month follow-up evaluations.
- Epworth Sleepiness Scale (ESS) - mean and change from baseline in the ESS score at each evaluation. The ESS evaluates the self-reported likelihood of dozing or falling asleep in 8 daytime situations with likelihood rated No Chance (0), Slight (1), Moderate (2), or High Chance (3) administered at baseline and the 1-, 3-, 6-, 12-, and 24-month follow-up evaluations.
- Participant Satisfaction Assessment - Five question self-reported survey of satisfaction with the procedure and recommendation to others administered at the 3-, 6-, 12-, and 24-month follow-up evaluations.
- Change in amount of "as needed" (PRN) medication/device use for nasal obstruction symptoms - Self-reported assessment of an increase, no change, or decrease in as needed medications and/or devices being used for treatment of nasal symptoms at each evaluation compared to use prior to the procedure administered at the 1-, 3-, 6-, 12-, and 24-month follow-up evaluations.
- Medications - Medications associated with relief or treatment of nasal airway obstruction symptoms will be documented at baseline and updated as necessary at each evaluation. In addition, medications associated with treatment of adverse events will be documented.

3.3 Safety and Risk Profile

The safety and risk profile of the Vivaer procedure relative to the sham procedure will be evaluated with respect to overall incidence of adverse events and treatment-related adverse events.

4.0 Study Plan

4.1 Study Design

The study is designed as a multicenter (up to 20 sites in the U.S. and Europe), prospective, randomized, controlled superiority trial with a one-way crossover component available to participants randomized to the control arm. A 2:1 site-stratified randomization will be used to allocate participants with NAO to either the active treatment arm (Vivaer procedure) or the control arm (sham procedure) to provide up to 120 total participants in the following groups:

- 80 active treatment (Vivaer procedure)
- 40 inactive treatment (sham procedure)

All participants will be evaluated in-office prior to treatment and following treatment at week 4 (1 month) and week 13 (3 months). The 3-month evaluation will be used for the primary endpoint analysis.

Active treatment participants (Vivaer procedure) will have an extended follow-up with evaluations conducted in-office at 6 months (26 weeks) and remotely at 12 months (52 weeks) and 24 months (104 weeks).

Participants receiving the sham procedure may elect to crossover to the active treatment arm (Vivaer procedure) within 30 days after the 3-month follow-up evaluation provided they still meet all eligibility criteria. Continued follow-up will be conducted at 1, 3, 6, 12, and 24 months after the Vivaer procedure to provide additional information on longer-term efficacy and duration of treatment effect.

Participants that received the sham procedure and do not elect to crossover or no longer meet all eligibility criteria will be exited from the study following the 3-month evaluation.

4.2 Study Population

The target population for this study is adults suffering from symptoms attributed to nasal airway obstruction primarily due to internal nasal valve dysfunction, rather than hypertrophied turbinates. This study requires severe or extreme symptoms demonstrated by a NOSE Scale score ≥ 55 and determination by the investigator that the nasal valve is the primary or significant contributor to the nasal obstruction.

Patients who have had previous surgical treatment of the nasal valve are not eligible to enroll in this study; however, it is anticipated that many patients will have already undergone rhinoplasty, septoplasty, inferior turbinate reduction or other surgical procedures prior to being approached for participation in this study. Therefore, a history of those types of procedures does not exclude a patient from enrolling in this study. However, to ensure that changes in NOSE Scale score over the course of follow-up are the result of the Vivaer procedure, prior surgical procedures must have been performed at least 3 months before the patient is enrolled in this study and no additional procedures should take place on the day of the Vivaer procedure or in the next 6 months.

Patients must meet all inclusion and exclusion criteria listed below for participation in the study.

4.2.1 Inclusion Criteria

1. Age 18 to 85 years (inclusively).
2. Willing and able to provide informed consent.
3. Willing and able to comply with the subject-specific requirements outlined in the Study Protocol.

4. Seeking treatment for nasal obstruction and willing to undergo an office-based procedure.
5. Baseline Nasal Obstruction Symptom Evaluation (NOSE) Scale score ≥ 55.
6. Nasal valve is a primary or significant contributor to the patient's nasal obstruction as determined by the study investigator (based on clinical presentation, physical examination, nasal endoscopy, etc.) and the patient has a positive response to any of the following temporary measures (based on patient history or office exam):
    - Use of external nasal dilator strips (eg, Breathe Right Strips)
    - Use of internal nasal dilator cones
    - Modified Cottle Maneuver (manual elevation of the lateral nasal wall using a small instrument or cotton-tipped applicator to open the nasal valve)
    - Cottle Maneuver (manual lateral retraction of the cheek to open the nasal valve)
7. Dissatisfaction with medical management as judged by the patient.
   Defined as failed medical therapy (eg, decongestants, antihistamines, and/or nasal sprays for an appropriate period of time), but a positive response to internal or external nasal dilators.

4.2.2 Exclusion Criteria

1. Prior surgery of the lateral nasal wall, including cephalic resection of the lower lateral cartilage, dome division or suture plication, alar graft or spreader graft placement.
2. Rhinoplasty, septoplasty, inferior turbinate reduction or functional endoscopic sinus surgery (FESS) within the preceding 3 months.
3. Severe case of any of the following: septal deviation, turbinate hypertrophy, polyps, or ptotic nose tip believed to be the primary contributor to the patient's nasal obstruction symptoms and warranting surgical intervention.
4. Any adjunctive surgical nasal procedure planned on the same day or within 6 months after the Vivaer procedure.
5. Known or suspected to be pregnant or is lactating.
6. Participating in another clinical research study.
7. Other medical conditions which in the opinion of the investigator would predispose the patient to poor wound healing or increased surgical risk, or poor compliance with the requirements of the study.

4.3 Enrollment and Randomization

Patients must be diagnosed with NAO prior to entry into the study. The use of diagnostic procedures and screening tests to determine a diagnosis and assess whether patients are appropriate candidates for inclusion in the study is an appropriate pre-entry activity. All participants must provide written informed consent before undergoing any study related procedures. A participant will be considered enrolled after signing and dating the IRB/EC approved informed consent form. If a participant is enrolled in the study but subsequently does not meet the eligibility criteria, participation in the study will be terminated and the data may be excluded from all analysis.

Randomization will occur after the participant is enrolled, met all eligibility criteria, and prior to the treatment procedure allowing sufficient time to prepare the required treatment. The randomized assignment (active treatment arm or control arm) will be determined using a web-based service. Once the baseline assessments have been completed and if patient meets eligibility, results must be entered into the electronic data capture (EDC) system before the system will randomize the participant to a study assignment group. Participants will be assigned to the active treatment arm (Vivaer procedure) or the control arm (sham procedure) in a 2:1 allocation, using the computer-generated randomization scheme stratified by site. To help assure balance in treatment assignment within sites a block randomization scheme will be implemented. Sites will be trained at site initiation to follow detailed randomization instructions to assure strict adherence to the randomization process.

4.4 Blinding

It will not be possible to blind the investigator administering the treatment because of obvious differences in the active application of the RF energy versus the sham control. However, every effort should be made to keep the participant blinded as to the treatment received. Steps to help maintain blinding include:

- Following the same preparation procedures for all cases, including administration of anesthetics (topical and local).
- Application of the Vivaer ARC Stylus in the same manner (pressure, locations, timing) for both the active and sham procedures.
- Simulation of RF energy being applied by having the Aerin Console appear to make audible sounds even though RF energy is not being generated or delivered for the sham procedure.
- Use of a blinded evaluator (nontreating physician) to conduct the follow-up visit nasal assessment when feasible; however, this is not required. Medical personnel who are unaware of the treatment received are also preferred for overseeing and coordinating the collection of the participant reported outcome measures during the follow-up evaluations. At a minimum, the treating physician should not be present when the participant reported outcomes are being collected. Site training will include the importance of maintaining the

blinded nature of the study and caution against inadvertent revelation of the treatment assignment by study personnel.

4.5 Outcome Measures

4.5.1 Nasal Assessment

The target nasal valve area within each nostril will be visually assessed for this study. The use of an endoscope for visual assessment is required. Observations are categorized as not present, mild, moderate, or severe. Representative video of each nasal passage will be captured for each assessment. Endoscopic video of subject holding breath and during maximal inhalation to capture dynamic changes.

Assessments include:

- Saddle nose deformity
- Bruising around orbital area
- Soreness, pain
- Numbness

Endoscope required:

- Inflammation / generalized redness
- Swelling, edema
- Blanching (generalized whiteness)
- Bleeding at anesthetic injection site (not requiring physician intervention)
- Bleeding at treatment site (not requiring physician intervention)
- Nasal obstruction from tissue edema
- Disruption of mucosal flow / crusting

4.5.2 Nasal Obstruction Symptom Evaluation (NOSE) Scale

Evaluation of nasal valve obstruction is based on clinical observations of signs and symptoms with no easily obtained, reproducible objective measurement techniques of the valve.[3] Poor correlation and uncertainty between more objective measures of nasal patency (eg, nasal inspiratory peak flow, acoustic rhinometry, rhinomanometry, CT scans, physician assessment of anatomy) and subjective measures have generally been reported.[32-36] Since patient symptoms and perception of condition are the factors leading an individual to seek treatment, patient-reported subjective measures are cited as the most important determinates of treatment outcome.[3,32,33]

To evaluate the significance of a patient's nasal obstruction both before and after the procedure, this study will use the well-known subjective patient-

reported Nasal Obstruction Symptom Evaluation (NOSE) Scale for determining the primary endpoint of the study. The NOSE Scale is a validated disease-specific health status instrument used by clinicians to measure the outcome of patients treated for nasal obstruction.[37] The NOSE Scale consists of 5 items, each scored using a 5-point Likert scale to make a total score range of 0 through 100, where higher scores indicate worse obstruction. Severity of symptoms can be classified as mild (range, 5-25), moderate (range, 30-50), severe (range, 55-75), or extreme (range, 80-100) nasal obstruction, based on responses to the NOSE survey.[38]

Treatment responder based on NOSE Scale improvement

Individual participant success (responder) is defined as at least 1 Nasal Obstruction Symptom Evaluation (NOSE) Scale class improvement, (eg, going from a score in the severe range (55-75) at baseline to a score in the moderate range (30-50) at the 3-month evaluation), or an improvement (decrease) in NOSE Scale score of 20% or more from baseline at the 3-month evaluation.

4.5.3 Pain – Visual Analog Scale Pain Score

A horizontal 100 mm visual analog scale (VAS)[39] anchored on the left with the words "No Pain" and on the right with the words "Worst Pain Imaginable", will be used to measure nasal pain associated with the procedure. Scores are obtained by measuring the distance in millimeters from the left origin of the line (0) to the point indicated with a vertical slash placed by the participant to indicate their current level of pain in and around the nose.

4.5.4 Ease of Breathing – Visual Analog Scale Breathing Score

A horizontal 100 mm VAS anchored on the left with the words "No Difficulty Breathing" and on the right with the words "Extreme Difficulty Breathing", will be used to assess the perception of the ability to breathe through the nose. Scores are obtained by measuring the distance in millimeters from the left origin of the line (0) to the point indicated with a vertical slash placed by the participant to indicate their assessment of ease of breathing.

4.5.5 Epworth Sleepiness Scale (ESS)

The ESS evaluates the self-reported likelihood of dozing or falling asleep in 8 daytime situations with likelihood rated No Chance (0), Slight (1), Moderate (2), or High Chance (3).[40] The total of the scores across the 8 questions can be categorized and interpreted as:

- 0-7 It is unlikely that you are abnormally sleepy.
- 8-9 You have an average amount of daytime sleepiness.
- 10-15 You may be excessively sleepy depending on the situation. You may want to consider seeking medical attention.
- 16-24 You are excessively sleepy and should consider seeking medical attention.

This measure is included in the study because results from at least 1 study suggest that chronic nasal obstruction impairs quality of life, at least partially, through excessive daytime sleepiness possibly caused by sleep-disordered breathing.[1] Treatment effectiveness with the Vivaer procedure may be evident in improvement of the ESS score.

4.5.6 Participant Satisfaction Assessment

Five question self-reported survey of satisfaction using a 5-point scale to assess tolerability of the procedure, ease of recovery, breathing through nose, overall satisfaction with the procedure, and recommendation to others.

4.5.7 Change in amount of PRN medication/device use for nasal obstruction symptoms

Self-reported assessment of an increase, no change, or decrease from baseline in as needed medications and/or devices being used for treatment of nasal symptoms following the procedure. Medication/device use may be categorized for reporting purposes.

4.5.8 Medication and Other Therapies for Symptoms of Nasal Obstruction

The current use of medication, devices or other therapies for symptoms of nasal obstruction, medication name, frequency, and dose will be recorded at each evaluation visit. Medications may be categorized for reporting purposes.

4.5.9 Adverse Events

Adverse events will be documented according to Section 7.1.2.

4.6 Success/Failure Criteria

Determinations of the overall success of treatment will be based on two levels: (1) the individual participant level and (2) the overall treatment group success relative to the sham control group. Each level has its own criteria for success.

4.6.1 Participant Success

The primary outcome success measure for a participant in this study is based on an improvement (decrease) in the NOSE Scale score after the procedure compared to the baseline score. The improvement must reflect at least one category improvement or $\geq 20\%$ decrease in score at the 3-month evaluation for the participant to be considered a success (responder).

4.6.2 Participant Failure

A participant will be considered a nonresponder at the 3-month evaluation if neither success criterion has been attained.

4.6.3 Study Success

The study will be considered a success if the proportion of participants in the active treatment arm achieving a successful outcome (responder) is statistically significantly greater than the proportion of participants in the

control arm achieving a successful outcome when evaluated at 3 months after the procedure.

4.7 Duration of the Study

The primary endpoint will be evaluated at 3 months. In addition, evaluations at 6, 12, and 24 months after treatment will extend follow-up to 2 years for evaluation of longer-term efficacy. Participants receiving the sham procedure and meeting all eligibility requirements may elect to crossover and receive the active Vivaer procedure within 30 days after the 3-month evaluation with continued follow-up for 24 more months for a total of up to 28 months of follow-up. Study enrollment is anticipated to be completed within 12 months. Therefore, total study duration is anticipated to be approximately 40 months.

4.8 Site Staffing and Responsibilities of Study Personnel

The principal investigator is responsible for ensuring that s/he has sufficient and qualified staff to conduct the clinical study and that all study-related tasks have been appropriately delegated and documented. Roles may include:

- Treating physician – The treating physician will perform the procedure and postprocedure assessments. The treating physician must be a medical doctor with experience in ENT procedures and trained in administering the Vivaer procedure.
- Blinded physician evaluator (Not Required) – A physician experienced in ENT procedures, trained for participation in this study, and unaware of the treatment received, may be used to conduct the follow-up nasal assessment. The blinded evaluator may also be responsible for the assessment, treatment and/or management of adverse events; however, in some cases it may be necessary to refer the event to the treating physician. If a blinded evaluator is not available, the treating physician or principal investigator will conduct the follow-up assessments.
- Oversight of participant reported outcomes and other data collection – Medical or office staff with relevant knowledge and experience as determined by the principal investigator to interact with study participants to ensure collection of study data and participant reported outcomes. Ideally, these individuals would be unaware of the treatment received by the participants.

Due to differences between the active and sham control procedures, staff may also become aware of the treatment being administered. Staff with knowledge of the randomization assignment should not communicate any information to the participant or blinded evaluator (if used) in order to minimize any potential bias.

4.9 Device Description

The Vivaer procedure incorporates use of the Vivaer ARC Stylus (Model FG257), which is a cleared and CE-marked (FDA - K172529, CE 639608) disposable handheld device capable of delivering bipolar radiofrequency energy to tissue, and

the Aerin Console (Model FG226), a cleared and CE-marked (FDA - K162810, CE 639608) RF generator with temperature control capable of delivering very low doses of energy.

The Vivaer ARC Stylus (Figure 1) consists of a handle, shaft and treatment tip. An array of bipolar electrodes is positioned on a nonconductive tip (Figure 2) that is attached to the handle via a nonconductive shaft. A temperature sensor is located on the Stylus tip to monitor tissue temperature during RF energy delivery. The Stylus is powered by an external temperature-controlled radiofrequency generator via a flexible cable (Figure 3). The Stylus incorporates features to allow compatibility with and authentication by only the Aerin Console. The connector for the Vivaer ARC Stylus has a pin configuration that prevents its use with other RF generators, making it only compatible with the Aerin Console. Authentication of the Stylus is achieved via a crypto chip that is built into the Stylus handle assembly. The chip is read and written to by the Aerin Console. Information stored on the chip includes the Stylus model information, treatment parameters, usage timestamp data, and a count of the remaining treatment cycles (based upon pre-set maximum).

The Vivaer ARC Stylus is temporarily inserted into the nose to access the treatment area. The Stylus requires the application of conductive media (eg, saline gel) to the tip prior to use. The conductive media helps to ensure good contact with tissue at all points of the treatment tip to facilitate energy transmission. Application of the RF energy is controlled by a foot switch connected to the Aerin Console. The Vivaer ARC Stylus improves nasal breathing by modifying the tissues of the nasal airway using low doses of radiofrequency energy. The low-power radiofrequency energy generates heat within the tissue and creates a coagulation lesion. As the lesion heals, the tissue retracts and stiffens, thereby decreasing nasal airway obstruction and improving airflow.

The procedure requires local anesthesia only. The Stylus is manufactured and supplied sterile and for single use only by Aerin Medical and may be used to treat both nostrils of the patient.

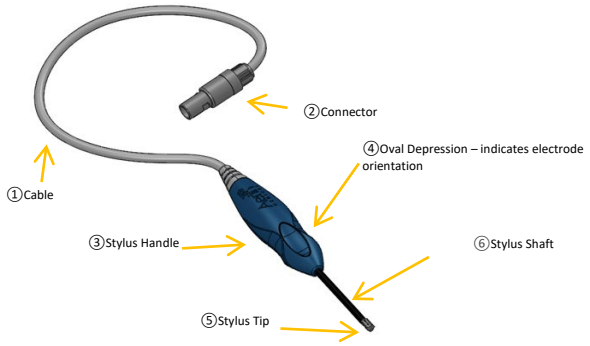


Figure 1. Vivaer ARC Stylus

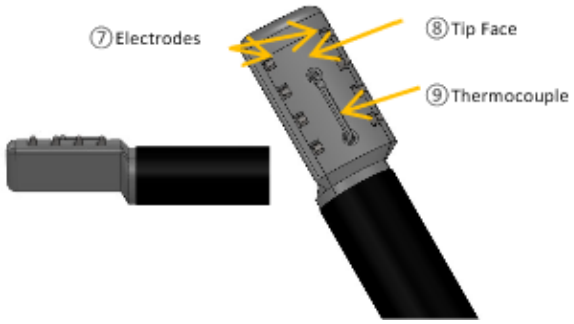


Figure 2. Vivaer ARC Stylus Tip

Figure 3. Aerin Console with Vivaer ARC Stylus

4.10 Risk/Benefit Analysis

4.10.1 Risks

Potential risks associated with the use of the Vivaer ARC Stylus do not differ from commonly used devices and treatments for nasal obstruction and snoring, but due to the nonsurgical nature of the therapy, small treatment area, low energy delivery, and lack of need for general anesthesia, the overall risk to the participant may be less than presented by other surgical treatments such as RF turbinoplasty, septoplasty, or functional rhinoplasty.

Potential risks associated with the use of the Vivaer ARC Stylus and the associated local anesthetics are listed below. Participants will be monitored closely as part of this study to allow for early detection of potential problems and prompt treatment if required.

Anticipated adverse events or side effects that may occur as a result of the treatment include:

- Infection
- Bleeding (other than during the treatment at treatment sites and greater than anticipated by the investigator)
- Mucosal changes
- Scar formation leading to nasal obstruction
- External deformity
- Sensory changes at treatment site
- Bruising including around the orbital area (black eyes)

Anticipated observations that are expected in and around the treatment area and are considered minor include:

- Inflammation / generalized redness
- Temporary swelling, edema
- Blanching (generalized whiteness)
- Temporary numbness/tingling
- Temporary soreness/pain
- Mild bleeding at anesthetic injection and/or treatment site (not requiring physician-level intervention, such as cautery)
- Temporary nasal obstruction from tissue edema
- Disruption of mucosal flow/intranasal crusting
- Scab formation

These observations will be assessed in the nasal assessment and recorded at study visits if they occur. Should any of the following require mitigation by the treating physician or be greater in severity or degree of incidence than anticipated, they will be considered an adverse event and will be recorded on the study Adverse Event Report eCRF.

Symptomatic improvements may not be achieved in all participants receiving the Vivaer procedure and may not be durable beyond the 3-month evaluation in all participants with relief at 3 months.

An additional risk to participants receiving the sham procedure is a potential for higher likelihood of the treatment not relieving their nasal obstruction symptoms compared to those receiving the Vivaer procedure.

4.10.2 Potential Risks to Participant Confidentiality

In all clinical studies, confidentiality of protected health information may be breached due to study-related activities beyond those of routine clinical care. This risk will be minimized by not entering personally identifying information into the EDC system through the study's electronic case report forms (eCRF). Risks to participant confidentiality are further minimized by allowing only authorized individuals to access the EDC system and the database that stores the electronically entered data. The 21 CRF Part 11 compliant and validated system maintains audit trails on all entries, changes or corrections to eCRFs. If a person with authority to complete but not sign eCRFs makes changes to an already signed eCRF, the investigator will be required to resign the eCRF, thereby protecting the integrity of the data collection process and the data.

4.10.3 Mitigation of Risks

The study was developed based on previous preclinical and clinical experience and includes a number of steps to minimize any additional risks to participants in the study:

- Preclinical mechanical and bench evaluations have been conducted to demonstrate that the design characteristics of the study device are appropriate for reliable clinical use of the device.
- The Vivaer ARC Stylus and Console have been cleared for use by the FDA based in part on prior clinical studies demonstrating safety and efficacy of their use and are CE-marked in the European Union.
- The study will be reviewed and approved by an Institutional Review Board(s)/Ethics Committee and conducted according to applicable regulations with ongoing review by the IRB/EC.
- Careful consideration has been given to the inclusion/exclusion criteria in order to select appropriate candidates for treatment.
- Patients will be fully informed of the study requirements prior to enrollment.
- Only physicians with experience in nasal surgical and minimally invasive procedures, and with specific training using the Vivaer ARC Stylus for performing the Vivaer procedure will be permitted to participate in the study.
- Study procedures, follow-up, and study monitoring are designed to closely manage adverse events in a timely manner.

- Participants receiving the sham control procedure will be offered the Vivaer procedure if they have not responded to the sham procedure by the 3-month evaluation.

4.10.4 Study Justification in Relation to Risk

The sponsor believes that any additional risks presented by participating in this study are very low and that adequate testing, safeguards, and risk monitoring have been incorporated into the study to further minimize and mitigate the risks relative to the potential benefits, including relief from symptoms of nasal obstruction, that may be realized by participation in this study.

4.10.5 Benefits

The potential benefit associated with the Vivaer procedure is to offer a minimally invasive treatment method that has been shown in a previous study to help alleviate symptoms of nasal obstruction and which has been cleared for use by the FDA and is CE-marked in the European Union. The Vivaer ARC Stylus improves nasal breathing by modifying the tissues of the nasal airway using low doses of radiofrequency energy. The low-power radiofrequency energy generates heat within the tissue and creates a coagulation lesion. As the lesion heals, the tissue retracts and stiffens, thereby decreasing nasal airway obstruction and improving airflow. In addition to symptom relief after correcting nasal obstruction, participants may also experience better sleep function and better psychological function. (eg, concentration, productivity and frustration). These benefits may last beyond the length of the study.

The procedure will be provided at no cost to participants. Participants randomized to the sham control procedure will be offered the opportunity to receive the Vivaer procedure within 30 days after the 3-month evaluation if the sham control procedure has not alleviated their symptoms.

5.0 Study Schedule and Procedures

This section provides summaries of the study schedule of events and flow of participants through the study, as well as more detailed information on study procedures and processes.

5.1 Schedule of Events

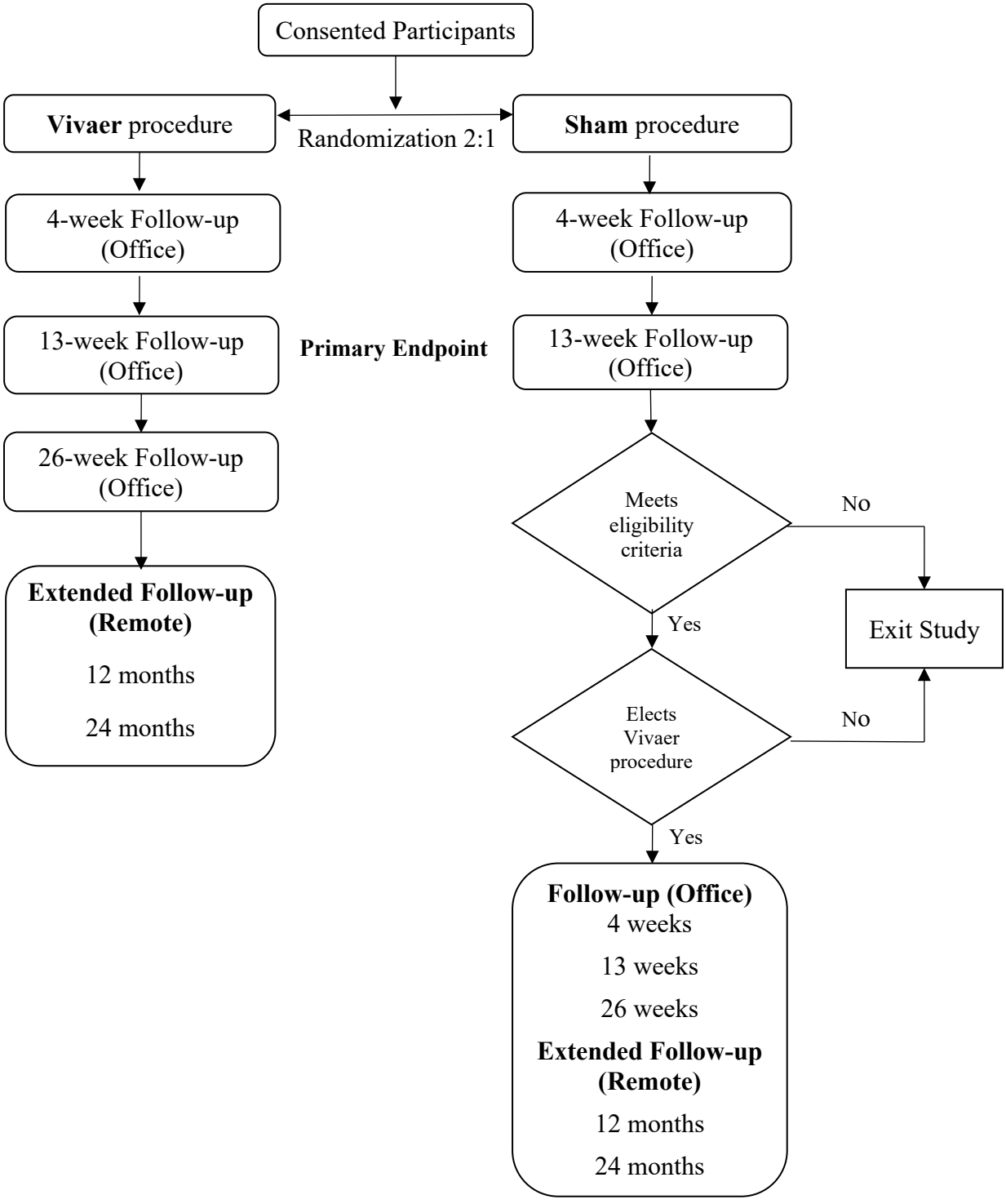
	Screening	Treatment		Follow-up (office)			Extended Follow-up (remote)	
		Procedure	Immediate Postprocedure	1 Month (4 weeks)	3 Months[1,2] (13 weeks)	6 Months (26 weeks)	12 Months (52 weeks)	24 Months (104 weeks)
Window (days)	**(-30)**	**(0)**	**(0)**	**(± 7)**	**(± 14)**	**(± 30)**	**(± 30)**	**(± 30)**
Activity / Assessment								
Eligibility	X							
Consent	X							
Demographics / Medical History	X							
Physician Evaluations								
Nasal Assessment (physical, endoscopic)	X	X[3]	X	X	X	X		
Current medication use (study relevant)	X	X[3]	X	X	X	X	X	X
Participant Evaluations								
NOSE Scale	X			X	X	X	X	X
VAS nasal pain			X	X	X			
VAS ease of breathing	X			X	X	X		
Epworth Sleepiness Scale	X			X	X	X	X	X
Participant Satisfaction Survey					X	X	X	X
Adverse Events	X	X[3]	X	X	X	X	X	X

[1]Primary analysis endpoint.

[2] Control participants eligible to crossover and receive Vivaer procedure.

[3]Repeat on day of treatment if screening and procedure occur on different days.

5.2 Participant Flowchart



5.3 Enrollment and Baseline Assessment

Screening

The investigator or designated research staff will perform an evaluation of the study candidate for study eligibility, which may include a history and physical examination of the nasal area, review of overall medical history, understanding of general health and discussion of any conservative measures used for nasal airway obstruction.

Patients must be diagnosed with nasal airway obstruction prior to entry into the study. The use of diagnostic procedures and screening tests to determine a diagnosis and assess whether patients are appropriate candidates for inclusion in the study is an appropriate pre-entry activity. While the availability of the study may be discussed with a prospective participant without first obtaining consent, informed consent must be obtained prior to initiation of any clinical procedures dictated by the protocol that are performed solely for the purpose of determining eligibility to participate in the study. Once the pretreatment assessments are completed the study procedure should be completed **within 30 days**.

Informed Consent

Informed consent must be obtained in accordance with FDA regulation 21 CFR Part 50 and ISO 14155. The investigator or designated staff member is responsible for ensuring that IRB/EC approved informed consent is obtained for each participant prior to participation in the study, or before undergoing any procedure specific to the clinical investigation. The patient must be fully counseled with an explanation of the study background, randomized nature of the study, study procedure, follow-up schedule, and informed of their options, risks and benefits, and have every opportunity to ask questions about participation in the study. Any new information obtained during the course of the study that may affect the health of the participant or their decision to continue in the study will be provided to the participant. This process includes a thorough explanation of the informed consent document that the patient will be asked to sign and date acknowledging that they understand and desire to participate in the study. The explanation and discussion should be conducted in such a way as to:

- answer the participant's questions,
- avoid coercion or influence of patient to participate in the study,
- ensure the patient understands that their legal rights are not waived at any time,
- use language at a level the patient can understand, and
- ensure the patient understands that after providing signature on the informed consent, the patient may still withdraw at any time before, during or after study treatment.

Evaluation of inclusion and exclusion criteria
The Screening Visit / Study Eligibility eCRF will be used to document the participant's eligibility status.

Pretreatment (baseline) data and assessments
The following data will be obtained prior to treatment and recorded on the Baseline Visit – Demographics & Treatment History eCRF:

- Demographics
  - Sex
  - Height (inches)
  - Weight (pounds)
  - Date of birth
  - Race / Ethnicity
- Medical history, Nasal Symptoms, History of Treatments, General Nasal Exam
  - History (duration) of nasal obstruction
  - History of nasal trauma
  - Related nasal symptoms
  - History of rhinitis (allergic, non-allergic), sinus disease, and/or obstructive sleep apnea
  - Medication/treatments used to address nasal obstruction and/or related symptoms (including CPAP)
  - Significant anatomic conditions that could affect treatment outcome (eg, severe septal deviation, turbinate enlargement, nasal polyps, ptotic nasal tip, and/or other external nasal deformity)
- Nasal assessment (physical and endoscopic exam) for each nostril including video. Representative video of each nasal passage will be captured for this assessment. Endoscopic video of subject holding breath and during maximal inhalation to capture dynamic changes. If treatment is not provided the same day as screening, then this assessment will be repeated on the day of the procedure immediately prior to treatment.
- Current use of medication, devices or other therapies for symptoms of nasal obstruction, including medication name, frequency, and dose will be detailed on the Concomitant Medication Log.
- NOSE Scale score (completed by participant).
- VAS ease of breathing score (completed by participant).
- Epworth Sleepiness Scale (completed by participant).

5.4 Treatment Visit and Procedure

Randomization will occur after the participant is enrolled, met all eligibility criteria, and prior to performing the procedure allowing enough time for preparation of the selected treatment.

The treatment procedure is summarized below. Consult the Vivaer procedure Investigator's Brochure and the Vivaer ARC Stylus and Aerin Console Instructions for Use (IFUs) for full detail of the treatment procedure and step-by-step instructions for preparation and use of the Vivaer ARC Stylus and Aerin Console.

Preparation

The procedure will be performed in the study clinic. The participant will be positioned in the exam chair according to personal comfort and study physician's preference (eg, upright, reclined or supine). A nasal assessment (physical and endoscopic exam) will be performed on each side of the nose and for each nostril, including video (only required if screening and procedure occur on different days). This is to assess the configuration of the structural components of the lateral nasal wall (including the upper and lower lateral cartilage, their junction and the overlying mucosa) and to allow the study physician to map out and plan the areas of treatment. Participants will undergo bilateral treatment of the nasal valves in a single study procedure session. Each side of the nose will be treated with up to four (4) non-overlapping applications of RF energy at the junction of the upper and lower lateral cartilage on the lateral nasal wall.

Figure 4. Vivaer ARC Stylus at the nasal valve

The study physician will anesthetize the treatment area by using a topical swab/gauze or spray of lidocaine to numb the mucosal tissue, wait approximately 20 minutes, and then inject anesthesia to the treatment area after initial numbness has occurred. The control group will undergo the same anesthetic protocol as the active treatment group.

Treatment Administration

A nasal speculum is inserted into the nostril and opened to visualize the treatment area on the lateral nasal wall. The Vivaer ARC Stylus will then be inserted to access the treatment area. The Stylus will be connected to the Aerin Console generator and the RF energy level will be set on the generator.

The default settings for the Vivaer ARC Stylus will be used for the study:

Temperature	60° C
Power	4 Watts
Treatment Time	18 secs
Cooling Time	12 secs

The Aerin Console is activated by depressing the foot pedal. With the Vivaer ARC Stylus pressed against the lateral nasal wall in the desired treatment location, the foot pedal is depressed and the Stylus is used to both gently displace the cartilage and mucosa of the lateral nasal wall and deliver RF energy to the tissues consistent with the IFU. A tone sounds when the Console is activated, signifying that energy is being delivered through the Stylus; this tone stops when the pedal is released and RF energy is no longer delivered.

When conducting a sham control procedure, the study physician will activate an audible tone mimicking the activation of the Aerin Console; however, no energy will be transmitted to the Stylus. The study physician should apply the Stylus to the lateral nasal wall in a similar fashion as would be done if energy was actually being delivered.

No repeat ("touch-up") procedures will be permitted during the study follow-up period.

Procedure data collection

Data relating to the procedure and the products used will be recorded on the Study Procedure eCRF. The following information will be recorded:

- Preprocedure nasal assessment (physical and endoscopic exam) for each nostril including video (only required if screening and procedure occur on different days).
- Procedure type, date of procedure
- Preprocedure and procedure medications
- Vivaer ARC Stylus and Aerin Console information
- Procedure start and end times
- Aerin Console settings
- Treatment duration
- Number of sites treated

- Occurrence of device malfunctions, protocol deviations, and/or adverse events
- Postprocedure nasal assessment (physical and endoscopic exam) for each nostril including video

5.5 Postprocedure Assessments and Care

Immediately postprocedure, a nasal assessment (physical and endoscopic exam) for each nostril including video will be conducted prior to discharging the participant and reported on the Study Procedure eCRF.

Participants will be asked to indicate the pain level experienced during the study procedure from anesthesia delivery to procedure completion using the VAS pain score instrument (vertical line marked on the 100 mm line) on the Pain VAS CRF.

At the discretion of the study physician, the following care may be provided:

- Apply compression to the treatment area internally for 5 minutes.
- Apply petroleum jelly to the treatment area as needed.
- Use of nasal saline spray or ointment as needed
- The participant should be instructed not to manipulate the treatment site for 24 hours with the exception of any necessary hemostasis.

Participants should have their first follow-up visit (4 weeks) scheduled within the visit window prior to release.

Participants should not receive other concomitant nasal treatment therapies or interventions after the procedure or during the study follow-up period to avoid confounding the evaluation of the effect of the treatment, unless the additional care is in response to an adverse event or is considered in the best interest of the participant. Therapies, interventions, and pain medication will be monitored at follow-up evaluations.

5.6 Follow-up Evaluations and Study Exit

Follow-up visit dates will be calculated from the study procedure date. Follow-up visits should be scheduled within the specified visit windows described in the Schedule of Events (Section 5.1) and Table 1 (Section 8.3.2). In-office follow-up evaluations are scheduled for 4 weeks (1 month), 13 weeks (3 months) and 26 weeks (6 months) after the procedure. In addition, follow-up evaluations at 12 and 24 months after the treatment procedure will be conducted remotely as a telephone assessment by site personnel. The timing of all follow-up evaluations is based on the date of the procedure and should not be altered based on the actual time of preceding follow-up visits. Participants who make nonstudy visits should be evaluated for possible adverse events and an Adverse Event Report eCRF should be submitted if appropriate.

Participants randomized to the control arm (sham procedure) may elect to crossover to the active treatment arm (Vivaer procedure) within 30 days after the 3-month

evaluation, once they have undergone their scheduled 3-month evaluation and continue to meet all of the eligibility criteria, including NOSE Scale score of ≥ 55. New baseline information will be collected prior to the Vivaer procedure. Crossover participants who choose to have the Vivaer procedure will maintain their original study ID and will follow the same pretreatment, treatment, and follow-up processes as any newly enrolled participant.

All participants who receive the Vivaer procedure, as well as sham procedure participants who choose to have the Vivaer procedure after their 3-month evaluation, should be followed through the final follow-up evaluation at 2 years postprocedure regardless of their success/failure classification. Sham procedure participants who choose not to have the Vivaer procedure or who fail to meet inclusion and exclusion criteria will be exited from the study following the 3-month evaluation. Every effort should be made to avoid having participants withdraw from the study (Section 9.6). If a participant does choose to withdraw from the study, it is very important to record information regarding the reason(s) and the last known status of the participant.

The following assessments will be conducted as indicated for each follow-up time point and recorded on the Follow-up Visit eCRF:

<u>In-office evaluations: 4-Weeks (1-month), 13-Weeks (3-month) and 26-weeks (6-months) follow-up:</u>

- Nasal assessment (physical and endoscopic exam) for each nostril including video
- Current use of medication, devices or other therapies for symptoms of nasal obstructions, including medication name, frequency, and dose
- Participant reported change in use of as needed medications and devices for nasal obstruction symptoms (completed by participant)
- NOSE Scale score (completed by participant)
- VAS pain score (completed by participant) (4-weeks and 13-weeks only)
- VAS ease of breathing score (completed by participant)
- Epworth Sleepiness Scale (completed by participant)
- Participant Satisfaction Survey (completed by participant) (13-weeks and 26-weeks only)
- Adverse events

<u>Remote (telephone) evaluations: 12-month (52-Weeks) and 24-month (104-Weeks) follow-up:</u>

- Current use of medication, devices or other therapies for symptoms of nasal obstruction, including medication name, frequency, and dose (study staff follow-up required if participant indicates change)

- Participant reported change in use of as needed medications and devices for nasal obstruction symptoms (verbal administration by site personnel)
- NOSE Scale score (verbal administration by site personnel)
- Epworth Sleepiness Scale (verbal administration by site personnel)
- Participant Satisfaction Survey (verbal administration by site personnel)
- Adverse events (study staff follow-up required if participant indicates changes)

Study Exit

Participants meeting the study requirements as planned will be exited from the study upon completion of the 24-month follow-up evaluation. If a participant reaches the 24-month follow-up evaluation and is experiencing a new or ongoing adverse event, the study sponsor should be contacted to discuss the need and/or methods for continued surveillance of the event.

5.7 Product Handling and Accountability

A system that allows tracking of orders, shipping and returns will be used to control Vivaer ARC Stylus and Aerin Console inventory. The devices will be packaged and labeled to clearly indicate that they are for clinical study use only and must only be used for participants enrolled in this study. All devices not used must be returned to the sponsor or disposed of in accordance with the sponsor's instructions. The investigator is responsible for adequate record keeping regarding the receipt, use, and final disposition of study inventory.

6.0 Statistical Considerations

6.1 Study Design

This is a prospective, multicenter, randomized, sham-controlled study to compare the Vivaer procedure for treatment of nasal airway obstruction with a sham procedure that simulates the actual procedure as closely as possible absent the delivery of radiofrequency (RF) energy to the nasal tissue. A 2:1 site-stratified randomization will be used to allocate participants with NAO to either the Vivaer procedure (active treatment) or a sham procedure (control). This study is designed to demonstrate the superiority of the active Vivaer treatment compared to the sham control.

6.2 Study Hypotheses

The null hypothesis (H_0) for this superiority study is that there is no difference between the success (responder) rate for the sham control and the success (responder) rate for the Vivaer procedure:

$$H_0: \pi_C - \pi_T = 0 \text{ vs. } H_1: \pi_C - \pi_T \neq 0$$

where:

π_C=proportion of responders in the sham procedure control group

π_T=proportion responders in the Vivaer procedure treatment group

Rejection of the two-sided null hypothesis in favor of the alternative (H_1) hypothesis means that there is evidence for a statistically significant difference in responder rates between the two groups.

6.3 Sample Size Estimate

The study will enroll up to 120 participants. The power analysis was performed such that there is adequate power to reject the null hypothesis of no difference between treatments. Sample size estimation was based on the test for differences between two proportions[41] using an Exact test and on the following assumptions:

- Significance level $\alpha = 0.05$ (two-sided)
- Power = 80%
- $\pi_C = 0.50$ (allowance for a 50% control responders)
- $\pi_T = 0.80$ (assumed 80% responders in the treated group)
- Treatment allocation is 2:1
- 10% dropout and nonevaluable

The 80% responder rate assumed for the active Vivaer procedure group is a conservative estimate based on the prior clinical study of this procedure in which all 50 participants were responders at 12 weeks and 46 of 49 (94%) were responders at 26 weeks. The lower 95% confidence bound on the estimate of 94% is 83.5%, which supports the conservative estimate of 80% responders assumed for the purpose of sample size calculation. The 50% responder rate assumed for the sham control procedure is based on literature for placebo and sham controls in therapeutic and device studies suggesting from 30% to 60% responder rates, with device studies tending to be at the higher end of the range[42]. A randomized study of a bioabsorbable implant treatment for nasal valve collapse reported a 54.7% responder rate in the sham procedure arm of the study.[20]

The minimum number of participants to achieve 80% power with a 2:1 active treatment to sham control allocation is 66 in the active treatment group and 33 in the sham. The sample size, allowing for 10% loss (nonevaluable) in each group and adjusting for a balanced distribution across 20 sites is 120 participants (80 active treatment (Vivaer procedure), 40 sham procedure control).

It is anticipated that participants will be enrolled at sites on a competitive basis; however, a reasonable balance of participants among sites may be maintained by potentially capping enrollment at individual sites based on the final number of participating sites.

6.4 Timing of Analysis

The primary evaluation phase of the study lasts until all participants have reached the primary endpoint at 13-weeks (3-month) postprocedure. The primary and secondary endpoints will be analyzed using the data from the primary evaluation phase for an interim study report when these data become available. Informational outcomes will be analyzed and included in interim reports after all participants have reached each of the successive follow-up time points. A final study report will be provided after all participants have reached the final 24-month (104-week) follow-up evaluation of the extended follow-up phase of the study, including sham procedure control participants who subsequently received the Vivaer procedure.

6.5 Analysis Populations

The primary endpoint analysis will be based on the intent to treat (ITT) principle. Participants will be analyzed in the originally randomized treatment group regardless of actual treatment received. The effects of protocol deviations will only be examined when the validity of the study conclusion is in question. All secondary and other analyses and reports will include an ITT population analysis. Following data reporting conventions, statistics on the per protocol population will also be reported. The per protocol population is defined as all participants who received treatments, with 13-week (3-month) follow-up data and no major protocol deviations.

6.6 Missing Data

All missing data in each treatment group will be imputed for the primary endpoint by assuming the missing outcomes are nonresponders. In addition, a post hoc sensitivity analyses may be performed, including a worst-case analysis (all missing primary outcomes in the Vivaer procedure group are considered nonresponders and all missing outcomes in the sham procedure control group are responders) and/or a change-point analysis, to assess the effect of missing data on the primary analysis. The results of the sensitivity analysis will not be used to adjust the conclusions drawn from the primary analysis.

Secondary outcome measures and additional observational measurements will be analyzed by using available data only.

6.7 Pooling

All study data will be pooled across study sites to facilitate hypothesis testing in accordance with the sample size estimation and power analysis (Section 6.3). Comparability between study sites may be shown using summary statistics calculated by site.

6.8 Participant Disposition

A detailed description of participant disposition will be provided by treatment group using a CONSORT diagram and summaries of participants falling in various subgroups of interest, such as, enrolled but not treated with any study treatment, not treated as randomized, discontinued, excluded from ITT, protocol deviations,

deaths, and withdrawals. All study population exclusions and reasons will be summarized. All randomized participants entered in the study will be accounted for in the summary. Follow-up by visit will be presented, showing theoretical, expected, and actual follow-up visits.

6.9 Demographics and Characteristics

Demography, baseline characteristics and the comparability of active treatment group and sham control group participants will be summarized using frequencies and percentages for categorical factors and mean, median, standard deviation, minimum and maximum for continuous factors. Demographic characteristics will be reported to describe the profile of samples. Comparability between treatment groups will not be statistically assessed in this prospective randomized clinical trial.

There are no preplanned subgroup analyses; however, potential baseline covariates with possible impact on outcomes at 3 months are:

- Age
- Race
- Sex
- BMI
- Allergic status (allergic rhinitis - nonallergic rhinitis)

Results may be evaluated by allergic status if sufficient numbers are obtained in both categories.

6.10 Primary Endpoint Analysis

Primary efficacy will be evaluated using the proportions of successful outcomes (responders) on the primary outcome measure (1 NOSE class improvement or improvement (decrease) in NOSE Scale score of ≥ 20% from baseline) at 13 weeks.

The proportions of successful participants at 13 weeks in each group will be compared using Fisher's Exact test.

Confidence intervals (95%) will be provided for all proportions and comparisons.

6.11 Secondary Endpoint Analyses

Secondary endpoints will be tested only after the primary objective of the study is met. Confidence intervals (95%) will be included for all secondary outcome measures.

- NOSE Scale score change from baseline to 13 weeks
  The mean changes from baseline at 13 weeks in each group will be compared with a 2-sided t-test with a null hypothesis of no difference between groups.

- Device-related and procedure-related serious adverse events through 13 weeks
  The proportions of device-related and procedure-related serious adverse events through 13 weeks in each group will be compared using Fisher's Exact test.

6.12 Other Outcome Measures Analyses

Additional outcome measures will be collected for information and hypothesis generating purposes. The primary analysis methods will be descriptive and exploratory and presented by evaluation to more completely understand the time course of treatment effect. Measures will be summarized using frequencies and percentages for categorical measures and mean, median, standard deviation, minimum and maximum for continuous factors. Confidence intervals for differences between treatment groups will be included where appropriate. Statistical comparisons will either not be performed or used for information purposes. Proportions may be compared using exact tests or chi-square tests. Continuous outcomes may be compared using t-tests, ANOVA or nonparametric equivalents. Repeated measures ANOVA may be used for longitudinal analysis across evaluations.

Other outcome measures include:

- Nasal Assessment - The visual physical and endoscopic assessment factors will be summarized to include frequency and percentage of responses in each category for each component of the nasal assessment by treatment group at baseline, just prior to procedure (if screening and procedure occur on different days), immediately after procedure, at 1 month, 3 months, and at 6 months after the procedure.
- NOSE Scale score - Categorical responses and scores on the NOSE Scale and its individual components will be subject to multiple summary methods and analyses including the:
  - Mean and mean change from baseline at the 3-, 6-, 12-, and 24-month follow-up evaluations.
  - Distribution of NOSE Scale score severity categories (mild, moderate, severe, extreme) at the 3-, 6-, 12-, and 24-month follow-up evaluations for each group.
  - Mean, change from baseline in mean, and response distribution of the 5 components of the NOSE Scale score (nasal congestion, nasal blockage, trouble breathing, trouble sleeping, and getting enough air during exercise) at the 3-, 6-, 12-, and 24-month follow-up evaluations for each group.
  - Proportion of responders based on improvement in NOSE Scale score at the 3-, 6-, 12-, and 24-month follow-up evaluations for each group.

- Visual analog scale (VAS) for pain - Summary will include mean VAS pain scores assessed postprocedure, 1 month, and at 3 months for both groups.
- Visual analog scale (VAS) for ease of breathing - Summary will include mean ease of breathing scores assessed at baseline, 1 month, 3 months, and at 6 months for both groups.
- Epworth Sleepiness Scale (ESS) - mean and change from baseline in mean ESS score and categorical responses will be summarized for both groups at baseline and the 1-, 3-, 6-, 12-, and 24-month follow-up evaluations.
- Participant Satisfaction Assessment - mean response for each of the five survey questions will be summarized by group at the 3-, 6-, 12-, and 24-month follow-up evaluations.
- Change in amount of PRN medication/device use for nasal obstruction symptoms - Proportions of participants reporting increase, decrease, or no change in use the categories of PRN medication or devices prior to procedure will be summarized by group at the 1-, 3-, 6-, 12-, and 24-month follow-up evaluations.
- Medications - Medications associated with relief or treatment of nasal airway obstruction symptoms or associated with the treatment of adverse events will be provided by group and documented at baseline and updated as necessary at each evaluation. Medication use by categories may also be presented as percentages of participants in each group.

6.13 Safety Analysis

All adverse events will be analyzed for all participants. Adverse events will be coded using a custom Aerin Medical dictionary so that adverse events may be categorized for analysis at an appropriate level of detail. Listings will be provided to detail individual events. The number of participants, number of AEs, and the proportion of participants reporting each AE will be summarized. Seriousness and severity of AEs and their relationship to the device and procedure will be summarized. A time course of adverse events will be presented. Any unexpected adverse device experiences or adverse events that occur at an unexpectedly high incidence rate will receive detailed analyses. Narratives will be presented for all deaths, serious adverse events, unexpected adverse device experiences, and participants withdrawn due to an adverse event.

6.14 Extension Phase Analysis

The extension phase analyses will be similar to those detailed above with a particular emphasis on the summarization of all adverse events occurring throughout the entire study and the maintenance of the treatment effect over time. Missing data analyses and imputation will not be performed on data collected during the extension phase.

6.15 Standard Methods of Report

Summary descriptive statistics including means, medians, standard deviations and histograms for continuous measures, and frequencies and percentages for categorical outcomes will be presented for all variables of interest. Outcome measures (primary, secondary, and informational) will be presented by treatment group and time.

7.0 Adverse Events and Product Complaints / Device Deficiencies

7.1 Adverse Events

Adverse events (AEs) may occur during the treatment phase or during the follow-up phase. Adverse events occurring after the baseline assessment but before the procedure will be documented in the participant's medical record but will not count as related to the study device or procedure.

7.1.1 Definitions

Following are definitions associated with adverse events:

Adverse Event (AE) - any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated (per ISO 14155:2020).

Note: This definition includes events related to the investigational medical device or the comparator. This definition also includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to the use of investigational medical devices.

Serious Adverse Event (SAE) - an adverse event that led to any of the following (per ISO 14155:2020):

a) death,

b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:

   1) a life-threatening illness or injury, or

   2) a permanent impairment of a body structure or a body function including chronic disease, or

   3) in-patient or prolonged hospitalization, or

   4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) fetal distress, fetal death, or a congenital abnormality, or birth defect including physical or mental impairment

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Adverse Device Effect (ADE) – adverse event related to the use of an investigational medical device.

Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes comparator if the comparator is a medical device (per ISO 14155:2020).

Serious Adverse Device Effect (SADE) - an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (per ISO 14155:2020).

Unanticipated Adverse Device Effect (UADE) - 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 (per 21 CFR 812.3(s)).

Relationship to device and procedure
The potential relationship of the event to the device or procedure will be categorized by the investigator as follows:

- Not related

  An adverse event for which sufficient information exists to indicate that there is no causal connection between the event and the device or procedure. The adverse event is due to and readily explained by the participant's underlying disease state or is due to concomitant medication or therapy not related to the use of the device or the procedure. In addition, the adverse event may not follow a reasonable temporal sequence following the procedure.

- Unlikely

  The relationship with the use of the device or procedure seems not relevant and/or the adverse event can be reasonably explained by another cause, but additional information may be obtained.

- Possibly related

  There is a reasonable possibility that the adverse event may have been primarily caused by the device or procedure. The adverse event has a reasonable temporal relationship to the use of the device or the

procedure and follows a known or expected response pattern to the device or procedure, but alternative etiology is equally or more likely compared to the potential relationship to the use of the device or the procedure.

- Probably related

  There is a reasonable probability that the adverse event may have been primarily caused by the device or procedure. The adverse event has a reasonable temporal relationship to the use of the device or the procedure and follows a known or expected response pattern to the device or procedure, and an alternative etiology is unlikely or significantly less likely.

- Definitely related

  The adverse event has a strong causal relationship to the device or procedure. The adverse event follows a strong temporal relationship to the use of the device or the procedure, follows a known response pattern to the device or procedure, and cannot be reasonably explained by known characteristics of the participant's clinical state or other therapies.

Every effort should be made to determine the cause of each adverse event, because a judgment must be made as to the relationship to the device or procedure. If an investigator cannot assign a causality category the event will be considered possibly related for reporting and analysis.

Note: The occurrence of a diagnostic or elective surgical procedure for a pre-existing condition, unless the condition becomes more severe or increases in frequency, would not be considered procedure or device related.

Intensity of adverse events:

- Mild

  The adverse event is noticeable to the participant but does not interfere with routine activity.

- Moderate

  The adverse event interferes with routine activity but responds to symptomatic therapy or rest.

- Severe

  The adverse event significantly limits the participant's ability to perform routine activities despite symptomatic therapy. The adverse event requires medical or surgical treatment or results in hospitalization.

7.1.2 Documentation and Reporting of Adverse Events

All adverse events will be monitored from the time of enrollment through study exit. All adverse events must be reported on the Adverse Event Report eCRF. A description of the event, including onset date, resolution date, action taken, and the outcome should be provided. All adverse events will be followed until they are adequately resolved or reach a chronic, stable state. If a participant reaches the 24-month follow-up visit and is experiencing a new or ongoing adverse event, the sponsor should be contacted to discuss the need and/or methods for continued surveillance of the event. Adverse events will be evaluated by the investigator and differentiated by:

- Seriousness
- Intensity (mild, moderate, severe)
- Causality (in relation to the device or procedure)
- Unexpectedness

Signs and symptoms considered normal postprocedure recovery (eg, postprocedure pain, transient sensory symptoms, fever, postanesthesia symptoms) do not have to be reported as adverse events. If these events require treatment outside that which is considered normal or if the event lasted longer in duration than normal, they should be reported as adverse events.

All adverse events classified as an Unanticipated Adverse Device Effect, Serious Adverse Device Effect, or Serious Adverse Event must be reported to the sponsor within 24 hours of learning of the event.

Sponsor Contact: Anais Laborde
Phone: 650-518-9624
Email: alaborde@aerinmedical.com

Investigators must also report promptly all unanticipated problems to their IRB/EC and/or regulatory authority involving risks to participants or others and report adverse events according to the local or national reporting requirements. Reporting instructions and contact information will be provided in the site's Regulatory Binder for this study.

7.2 Product Complaints / Device Deficiencies

7.2.1 Definitions

Product Complaint - Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of an Aerin product (medical device) after it is released for distribution (per 21 820.3(b)).

Complaint – written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety or performance of a medical device that has been released from the

organization's control or related to a service that affects the performance of such medical device (per ISO 13485:2016).

Reportable Complaint – Any product complaint that represents an event, which must be reported to a regulatory agency including:

- US Food and Drug Administration (per 21 CFR Part 803)
- A Competent Authority within the European Community or a Notified Body (MDD)
- The Canadian HPFB
- Any regulatory agency, within the country of distribution

Device Deficiency – inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling. This definition includes device deficiencies related to the investigational medical device or the comparator (per ISO 14155:2020).

7.2.2 Documentation and Reporting of Complaints / Device Deficiencies

All product complaints, deficiencies and malfunctions associated with devices will be documented on the appropriate eCRF and/or communicated to the sponsor within 24 hours of first becoming aware of the event.

8.0 Study Administration

This study will be conducted in accordance with elements of ICH E6 Guideline for Good Clinical Practice, Abbreviated Requirements of 21 CFR 812 for NSR device studies, the European Standard ISO 14155, the Declaration of Helsinki, the Belmont Report, and any applicable regional or national regulations.

The sponsor has the overall responsibility for the conduct of the study according to all applicable regulatory requirements. The sponsor will have certain direct responsibilities and will delegate other responsibilities to the investigator and study site. The sponsor and investigator will ensure that the study is conducted according to all applicable regulations. All personnel participating in the conduct of this study will be qualified by education and experience to perform their tasks.

The sponsor, treating physician, or any person acting for or on behalf of the sponsor or investigator shall act in accordance the applicable standards, guidelines and regulations.

This study is funded by Aerin Medical. The Clinical Trial Agreement (CTA), mutually signed by the study site and Aerin Medical, describes the agreement between sponsor and site with respect to study financing.

8.1 Investigator Training

Site initiation training will occur prior to the first procedure at a site. Investigators will be trained on the procedure and use of the Vivaer ARC Stylus and Aerin Console. All study staff will be trained, as necessary, to ensure compliance with the protocol and regulatory requirements, as well as to ensure accurate data collection. Site training will include a detailed review of this protocol, use of the EDC system, eCRF completion instructions, adverse event reporting, product handling and inventory, randomization instructions, monitoring logistics, and regulatory requirements.

8.2 Study Monitoring

Study monitoring will be carried out in compliance with FDA regulations, ISO 14155, and GCP guidelines. The monitoring for this study will be carried out by monitors qualified by experience and training who are Aerin Medical employees or individuals contracted by Aerin to conduct monitoring activities. The study monitors will oversee the conduct of the study and evaluate compliance with the protocol, any specific recommendations made by the site's IRB/EC and the signed Investigator Agreement. During the study, phone contacts and site visits will be conducted to ensure protocol compliance. Monitoring will include a verification the informed consent was properly obtained for all study participants, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results, a review of source documents, and ensuring adverse events, protocol deviations and device usage are properly documented. The monitor will conduct source data verification by verifying eCRFs are consistent with source documents. The investigator will make available to the monitor for review the informed consent forms, source documents, and any other relevant records for all study participants at the site. The investigator and other site personnel will be accessible to the monitor during visits and sufficient time is provided to conduct the visits and address questions. If the monitor becomes aware of any deficiencies during the course of the study, the monitor will discuss with the sponsor and investigator to ensure compliance is maintained. A final close-out monitoring visit will occur when the study has been completed or terminated.

8.3 Documentation of Study Findings

8.3.1 Data Management

A secure Electronic Data Capture (EDC) and management system will be used for entry, storage, review, and management of study data. The system will use the Medrio EDC platform (Medrio, Inc. San Francisco, CA) and be compliant with applicable GCP and regulatory requirements. Investigators are responsible for accurate completion and timely submission of the data collected during the study. Sites will be trained in the use of the system for entering study data and uploading supporting documents and will be given access for this purpose. Data monitoring will be performed to identify missing data, verify data accuracy, and ensure queries are resolved. Any data issues are to be promptly addressed with the investigator. Quality assurance

procedures will be established to ensure that complete, accurate and timely data are submitted, protocol requirements are followed, and that complications, adverse events and adverse device effects are correctly reported and investigated as appropriate. The management and retention of these data will be compliant with applicable regulatory requirements.

8.3.2 Case Report Forms

Standardized electronic case report forms will be used at all participating study sites to collect complete and accurate records of the clinical data. All study data will be entered by study personnel through eCRFs for each participant enrolled in the study. A unique ID number will be assigned to each participant.

The following eCRFs and log will be used in this study and submitted at the intervals outlined in Table 1:

- Screening Visit / Study Eligibility (01)
- Baseline Visit – Demographics & Treatment History (02)
- Nasal Obstruction Symptom Evaluation (NOSE) Scale (03)
- Ease of Breathing VAS – Participant form (04A)
- Ease of Breathing VAS – Site form (04B)
- Epworth Sleepiness Scale (05)
- Study Procedure (06)
- Pain VAS – Participant form (07A)
- Pain VAS – Site form (07B)
- Follow-up Visit (08)
- Participant Satisfaction Survey (09)
- Study Exit (10)
- Device Malfunction Report (11)
- Protocol Deviation (12)
- Adverse Event Report (13A) (reference AE Code List (13B))
- Serious Adverse Event / Unanticipated Adverse Device Effect (SAE / UADE) Report (14)
- Concomitant Medication Log (L3)

Table 1. Schedule of case report forms and related materials.

Visit	Visit Window (days)	eCRF	Other
Screening / Baseline	n/a	01, 02, 03, 04A, 04B, 05, L3	Informed Consent Nasal assessment images†
Study Procedure	within 30 days of Baseline‡	06	Nasal assessment images†
Postprocedure	0	06, 07A, 07B	Nasal assessment images†
4-Week (In-office)	±7	03, 04A, 04B, 05, 07A, 07B, 08	Nasal assessment images†
13-Week (In-office)	±14	03, 04A, 04B, 05, 07A, 07B, 08, 09	Nasal assessment images†
6-Month (In-office)	±30	03, 04A, 04B, 05, 08, 09	Nasal assessment images†
12-Month (Remote)	±30	03, 05, 08, 09,	
24-Month (Remote)	±30	03, 05, 08, 09, 10	
As Needed	n/a	11, 12, 13, 14, L3	

†Copy deidentified endoscopic video/images collected for study records to USB flash drive and provide to sponsor.

‡If the procedure does not occur on the same day as screening, the Nasal Assessment will be repeated prior to the procedure.

8.3.3 Investigator Responsibilities, Records, and Reports

Responsibilities

The investigator is responsible for ensuring that the study is conducted according to the protocol and all IRB/EC requirements. In addition, the investigator is responsible for obtaining participant's written informed consent and for U.S. study sites, participant's written authorization for disclosure and use of health information as required under the Health Insurance Portability and Accountability Act (HIPAA; 45 CFR Parts 160 and 164), or other documentation as required by the IRB/EC and national regulations.

Records

The investigator will maintain complete, accurate and current study records. Investigator records including:

1. Relevant communication that documents any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, or adverse event reporting, including that with the IRB/EC, the sponsor, the study monitors, other investigators, and regulatory agencies.
2. Device accountability records that will track device usage for all study participants. Information tracked will include date of receipt, lot or serial number, expiration date, date of device usage, subject ID, and disposition of all study products, including the type and quantity of the

product, the dates of their return, if applicable, the occurrence of any device malfunctions, and initials of study personnel conducting device accountability.

3. Participant records, including the participant's informed consent form, case history, procedure dictation, adverse events, progress notes, follow-up evaluations, case report forms and all supporting documents, such as diagnostic studies.
4. Study protocol, amendments, and documentation (dates and reasons) of any deviations from the protocol.
5. IRB/EC records, including original and ongoing study approvals, all correspondence, and the approved informed consent form(s).
6. IRB/EC membership list, FWA# as applicable, statement of compliance and written procedures pertaining to AE and PD reporting (if available).
7. Study agreement, curricula vitae of investigator(s), financial disclosure, signature authorization log (delegation of responsibility), protocol signature page, and patient screening/enrollment log.
8. Reports (including safety reports, progress reports and a final report from the investigator).
9. Any other records, as required by the IRB/EC and the sponsor.

Reports

Investigators are required to prepare and submit the following reports in a complete, accurate, and timely fashion:

1. In the event of an adverse experience that is serious or unanticipated, or which requires action by sponsor to prevent an unreasonable risk of substantial harm to public health, notice shall be given immediately (but in no event later than 24 hours after learning of such experience) by telephone or e-mail to the sponsor and the IRB/EC. Any notices made by telephone shall be confirmed in writing within 2 days of the initial notification. The site shall provide all associated documentation (eg, lab reports, death summary, operative reports, etc.) for each adverse experience.
2. Unanticipated adverse device effects and serious adverse events should be reported to the sponsor within 24 hours of event discovery. If the adverse event is alarming, the investigator shall report the event immediately.
3. Investigators shall promptly report to the IRB/EC all changes in the research activity and all unanticipated problems involving risk to participants and others, and that s/he will not make any changes in the

research without IRB/EC approval, except where necessary to eliminate apparent hazards to the participants.

4. Withdrawal of IRB/EC approval reported to the sponsor within 5 working days. The report will include a complete description of the reason that approval was withdrawn.
5. Progress reports must be submitted to the IRB/EC at regular intervals dictated by the IRB/EC but no less than annually.
6. A final report must be submitted to the IRB/EC within 3 months after 1) termination or completion of the study; or 2) the investigator's work on the study ceases.
7. Any deviation from the protocol to protect the life or physical well-being of a participant in an emergency is to be reported to the sponsor and IRB/EC no later than 5 working days after the emergency occurs. Deviations to the informed consent process (eg, use of study product without informed consent) must be reported to the sponsor and the IRB/EC immediately but no later than 5 working days after the use occurs. Deviations from the randomization scheme must be reported to the sponsor as soon as possible after they are recognized.
8. Other: upon request, the investigator will supply accurate, complete and current information about any aspect of the study to the sponsor.

8.3.4 Retention of Study Records

The sponsor must ensure that all study participant records are stored for at least 2 years after the later of the following two dates: the date on which the study is terminated or completed (all study participants through final follow-up), or the date that the records are no longer required by the study site record retention policy or per applicable regulatory requirements. To avoid error, the site should contact the sponsor prior to the destruction of study records to ensure that they no longer need to be retained. In addition, the sponsor should be contacted if the study site is acquired or shuts down so that arrangements can be made for the handling or transfer of study records.

8.3.5 Data Quality Assurance

The sponsor, or the sponsor’s representative, may conduct audits at the study sites. Audits may include, but are not limited to, device supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time, in a reasonable manner.

8.3.6 Confidentiality

All information provided to investigators, IRBs/ECs, and generated in this study must be considered highly confidential and must not be disclosed to any persons not directly involved with the study without prior written permission

from the sponsor. However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All study products must be used solely in accordance with this protocol. Privacy and confidentiality of information about each participant shall be preserved in the reports and in any publication. Each participant in this study will be assigned a unique identifier. All data will be tracked, evaluated, and stored using only this unique identifier.

The study site will maintain a confidential list (paper or electronic) identifying all participants. This list will contain the assigned participant's unique identifier and name. The investigator is responsible for keeping this list confidential. This list will not be provided to the study sponsor and is only to be used at the study site.

Monitors and auditors will have access to the study patient list and other personally identifying information of participants to ensure that data reported corresponds to the person who signed the informed consent form and the information contained in original source documents. Such personal identifying information may include, but is not limited to the participant's name, address, date of birth, gender, race and medical record number.

8.3.7 Publication Policies

The Clinical Trial Agreement mutually signed by the investigator(s) and Aerin Medical, defines and describes the nature of the study agreement. The data and results from this study are the sole property of Aerin Medical. Aerin Medical shall have the right to access and use all data and results generated during the clinical investigations now and in the future for presentation or publication at the sponsor's discretion or for submission to governmental agencies. Publication authorship will be established according to the International Committee of Medical Journal Editors (ICMJE) guidelines and Aerin Medical policy. Clinical study design will be publicly disclosed on ClinicalTrials.gov, and summary results posted per FDAAA 801 Requirements, and in accordance with national regulations as required by other regulatory agencies. Additionally, an investigator may only publish data generated by this trial in accordance with the terms of the Clinical Trial Agreement.

It is Aerin Medical's intent to encourage and facilitate the publications of scientifically important results, while simultaneously ensuring minimization of duplicative data publication and the priority publications of multicenter results ahead of single-center investigations.

Aerin Medical intends to provide research sites with a standardized study report containing aggregated site study data.

8.4 Study Suspension or Early Termination

The study can be suspended or discontinued at the discretion of the sponsor for reasons including, but not limited to, the following:

- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of patients
- Unanticipated adverse device effect presenting an unreasonable risk to patients
- Persistent noncompliance with the protocol and/or IRB/EC or regulatory authority requirements

If the study is discontinued or suspended prematurely, the sponsor shall promptly inform all participating study sites and treating physicians of the termination or suspension and the reason(s) for the termination or suspension. The IRB/EC shall also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor. The investigator shall promptly inform enrolled participants at his/her study site, if appropriate. Regulatory authorities and the personal physicians of the participants may also need to be informed if deemed necessary. All applicable study documents will be subject to the same retention policy as detailed in Section 8.3.4.

9.0 Ethics

9.1 Institutional Review Board/Ethics Committee

This study may not be initiated at a site until applicable Institutional Review Board/Ethics Committee, or regulatory authority approval/favorable opinion is obtained. The study protocol, all study protocol amendments, written study participant information, informed consent form, and any other appropriate study-related information must be reviewed and approved by the IRB/EC. Any additional requirements or conditions imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

To assure proper review and study oversight, the IRB/EC must comply with the responsibilities, functions, and records requirements defined in U.S. FDA regulations (21 CFR Part 56) or per their regulatory authority.

The investigator at each site is responsible for submitting the appropriate study documentation to the IRB/EC for review and approval in accordance with applicable regulations. The investigator is responsible for providing accurate, complete, and current information to the IRB/EC throughout the course of the study.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements governing clinical studies of marketed products. Compliance with these requirements also constitutes conformity with the ethical principles that have their origin in the Declaration of Helsinki and the rights, safety and wellbeing of study subjects shall be protected consistent with these principles.

The sponsor will promptly review all information relevant to the safety of the product that is received and comply with all regulatory device safety reporting requirements.

9.3 Participant Privacy

The privacy of participants in this study will be protected by all reasonable means. The investigator is responsible for study records at the study site and must only disclose information as provided for in the site's Authorization to Use and Disclose Health Information, or in accordance with EC policies and national regulations. Each participant must give permission for use and disclosure of their information by signing the Authorization to Use and Disclose Health Information, or other document as required by the EC and/or regulatory authority. This form may be a separate document from the informed consent form or it may be contained within or as an addendum to the informed consent form. Although the sponsor is not a covered entity under HIPAA, access to study records, particularly participant information, will be strictly limited by the sponsor to the investigator, the sponsor's clinical research personnel, authorized representatives of the sponsor, the Food and Drug Administration under applicable federal regulations, or other regulatory authority as required per national regulations. No public reporting or publications of the results of this study will contain identifiable references to individual participants in the study.

9.4 Participant Insurance

It is the responsibility of the sponsor to provide insurance covering the cost of treatment of participants in the event of clinical-investigation-related injuries, in accordance with the national regulations, as applicable.

9.5 Participant Reimbursement

Participants may be reimbursed for their time for completing questionnaires as allowed by the IRB/EC and study site policies. Participants will not be reimbursed for questionnaires not completed.

9.6 Participant Withdrawal

Participants may voluntarily withdraw from the study at any time for any reason without impact to their future medical care at the study site. In addition, the investigator may withdraw a participant from the study, if in the investigator's opinion, it is not in the best interest of the participant to continue in the study. Any participant withdrawing from the study for any reason will continue to receive medically necessary follow up care as determined by the investigator. Every attempt should be made to follow a participant withdrawing either because they failed to obtain a desired effect or suffered an adverse event.

When a participant chooses to withdraw, the investigator or designee will make all possible efforts to collect and report the final visit observations. If the investigator has made 3 documented attempts to contact the participant and received no response, the participant may be considered to be lost to follow-up. A participant

who misses a study visit, but attends a subsequent visit will no longer be considered lost to follow-up. All reasons for withdrawals and documentation will be recorded in source documentation and the appropriate case report form. In addition, within the informed consent process, participants will be asked to provide consent for the study staff to contact them by mail or phone to follow up on safety-related issues as appropriate.

9.7 Protocol Modifications

This protocol shall not be amended without the approval of the sponsor. The sponsor may amend the protocol to clarify study procedures or to implement changes to the protocol that do not affect the validity of the data; the risk to benefit ratio; the scientific soundness of the protocol; or the rights, safety, or welfare of the participants. All modifications must be reviewed and approved by the IRB/EC before implementation.

9.8 Protocol Adherence and Deviations

9.8.1 Definition

Deviation – instance of failure to follow, intentionally or unintentionally, the requirements of the protocol (per ISO 14155:2020).

9.8.2 Documentation and Reporting of Deviations

The investigator(s) agree to conduct the study in accordance with this protocol. An investigator must not make any changes in the study without first receiving agreement by the sponsor and approval in writing from the IRB/EC, except when necessary to eliminate apparent immediate hazards to a participant. Investigators will also adhere to procedures for reporting study deviations to their IRB/EC in accordance with their specific IRB/EC reporting policies and procedures. Deviations will also be reported to the regulatory authority as required per national regulations.

Deviations must be reported to the sponsor regardless of whether medically justifiable, pre-approved, or performed to protect the participant in an emergency. The investigator will document and explain the reason for the deviation. Participant specific deviations will be reported using the Protocol Deviation eCRF.

10.0 References

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