AERWAY

A Prospective, Multicenter Study of the **AER**in Medical Vivaer® ARC Stylus for Nasal Air**WAY** Obstruction **(AERWAY)**

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Protocol Version:	E
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1.0 PROTOCOL SYNOPSIS

Study Title:	A Prospective, Multicenter Study of the **AER**in Medical Vivaer® ARC Stylus for Nasal Air**WAY** Obstruction (AERWAY)
Device:	Vivaer® ARC Stylus
Device Description:	The Vivaer® ARC Stylus is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue.
Device Regulatory Status:	The Vivaer® ARC Stylus was cleared by the FDA under 510(k) #K172529 and the Aerin Console was cleared under K162810 both are also CE marked.
Study Objective:	The primary objective of this post-market study is to continue to evaluate the effectiveness of the Vivaer® ARC Stylus for treating the nasal valve area to improve symptoms in those diagnosed with nasal airway obstruction.
Study Design:	A Prospective, Multicenter Study of the Aerin Medical Vivaer® ARC Stylus for Nasal Airway Obstruction
Subject Population:	Male and female subjects who present with symptoms associated with nasal airway obstruction and meet the protocol eligibility criteria
Study Procedure:	Subjects will be followed from the Vivaer® treatment date out to 36 months post index procedure.
Observational Evaluation:	• Evaluate changes in subject-reported Nasal Obstruction Symptom Evaluation (NOSE) Score. • Evaluate physicians' visual assessment of nasal airway at treatment and 3-months post index procedure • Evaluate the average anatomical Vivaer® treatment locations and number of placements per nostril per treatment session. • Evaluate Quality of Life questionnaire(s) at follow up timepoints to better understand improvement and pain associated with treatment over time. • Change in medication use reported at follow up timepoints in comparison to reported medications used for nasal obstruction symptoms prior to treatment. • Evaluate profile by characterizing the type and frequency of adverse events reported at or following the study procedure, and throughout the follow-up period.
Additional Evaluations:	• Nasal treatment history • Subject Demographic information
Study Size:	Up to 125 subjects
Number of Sites:	Up to 15 sites

Study Visits:	Pre-Procedure, Treatment, and 3 month follow-up
Study Subject Follow-up:	3, 6, 12, 24 and 36 months after Vivaer® Treatment
Study Eligibility Criteria:	Inclusion Criteria: Eligible subject will meet all the following: 1. Age 18 or older 2. Willing and able to provide informed consent 3. Willing and able to comply with the study protocol 4. Seeking treatment for nasal obstruction 5. NOSE score of ≥ 60 at Baseline 6. Nasal valve is a primary or significant contributor to the subject's nasal obstruction as determined by the study investigator (based on clinical presentation, physical examination, nasal endoscopy, etc.) and the subject has a positive response to any of the following temporary measures (based on patient history or office exam): • Use of external nasal dilator strips (e.g., Breathe Right Strips) • Q-Tip test (manual intranasal lateralization) • Use of nasal stents • Cottle Maneuver (manual lateral retraction of the cheek) Exclusion Criteria: Eligible subjects will NOT meet any of the following: 1. Prior surgical treatment of the nasal valve 2. Rhinoplasty, septoplasty, inferior turbinate reduction or other surgical nasal procedures within the past three (3) months 3. Anatomy that requires an adjunctive surgical nasal procedure on the same day or 3 months after the Vivaer procedure 4. Medical conditions which in the opinion of the treating physician would predispose the subject to poor wound healing or increased surgical risk.

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2.0 INTRODUCTION AND LITERATURE REVIEW

2.1 Introduction

Nasal airway obstruction affects the upper airway system causing restriction in normal airflow into the nasal cavity. This nasal condition can be caused by a diversity of mucosal and structural disorders in the nasal cavity. Nasal diseases such as acute and/or chronic rhinosinusitis can cause nasal polyps, turbinate hypertrophy and other soft tissue responses. Structural anomalies such as severe septal deviation, nasal valve angle changes or nasal valve collapse are among the dysfunctions that are common causes of nasal obstruction (Udaka, Suzuki et al. 2006, Wittkopf, Wittkopf et al. 2008, Chandra, Patadia et al. 2009, Fraser and Kelly 2009).

Chronic nasal obstruction can elicit many symptoms, including congestion, stuffiness, headache, fatigue, sleep disturbance, daytime sleepiness, snoring and a decline in health-related quality of life (QOL) (Rhee, Book et al. 2003). In recent years, there has been growing awareness that nasal obstruction may impair various daily and social activities (Udaka, Suzuki et al. 2006) and result in a degradation of the patient's overall quality of life (Rhee, Weaver et al. 2010).

2.2 Nasal Anatomy

The nose is a respiratory organ that performs a prominent airflow regulatory role. Air enters the nasal cavity, where it is warmed to a temperature of approximately 31°C to 34°C, regardless of outside temperature. The nose also humidifies the inspired air to a relative humidity of 90% to 95% (Behrbohm 2004). These functions prevent drying of the distal airways, which allows optimal gas exchange, and helps maintain healthy body temperature.

The nasal anatomy is illustrated in Figure 1. The nasal valve area (V) represents the narrowest segment of the nasal airway. It is defined as the area bounded by the caudal end of the upper lateral cartilage (ULC), cartilaginous nasal septum (S) and head of the inferior turbinate (T) (Cole 2003, Wexler and Davidson 2004, Weaver 2012). The nasal valve, which is a portion of the nasal valve area, is the area of highest airway resistance in the nasal passage. A decrease in the cross-section of this area leads to restriction of airflow and can cause nasal obstruction symptoms.

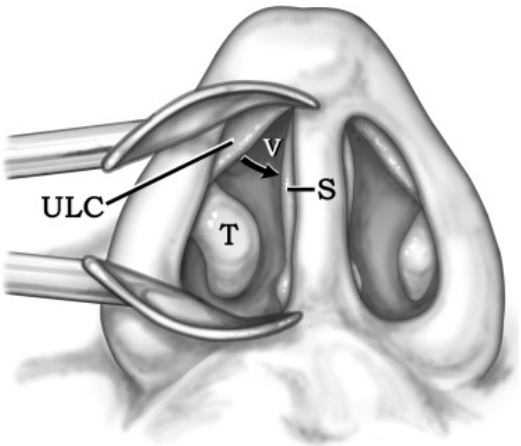

Figure 1. Nasal Anatomy
(from Weaver 2012, Figure 1)

The nasal valve angle is the angle between the upper lateral cartilage and the nasal septum. Anatomical studies have shown that this angle classically ranges between 10° and 15° in the nose of Caucasian individuals. One of the most common causes of nasal obstruction is internal nasal valve dysfunction wherein the upper lateral cartilage moves towards the septum, increasing airway resistance upon inspiration (Cole 2003, Wexler and Davidson 2004).

3.0 NASAL VALVE OBSTRUCTION MEASUREMENT AND TREATMENT

3.1 Physical Assessment

Self-diagnosis is common with patients experiencing decreased nasal airflow. The first-line treatment may be over-the-counter remedies such as nasal dilator sprays, humidifiers and/or external nasal dilator strips (e.g., “Breathe Right” nasal strips) which temporarily expand the sidewalls of the nose at the level of the nasal valve. As these temporary solutions fail to resolve chronic nasal airway obstruction, patients may then seek professional diagnosis from an otorhinolaryngology (ENT) specialist.

The physician will typically conduct a history of nasal obstruction symptoms and assessment of nasal pathology to rule out concomitant causes of nasal obstruction and to understand prior otorhinolaryngologic treatment and surgical history. Common causes of chronic decreased airway flow can be a response from year-round allergic and non-allergic triggers, chronic sinusitis and/or abnormal nasal pathology such as severe deviated septum, enlarged inferior turbinates, nasal polyps, etc. As each of these factors is ruled out and the nasal valve angle is determined to be the likely cause of nasal obstruction symptoms, conservative measures are discussed prior to surgical treatment (Jessen and Malm 1997).

3.2 Nasal Obstruction Measurement

Patients presenting with decreased airway flow with suspicion of nasal valve angle changes or compromise may be evaluated by the Cottle Maneuver to understand the direct cause of nasal airway obstruction. This maneuver temporarily enlarges the radius of the nasal valve area increasing nasal airflow as the nasal valve area is manually widened. A positive response can be an indicator that patients will respond well to a nasal valve angle increase (Kern and Wang 1993).

Figure 2 demonstrates the Cottle Maneuver in which the physician temporarily lifts and lateralizes the skin around the nose and cheek, increasing the nasal valve angle.

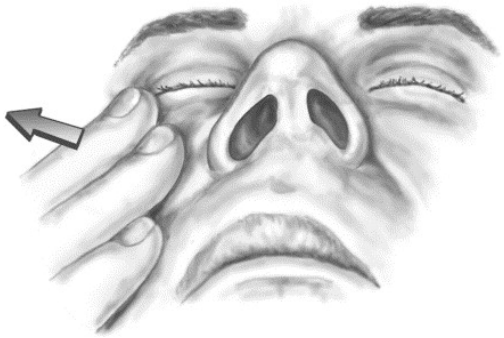

Figure 2. Cottle Maneuver

Nasal valve collapse may occur during inspiration. The modified Cottle Maneuver is effective in diagnosis. A fine instrument, such as a cerumen loop, is placed gently within the nares against the lateral nasal wall at the level of maximal observable collapse. The patient is then asked to breathe in through the nose. Collapse is stented by the instrument, which should be held lightly to prevent distortion. This maneuver may predict the potential benefit of surgical nasal valve correction (Constantinides, Adamson et al. 1996). The procedure is performed both before and after decongestion to determine the effect of mucosal swelling in symptomatology.

3.3 Subjective Assessment

A validated disease-specific health status instrument may be used by clinicians to measure the outcome of subjects treated for nasal obstruction. One well-known and recognized tool is the Nasal Obstruction Symptom Evaluation (NOSE) Scale, which is a validated 5-item instrument using a 5-point Likert Scale (Stewart, Witsell et al. 2004). This outcome assessment has been used to measure improvements in quality of life (QOL) following septoplasty, functional septorhinoplasty and nasal valve surgery (Dolan 2010, Chambers, Horstkotte et al. 2015, Yeung, Hassouneh et al. 2015, Camacho, Zaghi et al. 2016).

3.4 Current Treatments

Nasal Valve Dilators

Multiple devices available on the market are designed to increase the size of the nasal passage at the nasal valve area. These products target people with poor nasal breathing, snoring difficulties or increased nasal breathing demands (e.g., athletes). Adhesive external nasal dilator strips are applied to the skin of the nose by gently folding the strip to contour to the external nasal shape at the level of the nasal valve. Flexible polyester springs within the strip recoil outward from the bent position. Because the strip is firmly adhered to the skin, the recoil generates a force on the external nasal valve causing it to open. These devices have been found to dilate the nasal airway significantly thereby reducing airway resistance, and stiffened the lateral nasal wall preventing inspiratory collapse (Kirkness, Wheatley et al. 2000, Peltonen, Vento et al. 2004).

Roithmann and Chapnik (Roithmann, Chapnik et al. 1998) found that 33 patients with nasal obstruction, compared with 51 healthy controls, had significant increase in airway patency with the adhesive external nasal dilator strip. All subjects showed objective measures of increased patency and experienced subjective improvement in sensation of airflow.

Another available product is the Nozovent™ nasal alar dilator. This consists of a semicircle of plastic with flattened free edges. The semicircle is squeezed and introduced into the nasal cavity with the flat free edges lying against the nasal wall at the level of the nasal valve. As the plastic ring is released it recoils outward, exerting a lateral force on the internal nasal valve, thereby expanding it. Although it is not as well tolerated, increased nasal patency and decreased resistance similar to (and occasionally better than) the external adhesive strips have been found (Ellegard 2006). While effective, nasal valve dilating devices require significant patient compliance.

Surgical Therapy

Typical surgical treatments are alar batten grafts, spreader grafts, and splay grafts, all involving implantation of a cartilage graft (typically harvested from the nasal septum or ear) or a biocompatible material (Khosh, Jen et al. 2004, Fischer and Gubisch 2006, Spielmann, White et al.

2009). Suturing techniques (suspension sutures, flaring sutures) are also used alone or in conjunction with grafts.

Another surgical treatment is a absorbable nasal implant, LATERA®, which is used to support upper and lower lateral cartilage in the nose, reinforcing the nasal wall like traditional cartilage and polymer grafts.

Surgical procedures are efficacious, but can be associated with long recovery periods and complications such as intranasal adhesions, scarring, infection, and graft migration, resorption or extrusion (Rhee, Arganbright et al. 2008, Sufyan, Ziebarth et al. 2012, Cheng, Atfeh et al. 2014).

4.0 CURRENT USE OF RADIOFREQUENCY ENERGY IN THE NOSE

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

ENT surgeons currently use radiofrequency energy daily in numerous nasal therapies. 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 energy to create heat within the submucosal tissue of the turbinate, reducing tissue volume with minimal impact on surrounding tissues (Coste, Yona et al. 2001). Radiofrequency turbinate reduction differs fundamentally from traditional surgical methods by using low-power radiofrequency energy to provide a relatively quick and painless procedure for tissue coagulation and/or ablation.

There have been multiple studies analyzing the safety and outcomes of using radiofrequency energy in the RFTR procedure. In 2009, Hytonen, et al. (Hytonen, Back et al. 2009) completed a systematic literature review of the RFTR technique and concluded that the technique is well tolerated and effective.

Numerous studies have demonstrated that radiofrequency tissue therapy in the nasal passage can be safe and effective in improving nasal obstruction and in preserving nasal function (Sapci, Sahin et al. 2003). Kezirian (Kezirian, Powell et al. 2005) reported 1 minor complication of crusting in 89 adult patients treated with radiofrequency ablation of the turbinates. The same authors also reported no moderate or major complications after RF turbinate reduction based on a review of published literature results.

5.0 PRIOR INVESTIGATIONS

Aerin Medical has identified a patient population whose nasal obstruction is primarily due to internal nasal valve dysfunction, rather than hypertrophied turbinates. A weakened upper lateral cartilage (ULC) can collapse or protrude into the nasal airway, causing restriction of airflow through the nasal valve area. Figure 3 illustrates a ULC that is protruding slightly into the nasal airway.

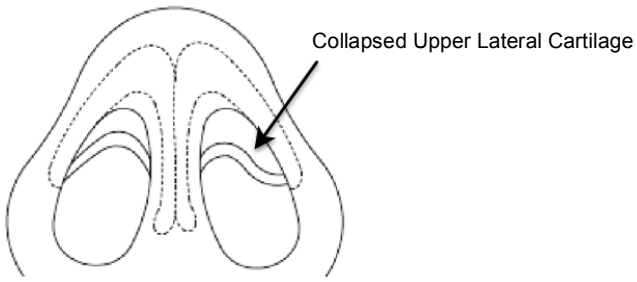

Figure 3. Internal Nasal Valve Dysfunction

(from Stupak 2011, Figure 3A)

It is known that a small change in nasal airway diameter can result in significant changes in airflow; this has been well-described by Bloching with reference to Poiseuille's law (Bloching 2007). Thus, even a slight narrowing or collapse of the ULC (as illustrated in Figure 3 and Figure 4) can result in symptoms of nasal obstruction. Since current non-surgical treatments, such as adhesive external nasal dilator strips and nasal alar dilators, provide relief only while the device is being used, and surgical treatments are not likely to be considered by patients unless their condition is severe and/or they desire cosmetic revision as well (Dolan 2010), there is an unmet need for a non-surgical method of strengthening, shaping and/or supporting an incompetent ULC.

Several researchers have shown through *in vitro* testing that radiofrequency heating can be used to reshape cartilage (Keefe, Rasouli et al. 2003, Manuel, Foulad et al. 2010, Zemek, Protsenko et al. 2012). Targeted radiofrequency heating of the lateral cartilaginous nasal wall, with the intent of causing tissue retraction and volume reduction, has also been used in patients with inspiratory nasal valve collapse (Seren 2009).

Prospective, Non Randomized Multicenter Study – Pivotal Trial

Aerin Medical conducted a prospective, non-randomized, multicenter 26-week trial in September 2016 at 8 study centers in the United States with the primary objective to evaluate safety and efficacy of the Vivaer® ARC Stylus for treating the nasal valve area to improve the symptoms in those diagnosed with nasal airway breathing. Fifty subjects participated in the study. Subjects exhibited significant symptoms of nasal obstruction attributed to internal nasal valve dysfunction. The nasal valve was determined to be the primary or significant contributor to subjects' nasal obstruction based on clinical presentation, physical examination, and nasal endoscopy. Subjects were required to have a nasal obstruction symptom evaluation (NOSE) score ≥60 to be included in the study.

The Vivaer® ARC Stylus was used to apply lateral pressure to a weakened ULC, repositioning the tissue while heating it and thereby widening the nasal airway (see Figure 5). Contraction of the treated area during the healing process would serve to curve the treated portion of the ULC, creating a wider nasal airway and a stiffer nasal valve wall (Figure 6).

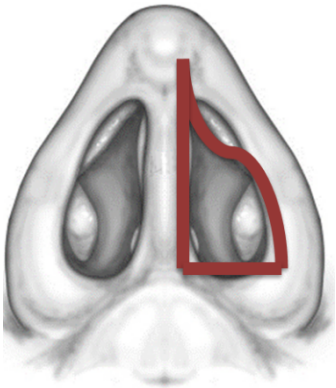

Figure 4. Obstructed Nasal Valve

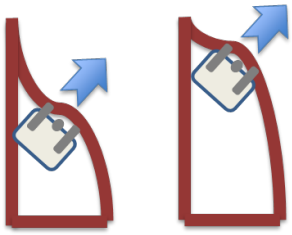

Figure 5. Vivaer® repositioning and treating ULC

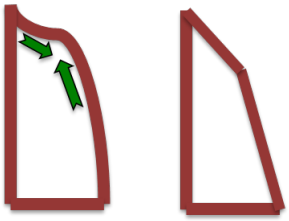

Figure 6. Contraction of ULC (left) and Healed ULC (right)

Of the 50 subjects enrolled in the study, 49 underwent the procedure on both nostrils and 1 subject had the procedure on one nostril only. Forty-nine subjects were available for the primary analysis at the 26-week evaluation. One subject was unavailable for the 26-week evaluation

Safety was evaluated by nasal status assessment, including both a physical assessment and an endoscopic visual assessment of the target nasal valve area within each nostril was done at baseline, immediately prior to and after the procedure, and at each subsequent follow-up visit. Other safety measures were a post procedure pain assessment using a visual analog scale (VAS) and monitoring of medications.
There were no deaths in the study. There were 36 adverse events reported from 20 subjects. 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. Two serious adverse events were reported from 2 subjects. Neither was related to the device or procedure. There were no unanticipated adverse events and no adverse device effects.

Primary efficacy measure and the primary efficacy endpoint was the mean NOSE score change from baseline at the 26-week evaluation. The secondary efficacy endpoint was the proportion of treatment responders at 26 weeks, where responders were defined as subjects with at least a 15-point decrease in the NOSE score. NOSE scores were also collected at each follow-up evaluation. Other efficacy measures included alternatively defined measures of treatment responder and a patient reported satisfaction questionnaire collected at the 26-week evaluation. The mean NOSE score at baseline was 79.9 (SD 0.8) and all subjects had nasal obstruction categorized as either severe (46%) or extreme (54%). The mean NOSE score improved to 24.7 (SD 20.4) at the 26-week endpoint with a mean change from baseline of 54.8 (SD 21.9). This improvement represented a successful outcome for the primary efficacy endpoint as the null hypothesis was rejected and as the mean improvement exceeded 15 points on the NOSE score (paired t-test, $p<0.0001$, lower 95% confidence bound=49.6). At 26 weeks, severe and extreme nasal obstruction rates had decreased from 100% to 10% of the subjects.

Ninety-six percent of subjects were treatment responders at 4 weeks and 100% at 12 weeks. At the 26-week secondary endpoint there were 3 non-responders. The 94% 26-week responder rate demonstrated success for this endpoint by being significantly greater than the success definition of a 55% responder rate.

Subject opinion of the procedure was generally favorable. The mean score response on a 10-point scale to each of the 5 satisfaction survey questions ranged from 7.3 to 8.7, where a higher score indicates a more favorable response.

Long Term Follow Up Study

An ongoing follow up study after the prospective, nonrandomized, multicenter 26-week (pivotal) trial was performed to continue to follow subjects for 2 years after the primary treatment. The objective of the study was to evaluate the long-term durability of benefits associated with the treatment procedure using the Vivaer® ARC Stylus for nasal airway obstruction. The Nasal Obstruction Symptoms Evaluation (NOSE) survey and a Quality of Life survey developed by Aerin Medical were administered at 12, 18, and 24 months after the subjects treatment procedure to subjects who agreed to participate and provided informed consent for the long-term data collection. Subjects completed the NOSE and Aerin Medical Quality of Life surveys in person with a study representative, by telephone, or by mail-in response.

Of the original 50 patients in the pivotal trial, 49 were eligible to participate in the long-term follow-up study and 39 enrolled in the study. Subjects from all original pivotal study sites were enrolled.

The mean NOSE score at baseline was 80.8 (SD 10.7) for subjects participating in this study. All subjects had nasal obstruction at baseline categorized as either severe (46%) or extreme (54%). The mean NOSE score for subjects in this study had significantly improved ($p<0.001$) 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). Significant improvement ($p<0.001$) in mean NOSE score was maintained through the 12-, 18-, and 24-month evaluations (27.5, 32.7, and 26.5, respectively). At 26 weeks, severe and extreme nasal obstruction rates had decreased from 100% to 10% (4 of 39) of subjects, and at 12-, 18-, and 24-months, 17%, 26% and 17% of subjects had severe or extreme nasal obstruction, respectively.

Using the definition of responder of at least a 15-point improvement in NOSE score, 92% of subjects participating in this study were classified as responders at 26 weeks and at 12 months 94% were classified as responders (3 subjects were not evaluated at 12 months). There were 3 participating subjects classified as non-responders at 26 weeks who met responder status at 12 months and 2 subjects classified as responders at 26 weeks who became non-responders at 12 months. All 39 subjects were evaluated at 18 months with a responder rate of 87% and at 24 months 36 of 39 subjects were evaluated and had a responder rate of 97%.

Both the improvement in NOSE score and responder rate through 24 months continued to meet the success criteria established for the 26-week endpoint of the pivotal study. 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 Aerin Medical Vivaer® Stylus was demonstrated to provide durable relief through 24 months as determined by maintenance of improvement in the NOSE score mean and responder rate similar to those achieved at 26 weeks. Response to the Aerin Medical Quality of Life survey provided additional support for the durability and benefits of the treatment.

6.0 STUDY RATIONALE

Given the significant QOL impact of nasal obstruction, it is important to measure not only the physical symptoms (congestion, obstruction and ability to breathe) but also the impact of those symptoms on the patient's ability to sleep and the related consequences on rest, productivity, concentration and ability to participate in the normal daily activities of work and life.

In addition to the physical benefits of increased nasal patency, there are significant quality of life benefits that are associated with better breathing. After correcting nasal obstruction patients report significantly better sleep function (e.g. better night's sleep; waking up during the night and difficulty falling asleep) as well as better psychological function (e.g. concentration, productivity and frustration). (Brown, Hopkins, et. al). We believe that these benefits may well be durable beyond the initial six months of the study in terms of sustained quality of life impact.

The purpose of this study is to continue to evaluate additional subjects for treatment with the Vivaer® ARC Stylus for up to 36 months post-procedure.

7.0 SUMMARY DEVICE DESCRIPTION

The System is comprised of the Vivaer® ARC Stylus (Figure 7, Figure 8) which is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue, and the Aerin Console, a FDA cleared generator (K162810) with temperature control capable of delivering very low doses of energy (Figure 9). The Aerin Console with the Vivaer® ARC Stylus (Figure 9) make up the Vivaer® System.

The Vivaer® ARC Stylus is a cleared device (K172529) and consists of a handle, shaft and treatment tip. An array of bipolar electrodes is positioned on a non-conductive tip which is attached to a handle via a non-conductive shaft. A temperature sensor is located on the tip to monitor tissue temperature. The Stylus is attached to a temperature-controlled radiofrequency generator via a flexible cable. The Vivaer® ARC Stylus temporarily inserted into the nose to access the treated area. It modifies the soft tissues of the nasal airway through the use of low doses of radiofrequency energy. The low-power radiofrequency generates heat within the submucosal tissue, creating a localized lesion. As the lesion heals, the tissue retracts and stiffens. This decreases the nasal airflow resistance thereby improving inflow of air through the nose.

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

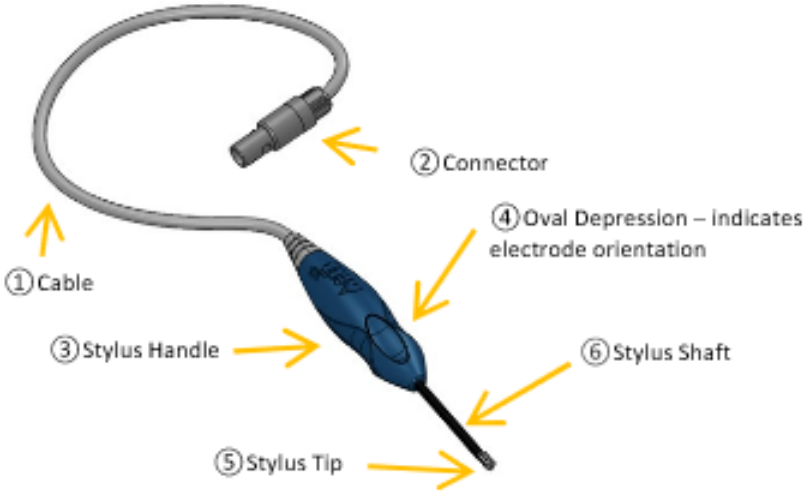

Figure 7. Vivaer® ARC Stylus

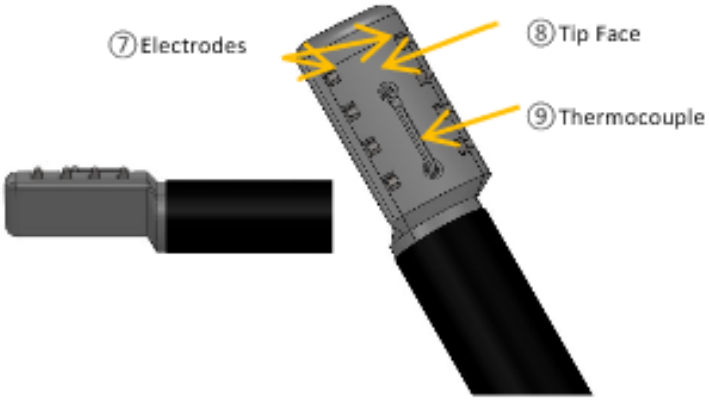

Figure 8. Vivaer® ARC Stylus Tip

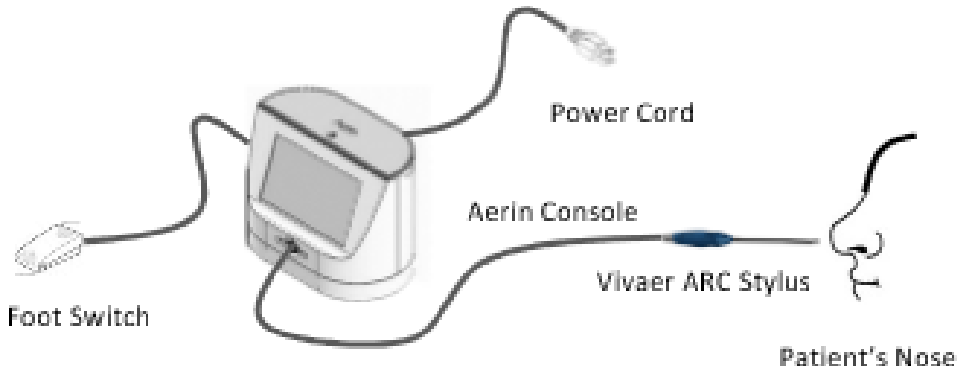

Figure 9. Aerin Console with Vivaer® ARC Stylus

8.0 STUDY DESIGN AND ENROLLMENT

8.1 Study Design and Objectives

A Prospective, Multicenter Study of the Aerin Medical Vivaer® ARC Stylus for Nasal Airway Obstruction. The primary objective of this study is to continue to evaluate the effectiveness of the Vivaer® ARC Stylus for treating the nasal valve area to improve symptoms in those diagnosed with nasal airway obstruction.

8.2 Subject Population

The population being approached for this study are male and female subjects who present with symptoms associated with nasal airway obstruction and meet the protocol eligibility criteria.

Eligible subjects must meet the inclusion and exclusion criteria described in Sections 8.3 and 8.4.

Up to 125 treated patients will be enrolled in the study at up to 20 sites in the United States.

8.3 Inclusion Criteria

To be eligible to participate in this clinical investigation, a patient must meet all of the following criteria:

1. Age 18 or older
2. Willing and able to provide informed consent
3. Willing and able to comply with the study protocol
4. Seeking treatment for nasal obstruction
5. NOSE score of ≥ 60 at Baseline
6. Nasal valve is a primary or significant contributor to the subject's nasal obstruction as determined by the study investigator (based on clinical presentation, physical examination, nasal endoscopy, etc.) and the subject has a positive response to any of the following temporary measures (based on patient history or office exam):

- Use of external nasal dilator strips (e.g., Breathe Right Strips)
- Q-Tip test (manual intranasal lateralization)
- Use of nasal stents
- Cottle Maneuver (manual lateral retraction of the cheek)

8.4 Exclusion Criteria

A patient who meets any of the following criteria is not eligible to participate in the study:

1. Prior surgical treatment of the nasal valve
2. Rhinoplasty, septoplasty, inferior turbinate reduction or other surgical nasal procedures within the past three (3) months
3. Anatomy that requires an adjunctive surgical nasal procedure on the same day or 3 months after the Vivaer procedure
4. Medical conditions which in the opinion of the treating physician would predispose the subject to poor wound healing or increased surgical risk.

9.0 STUDY PHASES

The study will be conducted in five phases:

Phase 1: Enrollment (Screening & Consent)
Phase 2: Vivaer® Treatment
Phase 3: Investigator Assessment and Subject Follow-Up, Questionnaires (QOL, NOSE and VAS) scales at 3 months
Phase 4: Subject Follow-up Questionnaires (NOSE and QOL) at 6, 12, 24 and 36 months
Phase 5: Study Exit

Study Assessments are defined in Section 9.6.

9.1 PHASE 1: ENROLLMENT (Screening & Consent)

The treating physician or designated research staff will perform a formal 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.

The following data will be collected:

- Patient demographics
- Medical history including prior medication use, tests and treatments for nasal airway obstruction
- NOSE Score
- Treating physician pre-treatment visual assessment of the area to be treated
- Photographs/videos of each nostril will be captured

The investigator or designated staff will review all aspects of the study with the patient including the protocol, associated documents, and the follow-up process. Once the study has been explained and any questions have been answered the patient will complete and sign the Informed Consent Form (ICF).

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other remote platforms such as video conferencing used in compliance with site policy) per the discretion of the investigator and with the agreement of the subject/consent designee. Whether in person or remote, the privacy and confidentiality of the subject will be maintained. The person explaining consent (and subject/consent designee, when in person) will be located in a private area (e.g., clinic consult room).

When consent is conducted remotely, the subject/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed. The subject should be informed of approximately how long the process will take and what information will be presented. The subject and person explaining consent will view individual copies of the approved consent document on screens at their respective locations; the same screen may be used when both the person explaining consent and the subject are co-located but this is not required. When remote, consent will be documented with required signatures on the electronic document. When an electronic document with a digital signature is used for the documentation of consent, this study will use the Adobe Acrobat platform, which is 21 CFR Part 11 compliant to obtain the required signatures. The identity of the subject will be determined by a prompt, which will require the provision of information from an official identification document and to answer security questions, prior to obtaining the signature. An electronic signature with a timestamp will be provided by the required parties through system prompts. Both the person explaining informed consent and the subject must sign the electronic document.

Whether the consent is obtained from the subject in person or remotely, the consent process must provide sufficient opportunity for the subject to consider whether to participate and to ask questions. A copy (paper or electronic) of the signed and dated consent must be provided to the subject.

9.2 PHASE 2: VIVAER® TREATMENT

Subjects will have their nasal valve treated in a single Vivaer® treatment session and will be considered enrolled once the device has entered the nasal cavity. The procedure will be performed in accordance to its intended use. The area planned for treatment will be visually assessed by the physician immediately before and after the treatment session. Subjects should be scheduled for Vivaer treatment within 30 days after their baseline assessment.

The following data will be collected:

- Physician Physical Examination of the Nasal Area
- Treatment Information
- Endoscopic Nasal Examination
- Photographs/videos of each nostril will be captured
- Evaluate Treatment Adverse Events

The follow-up period will begin after the study treatment session.

9.3 PHASE 3: INVESTIGATOR ASSESSMENT AND SUBJECT FOLLOW-UP AT 3 MONTH

The following data will be collected at the 3 month clinic visit:

- Physician Physical Examination of the Nasal Area
- Endoscopic Nasal Examination
- Photographs/videos of each nostril will be captured
- Evaluate for any Adverse Events

Study subjects will be asked to complete the following self-reported questionnaires:

- NOSE Score
- Quality of Life (QOL) Questionnaire
- Visual Analog Scale (VAS) for Pain related to the treated area

9.4 PHASE 4: SUBJECT FOLLOW-UP QUESTIONNAIRES AT 6, 12, 24 and 36 MONTHS

Subjects will be contacted for follow-up data collection at **6, 12, 24 and 36 months** calculated from the treatment date.

Study subjects will be asked to complete the following self-reported questionnaires:

- NOSE Score
- Quality of Life (QOL) Questionnaire

If any changes in medication, health status or subject received another nasal procedure, the subject will be instructed to contact the study staff.

9.5 PHASE 5: STUDY EXIT

Subjects will be determined exited from the study when they complete the questionnaires for each required follow up or are determined as exited if a circumstance removes them for a specific reason earlier than planned. Subjects meeting the study requirements as planned will be exited from the study after the 36 month follow-up data collection. If a subject reaches the 36 month follow-up point and is experiencing new or ongoing adverse event, the study sponsor and treating investigator should be contacted to discuss the need and/or methods for continued surveillance of the event.

Subjects that completed the 24-month follow-up and exited per protocol version D will be invited to continue participation in the study through their 36 month post Vivaer procedure date. Subjects who elect to continue with the study will be asked to re-consent for their participation through 36 months. Subjects that decline 36-month follow-up participation or re-consent, will be exited from the study after their 24 month follow-up data collection. Reasons for declining participation in the 36 month extension will be recorded in the eCRF.

9.6 STUDY ASSESSMENTS

The following study assessments will be collected at the specific time-points mentioned in the above phases.

Visual Assessment of Treatment Area (Nasal Evaluation): The treated area within each nostril will be visually assessed. The use of an endoscope for visual assessment is required. For consistency in reporting across sites, a study CRF will outline specific observations to be assessed. In addition, representative still photographs of each nostril will be captured at each visit

The following assessments will be obtained from the study subjects.

Nasal Obstruction Severity Effectiveness (NOSE) Scale: A validated disease specific health status instrument to measure the outcome of subjects treated for nasal obstruction is a well-known and recognized validated 5-item instrument using a 5-point Likert Scale for patients with nasal obstruction. This outcome assessment has been used to measure improvements in QOL in septoplasty, functional septorhinoplasty and nasal valve surgery.

Visual Analog Scale (VAS) for Pain Intensity: The Pain VAS will be used to rate pain associated with the treatment (Hawker, Mian et al. 2011). Subjects will be asked to mark their pain level on a 10 cm line anchored by verbal descriptors: 0 = no pain and 10 = worst pain imaginable. The study staff will measure with a metric ruler from the 0, the beginning of the line, to the vertical mark made by the subject. The result, expressed in millimeters, will represent the subject's VAS Pain Score.

Adverse Event Evaluation: Subjects will be asked about any side effects or adverse experiences related to the Vivaer® treatment that they may have been experienced. All device related events will be documented on the proper Adverse Event Log and Adverse Event data form.

Medications: Updates to current medications or any new or changed medications will be asked. The medication log will be updated to reflect any changes. In addition, any medications as a result of intervention related to the study treatment will be documented and will correlate with the Adverse Event Case Report Form.

Quality of Life Questionnaire: Study-Specific Quality of Life (QOL) Questionnaire – The QOL questionnaire will be used to gain better understanding of the impact of nasal obstruction on the subject's daily activities, feelings, symptoms and medication use.

Table 1. Schedule of Assessments

Assessments	Prior to Nasal Valve Treatment	Nasal Valve, Treatment	Investigator Visual Assessment & subject follow-up at 3 months (+/- 2 weeks)	6, 12, 24 and 36 month Follow-ups (+/- 1 month)
Demographics and Medical History	X			
Nasal Evaluation	X	X	X	
Medication Review	X	X	X	X
Visual Assessment of Treatment Area & Photographs/videos	X	X	X	
Vivaer ARC Stylus Treatment		X		
NOSE Score	X		X	X
Visual Analog Scale (VAS)			X	
Subject QOL Questionnaire			X	X
Adverse Event Review		X	X	X
Study Exit				X*

*At 36 month visit

10.0 ADVERSE EVENTS AND PRODUCT COMPLAINTS

10.1 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 treatment procedure will be documented in the subject's medical record but will not count as related to the study device or procedure.

Each adverse event will be recorded in the corresponding subject's CRF. Each adverse event will be judged by the Investigator as to its relationship and level of relatedness to the study device and/or study procedure. In addition, the Investigator will identify the date of onset, severity and duration of the AE. All adverse events will be monitored until they are adequately resolved or explained. If a subject reaches the 36 month follow-up visit 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.

The Investigator must submit to the Sponsor a report of any Serious Adverse Event (SAE), Serious Adverse Device Effect (SADE) or Unanticipated Adverse Device Effect (UADE) within 24 hours of knowledge of the event.

Sponsor Contact:	Desiree Hollemon, MSN, MPH
Telephone:	(503) 686-8972
Email:	dhollemon@aerinmedical.com

In addition, the Investigator will report adverse events to the reviewing IRB / EC *(as applicable)* according to the local reporting requirements.

Adverse Events
Adverse Event (AE) – any untoward medical occurrence in a subject (ISO 14155).

NOTE: This definition does not imply that there is a relationship between the adverse event and the device under investigation.

Serious Adverse Event (SAE) – an adverse event that (ISO 14155):

- led to a death,
- led to a serious deterioration in the health of the subject,
- resulted in a life-threatening illness or injury,
- resulted in a permanent impairment of a body structure or a body function,
- required hospitalization or prolongation of existing hospitalization,
- resulted in medical or surgical intervention to prevent permanent impairment to body structure or function,
- led to fetal distress, fetal death, a congenital abnormality, or birth defect.

Adverse Device Effect (ADE) – any untoward and unintended response to a medical device (ISO 14155)

NOTE: This includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition also includes any event that is a result of user error.

Serious Adverse Device Effect (SADE) – an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune (ISO 14155).

Anticipated Adverse Device Effect (AADE) – an adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the previously identified in nature, severity, or degree of incidence in the investigational plan or application

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 (21 CFR 812.3(s) and ISO 14155).

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.

10.2 Product Complaints

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 CFR 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.

11.0 SUBJECT REIMBURSEMENT

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

12.0 RISK-BENEFITS

12.1 Potential Risks to Patient Confidentiality

Risks to patient confidentiality are minimized by only allowing authorized individuals to access the EDC system, which is 21 CFR Part 11 compliant. The validated system maintains an audit trail on all entries, changes or corrections to eCRFs. If a person only authorized to complete 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.

The electronically driven subject reported questionnaire system enables subject privacy protection and full data attribution through the use of a unique username, password and provides a full audit trail. The system employs Advanced Encryption Standard (AES) for data in transit, at rest and in system backups. The data collection process uses encryption with, at least, 256-bit Secure Sockets Layer (SSL) and 2048 bit RSA public keys while providing the subject a user-friendly method to provide patient reported outcomes (PRO)'s.

12.2 Minimization of Anticipated Risks

Risks associated with the Vivaer® ARC Stylus are minimized by design. In addition, risks will be minimized through the use of a treating physician with a high degree of experience in nasal surgical and minimally invasive procedures. The treating physician will have received new customer training in proper use of the device prior to study start.

12.3 Potential Benefits

Potential benefit, associated with the Vivaer® treatment, is to offer a safe, minimally invasive treatment method to alleviate the symptoms of nasal obstruction. 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.

13.0 STUDY MANAGEMENT

This study will be conducted in accordance with elements of E6 Good Clinical Practice Consolidated Guidance, ICH, April 1996, Abbreviated Requirements of 21 CFR 812 for NSR device studies, the Declaration of Helsinki, the Belmont Report and any conditions imposed by the reviewing IRB **or** US FDA or other regulatory agency.

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

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

14.0 ETHICAL CONSIDERATIONS

The rights, safety and wellbeing of clinical study subjects shall be protected consistent with the ethical principles outlined in the Declaration of Helsinki. This shall be understood, observed and applied at every step in this clinical investigation.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The Sponsor and the treating physician shall avoid improper influence or inducement of the patient, study monitor, treating physician or other parties participating in or contributing to the clinical study.

15.0 PROTECTION OF PATIENT CONFIDENTIALITY

At all times throughout the clinical investigation, confidentiality will be observed by all parties involved. All data shall be secured against unauthorized access. Privacy and confidentiality of information about each patient shall be preserved in the reports and in any publication. Each patient participating in this study will be assigned a unique identifier. All data will be tracked, evaluated, and stored using only this unique identifier. See Sec. 16.0 for more details.

The study site will maintain a confidential study patient list (paper or electronic) identifying all enrolled patients. This list will contain the assigned study patient's unique identifier and name. The treating physician bears responsibility for keeping this list confidential. This list will not be provided to the study sponsor and is only to be used at the study center.

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

16.0 DATA COLLECTION

Subject data will be collected in a secure electronic data capture (EDC) system via the internet. All baseline, index procedure and 3-month data will be entered by the study site personnel in the electronic Case Report Forms (eCRFs). A unique subject ID number will be assigned to each subject. Every reasonable effort should be made to complete data entry within 10 business days of data collection. Any discrepancies may be queried during routine monitoring visits. Data monitoring will be performed to verify data accuracy and ensure queries are resolved.

Subject reported outcomes obtained via EDC system are considered to be source documents for this study.

17.0 PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the trial according to the protocol or the investigator agreement. Deviations must be reported to Aerin Medical regardless of whether medically justifiable, pre-approved, or performed to protect the subject in an

emergency. Examples of deviations that are required to be reported to Aerin Medical include, but not limited to the following:

- Informed Consent Form is not obtained before data collection
- Subjects are enrolled that have not met the eligibility criteria
- Subject misses the 3-month Investigator Visual Assessment Follow-up Visit

Investigators are required to report deviations to Aerin Medical by completing a Protocol Deviation eCRF. The investigator is obliged to comply with IRB procedures and/or local laws for reporting deviations. Aerin Medical shall review reported deviations upon receipt and determine appropriate action and regulatory reporting requirements.

18.0 STUDY SUSPENSION OR EARLY TERMINATION

The study can be 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
- Persistent non-compliance with the protocol

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform all participating study sites and treating physicians / investigational center(s) of the termination or suspension and the reason(s) for this. The IRB/EC shall also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor. Regulatory authorities and the personal physicians of the patients may also need to be informed if deemed necessary.

19.0 RESPONSIBILITIES

Aerin Medical Inc. is the manufacturer of the Vivaer® ARC Stylus and the Sponsor of this study. The Sponsor has the overall responsibility of the study and will work to ensure compliance with the Investigational Plan, elements of Good Clinical Practice: Consolidated Guidance (ICH, April 1996), signed study agreements and 21 CFR 812.2(b), *Abbreviated Requirements*.

The sponsor will be responsible for, but not limited to, conducting the following tasks:

- Ensuring the treating physicians are trained to the Vivaer® ARC Stylus
- Provide appropriate information to treating physicians and clinic staff
- Promptly inform the treating physicians and where applicable any regulatory authorities and Ethics Committees, if the study is prematurely terminated or suspended and the reason for the termination or suspension
- Provide protocol initiation training to include the study protocol, data completion guidelines, and guidelines for obtaining informed consent
- Coordinate ongoing communication with consultants and study sites to resolve any problems concerning the protocol or data collection. Every effort will be made to ensure compliance with the protocol

- Retain ownership of all clinical data generated in this study, and control the use of the data for purposes of regulatory submissions to the US and other regulatory agencies
- Protect patient confidentiality

The Sponsor will be responsible for **maintaining study records** per 21 CFR 812.140(a) and Good Clinical Practice: Consolidated Guidance (ICH, April 1996), Section 4.9.

The Sponsor will allow auditing of their clinical investigation or study procedure(s).

The Sponsor is responsible for maintaining study records for every patient participating in study (including information maintained electronically. The Sponsor will also maintain any ***original*** source documents from which study-related data are derived, which may include, but are not limited to:

- Notes of phone calls and/or correspondence indicating site's attempts to contact and follow a study patient at the required follow-up time points until such time a subject is determined to be lost-to-follow-up.

The Sponsor must ensure that all study patient records are stored for at least 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of this study or a notice of completion of a product development protocol. 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 site is acquired or shuts down so that arrangements can be made for the handling or transfer of study records.

20.0 PUBLICATION POLICIES

The Clinical Trial Agreement (CTA) mutually signed by the Investigator(s) and Aerin Medical, defines and describes the nature of the study agreement. The data and results from the AERWAY 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. Publication authorship will be established according to 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. 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 multi-center results ahead of single-center investigations.

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

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