

# A Prospective, Multi-Center, Non-Randomized Study to Evaluate Treatment of Nasal Airway Obstruction Using the Aerin Medical Device

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## TABLE OF CONTENTS

<b>1.0</b>	<b>PROTOCOL SYNOPSIS .....</b>	<b>4</b>
<b>2.0</b>	<b>INTRODUCTION AND LITERATURE REVIEW .....</b>	<b>6</b>
2.1	Introduction .....	6
2.2	Nasal Anatomy .....	6
<b>3.0</b>	<b>NASAL VALVE OBSTRUCTION MEASUREMENT AND TREATMENT .....</b>	<b>7</b>
3.1	Physical Assessment .....	7
3.2	Nasal Obstruction Measurement .....	7
3.3	Subjective Assessment .....	8
3.4	Current Treatments .....	8
<b>4.0</b>	<b>CURRENT USE OF RADIOFREQUENCY ENERGY IN THE NOSE .....</b>	<b>9</b>
<b>5.0</b>	<b>STUDY RATIONALE .....</b>	<b>9</b>
<b>6.0</b>	<b>SUMMARY DEVICE DESCRIPTION .....</b>	<b>10</b>
<b>7.0</b>	<b>CLINICAL STUDY DESIGN AND ENROLLMENT .....</b>	<b>12</b>
7.1	Study Design and Objectives .....	12
7.2	Subject Population .....	12
7.3	Inclusion Criteria .....	13
7.4	Exclusion Criteria .....	13
<b>8.0</b>	<b>STUDY PHASES .....</b>	<b>14</b>
8.1	Phase 1: Pre-Screen and Informed Consent Process .....	14
8.2	Phase 2: Screening and Baseline Evaluation .....	14
8.3	Phase 3: Enrollment and Study Procedure .....	15
8.4	Phase 4: Follow-Up and Study Exit .....	16
8.5	Types of Assessments .....	16
<b>9.0</b>	<b>SUBJECT REIMBURSEMENT .....</b>	<b>18</b>
<b>10.0</b>	<b>STUDY WITHDRAWAL .....</b>	<b>18</b>
<b>11.0</b>	<b>ADVERSE EVENTS .....</b>	<b>18</b>
<b>12.0</b>	<b>RISK – BENEFIT ASSESSMENT .....</b>	<b>19</b>
12.1	Potential Risks .....	19
12.2	Potential Benefit .....	20
12.3	Minimization of Anticipated Risks .....	20
12.4	Potential Risks to Patient Confidentiality .....	20
<b>13.0</b>	<b>STATISTICAL ANALYSIS .....</b>	<b>20</b>
13.1	Sample Size Determination .....	20
13.2	Hypothesis Testing .....	21
13.3	Definition of Populations .....	21
13.4	Primary Endpoint – Efficacy Analysis .....	21
13.5	Secondary Endpoint – NOSE Responder Rate .....	21
13.6	Secondary Endpoint – Safety Analysis .....	21
13.7	Adverse Events .....	21
13.8	Statistical and Analytical Methods .....	22
<b>14.0</b>	<b>SAFETY RELATED STOPPING RULES .....</b>	<b>23</b>

15.0	QUALITY ASSURANCE AND SUPERVISION BY AUTHORITIES .....	23
16.0	STUDY MANAGEMENT .....	23
17.0	INVESTIGATIONAL DEVICE MANAGEMENT .....	24
18.0	REQUIRED DOCUMENTS FROM THE INVESTIGATOR (PRIOR TO STUDY START) .....	24
19.0	TRAINING .....	24
20.0	ETHICAL CONSIDERATIONS .....	24
21.0	PROTECTION OF PATIENT CONFIDENTIALITY .....	25
22.0	DATA COLLECTION .....	25
23.0	SOURCE DATA VERIFICATION .....	25
24.0	STUDY SUSPENSION OR EARLY TERMINATION .....	25
25.0	SITE CLOSE-OUT .....	26
26.0	RESPONSIBILITIES .....	26
27.0	SPONSOR MAINTENANCE OF STUDY RECORDS .....	27
28.0	INVESTIGATOR MAINTENANCE OF STUDY RECORDS .....	27
29.0	INVESTIGATOR REPORTS .....	28
30.0	DATA MANAGEMENT .....	28
30.1	Data Entry .....	28
30.2	Data Cleaning .....	28
30.3	Data Back-up .....	29
30.4	Confidentiality and Security .....	29
30.5	Final Report .....	29
30.6	Publication Policy .....	29
31.0	DEFINITIONS AND ACRONYMS .....	29

## 1.0 PROTOCOL SYNOPSIS

<b>Study Title:</b>	Prospective, Multi-Center, Non-Randomized Study to Evaluate Treatment of Nasal Airway Obstruction Using the Aerin Medical Device
<b>Investigational Device:</b>	Aerin Medical Vivaer™ Stylus
<b>Device Description:</b>	The Vivaer Stylus is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue.
<b>Proposed Indication:</b>	The Vivaer Stylus is indicated for the treatment of nasal obstruction by the modification of submucosal tissue including cartilage in the internal nasal valve area.
<b>Study Objective:</b>	The primary objective of this study is to evaluate the safety and efficacy of the Vivaer System for treating the nasal valve area to improve symptoms in those diagnosed with nasal airway obstruction.
<b>Study Design:</b>	Prospective, multi-center, non-randomized, Non-Significant Risk (NSR) safety and efficacy study.
<b>Subject Population:</b>	Male and female subjects who present with symptoms associated with nasal airway obstruction and meet the protocol eligibility criteria.
<b>Study Procedure:</b>	Subjects will have both nasal valves treated in a single treatment session. Follow-up visits will be scheduled and calculated from the treatment date. No repeat ("touch-up") procedures will be permitted during the 6-month (26-week) follow-up period.
<b>Study Endpoints:</b>	<p><u>Primary Endpoint – Efficacy:</u> Improvement in subject-reported Nasal Obstruction Symptom Evaluation (NOSE) Score from Baseline to 26 weeks post study procedure. The primary efficacy endpoint will utilize the mean change in NOSE score from Baseline to 26 weeks post study procedure. The mean improvement in this score must be statistically significantly greater than 15 points for study success.</p> <p><u>Secondary Endpoint – NOSE Responder Rate:</u> A responder is defined as a treated subject who experiences at least a 15-point improvement in NOSE score from Baseline to 26 weeks post treatment. Success for this endpoint is defined as a responder rate of 55% or greater.</p> <p><u>Secondary Endpoint – Safety:</u> Safety will be assessed by characterizing the type and frequency of adverse events reported at or following the study procedure, throughout the follow-up period.</p>
<b>Additional Evaluations:</b>	<p>Subject-reported NOSE score at 4-week and 12-week follow-up visits.</p> <p>Subject-reported pain related to the study procedure by Visual Analog Scale immediately post-procedure and at 4-week and 12-week follow-up visits.</p> <p>Patient Satisfaction with the study procedure 26 weeks post procedure.</p>

<b>Study Size:</b>	50 subjects
<b>Study Size Determination:</b>	Prior study data were used to estimate the expected mean change (28.5) and standard deviation (30.3) for the change in NOSE score from baseline to 26 weeks. N=45 subjects would provide 90% power to test the study hypothesis at the one-sided alpha level of 0.05. To allow for up to 10% attrition, a total of 50 subjects will be enrolled.
<b>Number of Sites:</b>	Up to 10 study sites
<b>Anticipated Study Duration:</b>	Enrollment completion – Q4 2016; Follow-Up completion – Q3 2017
<b>Study Visits:</b>	Screening/Baseline, Study Procedure, 4 weeks, 12 weeks, 26 weeks
<b>Study Eligibility Criteria:</b>	<p><u>Inclusion Criteria:</u> Eligible subject <u>will meet all</u> the following:</p> <ol style="list-style-type: none"><li>1. Age 22 to 75 years (inclusively)</li><li>2. Willing and able to provide informed consent</li><li>3. Willing and able to comply with the subject-specific requirements outlined in the study protocol</li><li>4. Seeking treatment for nasal obstruction and willing to undergo an office-based procedure</li><li>5. NOSE score of <math>\geq 60</math> at Baseline</li><li>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):<ul style="list-style-type: none"><li>• Use of external nasal dilator strips (e.g., Breathe Right Strips)</li><li>• Q-Tip test (manual intranasal lateralization)</li><li>• Use of nasal stents</li><li>• Cottle Maneuver (manual lateral retraction of the cheek)</li></ul></li></ol> <p><u>Exclusion Criteria:</u> Subject <u>will not be enrolled</u> if they meet any of the following:</p> <ol style="list-style-type: none"><li>1. Prior surgical treatment of the nasal valve</li><li>2. Rhinoplasty, septoplasty, inferior turbinate reduction or other surgical nasal procedures within the past twelve (12) months</li><li>3. Severe and/or chronic sinusitis, recurrent sinusitis, or allergies leading to nasal obstruction and currently requiring oral corticosteroid therapy</li><li>4. Severe case of any of the following; septal deviation, turbinate hypertrophy, polyps, or ptotic nose tip believed to be the primary contributor to the subject's nasal obstruction symptoms and warranting surgical intervention</li><li>5. Known or suspected allergies or contraindications to the anesthetic agents and/or antibiotic medications to be used during the study procedure session</li><li>6. Known or suspected to be pregnant, or is lactating</li><li>7. Other medical conditions which in the opinion of the investigator would predispose the subject to poor wound healing or increased surgical risk.</li></ol>

## 2.0 INTRODUCTION AND LITERATURE REVIEW

### 2.1 Introduction

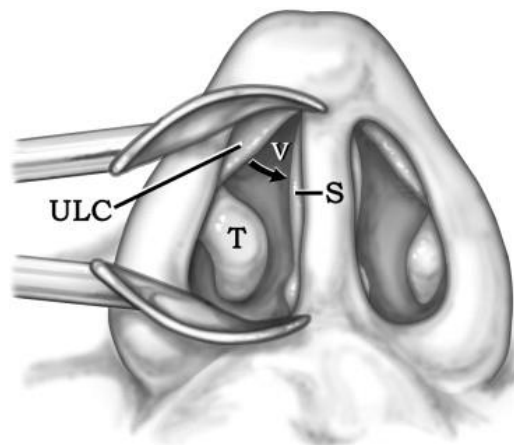
Nasal airway obstruction affects the upper airway system causing restriction in normal airflow into the nasal cavity. This nasal condition can be caused by a diversity of mucosal and structural disorders in the nasal cavity. Nasal diseases such as acute and/or chronic rhinosinusitis can cause nasal polyps, 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

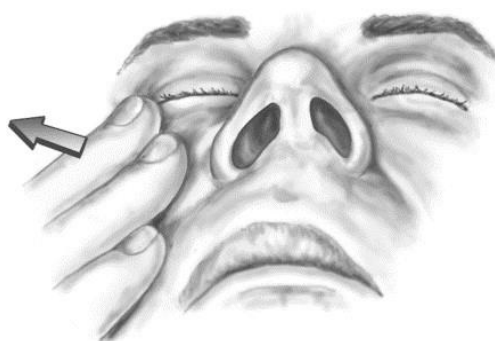
Self-diagnosis is common with patients experiencing decreased nasal airflow. The first-line treatment may be over-the-counter remedies such as nasal dilator sprays, humidifiers and/or external nasal dilator strips (e.g., “Breathe Right” nasal strips) which temporarily expand the sidewalls of the nose 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. 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, Affeh 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.

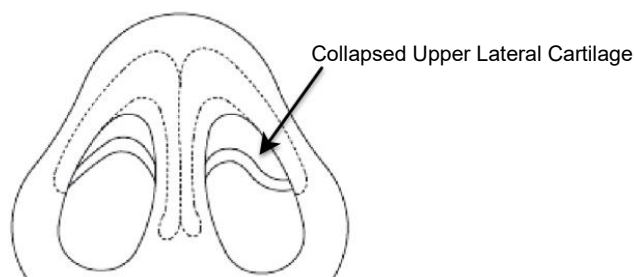
ENT surgeons currently use radiofrequency energy daily in numerous nasal therapies. Radiofrequency turbinate reduction (RFTR), for instance, is a minimally invasive surgical option that can reduce tissue volume in a precise, targeted manner. This technique uses radiofrequency energy to create heat within 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 STUDY RATIONALE

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).

Aerin Medical believes the Vivaer™ Stylus can be 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).

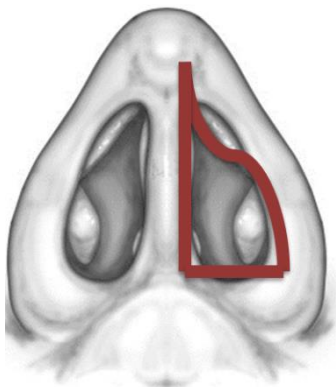


Figure 4. Obstructed Nasal Valve

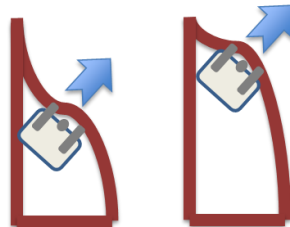


Figure 5. Vivaer repositioning and treating ULC

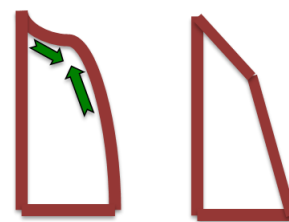


Figure 6. Contraction of ULC (left) and Healed ULC (right)

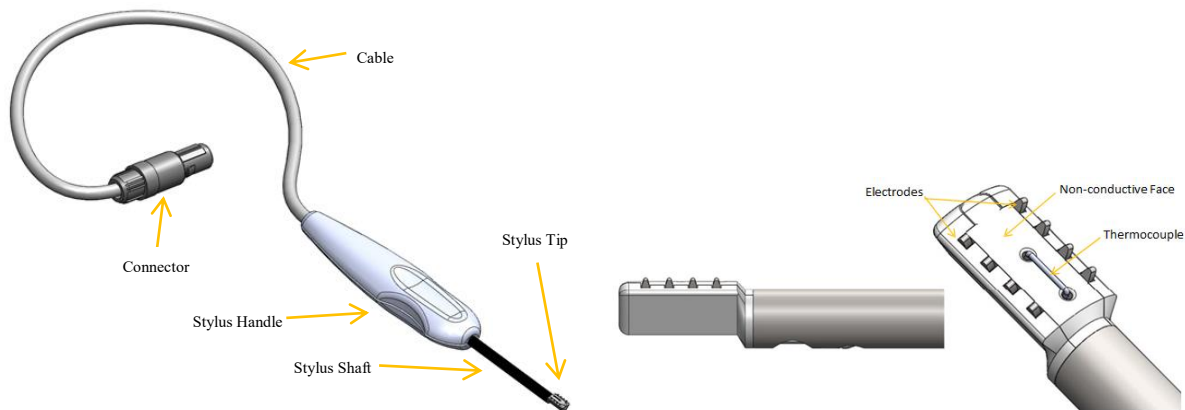
## 6.0 SUMMARY DEVICE DESCRIPTION

The Aerin Medical Vivaer™ System is an investigational device intended to improve nasal breathing by modifying soft tissues of the nasal airway. The System is comprised of the Vivaer Stylus (Figure 7) which is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue, and a radiofrequency generator, Smith and Nephew ORA-50 S, a FDA cleared generator (K990474) with temperature control capable of delivering very low doses of energy (Figure 8). The ORA-50 S generator's technical specifications comply with those required by Aerin Medical's Product Specification PS010.

The Vivaer Stylus 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™ Stylus 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 coagulation 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 Vivaer Stylus tip is temporarily inserted into the nose to access the treated area. The procedure requires local anesthesia only. The stylus is manufactured and supplied by the Sponsor and may be used to treat both nostrils of the patient.



**Figure 7. Vivaer Stylus**



**Figure 8. Ora-50 S RF Generator**

## 7.0 CLINICAL STUDY DESIGN AND ENROLLMENT

### 7.1 Study Design and Objectives

This study is a prospective, multi-center, non-randomized, single arm, non-significant risk device evaluation of the Aerin Medical Vivaer™ Stylus. The primary objective of this study is to evaluate the safety and efficacy of the Vivaer System for treating the nasal valve area to improve symptoms in those diagnosed with nasal airway obstruction, to support the following proposed indication for use:

*The Vivaer Stylus is indicated for the treatment of nasal obstruction by the modification of submucosal tissue including cartilage in the internal nasal valve area.*

### 7.2 Subject Population

The population being targeted for this therapy consists of patients who exhibit significant symptoms of nasal obstruction attributed to internal nasal valve dysfunction. To evaluate the significance of a patient's nasal obstruction both before and after the investigational procedure, this study will use a subjective measure, the Nasal Obstruction Symptom Evaluation (NOSE) scale. No objective measures will be used, as the published literature reports poor correlation between objective measures of nasal patency (e.g., nasal inspiratory peak flow, acoustic rhinometry, rhinomanometry, CT scans, physician assessment of anatomy) and subjective measures (Stewart and Smith 2005, Lam, James et al. 2006, Andre, Vuyk et al. 2009, Dadgarnia, Baradaranfar et al. 2013, Andrews, Choudhury et al. 2015). 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 (Stewart and Smith 2005, Lam, James et al. 2006, Rhee, Weaver et al. 2010).

Aerin Medical has chosen a baseline NOSE score inclusion criterion of  $\geq 60$  to ensure that enrolled subjects are suffering from significant nasal obstruction symptoms. This criterion takes into consideration the nasal obstruction severity classification system developed by Lipan and Most (Lipan and Most 2013) which classifies a NOSE score of  $\geq 55$  as indicative of severe to extreme nasal obstruction. As additional support for this threshold, average pretreatment NOSE scores ranging from 57 to 77 were seen in publications describing surgical treatments for nasal airway obstruction (Rhee, Sullivan et al. 2014).

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 trial. However, to ensure that changes in NOSE score over the course of follow-up are the result of the investigational procedure, prior surgical procedures must have been performed at least 12 months before the patient is enrolled in this study. Patients who have had previous surgical treatment of the nasal valve are not eligible to enroll in this trial.

Eligible subjects must meet the inclusion and exclusion criteria described in Sections 7.3 and 7.4. Any questions regarding a potential subject's eligibility for enrollment must be discussed with the Sponsor prior to scheduling the subject for the investigational procedure.

An estimated 45 treated subjects who complete the 26-week follow-up will be necessary to fulfill the primary endpoint data analysis. To allow for up to 10% attrition over the course of the study, a total of 50 subjects will be enrolled.

### 7.3 Inclusion Criteria

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

1. Age 22 to 75 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. NOSE score of  $\geq 60$  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)

### 7.4 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 twelve (12) months
3. Severe and/or chronic sinusitis, recurrent sinusitis, or allergies leading to nasal obstruction and currently requiring oral corticosteroid therapy
4. Severe case of any of the following; septal deviation, turbinate hypertrophy, polyps, or ptotic nose tip believed to be the primary contributor to the subject's nasal obstruction symptoms and warranting surgical intervention
5. Known or suspected allergies or contraindications to the anesthetic agents and/or antibiotic medications to be used during the study procedure session
6. Known or suspected to be pregnant, or is lactating
7. Other medical conditions which in the opinion of the investigator would predispose the subject to poor wound healing or increased surgical risk.

## 8.0 STUDY PHASES

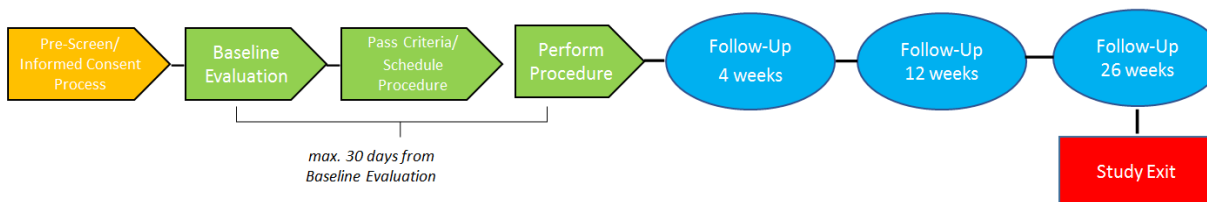
The study will be conducted in four phases as subjects are consented, evaluated for eligibility, treated and followed until study exit:

Phase 1 - Pre-Screen / Informed Consent Process

Phase 2 - Screening / Baseline Evaluation

Phase 3 - Enrollment / Study Procedure

Phase 4 - Follow-up / Study Exit



The different study phases are described in Sections 8.1 through 8.4. Section 8.5 provides a table of required study visits, the visit windows, and the assessments to be done at each visit, as well as a description of each assessment type.

### 8.1 Phase 1: Pre-Screen and Informed Consent Process

Patients presenting with symptoms associated with nasal airway obstruction will be approached with the study and asked if they are willing to volunteer participation. Patients will initially be asked about duration of symptoms and conservative measures used for their condition. Any known concomitant nasal conditions and past nasal surgeries will be discussed to understand if they are potential candidates for the study.

#### Informed Consent

Informed consent will be obtained as outlined in 21 CFR Part 50 and the Good Clinical Practice: Consolidated Guidance (ICH, April 1996).

A research study member at the approved study site will speak with the study candidate about the purpose of the study and investigational research. Explanation of the study background, study procedure, follow up visit schedule, study procedure risks and benefits will be reviewed in detail with the patient. Patients will be given the time they need to read through the study information and informed consent document and ask as many questions as necessary to make them comfortable with the study and the requirements. For those potential candidates who agree to participate in the study by signing the IRB approved Informed Consent Form (ICF), a baseline evaluation will be conducted.

### 8.2 Phase 2: Screening and Baseline Evaluation

During the screening/baseline visit in the study clinic, the Investigator or designated research staff will perform a formal evaluation of the study candidate for study eligibility, which will 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 tests and treatments for nasal airway obstruction
- Physical exam and vital signs
- NOSE questionnaire (completed by the subject)
- Investigator visual assessment (using an endoscope) of nasal valve area to be treated

Subjects who agree to participate and meet the enrollment criteria must be scheduled to undergo the study procedure **within 30 days** of the baseline visit.

### 8.3 Phase 3: Enrollment and Study Procedure

Study subjects will be considered enrolled once they arrive at the study clinic to undergo the investigational procedure. At this time a study subject identification number will assigned along with the study subject binder. The investigational procedure will be performed in the study clinic. Subjects will have both nasal valves treated in a single study procedure session. Each nostril will be treated at up to 3 non-overlapping positions along the upper lateral nasal valve region.

Treatment settings to be used are:

Temperature ..... 60°C

Power ..... 4 Watts

Treatment Time ..... 18 secs

Cooling Time..... 12 secs

No repeat ("touch-up") procedures will be permitted during the 26-week follow-up period. 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 Table 1.

#### Immediate Post-Procedure Care (prior to leaving the clinic)

Subjects will be asked to mark a vertical line on a 10 cm VAS scale to represent the pain level experienced on the Left Side and a separate VAS for pain experienced on the Right Side during the study procedure session. The score will include the overall pain experience from anesthesia delivery to procedure completion.

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

- Apply compression to the treatment area with or without topical anesthetic, internally for 5 minutes.
- Apply petroleum jelly to the treatment area as needed.
- The patient should be instructed not to manipulate the treatment site for 24 hours with the exception of any necessary hemostasis.

Study subjects will be reminded of their next follow-up visit and will be scheduled within the study window.

**NOTE: Device Malfunction or Failure**

If any component of the Vivaer™ System is associated with a malfunction or failure during a study procedure, the sponsor should be contacted immediately for instructions.

Sponsor Contact:	Andrew Frazier, VP of Research and Development
Telephone:	(650) 776-3061
Email:	afrazier@aerinmedical.com

**8.4 Phase 4: Follow-Up and Study Exit**

The follow-up period will begin after the study procedure session. Subjects will undergo follow-up visits at **4 weeks, 12 weeks, and 26 weeks** calculated from the study procedure date. Requirements for each follow-up visit are provided in Table 1. Subjects that meet the study requirements as planned will be exited from the study at the 26-week follow up visit.

If a subject reaches the 26-week 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.

**8.5 Types of Assessments**

Table 1 outlines the assessments to be performed at each required visit, and specifies the required visit windows.

The following assessments will be obtained from the study subjects at the specified study follow-up visits:

Visual Assessment of Treatment Area – The target nasal valve area within each nostril will be visually assessed at baseline and following the treatment procedure at the time points described in Table 1. 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.

Nasal Obstruction Severity Evaluation (NOSE) Scale – The NOSE Scale is a validated disease-specific health status instrument to measure the outcome of subjects treated for nasal obstruction. This outcome assessment has been used to measure improvements in QOL in septoplasty, functional septorhinoplasty and nasal valve surgery (Rhee, Weaver et al. 2010). The NOSE Scale will be utilized to evaluate the severity of the subject's nasal obstruction at baseline and follow-up time points.

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 possible side effects or adverse experiences related to the study procedure. All events will be documented on the proper Adverse Event Log and Adverse Event Case Report Form. Anticipated observations related to the study procedure will be tabulated, but will not be categorized as adverse events unless they require



mitigation by the treating physician or are greater in severity, duration or degree of incidence than anticipated. Refer to Table 2 for a listing of anticipated observations as well as anticipated frequency, severity and duration.

**Medications** – Updates to current medications or any new or changed medications will be requested at each follow-up visit. The medication log will be updated to reflect any changes. In addition, any medications required as a result of intervention related to the study procedure will be documented and will correlate with the Adverse Event Case Report Form.

**Table 1. Schedule of Assessments**

Assessments	Screening / Baseline	Study Procedure (within 30 days of Baseline visit)	Immediately Post-Treatment	4-Week Follow-Up (+/- 7 days)	12-Week Follow-Up (+/- 10 days)	26 Weeks Follow-Up (+/- 14 days)
Demographics and Medical History	X					
Physical Exam and Vital Signs	X					
Medication Review	X	X		X	X	X
Study Procedure		X				
Endoscopic Assessment of treatment area (with representative still photographs)	X	X	X	X	X	X
NOSE Score	X			X	X	X
Subjective Pain VAS			X	X	X	
Subject Satisfaction Questionnaire						X
Adverse Event review			X	X	X	X
Pregnancy test (if female)		X				

## 9.0 SUBJECT REIMBURSEMENT

Subjects may be reimbursed for their time and travel and any expenses associated with each study visit, as allowed by study site policies. Subjects will not be reimbursed for those scheduled study visits that they do not attend.

## 10.0 STUDY WITHDRAWAL

Subjects may be terminated or withdrawn from the study for the following reasons:

- Voluntary withdrawal – meaning that the subject voluntarily chooses not to further participate in the study
- \*Lost to follow-up – meaning that the subject is more than one month late (beyond the late visit window) to a study visit and 3 documented attempts to contact the subject are unsuccessful. A subject who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up.
- \*In the physician's opinion, it is not in the best interest of the subject to continue study participation.
- Subject death.

*\*Where possible, subjects will be followed for safety to study completion. Safety follow-up will include a review of adverse events (AEs). A safety follow-up assessment may be performed either via a phone or email contact or a physician visit.*

Any study subject who does not attend a scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment(s). The reason for the missed visit should be determined and documented in the subject's study records. All subjects enrolled (including those withdrawn or lost to follow-up) shall be accounted for with appropriate documentation.

## 11.0 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 investigational 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 investigational device and/or investigational 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 26-week 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: Scott Wolf, MD  
Telephone: (650) 605-3579  
Facsimile: (650) 605-3579  
Email: scott@aerinmedical.com

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

## 12.0 RISK – BENEFIT ASSESSMENT

### 12.1 Potential Risks

Potential risks associated with the use of the Vivaer™ System do not differ from those of the commonly used devices and procedures to treat nasal obstruction and snoring discussed previously, but due to the non-surgical nature of the therapy, small treatment area, low-power delivery and lack of need for general anesthesia, the overall risk to the patient may be less than from other procedures such as RF turbinoplasty, septoplasty and/or functional rhinoplasty.

Potential risks associated with the use of the Vivaer System and/or the associated local anesthetics are outlined below. Subjects will be monitored closely as part of this study to allow for detection of symptoms, should they be present. This, in turn, should allow for early treatment or intervention, if necessary.

While there were no reports of these events in the previous feasibility study of this system, the following are adverse events or side effects that may occur as a result of the treatment:

- Infection
- Bleeding (other than intra-treatment at treatment sites and greater than anticipated by the investigator)
- Mucosal changes
- Scar formation leading to nasal obstruction
- Sensory changes at treatment site

Table 2 provides a list of anticipated observations that are expected in and around the treatment area. For reference, the incidence (reported as percentage of treated nostrils) observed in the previous feasibility study is also provided. These observations will be assessed and recorded at study visits if they occur but, being anticipated as a result of the procedure, will not be considered adverse events unless they require mitigation by the treating physician or are greater in severity, duration or degree of incidence than anticipated. If one of these types of observations is deemed to be an adverse event, it should be recorded on the study Adverse Event CRF.

**Table 2. Treatment Area Observations (Feasibility Study)**

Observation	Post-Procedure (% treated nostrils)		30-Day Follow-Up (% treated nostrils)		90-Day Follow-Up (% treated nostrils)	
Inflammation / redness	Mild	55.9	Mild Moderate	10.7 1.8	Mild	3.7
Swelling, edema	Mild	64.4	Mild Moderate	16.1 3.6	Mild	3.7
Blanching	Mild Moderate	66.1 3.4	Mild	3.6	Mild	3.7
Numbness	Mild	5.1	No reports		No reports	
Bruising around orbital area	No reports		No reports		No reports	
Soreness, pain	Mild	15.3	Mild Moderate	3.6 21.8	No reports	
Bleeding at anesthetic injection site	Mild	5.3	No reports		No reports	
Bleeding at treatment site	Mild	3.4	No reports		No reports	
Nasal obstruction from tissue edema	Mild	45.8	Mild Moderate	5.4 1.8	No reports	
Disruption of mucosal flow / crusting	Mild	1.7	Mild Moderate	10.7 1.8	No reports	

## 12.2 Potential Benefit

Potential benefit, associated with the use of the Vivaer™ System, is to offer a safe, minimally invasive treatment method to improve nasal breathing. Improved nasal breathing may have a positive effect on quality of life and health.

## 12.3 Minimization of Anticipated Risks

Risks associated with the Vivaer System are minimized by design. In addition, risks will be minimized through the use of an Investigator with a high degree of experience in nasal surgical and minimally invasive procedures. The Investigator will receive sponsor-led training in proper use of the device, prior to study initiation and as warranted throughout the study. The sponsor will monitor the study for any trends that would indicate a safety issue. Aerin Medical technical and/or clinical representatives will attend all procedures to ensure the device performs as intended.

## 12.4 Potential Risks to Patient 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 collecting personally identifying information on Case Report Forms (CRFs) or other study-related documentation to be provided to the study sponsor.

## 13.0 STATISTICAL ANALYSIS

### 13.1 Sample Size Determination

Prior study data was used to estimate the expected mean change (28.5) and standard deviation (30.3) for the change in NOSE score from baseline to 6 months (26 weeks). N=45 subjects would provide 90% power to test the study hypothesis at the one-sided alpha level of 0.05. To allow for up to 10% attrition, a total of 50 subjects will be enrolled.

### 13.2 Hypothesis Testing

The objective is to show that the mean improvement in NOSE score from baseline to 26 weeks exceeds 15 points. The null and alternative hypotheses are given by:

Ho:  $\mu_d \leq 15.0$

Ha:  $\mu_d > 15$ , where  $\mu_d$  represents the mean improvement in NOSE score from baseline to 26 weeks. The hypothesis is tested at the one-sided alpha 0.05 level.

### 13.3 Definition of Populations

Enrolled Subjects – all subjects enrolled in the study

Evaluable Subjects – all subjects that are enrolled in the study and have received the study procedure.

All enrolled subjects will be accounted for. If a subject is enrolled in the study and does not undergo the study procedure, a description of the reason will be provided. Analysis of study endpoints will be performed on all evaluable subjects.

### 13.4 Primary Endpoint – Efficacy Analysis

The study hypothesis will be tested by calculating the change in NOSE scores from baseline to 26 weeks (baseline – 26 weeks). The lower limit of the one-sided 95% confidence interval will be calculated using the t-distribution. Should the lower limit exceed 15.0, then the null hypothesis will be rejected in favor of the alternative.

### 13.5 Secondary Endpoint – NOSE Responder Rate

The secondary efficacy endpoint is the percent of subjects that are considered a responder, where responder is defined as achieving a 15 point or greater improvement in the NOSE score from baseline to 26 weeks. Success for this endpoint is defined as a responder rate of 55% or greater.

### 13.6 Secondary Endpoint – Safety Analysis

Safety will be assessed by characterizing the type and frequency of adverse events reported at or following the study procedure, throughout the follow-up period. The number of events as well as the percent of subjects experiencing each event type will be calculated.

### 13.7 Adverse Events

All adverse events for subjects in the safety population will be reported.

- Serious Adverse Events
- Non-serious Adverse Events
- Device Related Adverse Event
- Device Related Serious Adverse Events

The following time intervals, based on the date of the procedure, will be considered:

- 0 days to 4 weeks
- 4 weeks to 12 weeks

- 12 weeks to 26 weeks

Results will include the number of subjects experiencing each type of event as well as the number of events.

### **13.8 Statistical and Analytical Methods**

#### **13.8.1 Demographics**

Subject demographics will be summarized using descriptive statistics (mean, median, SD, minimum, maximum) and number of subjects for continuous variables (e.g., age), and frequency distributions (number and percentage of subjects) for categorical variables (e.g., gender, race).

#### **13.8.2 Handling Dropouts, Loss-to-Follow-up or Missing Data**

All efforts will be made to collect all data points in this study. The study hypothesis will be tested using all available data for the subjects in the efficacy patient population. If the primary endpoint is not available for all such subjects, then additional analyses will be performed in order to assess the potential effect of missing data on the study conclusions. First an analysis will be performed, treating all missing data points for the primary endpoint as 0 improvement. If the study conclusion is upheld using this type of worst-case scenario, no other analyses will be performed. Otherwise, a multiple imputation approach will be used. The propensity method will be used including the baseline, 4 week and 12 week NOSE scores if they are available. Fifteen imputed datasets will be generated and the study hypothesis will be repeated on the imputed dataset to determine if the study hypothesis is upheld.

#### **13.8.3 Multicenter Study**

Data from up to 10 investigational sites will be pooled for this study. The justification for pooling is made on a clinical basis (Meinert and Tonascia 1986). This study will be conducted such that: 1) the same protocol will be used at each site; 2) site investigators and personnel will receive uniform training; and 3) central data management and monitoring will be consistent and applied with equal rigor at all sites. The diversity of hospital and clinical practice settings will add to the scientific validity and generalizability of the findings.

An analysis of the consistency of the “treatment effect” across sites cannot be made directly in this study since it is a single arm study. Observed differences across sites could be due to differences in patient populations or in the performance of the device. The primary endpoint results will be stratified by clinical center. If any sites have fewer than 5 subjects in the analysis group, they will be pooled together (if there are more than one), or with the next smallest site if there is only one. The mean changes in NOSE score will be compared statistically using analysis of variance. The p-value for statistically significant differences across sites will be set at the 0.15 level.

Demographics and baseline characteristics will also be stratified by site. Should the comparison in mean change for the primary endpoint result in a significant difference across sites, then the demographics and baseline characteristics will also be compared statistically across sites. Fisher’s Exact test will be used for categorical outcomes, and analysis of variance for continuous outcomes. Any characteristics found to be statistically significant at the 0.15 level will be included in the model comparing the primary endpoint outcome across sites. A generalized linear model will be used with change in NOSE score playing the role of the

dependent variable and site and statistically significant characteristics as independent variables. The differences in outcome across sites, after adjusting for differences in baseline characteristics will be assessed. A p-value > 0.15 will indicate no significant differences across sites.

#### 14.0 SAFETY RELATED STOPPING RULES

The study sponsor will be charged with monitoring the study for safety and for auditing the quality of the data. If there are any perceived safety concerns related to the Vivaer™ System or procedure, the trial may be terminated.

#### 15.0 QUALITY ASSURANCE AND SUPERVISION BY AUTHORITIES

This study will be conducted in accordance with elements of E6 Good Clinical Practice Consolidated Guidance, ICH, April 1996, abbreviated requirements of 21 CFR 812.2(b) for Non-significant Risk (NSR) device studies, the Declaration of Helsinki, the Belmont Report, and IRB/EC requirements.

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the patient's privacy as far as reasonably practicable. The Sponsor and representatives of the FDA or other regulatory authorities are permitted to inspect the study documents (e.g., study protocol, CRFs, and original study-relevant medical records/files) as needed. All attempts will be made to preserve patient confidentiality.

All clinical sites are subject to audit by study sponsor personnel or designee for protocol adherence, accuracy of CRFs and compliance with applicable regulations. Any evident pattern of non-compliance with respect to these standards will be cause for corrective action.

The study protocol, data-recording procedures, data handling as well as study reports are subject to an independent clinical Quality Assurance audit by the study sponsor, its designee, or health authorities.

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

## 17.0 INVESTIGATIONAL DEVICE MANAGEMENT

The Vivaer™ System is investigational and is not approved for commercial use in the United States. The investigator shall maintain adequate records of the receipt and disposition of all investigational devices. When trial enrollment is complete, the investigator shall return any unused devices to the sponsor or their designee. The device will only be used as part of this clinical trial in eligible patients and will be used according to its intended use. A copy of the Instructions for Use (IFU) accompanies each study device.

## 18.0 REQUIRED DOCUMENTS FROM THE INVESTIGATOR (PRIOR TO STUDY START)

At a minimum, the following documents will be provided by the investigational site to the study sponsor:

- Signed Investigator Agreement
- Signed Clinical Investigational Plan (CIP) Signature Page
- IRB/EC approval
- IRB/EC approved Informed Consent Form (ICF)
- Investigator and Co-Investigator's current Curriculum Vitae
- Investigator and Co-Investigator's current Medical Licenses

A site may not begin study participation until all of the above listed documents have been provided to the study sponsor.

## 19.0 TRAINING

The Vivaer™ System is intended for use by experienced medical personnel. The Investigator will be provided training by the study sponsor in the use of the device to familiarize them with the use of the Vivaer System prior to their participation in the clinical study.

Each study center will undergo protocol initiation including but not limited to a review of the following:

- Procedures for obtaining Informed Consent
- Procedures for completing Informed Consent Form
- Device usage instructions
- Reporting requirements
- CRF completion and correction procedures
- Vivaer System overview
- Protection of patient confidentiality

## 20.0 ETHICAL CONSIDERATIONS

The rights, safety and wellbeing of clinical investigation 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 Investigator shall avoid improper influence or inducement of the patient, study monitor, clinical investigator or other parties participating in or contributing to the clinical investigation.

## 21.0 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 CRFs will be tracked, evaluated, and stored using only this unique identifier.

The investigational 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 Site Principal Investigator (PI) 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 in the CRF 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.

*NOTE: The patient's name, medical record number or address will NOT be recorded in the monitor's visit report or the database; demographic data that may be recorded includes age, race, and gender.*

Any source documents copied for monitoring purposes by the Sponsor will have patient identifiable information redacted and be identified by using the assigned patient's unique identifier in an effort to protect patient confidentiality.

## 22.0 DATA COLLECTION

Study data will be collected using standardized Case Report Forms (CRFs). The CRFs are designed to accommodate the specific features of the trial design. Modification of CRFs will only be made if deemed necessary by the study sponsor.

## 23.0 SOURCE DATA VERIFICATION

At a minimum, source data verification will be performed on all primary endpoint, secondary endpoint and safety data for each patient enrolled in this study.

## 24.0 STUDY SUSPENSION OR EARLY TERMINATION

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

- Occurrence of adverse events unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known adverse events
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of patients
- Unanticipated adverse device effect (UADE) presenting an unreasonable risk to patients (Sponsor may terminate the study immediately)
- Persistent non-compliance with the protocol
- Persistent non-compliance with IRB/EC or regulatory requirements

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigator(s) / 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 or by the Site PI / investigational center(s). Regulatory authorities and the personal physicians of the patients may also need to be informed if deemed necessary.

## 25.0 SITE CLOSE-OUT

At the time of the site close-out visit, the site monitor or designee will collect all outstanding study documents, ensure that the Investigator's files are accurate and complete, review record retention requirements with the Investigator, make a final accounting of all study supplies, and ensure that all applicable requirements are met for the study. The observations and actions made at this visit will be documented in a final closeout report.

## 26.0 RESPONSIBILITIES

Aerin Medical Inc. is the manufacturer of the Vivaer™ System and the Sponsor of this study. The study 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:

- Select qualified Investigators
- Select qualified monitors and other contract study personnel
- Provide the Investigational Plan and any subsequent amendments
- Sign the protocol
- Provide appropriate information and device training to Investigators and study site staff
- Promptly inform the Investigators 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 review of the Vivaer System instructions for use, the Investigational Plan, CRF completion guidelines, and guidelines for obtaining informed consent

- Coordinate ongoing communication with CRO(s), 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
- Collect, store and keep secure, at a minimum, the following documents:
  - A current Curriculum Vitae and medical license of each Investigator
  - The name of the institutions where the study will be conducted
  - The IRB/EC opinion and / or approval, in writing, and relevant correspondence
  - Correspondence with authorities (as required)
  - Investigator Agreement
  - CIP Signature Page
  - Appropriate insurance certificates (as necessary)
  - IRB/EC Approved ICF
  - Names / contact information for study monitor(s)
  - Copies of signed and dated CRFs
  - Records of any adverse events and adverse device effects
  - Statistical analyses and underlying supporting data
  - Final report

## 27.0 SPONSOR MAINTENANCE OF STUDY RECORDS

The Sponsor will be responsible for **maintaining study records** per 21 CFR 812.140(b) and Good Clinical Practice: Consolidated Guidance (ICH, April 1996), Section 8.

The Sponsor will be responsible for **monitoring the investigation** per 21 CFR 812.46 and Good Clinical Practice: Consolidated Guidance (ICH, April 1996), Section 5.18.

The Sponsor will be responsible for **reporting** per 21 CFR 812.50(b).

## 28.0 INVESTIGATOR MAINTENANCE OF STUDY RECORDS

The Site PI 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 Site PI will allow auditing of their clinical investigation procedure(s).

Each investigator will provide a completed Financial Disclosure prior to study initiation and upon request at later time points in the study.

The Investigator is responsible for maintaining medical and study records for every patient participating in the clinical study (including information maintained electronically such as digital imaging). The study center

will also maintain **original** source documents from which study-related data are derived, which may include, but are not limited to:

- Clinic progress notes recording patient's medical history and medications
- Medical records regarding AEs, including treatment and clinical outcome
- Results of diagnostic examinations
- Notes of phone calls and/or correspondence indicating investigational site's attempts to contact and follow a study patient at the required follow-up visits until such time a subject is determined to be lost-to-follow-up.

The Investigator 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 supporting a premarket approval application or a notice of completion of a product development protocol. To avoid error, the study site should contact the study sponsor prior to the destruction of study records to ensure that they no longer need to be retained. In addition, the study sponsor should be contacted if the Investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

## 29.0 INVESTIGATOR REPORTS

The Site PI will be responsible for reporting per 21 CFR 812.150(a) and according to applicable IRB/EC requirements and Good Clinical Practice: Consolidated Guidance (ICH, April 1996), Section 4.11.

*NOTE: Reports must identify patients using the study's unique identifier to protect patient's confidentiality.*

The primary responsibility of the investigator is to protect the welfare of the study subjects. Other responsibilities, including adherence to the protocol, are defined in the Investigator Agreement.

## 30.0 DATA MANAGEMENT

Data will be handled as applicable, per Good Clinical Practice: Consolidated Guidance (ICH, April 1996), Section 5.5. To ensure proper tracking of Case Report Forms, a tracking system will be utilized.

### 30.1 Data Entry

Qualified personnel assigned by the principal investigator and/or the sponsor will perform data entry.

### 30.2 Data Cleaning

All CRF pages will be subject to initial inspection for omitted data, gross data inconsistencies, illegible data and deviations. Any deficiencies or deviations will be reviewed and any necessary action determined (e.g., data query, communication to the study center).

Intermittent data review will be performed and any discovered errors will be reported to the study site using the data correction and query process (as necessary). The study site will be expected to review the query, make any necessary corrections or comments, and return to Data Management where the correct response will be entered. The data cleaning cycle will be repeated until all data are considered clean.

### 30.3 Data Back-up

Incremental computer data backup will be performed on a regular basis. All hard copies of Case Report Forms and media will be stored in a secure location.

### 30.4 Confidentiality and Security

Passwords will be issued to appropriate personnel to insure confidentiality and protection of data.

### 30.5 Final Report

A final report will be completed, even if the study is prematurely terminated.

### 30.6 Publication Policy

At the conclusion of the trial, the results may be prepared and presented at a major meeting(s). The publication of results from any center experience within the trial is not allowed, unless there is written consent from the study sponsor.

## 31.0 DEFINITIONS AND ACRONYMS

### 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 (21CFR812.3.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.*

**Adverse Device Effect (ADE)**

See Adverse Events.

**Case Report Form (CRF)**

Printed, optical or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject

**Confidentiality**

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or a subject's identity (GCP Consolidated Guidance).

**Ethics Committee (EC) / Institutional Review Board (IRB)**

Synonyms. An independent body constituted of medical, scientific and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects (GCP Consolidated Guidance).

**Good Clinical Practice (GCP)**

An international quality standard for conducting clinical trials that is provided by International Conference on Harmonisation (ICH) to protect trial subjects rights, safety, and welfare, as well as provide integrity to the overall study data.

**Informed Consent**

The process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated consent form (GCP Consolidated Guidance).

**Informed Consent Form (ICF)**

A document disclosing the risks, benefits, and alternatives of a clinical trial and documents the subject's voluntary willingness to participate in a clinical trial.

**Monitoring**

The act of overseeing the progress of a trial, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, standard operating procedures (SOPs), and the applicable regulatory requirements.

**Serious Adverse Device Effect (SADE)**

See Adverse Events.

**Serious Adverse Event (SAE)**

See Adverse Events.

**Source Data**

All information in original and identified records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. Source data are contained in source documents (ISO 14155 and GCP Consolidated Guidance).

**Source Documents**

Original documents, data and records (ISO 14155).

*NOTE: This may be, for example, hospital records, laboratory notes, pharmacy dispensing records, copies or transcriptions certified after verification as being accurate copies, photographic negatives, radiographs, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical investigation.*

**Standard Operating Procedure (SOP)**

Detailed, written instructions to achieve uniformity of the performance of a specific function

**Unanticipated Adverse Device Effect (UADE)**

See Adverse Events.

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