Aerin Medical Inc. TP423 IRB Approved at the Protocol Level Jan 25, 2019

A Prospective, Non-Randomized Study to Evaluate Treatment Outcome of Nasal Airway Obstruction Using the Aerin Medical Vivaer™ Stylus

Protocol # / Version Date:	**TP423 / Version Date: 16 Jan 2019**
Study Sponsor:	**Aerin Medical Inc** Primary Contact: Scott Wolf, MD, CMO 232 E. Caribbean Drive Sunnyvale, CA 94089 Telephone: (650) 605-3579
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A complete list of investigators will be maintained and will be available upon request.

SIGNATURES

SPONSOR

Print Name: Scott Wolf, MD **Title:** Chief Medical Officer

Signature: [signature] **Date:** 2/11/19

INVESTIGATOR

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

Print Name: Brad Otto

Signature: [signature] **Date:** 2/11/19

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1.0 PROTOCOL SYNOPSIS

Study Title: A Prospective, Non-Randomized Study to Evaluate Treatment Outcome of Nasal Airway Obstruction Using the Aerin Medical Vivaer™ Stylus

Study Device: Aerin Medical Vivaer Stylus

Device Description: The Vivaer Stylus is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue.

Proposed Indication: 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.

Study Objective: The main objective of this research is to evaluate the outcome of treating nasal airway obstruction with the Aerin Medical Vivaer Stylus

Study Design: Prospective, non-randomized study to evaluate treatment outcome of nasal airway obstruction using the Aerin Medical Vivaer stylus

Subject Population: Male and female subjects who present with symptoms associated with chronic nasal obstruction

Study Procedures: Subjects will have both nasal valves treated in a single treatment session. Follow-Up and Study Exit will be at 90 Days, Post-Procedure. No repeat ("touch-up") procedures will be permitted during the 90 day follow-up period.

Study Endpoints: Primary Endpoint variable(s) – The primary symptom outcome variables include self-reported Nasal Obstruction Symptoms Evaluation (NOSE) score and Visual Analog Scale (VAS) of nasal obstruction. One-way ANOVA with repeated measures will be used to compare post-treatment vs. baseline measurements and determine the effectiveness of the treatment.

The primary independent endpoint variables include several categories: 1) variables that index general disease severity (Computerized Tomography (CT) staging and endoscopic examination score 2) peak inspiratory flow measurements of nasal physical resistance.

Secondary outcome variables will include age, gender, race, duration of the disease, and medical and smoking histories. The potential confounding effect of the secondary outcome variables will be examined.

Study Evaluations:

1. Nasal Obstruction Symptoms Evaluation (NOSE) score
2. Visual Analog Scale (VAS) of nasal obstruction

3. Endoscopic examination (video and pictures), Lund-Kennedy endoscopic scores
4. Peak nasal inspiratory flow
5. Cone beam CT scan (clinical or research)
6. Sino-Nasal Outcome Test (SNOT-22)
7. Computational modeling of nasal airflow based on CT scan of each visit.

Study Size: **Up to** 20 patients meeting the inclusion/exclusion criteria will be recruited.

Anticipated Duration: Enrollment completion/Q2 2019; Follow-Up completion/Q3 2019

Study Visits: Phase 1 - Pre-Admission Evaluation/Patient Consent
Phase 2 – Baseline/Treatment
Phase 3 – Follow-Up 90 Days Post-Procedure / Study Exit

Study Eligibility Criteria:

Inclusion Criteria:

Eligible subjects will meet all the following:

1. Age 18 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. Complaints of nasal obstruction for at least 1 year
5. Failed maximum medical therapy (4-6 weeks of steroids)
6. Nasal Obstruction Symptom Evaluation (NOSE) score of $\geq$ 60 at Baseline
7. 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 during office exam):
    a. Use of external nasal dilator strips (e.g., Breathe Right Strips)
    b. Q-Tip test (manual intranasal lateralization)
    c. Use of nasal stents
    d. Cottle Maneuver (manual lateral retraction of the cheek)

Exclusion Criteria:

Subjects will not be enrolled if they 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. 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 could predispose the subject to poor wound healing or increased surgical risk.

2.0 OVERALL OBJECTIVES

The study will evaluate the outcome of nasal obstruction treated with the Vivaer™ Stylus, and also attempt to use computational aerodynamics simulation and sensory measurements to identify and predict patients' treatment outcome. The ability to envisage variables that will lead to best outcome may have potential to assist patients and clinicians in planning effective, well-informed, personalized treatment/surgery strategies.

2.1 Primary outcome variables

The primary symptom outcome variables include self-reported Nasal Obstruction Symptoms Evaluation (NOSE) score and VAS of nasal obstruction.

The primary independent objective variables include several categories: 1) variables that index general disease severity (Computerized Tomography (CT) staging and endoscopic examination score), 2) peak inspiratory flow measurements of nasal physical resistance.

2.2 Secondary outcome variables

Secondary outcome variables will include age, gender, race, duration of the disease, and medical and smoking histories. The potential confounding effect of the secondary outcome variables will be examined.

3.0 BACKGROUND AND RATIONALE

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) (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. The nasal valve is a critical site for nasal resistance and for nasal obstruction symptoms. 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 and leading to nasal obstruction.

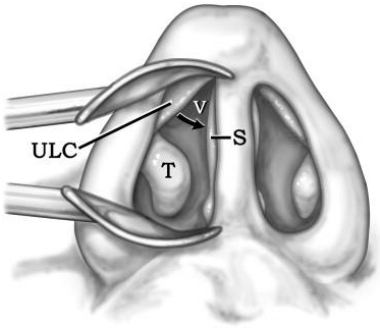

Figure 1. Nasal Anatomy
(from Weaver 2012[1], Figure 1)

Airway remodeling in the nasal valve region may have significant benefit for patients with a narrow nasal valve. Over-the-counter remedies such as external breathing strips can provide patients with temporary relief. However, a long-term solution to chronic nasal airway obstruction associated with the nasal valve usually involves extensive surgery. One of the common surgical procedures targeting the nasal valve is the implantation of alar batten grafts; i.e., curved cartilage supports placed into areas of the nasal valve area to enlarge and strengthen it. Although batten graft surgical outcomes are generally successful, the procedure requires the harvesting of a cartilage graft from another anatomic site, a difficult and time-consuming procedure. Overall, current surgical therapy on the nasal valve is efficacious, but is invasive and associated with long recovery periods and the risk of complications, e.g., hemorrhage.

The use of radiofrequency energy has been common for decades in the fields of otolaryngology, neurosurgery, cardiology, urology and general surgery. For instance, radiofrequency turbinate reduction (RFTR) uses radiofrequency to create heat within the submucosal tissue of the turbinate, reducing tissue volume with minimal impact on surrounding tissues. Numerous studies have demonstrated that radiofrequency therapy in the nasal passage can be safe and effective in improving nasal obstruction and in preserving nasal function.[2,3]

The Aerin Medical Vivaer™ System an investigational device that is capable of delivering bipolar radiofrequency energy to improve nasal breathing by modifying soft tissues of the nasal valve. The System is comprised of the Vivaer Stylus (Figure 2), a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue, and a radiofrequency generator (Figure 3).

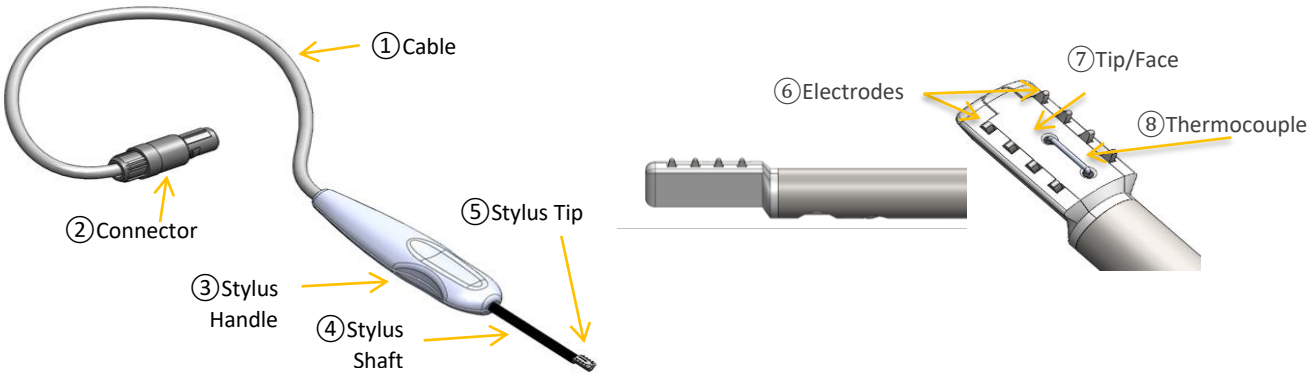

Figure 2. Vivaer™ Stylus

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 the handle via a non-conductive shaft. A temperature sensor (thermocouple) 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 valve 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, slightly widening the nasal valve area. This decreases the nasal airflow resistance thereby improving inflow of air through the nose (as demonstrated in earlier pre-clinical and pilot studies). The procedure requires local anesthesia only, and is much less invasive than current surgical approaches.

This clinical study plans to use computational fluid dynamics (CFD) and various sensory testing techniques to examine the factors contributing to patients' outcome after Aerin treatment. The efficacy and safety of the Vivaer Stylus treatment will be recorded.

1) Aerin Console unit
2) Power Cord
3) Foot Switch

Figure 3. Aerin Console

4.0 PROCEDURES

4.1 Research Design

The study will be conducted by the Department of Otolaryngology, The Ohio State University School of Medicine, in conjunction with Aerin Medical. This study is a prospective, case series design, involving a group of patients with chronic nasal obstruction symptoms. The study is a longitudinal design, involving two test sessions: one at baseline (pre-treatment) and one at 90 days post-treatment.

4.2 Study Size

Up to Twenty (20) patients meeting the inclusion/exclusion criteria will be recruited.

4.3 Inclusion Criteria

Eligible subjects will meet all the following:

1. Age 18 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. Complaints of nasal obstruction for at least 1 year
5. Failed maximum medical therapy (4-6 weeks of steroids)
6. Nasal Obstruction Symptom Evaluation (NOSE) score of $\geq$ 60 at Baseline
7. 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 during office exam):
   a. Use of external nasal dilator strips (e.g., Breathe Right Strips)
   b. Q-Tip test (manual intranasal lateralization)
   c. Use of nasal stents
   d. Cottle Maneuver (manual lateral retraction of the cheek; see Figure 4)

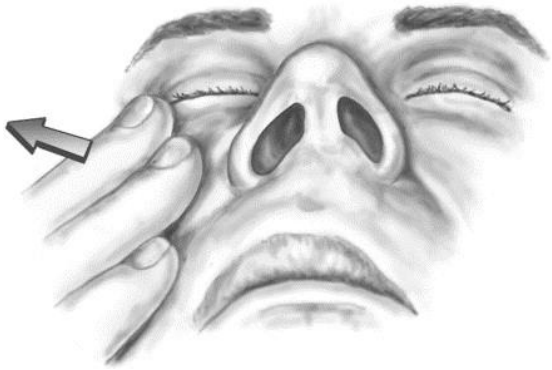

Figure 4. Cottle Maneuver

Figure 4 demonstrates the Cottle Maneuver as the patient or the physician temporarily lifts and lateralizes the skin around the nose and cheek, increasing the nasal valve angle, and potentially increasing nasal airflow. A positive response can be an indicator that the patient will respond well to an increase in nasal valve angle.

The Q-Tip test is another evaluation of potential positive response. A Q-tip is placed gently within the nares against the lateral nasal wall at the location of the narrowest nasal valve region and is pushed outward lightly to expand the nasal valve angle. A positive response to this maneuver may also predict the potential benefit of nasal valve correction.

4.4 Exclusion Criteria

Subjects will not be enrolled if they 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. 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 could predispose the subject to poor wound healing or increased surgical risk.

4.5 Subject recruitment

Patients will be primarily recruited from the clinical population being seen by physicians as part of their practice in the Department of Otolaryngology, The Ohio State University School of Medicine. In order to ensure the subject population has adequate access to the recruitment materials, IRB approved flyers will be available in the patient waiting area, and on the department's website / Facebook page.

4.6 Measurement / Instrumentation

Endoscopic Examination
Patients will receive endoscopic examination as part of their standard clinical care. The severity of disease will be scored based on endoscopic examination (Lund-Kennedy endoscopic scores).

Study Procedures
Each visit is expected to last 2-3 hours and may include the following procedures. (These procedures are routinely performed for research purposes; however, none of them should be considered standard clinical care. The differences will be explained to the participants during the consent process.)

1. All participants will be asked to fill out a medical history questionnaire, as well as the Sino-Nasal Outcome Test (SNOT-22) questionnaire, the NOSE score and the Visual Analog Scale for nasal obstruction. The SNOT-22 and NOSE are two commonly used validated outcome questionnaires to evaluate change in rhinosinusitis and/or nasal obstruction symptoms in patients. The VAS is a self-rating of nasal obstruction on a linear scale (range 0-10; 0 being completely clear and 10 being completely blocked) using both nostrils and then with the left and right nostril separately.

2. Peak nasal inspiratory flow: A mask attached to a spirometer is fitted tightly on each subject´s face without touching the nose. The subject is instructed to inhale as strongly as possible, and the peak flow rate is then recorded. The test will be repeated three (3) times and the results averaged. For unilateral recording, one nostril is blocked with a tape, so that the subject can only inhale through the other nostril.

3. Research CT scans: The subject may receive a CT scan for non-clinical purposes with a cone beam office CT scanner (3D Accuitomo 170, J. Morita USA, Inc.) at the Department of Otolaryngology at The Ohio State University School of Medicine. This scan has a radiation dosage of roughly 12% that of a conventional head CT scan with a significantly lower associated health risk, while retaining excellent air-mucus contrast for CFD modeling. The recruitment strategy will reduce the need for research CTs and unnecessary radiation by recruiting patients who have been prescribed a sinus CT clinically, which will serve as the subject's baseline CT. Furthermore, if a post-treatment/surgery CT scan is clinically necessary for a patient after enrollment, it will be scheduled for the subject's second study visit. Through these measures, the need for research CT scans will be reduced to limit the number of research CT scans for all patients to one (1).

4. CFD Modeling: 3D numerical nasal models that are suitable for numerical simulation of nasal airflow and odorant transport will be constructed based on each subject/patient's CT scan and according to the method described by Zhao[8]. In brief, first the interface between the nasal mucosa and the air is delineated (using AMIRA®) on the CT scans. Then, the nasal cavity air space is filled with tetrahedral elements (ICEMCFD®). A finer mesh (prism layer) is created near the mucosal surface to more accurately model the rapidly changing near-wall air velocity and odorant concentration. Next, inspiratory and expiratory quasi-steady laminar nasal airflow[8,9] is simulated (Fluent©, Ansys Inc, USA) by applying a physiologically realistic pressure drop between the nostrils and the nasal pharynx. By varying the pressure drop and computing the changes in total airflow through the nose, the total nasal resistance can be determined, a numerical method of rhinomanometry. Through simulation, the following variables will be obtained: numerical nasal resistance, nasal mucosal cooling rate, and nasal airflow distribution patterns.

5. 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.

7. 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.

8. General Health Survey Subject will be asked to complete the SF-36 before and after treatment. The SF-36 is one of the most widely used generic measures of health-related quality of life and has been shown to discriminate between subjects with different chronic conditions and between subjects with different severity levels of the same disease. The SF-36 has also demonstrated sensitivity to significant treatment effects in a variety of patient populations.

4.7 Study Phases

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

Phase 1 - Pre-Admission Evaluation/Patient Consent
Phase 2 – Baseline/Treatment
Phase 3 – Follow-Up 90 Days (+/- 15 days) Post-Procedure / Study Exit

The assessments to be performed during each phase are listed in Table 1.

Pre-Admission Evaluation/Patient Consent

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.

Table 1. Schedule of Assessments

Assessments	Screening / Evaluation	Baseline/Study Procedure	Immediately Post-Treatment	90 day Follow-Up / Study Exit (+/- 15 days)
Informed Consent	X			
Demographics and Medical History	X			
Physical Exam and Vital Signs		X		
Medication Review		X		X
SF-36 Quality of Life Questionnaire		X		X
NOSE Score	X			X
Study Procedure		X		
Endoscopic Assessment of treatment area (with representative still photographs)		X	X	X
Cone beam CT scan (clinical or research)		X		X
Sino-Nasal Outcome Test (SNOT-22)		X		X
Peak Nasal Inspiratory Flow (PNIF)		X		X
Visual Analog Scale (VAS) of nasal obstruction		X		X
Adverse Event review			X	X
Pregnancy test (if female of child bearing potential)		X		

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, and 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 to ask as many questions as necessary to make them comfortable with the study and the requirements. A patient willing to participate after undergoing the informed consent process will then be asked to sign the consent form and given a copy. The original will be kept on file.

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. Subjects will be considered enrolled once they arrive at the study clinic to undergo the procedure. At this time a subject identification number will be assigned along with the subject binder.

<u>During the baseline and follow-up visits, the procedures listed below will occur</u>

1. Endoscopic examination (video and pictures), Lund-Kennedy endoscopic scores
2. Peak nasal inspiratory flow
3. Cone beam CT scan (clinical CT at baseline; clinical or research CT at 90-day follow-up visit)
4. Nasal Obstruction Symptom Evaluation (NOSE) scale
5. Sino-Nasal Outcome Test (SNOT-22)
6. Visual analogue scale (VAS) rating severity of nasal obstruction
7. Computational modeling of nasal airflow based on CT scan of each visit.

During the baseline visit, data collection will be performed first, and then the Aerin Vivaer™ Treatment will be provided in the clinic by the physician. The styluses used in this study will be manufactured and supplied by the sponsor.

During the treatment, 0.5 ml of local anesthesia (lidocaine 1% with epinephrine 1:100,000) will be injected into the target tissue. The Vivaer stylus will be inserted into the nose and the electrode-containing tip will be positioned against the target tissue.

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

Accurate positioning will be confirmed by observing the temperature change on the RF generator screen as the stylus tip comes in contact with the target tissue.

No repeat ("touch-up") procedures will be permitted during the 90-day follow-up period.

<u>Immediate Post-Procedure Care (prior to leaving the clinic)</u>
At the discretion of the physician, the following care and instructions may be provided:

- 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 (90 ± 15 days).

Adverse events (AEs) may occur during the treatment phase or during the follow-up phase. Adverse events occurring during the baseline assessment will be documented in the subject's medical record but will not count as related to the device or procedure. Each adverse event will be recorded and judged by the Investigator as to its relationship and level of relatedness to the device and/or procedure. In addition, the Investigator will identify the date of onset, severity and duration. All adverse events will be monitored until they are adequately resolved or explained.

4.8 Internal Validity

The participating physicians will ensure that the recruitment material is well distributed to all potential subject/patient populations. In the recruitment process, they will specifically emphasize to all potential subjects/patients that whether or not they agree to participate will not have any impact on their continuing treatment and interactions at the Department of Otolaryngology, The Ohio State University School of Medicine.

4.9 Data Analysis

Treatment effectiveness
Outcome variables: patient's ratings of nasal obstruction via a VAS and NOSE score as well as the SNOT-22 questionnaire and peak inspiratory flow rate. One-way ANOVA with repeated measures will be used to compare post-treatment vs. baseline measurements and determine the effectiveness of the treatment.

Hypothesis:
Nasal valve region airflow and airflow induced cooling is critical for patients' subjective nasal patency.

Many publications suggest that sensory feedback is as important to perception of nasal obstruction as nasal resistance. For example: Topical or oral application of menthol produces the illusion of decongestion and improved nasal airflow without actually altering nasal resistance[10]. Topical application of local anesthetics results in an artificial sensation of nasal obstruction, presumably due to blocking of the trigeminal afferents[11].

The Ohio State University (OSU) staff have published a series of studies[6,12,13] with individualized Computational Fluid Dynamics models and demonstrated that nasal cooling during breathing at the nasal valve region and the nasal trigeminal nerve sensitivity are key to the perception or absence of nasal obstruction. The combination of these variables can predict the subject's ratings (excellent, normal and moderately obstructed) with 89.3% success. It is likely that nasal valve width and shape may have an optimal range in order to achieve both low nasal resistance and high regional mucosal cooling (see Fig. 5). This study will examine a broad list of factors that may contribute to patients' subjective outcomes, not just limited to nasal resistance alone, that include CFD simulation of nasal airflow, mucosa cooling and mucosa sensitivity responding to that cooling.

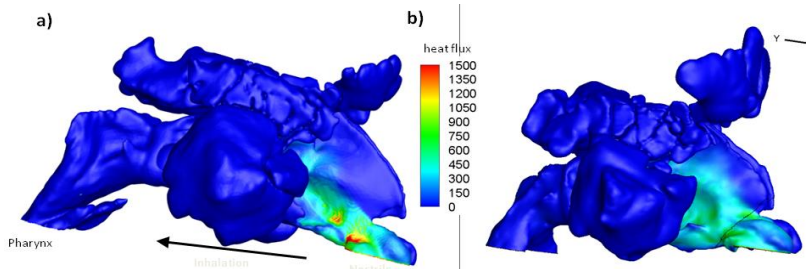

Figure 5. Computational simulation of nasal cooling
a) high regional cooling, no complaints
b) low nasal cooling with moderate ratings of nasal obstruction

Spearmen correlation and multiple regression will be used to screen for independent variables that significantly correlate with dependent variables, as well as potential non-linear relationships between the variables. Other potential confounding factors (e.g., age, duration of the disease, smoking history) will also be examined. The Holm Bonferroni correction will be applied to control for multiple comparisons. Finally, statistical learning methods such as linear discrimination analysis (LDA) and logistic regression will be applied for classification and discrimination of patient symptom categories (e.g., symptom-free, moderate and severe nasal obstruction) based on significant independent variables.

5.0 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.

6.0 STUDY WITHDRAWAL

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

- Voluntary withdrawal – the subject voluntarily chooses not to further participate in the study
- *Lost to follow-up – 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 the scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment. 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.

7.0 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. The Investigator will make a judgement 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 90-day 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 *(as applicable)* according to the local reporting requirements.

8.0 RISK – BENEFIT ASSESSMENT

8.1 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 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
- Vasovagal response secondary to the procedure

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 10.7 Moderate 1.8	Mild 3.7
Swelling, edema	Mild 64.4	Mild 16.1 Moderate 3.6	Mild 3.7
Blanching	Mild 66.1 Moderate 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 3.6 Moderate 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 5.4 Moderate 1.8	No reports
Disruption of mucosal flow / crusting	Mild 1.7	Mild 10.7 Moderate 1.8	No reports

8.2 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.

8.3 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.

8.4 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.

9.0 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 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.

The clinical site is 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.

10.0 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.

11.0 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.

12.0 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 approval
- IRB 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.

13.0 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

14.0 ETHICAL CONSIDERATIONS

The rights, safety and well-being 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.

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 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.

16.0 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.

17.0 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.

18.0 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 or regulatory requirements

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform the clinical investigator(s) / investigational centers of the termination or suspension and the reason(s) for this. The IRB 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. Regulatory authorities and the personal physicians of the patients may also need to be informed if deemed necessary.

19.0 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.

20.0 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 the Institutional Review Board, 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 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 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

21.0 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).

22.0 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.

23.0 INVESTIGATOR REPORTS

The Site PI will be responsible for reporting per 21 CFR 812.150(a) and according to applicable IRB 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.

24.0 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.

24.1 Data Entry

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

24.2 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.

24.3 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.

24.4 Confidentiality and Security

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

24.5 Final Report

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

24.6 Publication Policy

At the conclusion of the trial, the results may be prepared and presented at a major meeting(s).

25.0 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 (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.

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).

Institutional Review Board (IRB)
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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