



**Treatment Alternatives in Adult Rare Disease;  
Assessment of Options in Idiopathic Subglottic Stenosis**

**North American Airway Collaborative PR-02 Study (NoAAC PR-02 Study)**

NoAAC Protocol Number: PR-02  
PCORI Grant Number: 1409-22214  
Principal Investigator: Alexander Gelbard M.D.  
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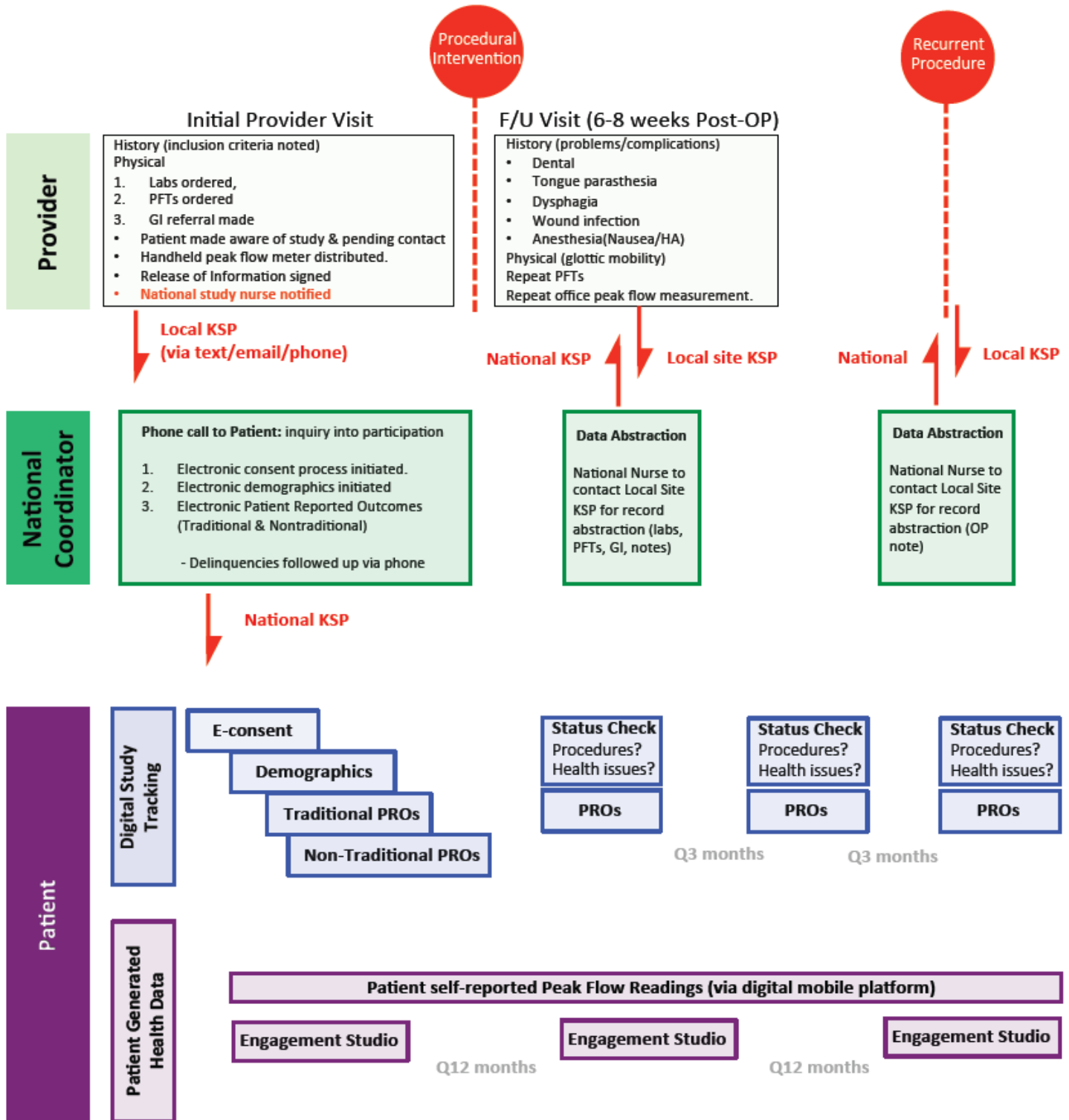
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## **STATEMENT OF COMPLIANCE**

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the PCORI Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

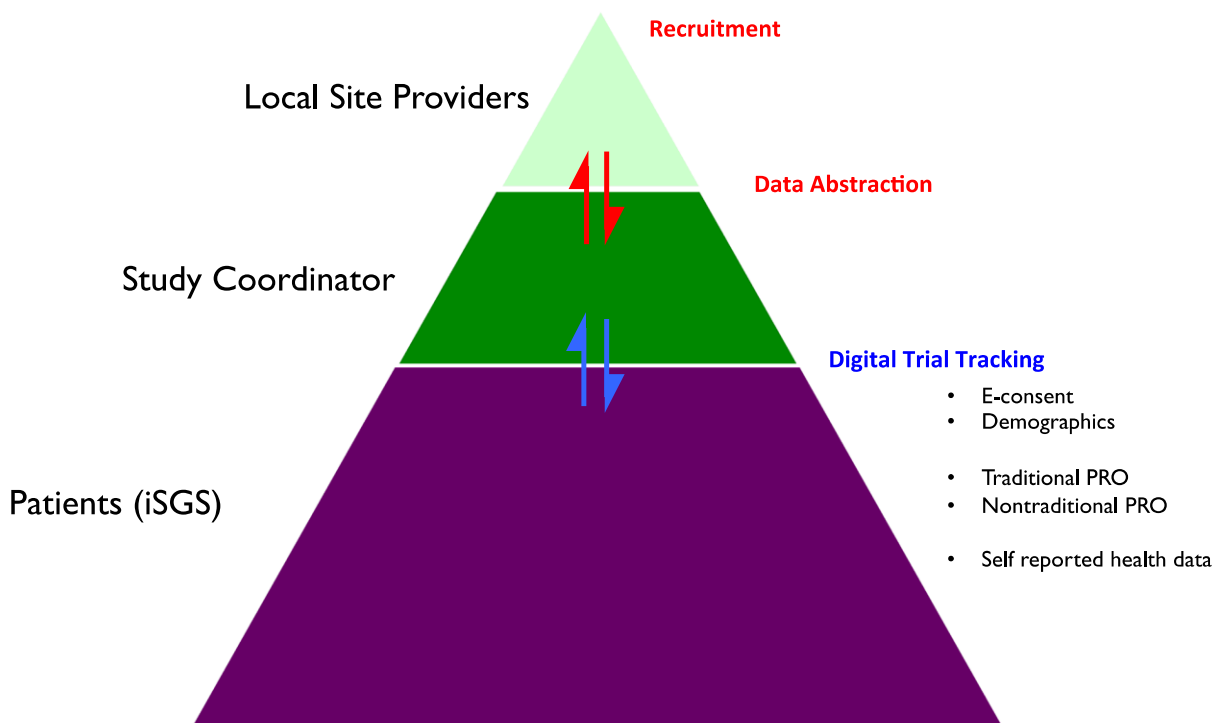
<b>Title:</b>	<b>Treatment Alternatives in Adult Rare Disease; Assessment of Options in Idiopathic Subglottic Stenosis</b>
<b>Précis:</b>	The proposed study intends to create an international, multi-institutional prospective cohort of iSGS patients. It will enable rigorous treatment strategy comparisons to determine how well the most commonly used treatments in iSGS “work”; and what quality of life trade-offs are associated with each approach.
<b>Objectives:</b>	<p>Prospective rigorous treatment comparisons to provide the critical information to patients to allow them to answer the questions,</p> <ol style="list-style-type: none"><li>1) “given my personal characteristics, conditions and preferences, what should I expect will happen to me?” and</li><li>2) “what are my options and what are the potential benefits and harms of these options?”</li></ol> <p><b>Primary Endpoint:</b> Treatment effectiveness: time to recurrent procedure and need for tracheostomy.</p> <p><b>Secondary Endpoint:</b> Health and quality of life tradeoffs: patient reported outcome measures in voice, swallowing, breathing, and global quality of life</p>
<b>Population:</b>	All clinically confirmed iSGS patients at the participating institutions are eligible for enrolment.
<b>Number of Sites:</b>	45 Sites
<b>Study Duration:</b>	60 months
<b>Subject Participation Duration:</b>	>6months
<b>Estimated Time to Complete Enrollment:</b>	24 months

**Schematic of Study Design:**



**Key Personnel and Study Responsibilities:**

NoAAC PR-02 Study Responsibilities



**Principal Investigator:** Dr. Alexander Gelbard M.D.

**PCORI Program Official:** Dr. Layla Lavasani Ph.D.

**Institutions:**

Vanderbilt University  
University of Virginia  
University of Utah  
Mayo Clinic  
Cleveland Clinic  
Johns Hopkins  
Massachusetts Eye & Ear Infirmary  
Oregon Health Science University  
Emory University  
University of Washington  
University of California San Francisco  
University of Colorado  
Baylor College of Medicine  
Louisiana State University  
Imperial College Health Care, Charring Cross  
University of Alabama Birmingham  
University of Wisconsin  
University of Michigan  
University of Nebraska  
University of Minnesota  
University of California San Diego  
University of Iowa  
University of Texas Southwestern  
Duke University  
University of North Carolina  
Augusta University  
University of California, Los Angeles  
University of Sydney  
University of California, Irvine  
University of Pittsburgh  
Loma Linda University  
Stanford University  
Emory University  
Ohio State University  
University of Southern California

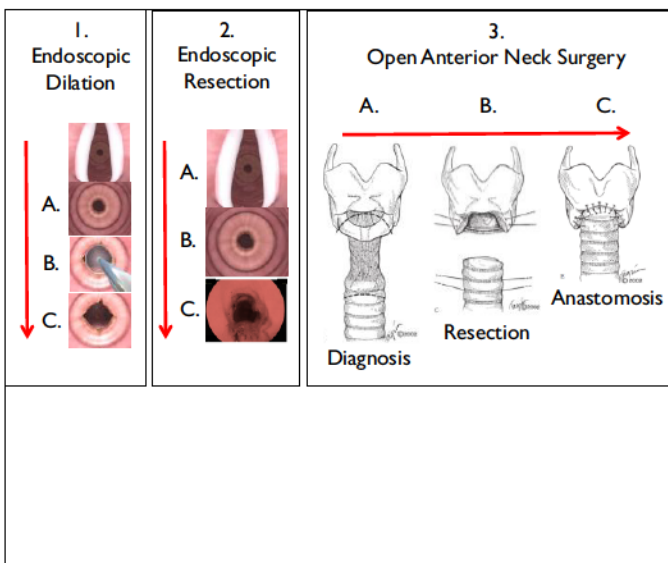
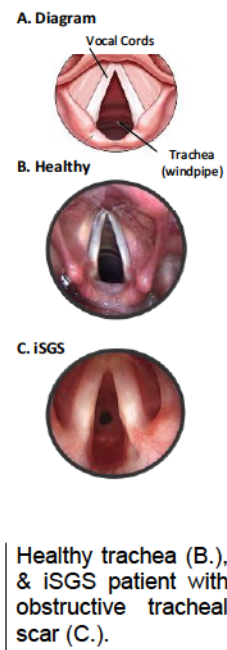
Temple University  
Medical College of Wisconsin  
Landspitali University Hospital  
Bastian Voice Institute  
New York University  
University of Cincinnati  
Columbia University  
University of Miami



## 1.0 Background

Idiopathic subglottic stenosis (iSGS) is a rare disease in which the trachea narrows for no known reason. Although uncommon (with an estimated incidence of 1:400,000 persons per year<sup>1</sup>), it is life-threatening and life-altering when severe. Both the disease and its therapies profoundly affect patients' ability to breathe, communicate<sup>3</sup> and swallow<sup>4</sup>. Breathing difficulties (i.e. dyspnea) is the hallmark symptom and the primary cause of death and disability<sup>5</sup>. However, patients can also experience debilitating voice changes<sup>3,6,7</sup> and swallowing problems<sup>8</sup> due to this condition (Figure 1) or its treatment.

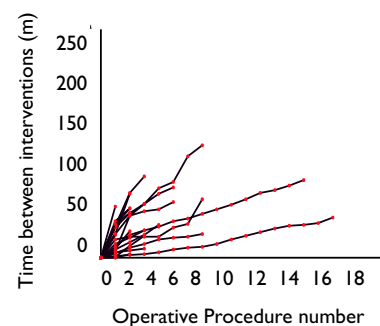
People with this disease often require several surgeries per year<sup>9</sup>. A variety of treatments have been advanced to manage this condition<sup>1,2,9</sup> but are generally categorized into: 1) endoscopic dilation of the tracheal stenosis (accomplished with rigid instruments or inflatable balloons); 2) endoscopic resection of the stenosis (often followed by prolonged medical therapy after surgery); or 3) open neck surgery with resection of the affected tracheal segment with end-to-end anastomosis (Figure 2). Each patient can require repeated surgeries to keep their trachea open, which increases the odds of treatment side effects and complications. All approaches have unique and often disabling associated side effects, which can significantly affect the patient's quality of life. However, comparative data on trade-offs have never been systematically



patients to find good information so that they can make a decision, particularly difficult because most patients present with severe symptoms, limiting their ability to explore options (as would be the case with a healthy trachea). Additionally, there is a general lack of high-quality, comparative data to aid in decision-making. Imperfect information and limited resources often lead to suboptimal decision-making as they try to balance survival, symptom relief, and quality of life considerations. In the absence of a clear standard of care, patients with a new diagnosis of iSGS face a limited number of therapeutic options, but are unable to explore them because it is urgent that they quickly relieve their breathing difficulty.

The proposed prospective study (NoAAC PR-02) is designed to fill this void, and leverages and builds upon our previous retrospective multi-institutional investigation, the North American Airway Collaborative RP-01 (NoAAC RP-01). In that study nearly 500 iSGS patients were identified and followed from ten expert tertiary care centers. Specifically, the need for repeat surgery, frequency of disease recurrence, and need for tracheostomy were identified as primary outcome measures.

Collaboration of experienced high volume centers in both the United States and the United Kingdom provided us with the largest and most representative signature of this disease’s epidemiology, natural history, and current management. Inclusion of patients across region and national borders ensured a racially/ethnically representative cohort spanning a range that includes socioeconomic disadvantaged and medically underserved patients. Interestingly, this condition was shown to be quite similar at the separate centers; as it nearly universally affects 40 – 60 year old women (median age 50.3, 95% CI 49.1 – 51.5) who undergo a median 1.75 surgeries per year (95% CI 0.8 – 2.6) (Figure 3). The NoAAC RP-01 study also found variation in the standard of care for iSGS at expert centers. Three basic treatment approaches were used (i.e. endoscopic dilation, endoscopic resection with adjuvant medical therapy, and open anterior neck surgery) despite an absence of randomized controlled trials (RCTs) or other rigorous comparative studies to assess their differential effectiveness at avoiding disease recurrence or tracheostomy.



**Figure 3.** Recurrent nature of interventions in iSGS. Operative procedure number vs. recurrence interval. Each line represents individual patient.

In contrast to the retrospective nature of RP-01, our proposed PR-02 prospective study design will directly compare effectiveness of contemporary treatments and assess their associated quality of life tradeoffs in iSGS patients. While evaluating treatment effectiveness is important, it is equally critical that the patient experience with the disease itself and its treatment be systematically characterized. This is imperative since patient and physician perspectives are often significantly discordant<sup>11</sup>. To this end, NoAAC PR-02 will collect patient-reported outcomes (PROs) in the cohort at initial presentation and at *a priori* determined intervals thereafter, (e.g. immediately pre-intervention, as well as 3, 6, and 12 months post-intervention) and conduct patient interviews and focus groups (labeled “engagement studios”) to better understand the patient experience with this condition.

Beyond the gaps in understanding of the relative effectiveness of clinical outcomes, no studies have explored health-related quality of life (HRQOL) or functional outcomes in iSGS. These endpoints are important to patients and are arguably a primary determinant in decision-making. For example, results show that endoscopic dilation is associated with a higher rate of disease recurrence and thus need for repeated surgery. Meanwhile, open cricotracheal resection is a major surgery with significant immediate perioperative risks and has been associated with alterations in voice<sup>3,6</sup> and swallowing<sup>4</sup>. Open surgery appears to reduce the risk of disease recurrence, but the degree of benefit, and the trade-offs associated with this invasive surgery are questions that demand prospective study.

## 2.0 Rationale and Specific Aims

Data from our prior retrospective multi-center study highlighted potential differential treatment effects based on reduced need for repeated surgery, while also providing insight into the typical disease course for iSGS patients. However, the need to systematically validate and expand upon these findings to provide patient-centered outcomes data requires longer-term prospective study. The proposed 5-year study will evaluate clinical outcomes data and generate novel information for iSGS patients beyond the currently available center-specific treatment outcome estimates to better guide clinicians and patients and they discuss treatment options.

*In summary, the proposed study will address the questions outlined above through 3 specific aims:*

*AIM I: We will build an international, multi-center prospective cohort of iSGS patients*

*AIM II: We will prospectively compare treatments in iSGS at multiple national and international centers to determine what “works” with respect to treatment outcomes of disease recurrence and tracheostomy.*

*AIM III: We will define the trade-offs in breathing, voice, swallowing and global quality of life between each treatment approach*

## 3.0 Inclusion/Exclusion Criteria

### **Inclusion Criteria:**

- >18 years of age.
- The lesion must involve the subglottis.

### **Exclusion Criteria**

- <18years of age
- Patients without capacity to consent for themselves
- History of significant laryngotracheal traumatic injury.
- History of endotracheal intubation or tracheotomy within 2 years of presentation.
- Major anterior neck surgery.
- History of neck irradiation.
- History of caustic or thermal injuries to the laryngotracheal complex.
- History of a clinically diagnosed vasculitis or collagen vascular disease.
- Positive antinuclear cytoplasmic antibody titers.

## 4.0 Randomization

There is no randomization as part of this study. This is a prospective observational multicenter study consisting of approximately 30 centers (Appendix 1). Each center enrolling patients will utilize a common diagnostic algorithm (Appendix 2), and then apply their explicitly defined standard of care. The patients will be prospectively tracked for outcomes with respect to disease recurrence, need for

additional surgery, tracheostomy, as well as subjective patient reported outcomes in breathing, voice, and swallowing.

## 5.0 Study Procedures

**Recruitment and Enrollment:** We anticipate a sample size of 800-1100 patients recruited across the participating centers. The target goal for Vanderbilt recruitment is 750-800 patients. There are currently 40 confirmed participating sites that will contribute patients (additional centers may be added in protocol amendments provided they meet defined study site selection criteria). Participating centers include those across all regions of the U.S. and international sites in the UK. Many are academic centers that are tertiary referral centers for adult laryngotracheal stenosis (LTS) and thus have significant experience treating this rare condition<sup>1,9,12-15</sup>. Nearly all LTS patients are ultimately referred for care and cluster at such high-volume centers, and thus we anticipate enrolling a representative patient cohort. Each research site has appropriate technological infrastructure for data collection and pathologic specimen tracking.

Study participants will be recruited via several mechanisms. Direct recruitment by participating clinician providers that diagnose and treat these patients will occur at each of the participating centers. It is expected that the majority of patients will be recruited through this approach. Patients will be identified by PI, Sub-I or Key study personnel and approached by a member of the research team at each institution regarding the study, or contacted by phone or email about the study. Participants may also be seen due to referrals in to participating sites/providers.

Additionally interested stakeholders can identify this study directly through its registration with ClinicalTrials.gov, the National Organization for Rare Disorders (NORD) website and rare disease database. Once recruited patients will undergo detailed discussion regarding risks and benefits of the trial, and informed consent will be obtained.

**Consent:** Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant, or reviewed with the patient by phone or email (i.e., econsent). Consent forms will be IRB-approved, and the participant will read and review the document or have the document read to him or her. The participant will sign the informed consent document prior to any study-related assessments or procedures, or agree to participation if consent is done by phone or email (i.e., econsent). Participants will be given the opportunity to discuss the study or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records, i.e. by mail, email, electronic link or in person. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

Given the observational nature of the study and the minimal risk involved to patients, we will utilize established methodology for electronic consent and phone consent as alternative options to consents obtained in providers offices. Electronic consenting of patients requires an alteration of the traditional consent model to fit within electronic delivery through email or for electronic capture of consent in a face to face encounter with participants. Retention of many elements of the traditional consent procedure to ensure participant protections are in place, and we will abide by the institutional guidelines regarding these alternative consent methods. (Appendix 4).

The investigator or designee will also be available to explain the research study to the participant and answer any additional questions that may arise. After informed consent, the patient will be considered to be a participant in the study.

**Protocol.** Once enrolled and consented, patients will receive standard of care treatment at the respective center (Appendix 1) and will be followed longitudinally for symptom changes, need for further treatment, complications, and will have PROs (Appendix 2) administered at *a priori* determined intervals.

**Data collection:** *Data collection for the proposed clinical cohort study will include the following case report forms (CRFs) (Appendix 3), implemented in an electronic data capture (EDC) system (please see further details, below, regarding EDC development and implementation).*

- Baseline. Baseline data will include such things as demographics, medical and surgical history, physical exam findings, and relevant diagnostics
- Procedure. Details of initial surgical procedure will be captured (e.g. site and degree of narrowing within the trachea). This information along with other procedure related information will be abstracted from the operative procedure note and clinical record into the EDC.
- Recurrence. At patient recurrence, information regarding the date of recurrence will be captured as for the initial procedure.
- Patient-reported outcomes (PROs). Validated PRO instruments will be utilized to assess patient quality of life. These relate to voice (VHI-10), dysphagia (EAT-10), breathing (COPD dyspnea), and general quality of life (SF-12). Additionally 4 “Non-traditional” PROs focused on 1) social support<sup>16</sup>, participatory decision-making style<sup>17</sup>, disease anxiety and burden<sup>18</sup> and fear of disease recurrence<sup>19</sup> will also be administered at the initial visit. Patients will be asked to complete “traditional” and “non-traditional PROs at baseline. The “traditional” PROs will be repeated at recurrence, and at routine intervals post-procedure (e.g., at 3, 6, and 12 months). For patients with Internet access and email connectivity, interval PRO completion may be done directly by the patient into the web-based data capture instrument, with automated email reminders to patients at each PRO interval. For patients without Internet/email access, completion of PROs will be via mailed or in person paper forms, or over the phone with a member of the research team; the research staff will then will transfer PRO data from paper to the EDC.

- Patient Generated Health Data (PGHD). Patient reported health data will be captured, an example of this is home peak flow measurements (obtained with a handheld asthma peak flow monitoring device supplied by the study) or number of steps taken during the week.
- Specimen. Biospecimens collected during routine standard of care from each patient (such as tracheal biopsies obtained during surgery, or surgical specimens generated thru open reconstructive surgeries), will be annotated in the EDC system with a minimum dataset to include date of specimen collection, specimen type (e.g., frozen biopsy tissue; FFPE block), and storage location. Additionally if blood is collected during standard of care, we may ask the participants to consent to providing a one-time blood specimen for research. We plan to obtain 30 mL of blood at a time when other medically indicated labs, operative or office-based procedures occur. A member of the research team will be present at the scheduled blood draw to obtain the necessary research blood and transport to a research lab for storage and analysis. We may examine excess tissue obtained at standard of care surgical biopsy for bacterial pathogens, inflammatory molecular markers, and protein alterations. Techniques will include immunohistochemistry, DNA isolation, PCR, Microarray. We will analyze blood samples for functional immunologic assays, Elispot for IFN-gamma secretion in response to peptide stimulation, flow cytometry for cellular subset abundance, and molecular studies for evidence of t-cell exhaustion and single nucleotide polymorphisms.

## 6.0 Data entry, collection, and quality control

*Data collection and management for the proposed project will be performed via a custom web-based electronic data capture system (EDC), implementing each of the CRFs described above in electronic format (eCRFs), and built using the Ruby on Rails (RoR) platform.*

This system is currently in place and actively functioning as the digital infrastructure for BetrNET, the NIH funded nationwide Barrett's disease monitoring network. The established HIPAA compliant technology has been actively in use for more than 5 years, as has a demonstrated track record of data privacy and fidelity. The system is based on *the Ruby on Rails (RoR) platform*. RoR is an open-source web application development framework for creating rich Internet applications that model complex data and reinforce data integrity through custom validations. The RoR framework for web-based data entry will be linked to a MySQL database for the data storage component. All data entry interfaces will utilize dropdown menus, radio buttons/checkboxes, and other structured variable formats whenever feasible, to enforce consistency of variable values in data entry. Also to support data quality control, extensive validations will be developed; these validations check records for internal consistency, conformity to any pre-specified data ranges, as well as compliance with any known inter-variable relationships. Support for longitudinal data will be provided through the use of a relational database architecture that models one-to-many relationships.

*In addition to the use of structured variables and validations to prevent data entry errors, other mechanisms for data quality control include:*

- Testing. The EDC will be tested extensively in both the development/staging and production environments. Automated testing is performed via scripted tests, to verify that observed

behavior of the system conforms to expected behavior. Manual testing of all system features will also be employed via the user interface and performed by dedicated testing personnel.

- Access controls. Access to the EDC will be restricted to authorized personnel. Data entry personnel and other users are provided secure access to the web-based application via standard Internet technologies (i.e., HTTPS), with tiered access permissions appropriate to their study role; such access is granted only when the following criteria are met: 1) request for access is authorized by a study principal investigator or other designated key study personnel and is accompanied by a designation of the user's role, to ensure appropriate level of access; and 2) the user completes training on system use, which may include a live training provided by our group and/or documented completion of a pre-recorded video training.

### **Patient Surveys:**

A critical component to understanding the patient experience with their disease is their own subjective input. This will be accomplished with established surveys of metrics for patient related health outcomes. The Vanderbilt University Office of Research will be used as a central location for data processing and management for these surveys. Vanderbilt University, with collaboration from a [consortium](#) of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. Two of those technologies are REDCap (Research Electronic Data Capture), a secure, web-based application that is flexible enough to be used for a variety of types of research and the BetrNet Ruby on Rails (ROR) platform. Both provide an intuitive user interface that streamlines project development and improves data entry through real-time validation rules (with automated data type and range checks). They also provide easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). In addition to traditional data capture functionality; REDCap and ROR survey capabilities are a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. All data collection projects rely on a thorough, study-specific data dictionary, defined by all members of the research team in an iterative, self-documenting process. This iterative development and testing process results in a well-planned and individualized data collection strategy. Surveys will either be completed via REDCap, the Ruby on Rails (RoR) platform or a combination.

### **Patient Generated Health Data:**

One important element of research is an understanding of the experiences of individual patients, and one of the ways to learn about those experiences is by collecting patient-generated data. Such information can be obtained in a variety of ways, including during medical visits, through use of smartphones and other electronic devices, and as part of research studies. These techniques will be employed during our study to capture patient self-reported peak-flow measurements. An established REDCap-based platform will be used to allow patients to input their data and provide the ability to track these measurements longitudinally over time. This technology utilizes smartphone reminders and automated voice algorithms for patient phone call, as well as having options for secure encrypted HTTPS data transfer over the web to the servers in the Data monitoring center.

The survey REDCap servers are housed in a local data center at Vanderbilt, and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to Vanderbilt researchers by both our Privacy Office and Institutional Review Board. REDCap has been disseminated for local use at more than 940 other academic/non-profit consortium partners in 75 countries. Vanderbilt leads the REDCap Consortium, which currently supports more than 99,000 projects and 128,000 users. More information about the consortium and system security can be found at <http://www.projectredcap.org/>.

## **7.0 Patient Reimbursement:**

None

## **8.0 Risks**

Minimal risk is anticipated. There are no investigational treatments under study in this project. Study patients will be asked to answer questions on self-administered hard copy electronic, mailed, or telephone surveys, and self-reported health data (i.e. peak flow breathing measurements).

Additionally, limited information from their routine medical care will be obtained. Patients will be informed that they can refuse to answer any of the questions. They will also be told that refusal to participate in the study will not in any way change or alter the care they will receive. Patients will be told that survey data are to be obtained for research purposes only and that no individual results will be reported. The data will be kept strictly confidential. No data of any sort will be released to anyone outside the study for any reason. Individual patients are never identified in publications.

Risks to the participants will be minimized by proper screening of potential candidates and strict adherence to confidentiality rules. In addition, access to the Electronic Data Capture (EDC) system will be strictly restricted to authorized personnel. Data entry personnel and other users are provided secure access to the web-based application via standard Internet technologies (i.e., HTTPS), with tiered access permissions appropriate to their study role; such access is granted only when the following criteria are met: 1) request for access is authorized by a study principal investigator or other designated key study personnel and is accompanied by a designation of the user's role, to ensure appropriate level of access; and 2) the user completes training on system use, which may include a live training provided by our group and/or documented completion of a pre-recorded video training. 3) The user has appropriate training for protection of human subjects.

All requests for user access, with documentation of fulfillment of the above criteria, are recorded in the permanent system documentation.

## **9.0 Benefits**

The risks for this study are minimal given the potential benefits to patients and society of any insights gained regarding the comparative effectiveness of idiopathic subglottic stenosis. Patients will be offered remuneration for study participation, as the various surveys will include roughly 25-100 items. There are no other direct benefits to the study patients, although some patients may gain



personal satisfaction through participation in research aimed at advancing knowledge of optimal treatment in a rare disease requiring repeated invasive operative interventions.

#### **10.0 Reporting of Adverse Events Involving Risk to Participants or Others**

This is a non-intervention study and there is no DSMB. The Principal Investigator is responsible for monitoring protocol conduct and reporting any adverse events related to study procedures. Adverse Events (AE) reporting will include the reporting of any unanticipated AE if it is probably or definitely related to being in this study. Although AEs are not anticipated on this study, if they should occur, they will be reported to the participating sites IRB board as well as the Vanderbilt Institutional Review Board by the Principal Investigator as required.

#### **11.0 Study Withdrawal/Discontinuation**

Study participants may withdraw from the study at any time by contacting the site specific PI, or the Coordinating Center PI Dr. Gelbard, or coordinating center research team staff.

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study subject's participation in the study if:

- Any medical condition, event or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

#### **12.0 Statistical Considerations**

##### **Study Hypotheses**

1. There is variation in Time to Recurrence (TTR) between centers using similar surgical approaches for iSGS
2. There is variation in TTR between centers using different surgical approaches for iSGS.
3. The different surgical approaches are associated with unique tradeoffs in terms of voice, swallowing, breathing, and global quality of life.

##### **Sample Size Considerations**

The primary endpoint of this trial is time to recurrence. The sample size estimation is completed using the 95% confidence interval (CI) method. With the proposed sample size of 1100 (endoscopic therapy  $\approx$  800, open surgery  $\approx$  100 and endoscopic resection  $\approx$  100), the half-width of

the 95% confidence interval for the time to recurrence function will be less than .24 for endoscopic resection and open surgery groups, and will be less than .13 for the endoscopic dilation group.

### **Final Analysis Plan**

**The primary objective:** The primary objective of this study is to evaluate the time to recurrence (TTR) among three possible treatment groups, i.e., open surgery, endoscopic dilation, and endoscopic resection.

**Data analysis plan for the primary endpoint:** Demographic information will be tabulated. Descriptive statistics, including means, standard deviations, and ranges for continuous parameters, as well as percents and frequencies for categorical parameters, will be presented. For the primary objective analysis, i.e., estimating the TTR with 95% confidence interval, the TTR time will be estimated using the Kaplan-Meier method with the 95% confidence interval (CI). The Rothman CI, CI's based on Greenwoods variance, Thomas and Grunkemeier CI and the simultaneous confidence bands by Nair and Hall and Wellner will be reported. The logrank test will be used to compare the equality of survival curves. The generalized Wilcoxon and log-likelihood tests will also be examined, as these tests weight the survival function differently from the logrank test, which gives more weight to later occurring events. The Cox proportional hazards model will be applied to investigate potential prognostic factors, such as age on the TTR data. The adjusted p-values as well as the adjusted 95% confidence intervals from the Cox model will be reported. The adjusted hazard ratios and 95% CIs will be reported.

**The secondary objective:** differential treatment quality of life trade-offs will be prospectively and systematically assessed using both validated “traditional” and “non-traditional” patient reported outcome measures (PRO). 4 “Traditional” PRO will measure disability related to voice (VHI-10<sup>1</sup>), swallowing (EAT-10<sup>2</sup>), breathing (COPD dyspnea<sup>3</sup>), and global quality of life (SF-12<sup>4</sup>) (IR4). 4 “Non-traditional” PROs focused on 1) social support<sup>5</sup>, participatory decision-making style<sup>6</sup>, disease anxiety and burden<sup>7</sup> and fear of disease recurrence<sup>8</sup> will also be administered at the initial visit. Responses to PROs tend to change in chronic disease states since severity of the measured concept is time-variable. This is particularly true for iSGS patients whose symptoms markedly improve after treatment and revert and worsen before subsequent treatments. To better understand the breadth of patient experience with this condition, PROs will employed at a priori determined intervals after diagnosis and treatment, (e.g. immediately pre-intervention, 3, 6, and 12, post-intervention), to obtain a more accurate portrait of the survivorship experience related to the different therapeutic modalities.

**Data analysis plan for secondary endpoints:** The secondary objective of this study is to evaluate the quality of life (QOL) scores, e.g., SF12, Dyspnea index, EAT-10, and VHI10, among three study groups. The 95% confidence interval (CI) method based on the Normal distribution will be applied to estimate the quality of life score among three study groups. The mixed effect model will be applied to exam the correlation between the quality of life score and the study groups.

The strategy to be used for developing the multivariable models for QOL involves the following steps: (1) Apply multiple imputation for missing covariate values to make good use of partial information. (2) Choose an appropriate statistical model based on the nature of the response variable.

(3) Decide on the allowable complexity of the model (i.e., the number of covariates) based on the effective sample size available. (4) Allow for nonlinear predictor effects using regression splines. (5) Incorporate pre-specified interactions. (6) Check distributional assumptions. (7) Adjust the variance-covariance matrix for multiple imputation. (8) Quantify the clinical utility (discrimination ability) of the model. (9) Internally validate the calibration and discrimination of the model using the bootstrap approach, e.g., .632+ bootstrap, to estimate the model's likely performance on a new set of subjects. The statistical analyses will be completed by either R 3.1.1 or SAS 9.4 statistical program in this project

**Statistical strategy for addressing missing data:** Given the enthusiasm of the iSGS population for this trial, we estimate a 90-95% response rate for the patient reported outcome measures in the cohort. Acknowledging this, it is possible that bias could be introduced due to missing data. To account for this, we will use two approaches in cases where participants are alive but are missing PRO data: the multiple imputation model based on the Markov chain Monte Carlo method described above<sup>9</sup> and a hierarchical hot-deck imputation approach<sup>10,11</sup>. We will perform sensitivity analyses compare the two methods to assess the validity of the two approaches. It is necessary to assume data are missing at random (MAR) to perform these types of pattern mixture imputation analyses<sup>11</sup>. In the hierarchical hot-deck imputation approach, participants with missing PRO data will be matched with at least 10 other participants with full data at the previous time point on the following variables: to voice (VHI-10), swallowing (EAT-10), breathing (COPD dyspnea), and general quality of life (SF-12), age, race, co-morbid disease, education and income. The order of matching will be determined by the dependent variable being examined. For the purposes of statistical testing, 10 complete data sets will be formed employing the hot-deck imputation approach<sup>11</sup>. Appropriate survey data analysis techniques will be performed using each data set, leading to 10 separate estimates of parameters and their covariances. We will use the `mianalyze.relimp` function in R to combine the parameter estimates and obtain covariance estimates which account for both within- and between-imputation sources of variation (*MD-5*). Inferences will be based on the combined parameter estimates and appropriate covariance structure. Our group has used this successfully in prior studies<sup>12,13</sup>.

**Strategy to address heterogeneity of treatment effect:** Subgroup analysis is the most commonly used analytic approach for examining HTE<sup>14</sup>, and we will utilize an exploratory variant of this analysis in our approach. Definition of subgroups, endpoints, hypotheses, and modeling parameters will be derived in response to the data. An example of this would be the use of a backward model selection approach to identify treatment by covariate interactions. Some of the important types of subgroup variables will be: (1) demographic variables (e.g., age); (2) pathophysiologic variables (e.g., timing after recurrence, disease grade); (3) comorbidities (e.g., presence of diabetes); and (4) concomitant exposures (e.g., hormone replacement therapy, proton pump inhibitors). Additionally, “non-traditional” characteristics that affect patient decision-making (e.g. social support, patient decision-making style, disease related anxiety, baseline quality of life) will be collected to improve risk-adjustment and increase the individualization of the results. Although it is extremely difficult to obtain the sampling properties of subgroup effect estimators (e.g., standard errors), post hoc exploratory subgroup analyses may identify promising hypotheses that will be subject to more rigorous future examination.

**Strategy to address confounding by selection bias:** Observational studies (like our proposed investigation) that lack randomization of subjects into treatment groups and must address selection bias to properly estimate the effect of treatment. We will apply a propensity scoring method (PSM) and instrumental variable (IV) method to adjust for observed and unobserved confounding, respectively. Propensity scoring will be used to mitigate the expected biases from observed confounding in the proposed observational study. It is a balancing score that effectively makes the distribution of measured baseline covariates similar between treatment groups. This is important because the apparent difference in outcome between those treated with endoscopic dilation versus those treated with endoscopic resection or open anterior neck surgery may depend on characteristics that affected whether or not a patient received a given treatment instead of due to the actual effect of the treatment. This issue is relevant to our study Aims #2 and #3, but for illustrative purposes, the specific analytic approach will be described in the context of Aim #2. Its objective is to determine factors that affect time to stenosis recurrence in patients with idiopathic subglottic stenosis. In this analysis, the dependent variable is time to recurrence and the primary independent variable is treatment type: endoscopic dilation versus endoscopic excision or open anterior neck surgery of the affected portion of the trachea.

There are three basic techniques for propensity score method: matching, stratification, and regression<sup>15</sup>. We plan to use two-step process of stratification and regression. Stratification consists of grouping subjects into strata determined by observed background characteristics; then comparing subjects between treatment groups directly. Propensity scoring on strata is particularly useful when there are large numbers of covariates, as is the case in this study. Conventionally, creation of five strata has been shown to remove 90% of bias due to the stratified variable<sup>16,17</sup>. The propensity score is then estimated using a logistic regression model, in which the treatment status is regressed on observed and stratified baseline characteristics. This allows for the formation of matched sets of patients who underwent endoscopic dilation, endoscopic resection or open anterior neck surgery for their iSGS based on similar propensity score values<sup>18</sup>. In essence, all collected and known confounding covariates will be collectively replaced by a single function of these covariates – the propensity score. Thus, the collection of known predictors is collapsed into a single predictor. Since time to recurrence is a continuous variable, the effect of treatment will be estimated as the difference between the mean time for patients in the endoscopic dilation versus endoscopic resection or open anterior neck surgery groups. Once treatment effect has been estimated using propensity scoring, variance of outcome effect and statistical significance can be estimated. Analysis of the propensity matched treatment groups can be accomplished by directly comparing outcomes between the three treatment groups. Multivariate regression will be performed to reduce bias due to residual differences in observed baseline covariates between groups.

All known and measurable covariates and confounders will be collected and considered in the propensity score model. Incorporation to the multivariate model will be determined *a priori* based on their potential to confound or modify the association between treatment and time to recurrence, and include **demographics** (age, sex, race, socioeconomic status, geographic location, marital status), **health** (Charlson-Deyo score, body mass index), **endocrinologic history** (age of first menses, number of pregnancies, onset of menopause, use of hormone replacement therapy), **Inflammatory biomarkers** (high sensitivity CRP, Antinuclear Antibodies, Antineutrophil

Antibodies, Renal filtration rate), **anatomic** characteristics (airway scar length, degree of luminal obstruction, distance from the glottis), **physiologic** (gastroesophageal reflux disease testing, pulmonary function testing), **social/behavioral** [Social Support (FSSQ), Quality of life (SF12), Decision-making style (PDMstyle), Fear of Progression (FoP-Q-SF)]. Provider-specific covariates will include the type of subspecialty training program, training location, procedural volume, and treatment criteria for open anterior neck surgery. In addition, the model will include interaction terms for the associations of age with endocrinologic history, Charlson-Deyo score, and facility regions based on statistical evidence of effect modification and theoretical plausibility.

Propensity scoring can only adjust for observed confounding variables such as those listed above not unobserved ones. Therefore, we will employ quantitative and limited variable (QLIM) to conduct instrumental variable analysis to adjust for unobserved confounding. The instrumental variable has to meet five specific assumptions: 1) potential outcomes for each patient are unrelated to treatment status of other patients, 2) instrument affects receipt of the treatment of interest, 3) this effect is always in the same direction, 4) instrument assigns treatment randomly, and 5) instrument has an effect on the outcome only through the treatment assignment<sup>19</sup>. The instrument that we plan to use in this analysis is distance from the patient's residence to the treating facility<sup>20,21</sup>. The assumption is that the association between distance to the hospital and time to recurrence is due only to the effect of relative distance on treatment assignment after controlling for observed variables and not directly correlated with time to recurrence. This process will involve a two-stage process that first uses the instrument variable and other covariates to predict the treatment. A second stage estimates the outcome by the predicted treatment (from the first model) and other covariates<sup>22</sup>. Using a two-stage approach has the advantage of incorporating the predicted treatment into the outcome model as it represents the portion of treatment selection related to distance from the treating facility. We will also adjust, when possible, for any instrument-outcome confounding, as confounding can still occur even with the instrumental variable procedure<sup>19</sup>. Other instruments will be considered if distance to treating facility is not found to meet the aforementioned assumptions or is found to significantly confound the outcome.

### 13.0 Ethics/Protection of Human Subjects:

**Ethical Standard.** The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6. Additionally, internationally, the investigator will ensure that this study is conducted in full conformity with the Declaration of Helsinki, CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002).

In adherence to the National Institutes of Health (NIH) policy on education in the protection of human subject participants in the conduct of research (Available at [grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html)), all key personnel will have documentation attesting to their completion of institutional curricula in ethical research and the protection of human subject participants.

**Institutional Review Board.** Each participating institutions must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. The protocol, informed consent form(s), recruitment materials and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

### *13.1.a: Risks to the subjects*

**Human Subjects Involvement and Characteristics:** Participants are primarily women (with a rare male) newly diagnosed with idiopathic subglottic stenosis identified through clinician providers at one of 30 international sites. There are no racial/ethnic restrictions to enrollment.

**Sources of Materials:** All eligible and willing patients will be asked to complete questionnaires (either written or by telephone, or email) at baseline, and at multiple time points after enrollment. Documented informed consent will be obtained from patients at the time of enrollment in the study, which will include permission to be contacted for future studies by KSP from participating centers.

**Potential Risks:** Minimal risk is anticipated. There are no investigational treatments under study in this project. Study patients will be asked to answer questions on self-administered electronic, mailed, or telephone surveys, and self-reported health data (i.e. peak flow breathing measurements). Additionally, limited information from their routine medical care will be obtained. Patients will be informed that they can refuse to answer any of the questions. They will also be told that refusal to participate in the study will not in any way change or alter the care they will receive. Patients will be told that survey data are to be obtained for research purposes only and that no individual results will be reported. The data will be kept strictly confidential. No data of any sort will be released to anyone outside the study for any reason. Individual patients are never identified in publications.

### *13.1.b Adequacy of protection against risks*

**Recruitment and Informed Consent:** All of the study letters, forms, protocols and procedures used will be approved by the appropriate local IRBs. After identification by the site investigator, informed consent will be obtained; the patients will be sent a baseline survey. Those who do not respond will be contacted by telephone, verbal informed consent obtained, eligibility assessed and the baseline telephone (or email) interview performed. At defined intervals post-enrolment, patients will be sent a follow-up electronic (or written) self-administered survey. Patients will be asked to complete these materials either digitally or in paper forms and return them in stamped, return addressed envelopes to the local study office..

**Protection against risk:** Risks to the participants will be minimized by proper screening of potential candidates and strict adherence to confidentiality rules. In addition, access to the Electronic Data Capture (EDC) system will be strictly restricted to authorized personnel. Data entry personnel and other users are provided secure access to the web-based application via standard Internet technologies (i.e., HTTPS), with tiered access permissions appropriate to their study role; such

access is granted only when the following criteria are met: 1) request for access is authorized by a study principal investigator or other designated key study personnel and is accompanied by a designation of the user's role, to ensure appropriate level of access; and 2) the user completes training on system use, which may include a live training provided by our group and/or documented completion of a pre-recorded video training. 3) The user has appropriate training for protection of human subjects.

All requests for user access, with documentation of fulfillment of the above criteria, are recorded in the permanent system documentation.

#### *13.1.c Potential benefits of the proposed research to subjects and others*

The risks for this study are minimal given the potential benefits to patients and society of any insights gained regarding the comparative effectiveness of idiopathic subglottic stenosis. There are no other direct benefits to the study patients, although some patients may gain personal satisfaction through participation in research aimed at advancing knowledge of a rare disease requiring repeated invasive operative interventions.

#### *13.1.d Importance of the knowledge to be gained*

Idiopathic subglottic stenosis (iSGS) is a rare disease manifesting in adults, characterized by severe airway obstruction. Affecting the upper tracheal airway, the condition is life threatening, and when survived, life altering. Both the disease and its therapies profoundly impact breathing<sup>2</sup>, communication<sup>3</sup> and swallowing in affected patients. Unfortunately, little is known about comparative effectiveness of the three most common therapies for iSGS; endoscopic dilation, endoscopic resection, and open anterior neck surgery. This research will generate new and important information that will help women with iSGS chose the optimal individualized therapy. Furthermore, it will provide a network and data infrastructure for future research into the etiology and optimal treatment strategy in iSGS. Given that minimal risk is involved in the study, the benefits greatly outweigh these risks.

*13.1.e Data and Safety Monitoring Plan:* Not applicable.

### **13.2 Inclusion of Women, Minorities and Children:**

#### *13.2.a Inclusion of Women*

Women are included in this study, and in fact, comprise the majority of patients affected with idiopathic subglottic stenosis.

#### *13.2.b Inclusion of Minorities*

Preliminary results from our initial multicenter retrospective study (the NoAAC RP-01) suggest iSGS preferentially affects Caucasians. However, all efforts will be made through this study to include affected patients of all racial/ethnic backgrounds. Given the number and geographic diversity of our study sites we believe we will generate a representative cohort of patients with

iSGS. We have no reason *a priori* to believe that results from this study will not be applicable to all patients affected with iSGS.

*13.2.c Inclusion of Children:* No children are included in this study as iSGS a disease of adults.

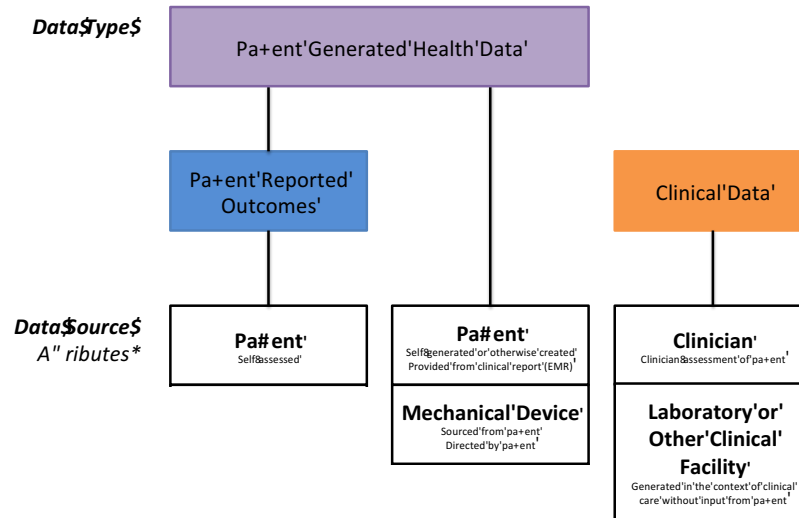
**14.0 Data Handling and Record Keeping.** The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The investigators will maintain adequate source documentation.

**Data Management Responsibilities.** Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports will be reviewed by the study team and data entry staff to ensure accuracy and completeness. Unanticipated problems must be reviewed by the investigator or designee.

**Types of Data.** Multiple types of data will be collected. Both clinical data (i.e. laboratory results, procedure notes etc.), as well as patient generated health data (i.e. surveys, patient reported health data, patient reported outcome measures), along with safety data (i.e. unanticipated problems) will be collected.



### NoAAC PR-02 Study: Data Types Collected



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#### 15.0 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Data collected from study participants will be maintained and stored in paper and electronic formats. Any paper study documents (such as signed consent forms, case report forms, or surveys and/or questionnaires) will be maintained in a secured location in the PI or Research Team's locked office.

The PI and his research team will conduct the study using Good Clinical Practice guidelines. All will respect the confidentiality of the records being accessed and the data being input. All authorized users will have individual usernames and passwords to access datasets. The database has security measures in place to protect the data as delineated: access to the Electronic Data Capture (EDC) system will be strictly restricted to authorized personnel. Data entry personnel and other users are provided secure access to the web-based application via standard Internet technologies (i.e., HTTPS), with tiered access permissions appropriate to their study role; such access is granted only when the following criteria are met: 1) request for access is authorized by a study principal investigator or other designated key study personnel and is accompanied by a designation of the user's role, to ensure appropriate level of access; and 2) the user completes training on system use, which may include a live training provided by our group and/or documented completion of a pre-recorded video training. 3) The user has appropriate training for protection of human subjects.

All requests for user access, with documentation of fulfillment of the above criteria, are recorded in the permanent system documentation.

Participant's personal information will remain confidential and will not be used if study information is published or presented at a scientific meeting.

## **16.0 Publication/Data Sharing Policy.**

This study will comply with Public Access Policy from both PCORI and the NIH, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive [PubMed Central](https://pubmed.ncbi.nlm.nih.gov/) upon acceptance for publication.

Like PCORI, the NoAAC study team is committed to promoting the principles of transparency, replication and reproducibility in research. As soon as we received notification of funding, we would update the protocol for the three-year follow-up. We would not finalize it, however, until after the initial meetings of the full study team to ensure we captured patient partner opinions and generated a protocol that reflected what we truly intended to do. This would be submitted to PCORI and made available to other researchers, after approval from the PI (and the rest of the NoAAC Steering Committee study team). Additional study documentation (e.g., database design, programming code, and data definitions) would be shared with PCORI in the final year of the grant, as well as with requesting researchers, and any requesting peer-reviewed journals.

We will share all a complete, cleaned, de-identified copy of the final data set with PCORI in the third year of the grant. Additionally, we will share all code books, meta-data related to the datasets and statistical programming code with PCORI in the third year of the grant and with any peer-reviewed journals who requested this information in support of manuscripts that resulted from the project. We plan this approach with the upcoming submission of the NoAAC RP-01 results, are prepared to do this again in the future.

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