



BTG

Interventional
Pulmonology

PneumRx

Elevair™ Endobronchial Coil System
Sponsor Executive Summary
June 14, 2018

Attachment 7: Proposed Post Approval Study Protocol

The table of contents can be found on page 6 of 43 or [click here](#).



Protocol Number:	CLN0022.p Draft
Protocol Name:	Elevair™ Endobronchial Coil System US Post-Approval Study
Phase:	Post-Approval Study
Sponsor:	PneumRx, Inc. 4255 Burton Drive Santa Clara, CA 95054 USA
Principal Investigator(s):	TBD
Study Device	Elevair™ Endobronchial Coil System

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Table 1: Protocol Revision History

<i>Draft NUMBER</i>	<i>AMENDMENT APPROVAL DATE</i>	<i>BRIEF DESCRIPTION OF CHANGES</i>
<i>01</i>	<i>N/A</i>	<i>Draft Version</i>
<i>02</i>	<i>N/A</i>	<i>Update in response to FDA deficiency letter:</i>



PROTOCOL APPROVAL & RELEASE SIGNATURE PAGE

Protocol Number:	CLN0022.p Draft
Protocol Name:	Elevair™ Endobronchial Coil System US Post-Approval Study
Protocol Version:	TBD
Protocol Approval Date:	TBD (DD/MMM/YYYY)

The above-referenced protocol was reviewed and approved for release by the following:

Approver	Signature	Date (DD/MMM/YYYY)
Principal Investigator	Not required for Draft Version	
Sponsor: Senior Manager Clinical Development	Not required for Draft Version	
Sponsor: Statistician	Not required for Draft Version	



PRINCIPAL INVESTIGATOR SIGNATURE

Protocol Number:	CLN0022.p.Draft
Protocol Name:	Elevair™ Endobronchial Coil System US Post-Approval Study
Protocol Version:	TBD
Protocol Approval Date:	TBD (DD/MMM/YYYY)

The Principal Investigator (undersigned) hereby declares that he/she has read this protocol and agrees to its contents.

The undersigned confirms that the trial will be conducted and documented in accordance with the US Federal, State and Local requirements for post-market human clinical study, the protocol, and the stipulations of the clinical trial agreement.

Investigator Name (please print): _____

Investigator Signature: _____

Date (DD/MMM/YYYY): _____



INVESTIGATOR PROTOCOL REVIEW STATEMENT

Protocol Number:	CLN0022.p.Draft
Protocol Short Title:	Elevair™ Endobronchial Coil System PAS
Protocol Version:	TBD
Protocol Approval Date:	TBD (DD/MMM/YYYY)

The site Principal Investigator (undersigned) hereby declares that he/she has read this protocol and agrees to its contents.

The undersigned confirms that the trial will be conducted and documented in accordance with the US Federal, State and Local requirements for post-market human clinical study, the protocol, and the stipulations of the clinical trial agreement.

By written consent to this protocol, the investigator agrees to the above and to fully co-operate with all monitoring and audits in relation to this trial by allowing direct access to all documentation, including source data, by authorized individuals representing PneumRx, Inc., IRBs and/or by the US Federal, State and local regulatory authorities.

Investigator Name (please print): _____

Investigator Signature: _____

Date (DD/MMM/YYYY): _____



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Table 2: Terms, Acronyms, Abbreviations

The following abbreviations and specialist terms are used in this protocol.

6MWT	Six Minute Walk Test
ABG	Arterial Blood Gasses
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ATS	American Thoracic Society
BUN	Blood Urea Nitrogen
CAO	Coil Associated Opacity
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
eCRF	Electronic Case Report Form

EDC	Electronic Data Capture
EKG	Electrocardiogram
ELEVAIR	The medical device that is the subject of this Study, consisting of the Elevair™ Endobronchial Coils and the Elevair™ Endobronchial Coil Delivery System.
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRCT	High Resolution Computed Tomography
ICF	Informed Consent Form
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
LVRs	Lung Volume Reduction Surgery
MedDRA	Medical Dictionary for Regulatory Activities
mMRC	Modified Medical Research Council (Dyspnea Scale)
O ₂	Oxygen
OTC	Over the Counter
OUS	Outside the US
PAS	Post-Approval Study
PFT	Pulmonary Function Testing

PI	Principal Investigator
PRO	Patient Reported Outcomes
PT	Prothrombin Time
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	SAS Institute, Inc., Cary, NC, USA
SDV	Source Data Verification
SGRQ	St. George's Respiratory Questionnaire
SOP	Standard Operating Procedure
SpO ₂	Oxygen Saturation By Pulse Oximetry
UADE	Unexpected Adverse Device Event
US	United States
WBC	White Blood Cell



PROTOCOL SYNOPSIS

Protocol Number	CLN0022.p.Draft
Protocol Title	Elevair™ Endobronchial Coil System (ELEVAIR System) US Post-Approval Study
Device	Elevair™ Endobronchial Coil System (ELEVAIR System)
Type of Protocol	Post Approval Study (PAS)
PAS Rationale	This PAS is designed to collect safety and effectiveness data in a post-approval setting of this US FDA-approved product. The ELEVAIR System will be used as intended and in accordance with FDA-approved labeling.
Objectives	<ol style="list-style-type: none"> 1. To demonstrate, in the post-approval setting, the safety of the ELEVAIR System for the treatment of severe emphysema by assessing the rate of device- or procedure related respiratory adverse events of interest (RAE). 2. To demonstrate, in the post-approval setting, the effectiveness of the ELEVAIR System for the treatment of severe emphysema by assessing the impact on subject Quality of Life (QOL) using the St. George's Respiratory Questionnaire (SGRQ).
Primary Endpoint(s)	<p>Safety Endpoint:</p> <p>Composite rate of device- or procedure-related serious RAEs through 12 months post-first implantation procedure. RAEs will be defined as AEs of the following types: Lower Respiratory Tract Infection/Pneumonia, COPD Exacerbation, Severe Hemoptysis, Pneumothorax, Respiratory failure</p> <p>Effectiveness Endpoint:</p> <p>Change in QOL, as measured by SGRQ, from baseline to 12 months post-first implantation procedure.</p>



Secondary Endpoint(s)	<p>Secondary Safety Endpoint:</p> <p>Frequency of individual device- or procedure-related RAEs through 12 months post-first implantation procedure in subjects treated with the ELEVAIR System.</p> <p>Secondary Effectiveness Endpoints:</p> <ol style="list-style-type: none"> 1. Changes in pulmonary function (including FEV₁, RV, RV/TLC) and exercise capacity (6MWT) from baseline to 12 months post-first implantation procedure. 2. Responder rates based on Minimum Clinically Important Difference (MCID) for SGRQ, selected pulmonary function and exercise capacity parameters. 3. Healthcare utilization during therapy and hospitalization throughout the Study.
PAS Duration	<p>All enrolled Subjects who undergo the ELEVAIR Coil procedure will be monitored for outcome data from baseline through 3 years post-first implant</p> <p>Expected enrollment start: 6 months after final protocol and PMA approval.</p> <p>Estimated study completion: five years after the first subject has enrolled (estimated two year enrollment for 300 subjects with 12-month primary endpoint and 3-year follow-up)</p>
PAS Design	<p>This PAS is a single-arm, prospective, multi-center Study. It is designed to assess 12-month safety and effectiveness of this FDA approved product in a post-approval setting, and to support the continued assessment of ELEVAIR Coil therapy for the treatment of severe emphysema in the United States. In addition, data will be collected to assess healthcare utilization of the therapy.</p> <p>Investigators will be physicians who are skilled in the use of therapeutic bronchoscopes, who have completed required training by a PneumRx representative, and are approved by PneumRx to perform the ELEVAIR Coil procedure (Approved Site). Approved sites will have facilities that support the practice of interventional bronchoscopy and have the appropriate infrastructure, equipment, and trained personnel to support advanced interventional pulmonary procedures.</p> <p>Participating sites will submit de-identified Subject data via electronic case report forms (eCRFs). The information collected by participating sites will be placed in an Electronic Data Capture (EDC) system.</p>

Study Population	<p>The study population will be in accordance with the FDA-approved labeling for this PMA product and who have met the treatment criteria as stated in the FDA-approved Instructions For Use (IFU).</p> <p>Enrollment in the Study will be available to all subjects eligible for treatment at an Approved Site once Institutional Review Board (IRB) approval is received and the subject meets study eligibility criteria.</p> <p>Written informed consent will be required for all Subjects prior to participation in the Study.</p>
Number of Subjects	<p>The Study will enroll a minimum of 300 subjects. The sample size is estimated to have adequate power to test the primary safety endpoint against the performance goal. The assumed 12-month Composite serious RAE rate is 44% based on the RENEW study and the performance goal is 55%. Using a one- sided 2.5% significance level, 300 subjects will provide greater than 90% power to demonstrate the Composite rate is below the performance goal using an exact binomial test.</p> <p>A sample size of 300 subjects will provide greater than 95% power to demonstrate that the primary effectiveness endpoint is less than or equal to a performance goal of -4 (e.g., improvement of SGRQ MCID or greater) using a single sample t-test of a mean change against the performance goal with a one sided Type 1 error rate of 0.025. The assumed mean (SD) primary effectiveness endpoint is -8 (12) based on the RENEW study.</p>
Number & Location of Sites	Up to 30 US sites are expected to participate in the Study
Inclusion / Exclusion Criteria	<p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Emphysema patients who are appropriate for ELEVAIR Coil treatment based on the US FDA-approved IFU requirements and are scheduled for the ELEVAIR Coil therapy procedure. 2. Subject has read, understood, agrees to participate in the Study, and signed the Informed Consent form (ICF). <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Subjects who are not appropriate for ELEVAIR Coil therapy based upon the US FDA-approved IFU requirements. 2. Subjects who have not signed the ICF.



Procedures in Screening / Baseline Period	<p>Baseline Visit:</p> <p>Subject is evaluated and selected for ELEVAIR Coil therapy and has met criteria for treatment per the FDA-approved IFU. Subject agrees to be a part of the Study and signs the ICF. This information will be entered into the EDC system.</p>		
Study Visits and Follow-up	<p>Procedure visit:</p> <p>Subject undergoes the ELEVAIR Coil procedure in accordance with the FDA-approved IFU. Procedure data will be collected and entered into the EDC system.</p> <p>The procedure visits will include 2 sessions: procedure for treatment of the first lung, followed by procedure for treatment of the contralateral lung, which should be scheduled at 1-3 months following the initial procedure.</p> <p>Follow-up Visit(s):</p> <p>Subject follow-up visits will occur in accordance with the institution's standard of care. Study-specific follow-up visits should be conducted at 6 and 12 months post-first procedure and then annually for up to 3 years from the date of the first procedure.</p> <p>Study specific follow-up visits should ideally occur at the hospital that performed the Coil implantation procedure and when the subject is in a clinically stable condition.</p>		
Study Visits and Follow-up (<i>cont.</i>)	<p>The eCRFs will be completed by the investigator (or an authorized member of the investigator's staff) at the participating site and entered into the EDC database per the schedule outlined below.</p>		
	Procedure/ Assessment	Bas eline	Treat ment
	Informed Consent	X	
	Baseline Assessment ¹	X	
	ELEVAIR Coil Procedure		X
	Medications	X	X
	AEs		X

	Effectiveness Measures ²	X		X
	¹ Includes demographics, medical history, physical exam, vital signs, and additional standard-of-care pre-treatment evaluations (e.g., HRCT). ² Measures include PFT, 6MWT, SGRQ, mMRC Dyspnea Scale performed per Standard-of-care at the individual institution.			
Management of Adverse Events	<p>Safety information in addition to mortality will be collected on an ongoing basis throughout the Study as participating centers become aware of device- and procedure-related Adverse Events.</p> <p>These events will be recorded on the AE form in the EDC system by the investigator or authorized designee. Event, date of onset, severity, seriousness, duration, and relationship to the procedure/device will be recorded. All reported device- and procedure-related adverse events will be followed until they are adequately resolved or stabilized or study completion/ or termination, whichever comes first.</p> <p>Safety Events will be summarized based on MedDRA codes and by relevant, discrete time periods including the Treatment recovery period (30 days from either therapy) and annually post-first implantation procedure.</p> <p>In addition, RAEs will be assessed and summarized. RAEs will be defined as AEs of the following types:</p> <ul style="list-style-type: none"> • Lower Respiratory Tract Infection/Pneumonia • COPD Exacerbation • Severe Hemoptysis • Pneumothorax • Respiratory failure <p>Additional information will be collected for Tissue Reaction, Localized (i.e., Coil Associated Opacity (CAO), a non-MedDRA term), and Coil migration and Coil removal, to facilitate appropriate event categorization, differentiation, and assessment.</p>			



<p>Statistical Analysis</p>	<p>The primary safety endpoint is the Composite Rate of device- or procedure-related serious RAEs which includes events summarized in the following major categories: COPD Exacerbation, Lower Respiratory Tract Infection/Pneumonia, Pneumothorax, Severe Hemoptysis, and Respiratory Failure. The primary effectiveness endpoint is QOL using the SGRQ.</p> <p>The primary safety and effectiveness endpoints will be analyzed using descriptive statistics with 95% confidence intervals in order to test the following hypotheses:</p> $H_0: S_{\text{rate}} \geq 55\%$ $H_a: S_{\text{rate}} < 55\%$ <p>where S_{rate} is the observed the 12-month Composite Rate of device- or procedure-related serious RAEs. The null hypothesis will be rejected and the primary safety endpoint performance goal will be met if the upper bound of the one-sided 97.5% exact confidence interval is less than 55%.</p> $H_0: \mu_E \geq -4$ $H_a: \mu_E < -4$ <p>where μ_E is the observed mean change from baseline to 12 months in SGRQ. The null hypothesis will be rejected and the primary effectiveness endpoint performance goal will be met if the upper bound of the one-sided 97.5% confidence interval is less than -4.</p> <p>Descriptive statistics and 95% confidence intervals will be used to summarize additional safety and effectiveness endpoints of interest including responder rates and change from baseline at each follow-up visit.</p> <p>The incidence of and total number of device- and procedure-related adverse events will be summarized by MedDRA preferred term and system organ class, overall and separately by follow-up visit windows, relatedness to device/procedure and seriousness.</p>
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The Study will be conducted and documented in accordance with the US Federal and Local requirements for post-market human clinical studies, the protocol, and the stipulations of the clinical trial agreement.

1. SCHEDULE OF VISITS

Procedure / Assessment	Baseline	Treatment	Follow-up Visit (s)
Informed Consent	X		
Baseline Assessment ¹	X		
ELEVAIR Coil Procedure		X	
Medications	X	X	X
AEs		X	X
Effectiveness Measures ²	X		X

¹Includes demographics, medical history, physical exam, vital signs, and additional standard-of-care pre-therapy evaluations (e.g., HRCT).

²Measures include PFT, 6MWT, SGRQ, mMRC Dyspnea Scale performed per Standard-of-care at the individual institution.

2. BACKGROUND

2.1. Disease background

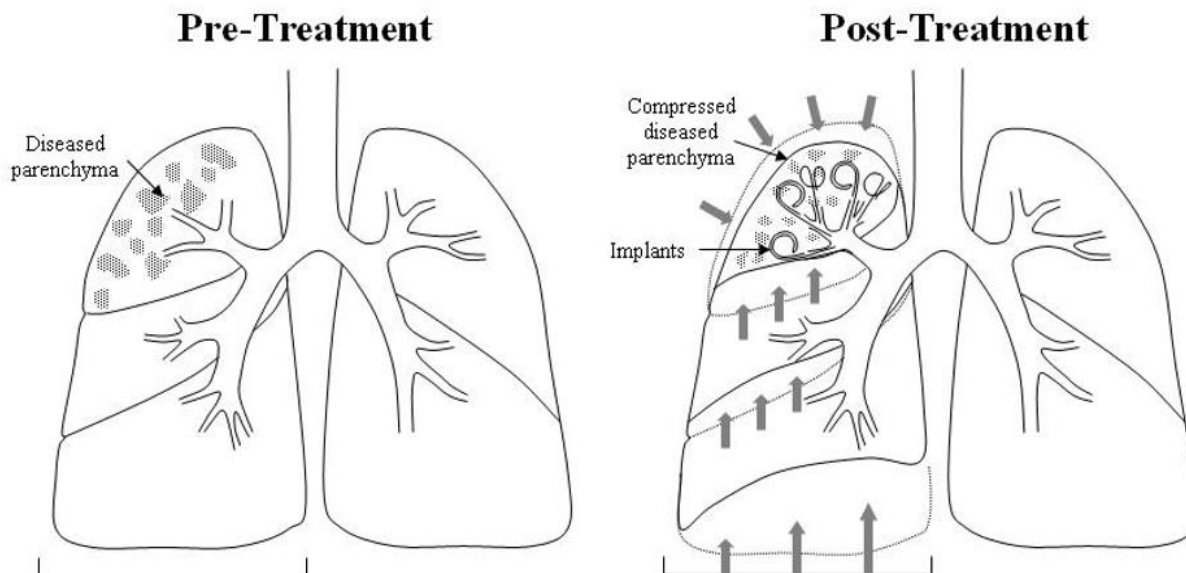
Emphysema is a chronic respiratory disease with an estimated prevalence of 4 million diagnosed adults in the US.¹ Emphysema is characterized by gradual destruction and disappearance of alveolar walls. This results in reduction in the elasticity and recoil pressure of the lungs, and allows the smaller airways to collapse prematurely during exhalation, resulting in hyperinflation, air trapping, and diaphragmatic flattening with decreased diaphragmatic efficiency. This hyperinflation worsens with rapid breathing associated with exercise. These effects are believed to be a primary contributor to the dyspnea experienced by emphysema patients.² The alveolar wall damage also creates large nonfunctional air pockets or bullae that become physiologic dead space in the thorax, preventing healthier portions of the lung from expanding and contracting normally. Patients with advanced emphysema also frequently demonstrate collateral ventilation both within the affected lobes and even across lobar fissures. As the disease progresses, the emphysema patient eventually becomes hypoxemic due to progressive loss of alveolar capillary membrane surface area. Hypoxemia and deconditioning contribute to muscle weakness and fatigue. The crippling effects of end-stage emphysema include severe dyspnea, severe limitation of activities, recurrent lung infections, and ultimately respiratory failure, which can result in death.

There are several treatments available for emphysema including smoking cessation, medications, physical therapy, supplemental oxygen, and surgery. Smoking cessation is an important step in the treatment of emphysema. While this will not treat emphysema directly, it will limit the rate of progression of the disease. Emphysema can be treated with inhaled bronchodilators, inhaled corticosteroids, anticholinergics, theophylline, phosphodiesterase-4 inhibitors and supplemental oxygen. Emphysema patients are prone to exacerbations, usually due to respiratory infections, which are usually treated with antibiotics and/or systemic corticosteroids and frequently require emergency room visits and/or hospitalizations. Emphysema patients may undergo pulmonary rehabilitation exercises and training. There are also two surgical procedures available for treatment of severe emphysema: lung transplantation and lung volume reduction surgery (LVRS). Lung transplantation is a seldom used option because of the limited availability of donor lungs, low transplantation priority for emphysema patients relative to other rapidly fatal pulmonary diseases, and because of the advanced age of most emphysema patients. Lung Volume Reduction Surgery is major surgery that carries the risk of morbidity and mortality. Recently, less invasive bronchoscopic approaches have been developed and several approaches are being actively investigated in human clinical trials in Europe and the US.

2.2. General Description of Investigational Device

The PneumRx, Inc. Elevair™ Endobronchial Coil System is designed to compress the areas of lung parenchyma most damaged by emphysema to allow more normal tissue to expand.^{3,4,5,6} The Coils restore lung tension to tether open and maintain airway patency; and also adjust lung compliance to shift preferential filling from diseased tissue to healthy tissue (Figure 1).

Figure 1: Diagram of the Lung Volume Reduction Procedure Using Coils



The Coil has been designed to treat the specific patho-physiologic challenges of the emphysema disease state. Emphysema is characterized by loss of the lung's natural elastic properties, which causes unsupported airways to collapse during exhalation. This, in turn, causes air trapping and increased lung volume, which makes breathing difficult. The Coil is intended to compress lung parenchyma, create tissue tension, and restore radial support, thereby tethering open the airways to reduce airway collapse and air trapping. The Coils also compress diseased tissue to prevent hyperinflation and shift preferential filling from diseased tissue to healthy tissue. Exhalation is facilitated, as re-tensioned lung tissue helps to maintain airway patency. By compressing the diseased tissue and reducing the negative effect of hyperinflation on breathing mechanics, the Coil also helps to regain diaphragm mobility, which also supports breathing function.

Because the Coil acts by a simple mechanical action of tissue tensioning and compression, the desired effects are achieved without collateral ventilation interfering with treatment outcome. The Coil is deployed using a minimally invasive approach through a bronchoscope and requires no incision. The Coil is designed to treat emphysema patients regardless of their disease distribution; it is suitable for patients with homogeneous and/or heterogeneous (either upper lobe predominant disease or lower lobe predominant) emphysema.

The PneumRx, Inc. Elevair™ Endobronchial Coil System has been shown to improve Quality of Life (QOL), exercise capacity, and pulmonary function in patients with severe emphysema.

2.3. Summary of Prior Clinical Experience with the Elevair™ Endobronchial Coil System

The Elevair™ Endobronchial Coil System received the CE mark on October 11, 2010 and has been commercially available throughout the EU since that date. ELEVAIR Coils have been implanted in over 6,000 patients in Europe and other markets where the ELEVAIR System is commercially available. Additionally, the ELEVAIR System has been studied in over 2,000 subjects across 8 clinical studies in the EU and North America, including a US pivotal randomized controlled study conducted to support FDA approval. A summary of the US pivotal study and other supporting clinical studies is available in the Summary of Safety and Effectiveness for the ELEVAIR System under PMA P170004.

3. STUDY OBJECTIVES, DESIGN AND ENDPOINTS

3.1. Study Objectives

1. To demonstrate, in the post-approval setting, the safety of the ELEVAIR System for the treatment of severe emphysema by assessing the rate of device- or procedure-related respiratory adverse events (RAE).
2. To demonstrate, in the post-approval setting, the effectiveness of the ELEVAIR System for the treatment of severe emphysema by assessing the impact on subject Quality of Life using the St. George's Respiratory Questionnaire (SGRQ).

3.2. Study Design

This PAS is a single-arm, prospective, multi-center Study. It is designed to assess the 12-month safety and effectiveness of this FDA approved product in a post-approval setting, and to support the continued assessment of the ELEVAIR Coil therapy for the treatment of severe emphysema in the United States. In addition, data will be collected to assess healthcare utilization of the ELEVAIR Coil therapy.

The PAS will enroll a minimum of 300 Subjects over a 2-year period. Up to 30 US sites are expected to participate in the Study. All enrolled Subjects who undergo the ELEVAIR Coil therapy procedure will be monitored for outcome data from baseline through 3 years following their first ELEVAIR Coil procedure.

The data collected in this Study will be entered into an electronic data capture system (EDC) using electronic case report forms (eCRFs). Subject data includes demographics, medical history, physical exam, vital signs, and additional standard-of-care pre-therapy evaluations (e.g., HRCT); therapy data; medication use; baseline and follow-up effectiveness measures including PFT, 6MWT, SGRQ, mMRC Dyspnea Scale performed per Standard-of-care at the individual institution; and device or procedure related adverse events (AEs) to include deaths, SAE and specific RAE of interest.

3.3. Safety and Effectiveness Endpoints

3.3.1. Primary Safety Endpoint:

Composite rate of device- or procedure-related serious RAE of interest through 12 months post-first implantation procedure. RAEs will be defined as AEs of the following types: Lower Respiratory Tract Infection/Pneumonia, COPD Exacerbation, Severe Hemoptysis, Pneumothorax, Respiratory failure.

3.3.2. Primary Effectiveness Endpoint:

Change in Quality of Life (QOL), as measured by SGRQ, from baseline to 12 months post-first implantation procedure.

3.3.3. Secondary Safety Endpoint:

Frequency of individual device- or procedure-related RAEs through 12 months post-first implantation procedure in subjects treated with ELEVAIR System.

3.3.4. Secondary Effectiveness Endpoints:

1. Changes in pulmonary function (including FEV₁, RV, RV/TLC) and exercise capacity (6MWT) from baseline to 12 months post-first implantation procedure.
2. Responder rates based on MCID for SGRQ, selected pulmonary function and exercise capacity parameters.
3. Healthcare utilization during therapy and hospitalization throughout the Study.

4. SITE AND SUBJECT SELECTION

4.1. Site Selection

Investigators will be physicians who are skilled in the use of therapeutic bronchoscopes, who have completed required training by a PneumRx representative, and are approved by PneumRx to perform the ELEVAIR Coil procedure (Approved Site). Approved sites will have facilities that support the practice of interventional bronchoscopy and have the appropriate infrastructure, equipment, and trained support personnel to support advanced interventional pulmonary procedures.

Up to 30 sites across the United States will be invited to participate. Sites will be selected based on their experience with ELEVAIR Coil technology, expertise in interventional bronchoscopy and operational and multidisciplinary resource availability.

4.2. Subject Population

4.2.1. Inclusion Criteria:

Patients with the following characteristics will be candidates for the Study:

1. Emphysema patients who are appropriate for ELEVAIR Coil treatment based on the US FDA-approved IFU requirements and are scheduled for the ELEVAIR Coil therapy procedure.
2. Subject has read, understood, agrees to participate in the Study, and signed the Informed Consent Form (ICF).

4.2.2. Exclusion Criteria:

Patients with the following characteristics will not be considered candidates for the Study:

1. Subjects who are not appropriate for ELEVAIR Coil therapy based upon the US FDA-approved IFU requirements.
2. Subjects who have not signed the ICF.

4.3. Subject Withdrawal

Subjects are free to withdraw from the Study at any time and will be withdrawn if they inform their PI that they no longer wish to participate. Subjects who are lost to follow-up will be considered withdrawn from the Study. Withdrawal data will be recorded in the EDC system along with the relevant reason(s) for withdrawal. Data collected prior to the subject's withdrawal will remain part of the study record.

5. TREATMENT OF SUBJECTS

5.1. ELEVAIR Coil Therapy

The Elevair™ Endobronchial Coil System is a US FDA-approved implantable device indicated for bronchoscopic placement of ELEVAIR Coil therapy Coils in subjects with severe emphysema (homogeneous and/or heterogeneous) and severe hyperinflation to improve QOL, lung function, and exercise capacity. The ELEVAIR System uses a minimally invasive technique to introduce nitinol Coils into the lungs to compress damaged tissue and re-tension lung tissue and reduce dynamic airway collapse in the remaining undamaged lung tissue.

5.1.1. Pre-implantation Subject Care

Procedural planning may be performed in accordance with the IFU by using high-resolution computed tomography (CT) for assessment of emphysematous lung tissue to identify the lung lobes most appropriate for therapy (i.e., the most damaged lobe (upper or lower) in each lung).

The subject should undergo a prophylactic regimen of antibiotics and corticosteroids administered per IFU/physician recommendation.

5.1.2. Implantation Procedure

The implant is delivered through a standard 2.8mm Inner Diameter therapeutic bronchoscope. The Elevair™ Endobronchial Coil System is a two-part system that consists of:

- 1) Sterile implants
- 2) Sterile, disposable, single-use (single-subject) Delivery System consisting of a Cartridge, a Catheter, a Guidewire and Forceps.

Each Coil implantation procedure must be performed under fluoroscopy in accordance with the IFU. Use of general anesthesia or sedation is at the discretion of the bronchoscopist and anesthesiologist. A complete therapy includes two procedures: the first side (upper or lower lobe Coil implantation) followed by therapy on the contralateral side. Procedures must be staggered (contralateral procedure should be scheduled 1 to 3 months after first therapy), such that both lungs are not treated during a single procedure.

The therapy is considered complete after the contralateral procedure. The investigator can decide to limit the therapy to one side if there are contraindications preventing the therapy of the contralateral side.

Follow-up visits can be scheduled after the completion of the final implantation procedure.

5.1.3. Post-implantation Procedure Management

It is recommended that the prophylactic regimen of antibiotics and corticosteroids continue according to the IFU and standard-of-care per the IFU, a chest X-ray or still fluoroscopy image should be performed post-procedure to verify Coil placement and to ensure no pneumothorax is present. A second, confirmatory chest X-ray should be performed a minimum of 4 hours following the first chest X-ray.

The Subject will be counseled on expected side-effects of the Coil procedure, including the potential AEs listed in Section 7.1.6. The Subject will be instructed to contact the treating physician immediately should any of the potential AEs be experienced. It is particularly important that Subjects be instructed at discharge to contact their implanting physician if they experience symptoms that may be indicative of pneumonia or Coil Associated Opacity syndrome (CAO), to ensure that appropriate therapy is delivered.

Post-procedure Subject follow-up will be per individual institution SOC and shall have as many follow-up visits as deemed necessary. Study specific follow-up visits are recommended to be conducted at 6 and 12 months and then annually for up to 3 years after the date of the first procedure.

5.1.4. Duration of Therapy and Follow-up

All enrolled subjects who undergo the ELEVAIR Coil therapy will be monitored for outcome data from baseline through 3 years following post-initial ELEVAIR Coil treatment.

6. MEASUREMENTS AND EVALUATIONS

6.1. Time and Event Schedule

The eCRFs will be completed by the investigator (or an authorized member of the investigator's staff) at the participating site and entered into the EDC database per the event schedule described below.

6.1.1. Baseline Visit

The potential study Subjects will be evaluated to ensure they are appropriate candidates for use of the ELEVAIR Coil therapy. Eligibility to enroll in the Study is assessed as described in Section 4. Subjects are enrolled in the Study after signing the ICF. The enrollment information will be entered into the EDC system. In addition, demographic, medical history, physical exam, vital signs and additional standard-of-care pre-therapy evaluations (e.g., HRCT) will be collected at the baseline visit and entered appropriately into the eCRFs. Baseline effectiveness measures, including PFT, 6MWT, SGRQ, and mMRC Dyspnea Scale, will be collected per the Standard-of-care at the individual institution.

6.1.2. Procedure/Implant Visit

Enrolled subjects will undergo the ELEVAIR Coil therapy in accordance with and the approved IFU. Procedure visits will include 2 sessions: therapy procedure for the first lung, followed by therapy procedure for the contralateral lung, which should be scheduled 1 to 3 months following the initial procedure. Per the IFU, a chest X-ray or still fluoroscopy image should be done post-procedure to verify Coil placement and to ensure no pneumothorax is present. A second, confirmatory chest X-ray should be done a minimum of 4 hours following the first chest X-ray.

6.1.3. Follow-up Visits

Post-procedure Subject follow-up will be per individual institution standard-of-care and shall have as many follow-up visits as deemed necessary. Study specific follow-up visits are recommended to be conducted at 6 and 12 months and then annually for 3 years after the date of the first procedure. Only Study specific visits performed at the site shall be entered into eCRFs. All safety information, including occurrence of AEs, SAEs reported at visits conducted at other times by referring physicians and other primary care physicians, should be entered into the eCRFs.

Study specific follow-up visits will ideally occur at the facility where the ELEVAIR Coil procedure was performed, and when the Subject is in a clinically stable condition.



6.1.4. Subject completion or early withdrawal

The subject completes the Study 3 years after the initial implantation procedure or when they choose to withdraw from the Study, if earlier than 3 years post-procedure. In the event of a continuing AE related to the ELEVAIR Coil therapy, the subject will be asked to return for follow-up until the AE has resolved or is deemed to be continuing indefinitely.

6.1.5. Data Collection

The eCRFs will be completed by the investigator (or an authorized member of the investigator's staff) at the participating site and entered into the EDC database per the schedule outlined below.

Procedure / Assessment	Baseline	Therapy	Follow-up Visit (s)
Informed Consent	X		
Baseline Assessment ¹	X		
ELEVAIR Coil Procedure		X	
Medications	X	X	X
AEs		X	X
Effectiveness Measures ²	X		X

¹Includes demographics, medical history, physical exam, vital signs, and additional standard-of-care pre-therapy evaluations (e.g., HRCT).

²Measures include PFT, 6MWT, SGRQ, mMRC Dyspnea Scale performed per Standard-of-care at the individual institution.

Physicians will be provided a process for assigning a de-identified number to the Subject and will be asked to keep any Study paperwork in a secure private area. Electronic audits will be in place to help ensure that data entered is within reasonable limits. This also allows the site to be queried regarding inappropriate data. The Study will also be monitored by PneumRx, Inc. and/or their designees for the duration of the Study to ensure accurate collection of data and compliance.

Study Evaluations and Procedures

6.1.6. Informed Consent Process

All Subjects must sign an ICF approved by the relevant IRB to be enrolled in the Study.



The investigator or delegate will review the treatment plans with the subject, and the subject will have an opportunity ask questions about trial procedures, the required visit schedule, risks and benefits of the Study treatments, and alternative therapy options prior to signature. The Subject will receive a copy of the signed ICF to keep for their records.

Subjects will be informed of any revisions of the ICF and any revisions must be signed and kept in the subject Study file.

Acquisition of the informed consent or any revisions should be documented in the subject's medical record and the ICF signed and dated by the individual who conducted the informed consent discussion.

6.1.7. Demographics

The following demographic data will be obtained: date of birth, gender, race, ethnicity, weight, and height.

6.1.8. Medical History

Medical history, including existing comorbidities deemed clinically significant (e.g., respiratory, pulmonary, cardiovascular, renal, liver, cerebral vascular, peripheral vascular, and psychiatric conditions and diseases) will be collected by the investigator.

Diagnosis and medical history for emphysema will be recorded separately from medical history, and will include at minimum the number of years since the subject was diagnosed with emphysema, characteristics of the emphysema, treatment history, and history of hospitalization events due to emphysema.

6.1.9. Pre-Treatment Evaluations

In addition to collecting demographics and medical history, the following evaluations will be performed during the pre-treatment baseline visit in accordance with the institution's SOC:

- Physical Exam
- Vital signs to include Blood Pressure, Pulse Rate, Respiratory Rate, and oxygen saturation by pulse oximetry (SpO2)
- Spirometry
- Lung volume measurement
- mMRC Dyspnea Scale
- 6-Minute Walk Test
- St. George's Respiratory Questionnaire (SGRQ)

The following evaluations may be performed during the pre-treatment baseline visit in accordance with the institution's SOC.

- Resting Electrocardiogram (EKG)
- Echocardiogram

- Blood tests (which may include: Hemoglobin, Hematocrit, White Blood Cell (WBC), Platelet count, Prothrombin Time/International Normalized Ratio (PT/INR), Sodium, Potassium, Chloride, Glucose, Total Protein, Albumin, Blood Urea Nitrogen (BUN), and Creatinine)
- Pregnancy test for females of child-bearing potential prior to radiographic procedures
- Room air Arterial Blood Gases (ABG)
- Diffusing Capacity
- Chest X-ray
- Chest CT scan

6.1.10. Eligibility Review

Subjects considered by the treating physician to be eligible to receive the ELEVAIR System and who are scheduled for the ELEVAIR Coil procedure, and who have signed the ICF, will be eligible for the Study. The determination of study eligibility will be recorded on the relevant eCRF.

6.1.11. Enrollment Event

Upon enrollment, each Subject will be assigned a unique numeric subject identity code by the site.

6.1.12. Implant Procedure Record

Details on the ELEVAIR Coil procedures performed on study subjects will be recorded in the relevant eCRF. Procedure data collected and entered into the EDC system will include at minimum the following:

- Treatment date
- Duration of bronchoscopy procedure
- Duration of fluroscopy
- Duration of hospital stay
- Lung lobe and location treated
- Number and size of implanted Coils
- Procedural AEs (see Section 7)
- Device deficiencies

6.1.13. Prophylactic Medication Record

Prophylactic medication (e.g., antibiotics, anti-inflammatories, bronchodilators, corticosteroids) administered to the Subject in preparation for the ELEVAIR Coil procedure will be recorded in the appropriate eCRF. Documentation will include dosage and start/stop dates.

6.1.14. Observation and Recording of Adverse Events

Subjects will be required to report AEs. At each Study visit, staff will ask general, open-ended, non-directed questions to obtain information about AEs. If the subject is unable to attend a Study visit, AEs can be collected by telephone contact.

The investigator should obtain all the information required to complete the AE form. Where possible, a diagnosis, rather than a list of signs or symptoms, should be recorded. Any medical management of an event and the resolution of an event must be recorded in source documentation and on the appropriate eCRF using medical terminology according to sponsor instructions.

6.1.15. Coil Removal

Coil removal following implantation (defined as removal of a Coil after termination of the Coil treatment procedure) must be medically indicated and performed in accordance with the IFU when possible. Each occurrence of post-procedure Coil removal will be recorded as an AE in the appropriate eCRF.

6.1.16. Quality of Life

QOL instruments suitable for subjects being treated for emphysema (i.e., SGRQ and mMRC Dyspnea Scale) will be administered at Study visits specified in the schedule of events.

6.1.17. Imaging

Chest X-rays performed post-procedure in accordance with the ELEVAIR IFU and the institution's SOC will be documented in the appropriate eCRF.

6.1.18. Effectiveness Measures

The following effectiveness measures will be performed during the follow-up visit in accordance with the institution's SOC:

- Spirometry
- Lung volume measurements
- 6 Minute Walk Test
- St. George's Respiratory Questionnaire (SGRQ)
- Modified Medical Research Council mMRC dyspnea scale

7. ADVERSE EVENTS

7.1. Adverse Event Definitions

Adverse experience will be considered synonymous with the term AE and vice versa.

An adverse event (AE) is any untoward medical occurrence in a study subject. This may include symptom(s), illness, clinically significant abnormal laboratory value or change in value, or worsening in a subject during a clinical study.

It is the responsibility of the investigator to report when he/she becomes aware of an AE that has occurred. AE information will be collected throughout the Study. AEs will be recorded on the eCRF by the investigator or authorized designee. Event, date of onset, duration, serious/non-serious, anticipated/not anticipated, severity, relationship to the procedure/device, outcome, and action taken will be recorded. Additional information on specific events may be requested in the eCRFs.

7.1.1. Definitions of SAE/UADE

Serious Adverse Event (SAE)

In accordance with 21 CFR Parts 803 and 812, a SAE is defined as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in subject hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or permanent damage,
- results in a congenital anomaly/birth defect, or
- requires intervention to prevent permanent impairment or damage.

Medical and scientific judgment should be exercised in deciding whether medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

An anticipated SAE is any SAE, the nature or severity of which is identified in the ELEVAIR IFU. Any other device related SAE will be considered an unanticipated adverse device effect (UADE).

NOTE: A planned hospitalization for a pre-existing condition, or a procedure required by the clinical protocol, without a serious deterioration in health, is not considered to be a SAE.

Unanticipated Adverse Device Event (UADE)

In accordance with 21 CFR Part 812, an UADE is 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

risk assessment, the ICF as well as the protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.1.2. Recording Adverse Events

All device- and procedure-related AEs will be documented from the date of the initial ELEVAIR System procedure until the subject completes the Study or withdraws.

In this Study, subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questions. At any time during the Study, the subject may volunteer information that resembles an AE. Once it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE form. Any medical management of an event and the date of resolution of the event must be recorded in the source document and on the appropriate eCRF using medical terminology according to sponsor instructions.

For each AE, the following information will be recorded:

- AE term
- Serious/non-serious
- Severity
- Action taken
- Relationship to ELEVAIR System
- Relationship to the Implant Procedure
- Anticipated/Unanticipated
- Date of onset
- Date of resolution

An anticipated AE is any AE the nature or severity of which is identified in the ELEVAIR System IFU.

Any AE experienced by a subject will be followed until the AE has resolved to the investigator's or physician sub-investigator's satisfaction or is considered stable. If a problem still exists, then the investigator or physician sub-investigator at his/her discretion will ask the subject to come back to the clinic for further evaluation. Any SAEs should be managed as discussed in Section 7.1.4.

7.1.3. Device and Procedure Causality Assessment

The investigator or physician sub-investigator must indicate whether he/she believes the AE is unrelated, possibly related (reasonable possibility that the investigational drug/device caused the AE), probably related, or definitely related to the device.

7.1.4. Expedited Safety Reports

All SAEs (defined above) and suspected UADEs must be reported via EDC to the sponsor within 24 hours of learning of the event.



The investigator must promptly inform the IRB of all UADEs and SAEs as needed per IRB requirements. These events will be reported by the sponsor, as appropriate, to the regulatory authorities according to relevant jurisdictional medical device regulations. As the Coil System is a PMA-approved and commercially available device in the US, Medical Device Reporting requirements (21 CFR 803) are applicable to adverse incidents reported through this Study.

7.1.5.Periodic Safety Reporting

Periodic safety reports prepared by the sponsor will be distributed across all Study centers. The investigator will be responsible for informing the IRB.

7.1.6.Reported Adverse Events

AEs reported during clinical study and post-market vigilance (in the EU and OUS regions) are detailed in the Instructions for Use. AEs which may be observed with endobronchial devices, systems for placement of these devices, and related procedures (including diagnostics and bronchoscopy procedures) and use of the ELEVAIR System include, but are not limited to, the events shown below. These events may vary in frequency and severity.

- | | | |
|-----------------------------|--|---|
| • Allergic Reaction | • Emphysema,
Subcutaneous | • Pneumonia* |
| • Aspiration | • Hemoptysis, including
severe hemoptysis | • Pneumonitis |
| • Bleeding or
Hemorrhage | • Hoarseness | • Pneumothorax |
| • Bronchial Blood Clot | • Hypertension | • Procedure-Related
Complication (e.g.,
fever, spasm) |
| • Bronchial Ulceration | • Hypotension | • Pulmonary embolism |
| • Bronchospasm | • Infection | • Respiratory Distress |
| • Cardiac Arrhythmias | • Inflammation | • Respiratory Failure |
| • COPD Exacerbation | • Lung Abscess | • Respiratory Tract
Infection |
| • Cough | • Pain | • Sedation-Related
Complication (e.g.,
nausea, vomiting,
headache) |
| • Death | • Painful Respiration | • Sepsis |
| • Device Dislocation | • Pleural Effusion | • Tissue Reaction,
Localized (a.k.a. Coil
Associated Opacity*) |
| • Dyspnea | • Pleural Fistula | • Tissue Trauma,
Procedural (e.g.,
tissue perforation,
dissection) |

Note: Additional interventional procedures may be necessary if subjects experience some of these potential AE(s) following ELEVAIR Coil treatment.

* There have been reports of non-infectious localized tissue reaction, also termed CAO, in the area of implanted ELEVAIR Coils. This is believed to be an inflammatory reaction that presents with pneumonia-like symptoms, including chest or pleuritic pain/discomfort, increased dyspnea, fatigue, and/or haze or infiltrates on chest X-ray, and may be difficult to distinguish from pneumonia. Therefore, subjects should be instructed at discharge to contact their implanting physician if they experience symptoms that may be indicative of pneumonia or CAO.

8. STATISTICAL CONSIDERATIONS

8.1. Determination of Sample Size

The Study will enroll a minimum of 300 subjects. The sample size is estimated to provide adequate power to test the primary safety endpoint against the performance goal. The assumed Composite Rate is 44% based on the RENEW study and the performance goal is 55%. Using a one-sided 2.5% significance level, 300 subjects will provide greater than 90% power to demonstrate the Composite Rate is below the performance goal using an exact binomial test.

A sample size of 300 subjects will provide greater than 95% power to demonstrate that the primary effectiveness endpoint is less than or equal to a performance goal of -4 (e.g., improvement of SGRQ MCID or greater) using a single sample t-test of a mean change against the performance goal with a one-sided Type 1 error rate of 0.025. The assumed mean (SD) primary effectiveness endpoint is -8 (12) based on the RENEW study.

8.2. Statistical Analysis

The primary safety endpoint is the Composite Rate of device-or procedure- related serious RAEs. RAEs include events summarized in the following major categories: COPD Exacerbation, Pneumonia, Pneumothorax, Severe Hemoptysis, and Respiratory Failure. The primary effectiveness endpoint is QOL using the SGRQ. The primary safety and effectiveness endpoints will be analyzed using descriptive statistics with 95% confidence intervals in order to test the following hypotheses:

H_0 : Srate \geq 55%

H_a : Srate $<$ 55%

where Srate is the observed the 12-month Composite Rate. The null hypothesis will be rejected and the primary safety endpoint performance goal will be met if the upper bound of the one-sided 97.5% exact confidence interval is less than 55%.

H_0 : $\mu_E \geq -4$

H_a : $\mu_E < -4$

where μ_E is the observed mean change from baseline to 12 months in SGRQ. The null hypothesis will be rejected and the primary effectiveness endpoint performance goal will be met if the upper bound of the one-sided 97.5% confidence interval is less than -4.

Descriptive statistics and 95% confidence intervals will be used to summarize additional safety and effectiveness endpoints of interest including responder rates and change from baseline at each follow-up visit.

The incidence of and total number of adverse events will be summarized by MedDRA preferred term and system organ class, overall and separately by follow-up visit windows, relatedness to device/procedure and seriousness.

8.3. Data Management

Data from the Study will be collected via EDC. Clinical data will be sent in a secured validated format to PneumRx on an ongoing basis.

Data will be entered in the eCRFs at the Study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the eCRF system and according to the eCRF instructions. The eCRF instructions will also provide the study site with data entry instructions. Risk-based monitoring of investigational site(s) will be conducted. Data entered in the eCRF will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed, edited and Source Data Verification (SDV) performed as specified per the clinical monitoring plan, the investigator will be notified to sign the eCRF electronically as per the agreed upon project process, and data will be locked to prevent further editing. A copy of the eCRF will be archived at the study site.

Data verification and data validation checks will be performed by PneumRx Data Management utilizing electronic edit checks comprised of validated computer programs and manual data review. Any data discrepancies will be referred back to the investigator. After the database has been declared clean it will be locked, and editing in the database will only be allowed with the proper documentation.

After database lock, data will be extracted to SAS® (SAS Institute, Inc., Cary, NC, USA) for analysis as defined in the SAP.

AEs will be coded according to the version of MedDRA agreed upon by PneumRx.

9. LEGAL/ETHICS and ADMINISTRATIVE PROCEDURES

9.1. Good Clinical Practice/Regulatory Compliance

The procedures set out in the this Study protocol, pertaining the conduct, evaluation, and documentation of this Study, are designed to ensure that the sponsor and investigators abide with US Food and Drug Administration (FDA) regulations in accordance with 21 CFR, Parts 50, 56, and 812; applicable state and local regulations; and the standard operating procedures (SOPs) of PneumRx, Inc., and its designee(s).

Independent Institutional Review Boards (IRBs) will provide oversight per local requirements for each study site and review documents associated with the Study to determine that they comply with all federal, state, and local laws and that the risks to subjects are minimized and reasonable in relation to anticipated benefits per the United States (US) Code of Federal Regulations (CFR), Title 21, Part 56, Section 56.111(a).

It is the investigator's responsibility to ensure that adequate time and appropriate resources are available at the Study site prior to making a commitment to participate in this Study. The investigator should also be able to estimate or demonstrate the potential for recruiting the required number of suitable subjects within the agreed upon recruitment period. The investigator will maintain a list of appropriately qualified personnel to whom the investigator has delegated significant Study-related tasks.

9.2. Study Site and Investigator Qualification

This Study will be performed by qualified investigators at 30 sites in the US.

All participating Study sites will be reviewed by the Study sponsor or designee to verify that they are able to conduct the Study. Each participating institution must have an established IRB and clinical protocol review process that is compliant with 21 CFR, Parts 50, 56, and 812, ensuring the clinical protocol and informed consent form can be adequately evaluated and approved at the institutional level.

9.2.1. Investigator CV

The investigator will provide the sponsor or designee with his/her current curriculum vitae and any revisions/updates, as well as those of any sub-investigator or staff personnel with significant Study responsibilities.

9.2.2. Statement of investigator

The investigator will be required to sign and date a Statement of Investigator form provided by the sponsor for the original and each subsequent amendment of the protocol and will return the original signed document to the sponsor. A copy of the signed form will be given to the investigator for his/her files.

9.2.3. Financial disclosure

Financial disclosure statements will be completed for the investigator and all sub-investigators to disclose potential conflicts of interest (per 21 CFR Part 54). The investigator is responsible for ensuring completed and signed financial disclosure forms are submitted to the sponsor or designee. A copy of the form(s) will be given to the investigators for their files. Financial disclosure information will be collected by the sponsor before the start of the Study and should be kept updated as necessary throughout the duration of the Study.

9.2.4. Investigator Recruitment

Investigators will be physicians who are skilled in the use of therapeutic bronchoscopes, who have completed required training by a PneumRx representative, and are approved by PneumRx to perform the ELEVAIR Coil procedure (Approved Site). Approved sites will have facilities that support the practice of interventional bronchoscopy and have the appropriate infrastructure, equipment, and trained support personnel to support advanced interventional pulmonary procedures..

One physician at each site will agree to act as the principal investigator. Additional physicians at each site may also participate as sub-investigators.

9.2.5. Investigator Training

Physician-investigators who wish to participate in this Study agree to satisfactorily complete a training program conducted by PneumRx. Training includes proper patient selection, implant procedure as well as training on the protocol. Investigators will conduct the Study under all applicable regulatory requirements. All participating investigators and co-investigators will be asked to sign a sponsor-generated Investigator's Agreement (as provided in contract), as well as any required institution-specific Investigator's Agreement. All participating study investigators must provide recent certification of GCP training.

9.2.6. Responsibilities

9.2.6.1. Sponsor Responsibilities

The sponsor of this Study is PneumRx, Inc. of Santa Clara, CA, U.S. The sponsor is committed to:

- Protecting the rights, health, safety and welfare of study Subjects by the review of IRB approvals and verification of the Subject informed consent process.
- Informing the clinical investigator of any new information that may affect the health, safety or welfare of the Subjects, or which may influence their decision to continue participating in the Study.
- Periodically reviewing the data to ensure that the investigator is in compliance with the protocol and the investigator's agreement.
- Providing the investigator with the study protocol and access to the EDC system and Study eCRFs.
- Selection and approval of investigators to participate in this Study.

- Maintaining a system of study documentation associated with the Study and corresponding sites and investigators.
- Providing training on key elements of the protocol, including Subject inclusion/exclusion criteria, EDC system, and what constitutes follow up.
- Review eCRF's to ensure completeness and accuracy of study data. Sites will be asked to resolve discrepancies via the EDC system.
- Acting as a resource for questions after training for the duration of the Study.

9.2.6.2. Responsibilities of the Principal Investigator

The investigator will affirm by his/her signature on the Investigator's Agreement that he/she will fulfill his/her responsibilities relative to the Study. The investigator will be responsible for:

- Ensuring that all Subjects entering the Study conform to the Subject inclusion criteria and that no exclusion criteria apply.
- Obtaining IRB approval from the respective institution to perform the procedure, prior to enrolling any Subjects in the Study. The informed consent document to be used will also be submitted by the investigator to the IRB for approval prior to initiation of the investigator's participation in the Study. The investigator is also responsible for providing any other additional documentation relevant to the Study as required by the IRB for their complete review. Written assurance of IRB approval of the Study plan and the informed consent document must be provided to PneumRx, Inc. prior to initiation of the Study at the site.
- Obtaining written Informed Consent from each Subject prior to enrollment and verifying that the correct and approved IRB version is used. The signed ICF will be maintained in the Subject's medical record, and a copy of the signed ICF will become an integral part of each case report file retained by the investigator. A copy of the signed ICF shall be given to the Subject who signed the ICF.
- The investigator will review, correct as needed, and sign off on the accuracy and completeness of the data entered in the EDC system. Original laboratory reports, procedure notes, etc. are to be retained by the investigator, and the resulting data shall be entered onto the appropriate eCRFs.

9.2.6.3. Site qualifications

The Institution must have appropriately qualified investigators and clinical / administrative support staff in place to adequately conduct the Study in compliance with the relevant guidelines and regulations (see section 9.1) and to treat emphysema with the ELEVAIR System.

9.3. Institutional Review Board (IRB)

9.3.1. Institutional approval of the protocol

It is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or designee), relevant supporting information and all types of subject recruitment information to the IRB for review and approval prior to site initiation. A copy of the

written approval of the protocol and ICF must be received by the sponsor prior to recruitment of subjects at the site.

Prior to implementing changes in the Study, the sponsor and IRB must also approve any revised informed consent documents and amendments to the protocol with documentation of the approvals submitted to the sponsor or designee. The approval document should clearly state the Study reference, date of review, and actions taken.

The investigator will be responsible for keeping the IRB apprised of the progress of the Study, any changes to the protocol, deviations from the protocol and SAEs or UADEs.

9.3.2.IRB Membership Roster

The investigator must submit a complete and current roster of the IRB to the sponsor or designee. Some institutions, due to reasons of confidentiality, may not release their roster. In such instances, the institution's General Assurance Number, assigned by the Department of Health and Human Services, is an acceptable substitute.

9.4. Informed Consent – Ethical Compliance

It is the responsibility of the investigator or a trained delegate to obtain written Informed Consent from subjects prior to the conduct of any Study procedures. All consent documentation must be consistent with applicable regulations and Good Clinical Practice. Each subject or the subject's legally authorized representative is requested to sign the ICF after the subject has received and read the written information and received an explanation of the Study, including but not limited to: a description of the Study, expected duration, statement of the Subject's right to decline to participate or to withdraw from the Study at any time and for any reason without fear of retribution, potential risks and benefits, limits of confidentiality, and contact information of the research personnel. A copy of the informed consent documentation (Consent Form or Subject Information and Consent Form, as applicable) must be given to the subject or the subject's legally authorized representative.

Acquisition of the Informed Consent should be documented in the subject medical record, and the ICF should be signed and personally dated by the subject and the individual who conducted the informed consent discussion. Signed consent forms must remain in each subject's study file and must be available for verification by Study Monitors at any time.

Each Investigator will provide the sponsor with a copy of the IRB-approved consent forms and a copy of the IRB written approval, prior to initiation of subject enrollment at the site. Additionally, if the IRB required modification of the sample Subject Information and Consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

The sponsor reserves the right to delay initiation of the Study at a site where the ICFs do not meet the standards of applicable regulations and guidelines.

9.5. Subject Privacy and Confidentiality

The sponsor and investigator affirm and uphold the principle for the subject's right to protection against invasion of privacy. Throughout this Study, all data collected and analyzed by the sponsor or designee will be treated confidentially and identified by an identification number.

To verify compliance with the protocol, the sponsor will require the investigator to permit its designee access to the subject's primary medical record to review those portions that directly concern this Study (including but not limited to laboratory test results, radiology images, and hospital and outsubject records).

As part of required content of the informed consent, the Subject must be informed that his/her records will be reviewed by the sponsor, sponsor representative and/or a representative of the appropriate regulatory agency. The informed consent or related document will also state that subject privacy will be maintained pursuant to the Health Insurance Portability and Accountability Act (HIPAA) and 21 CFR 21.

Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the investigator will obtain such permission in writing from the subject before the subject is entered in the Study.

Data collected during this Study may be used to support the development, approval or marketing of the ELEVAIR Coil System. Collected data may be reviewed by the sponsor and/or its representatives, independent auditors who validate the data on behalf of the sponsor, third parties with whom the sponsor may develop, register or market the ELEVAIR Coil System, national or local regulatory authorities, and the IRB(s) which granted approval for this Study to proceed.

9.6. Study Monitoring

Monitoring of the Study will be detailed in the Study clinical monitoring plan and will be performed by qualified personnel from the sponsor or sponsor designee. At the monitoring visits, the progress of the Study will be discussed with the investigator or his/her representative. The ICFs will be reviewed for signatures and the eCRFs checked for completeness and accuracy. Subject source data must be available for review. The investigator and his/her staff are expected to cooperate with the study monitor and be available during at least a portion of the monitoring visit to review the eCRFs and any queries/resolutions, answer questions, and provide any missing information.

The study monitor will record the date of each visit together with a summary of the status and progress of the Study at that site. Proposed actions will be confirmed with the investigator in writing.

Telephone and electronic mail contact will be made with the investigator and Study staff as necessary during the data collection and report writing periods.

9.7. Modification of the Protocol

All amendments to the protocol must be documented in writing, reviewed and approved by the investigator and sponsor, and submitted to the IRB for approval/positive vote prior to initiation. If the protocol amendment substantially alters the Study design or potential risk to the subject, new written informed consent must be obtained from each subject for continued participation in the Study.

9.8. Suspension or Termination of Study

If conditions arise requiring further clarification before the decision can be reached to proceed with or terminate the Study, the Study will be suspended until the situation has been resolved.

The sponsor has the right to terminate this Study and remove all Study material from the site at any time. Examples of situations where this might occur include:

- It becomes apparent that subject enrollment is unsatisfactory with respect to quality and/or quantity or data recording is chronically inaccurate and/or incomplete.
- The incidence and/or severity of AEs in the Study indicate a potential health hazard caused by the Study therapy.

9.9. Departure from Protocol

No deviation may be made from the protocol except to protect the health and welfare of a study Subject. Further, changes to the Study protocol will be implemented only after an amendment has been agreed to in writing by the sponsor, and the protocol amendment is approved by the IRB(s).

Protocol deviations will be tracked according to the following categories:

- Major protocol deviations
- Minor protocol deviations

Major protocol deviations are defined as:

- Enrollment eligibility criteria deviations
- Informed consent process was not followed
- ELEVAIR Coil treatment performed by an individual who was not trained by a PneumRx-authorized trainer and/or program.

All other protocol deviations will be classified as minor protocol deviations.

9.10. Potential Risks to Subjects

There are limited risks to Subjects as a result of having their data collected for this Study. The study procedures and data being collected are part of routine subject follow-up or Standard of Care.

9.11. Potential Benefits to Subjects and Society

In the future, subjects may benefit from results that lead to a better understanding of the safety and effectiveness of the ELEVAIR Coil System in the broader context of other options for treating emphysema.

The healthcare system may benefit from a better overall understanding of effectiveness and costs of this procedure.

This Study may also help define new standards of care for treatment of emphysema.

9.12. Financial Considerations

9.12.1. Subject Compensation:

Subjects will not be compensated for their participation in the Study.

Subjects participating in the Study may be reimbursed for travel expenses incurred at the 6-month, 12-month, 2-year, and 3-year follow-up visits.

9.12.2. Physician Compensation:

Participating sites will be compensated a reasonable amount, calculated to cover the costs of physician and staff time to enter data and administer the Study. Compensation will be provided for timely and completed eCRFs.

9.13. Recording, Access to and Retention of Source Data

Investigators are required to prepare and maintain adequate source documentation which includes:

- Documents relative to the subject medical history that verify eligibility criteria
- Records covering subject participation in the Study including basic identification information, results of physical examinations and diagnostic tests, original laboratory results (initialed and dated by investigator), therapy, Study therapy administration, concurrent medication information, pathology reports, and visit/consult notes.

All key data must be recorded in the subject's source documents including the Informed Consent acquisition.

The investigator must permit authorized representatives of the sponsor, the regulatory authorities, the IRB, and auditors to inspect facilities and records relevant to the Study.

The monitor (auditors, IRB or regulatory inspectors) may check the eCRF entries against the source documents. The consent form will include a statement by which the subjects allow the above-named access to source data that substantiate information recorded in the eCRFs. These personnel, bound by professional secrecy, will not disclose any personal information or personal medical information.

As described in the US FDA regulation 21 CFR 812.140, investigator records, including eCRFs, source documents, consent forms, laboratory test results, device inventory records, should be retained by the investigator until at least two years after 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. These documents may be retained for a longer period, however, if required by the applicable regulatory requirements or if so stated by an agreement with the sponsor. The investigator must obtain written permission from the sponsor prior to destruction of any Study document.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of FDA in accordance with 21 CFR 812 or by other regulatory authorities in accordance with regulatory requirements.

9.14. Electronic Case Report Forms

The investigator is responsible for maintaining adequate and accurate source documents from which accurate information will be transcribed into eCRFs that have been designed to capture all observations and other data pertinent to the clinical investigation. eCRFs should be completed by the investigator or delegate as stated on the Delegation of Authority Log. Overwriting of information or use of liquid correcting fluid is not allowed in source documentation.

Once the study monitor has verified the contents of the completed eCRF against the source data, queries may be raised if the data are unclear or contradictory. The eCRFs must be reviewed and electronically signed and dated by the investigator as required by the clinical monitoring plan, once all data has been entered and all queries resolved.

9.15. Publications

All manuscripts, abstracts or other modes of presentation arising from the results of the Study must be reviewed and approved in writing by the sponsor, in advance of submission, and in accordance with the sponsor's U.S. Study Publication Policy. The review is intended to protect sponsor proprietary information existing either at the date of commencement of the Study or generated during the Study. No individual investigator or group of investigators may publish results from his/her site(s) until after publication of a primary manuscript describing the full Study population.

The detailed obligations regarding the publication of any data, material results or other information that is generated or created in relation to the Study shall be set out in the sponsor's U.S. Study Publication Policy.

In accordance with recommendations from the International Committee of Medical Journal Editors, the Study will be listed in a publicly accessible repository of clinical studies such as clinicaltrials.gov.

9.16. Audit/Inspections

To ensure compliance with relevant regulations, data generated by this Study must be available for inspection upon request by representatives of the FDA, the sponsor and its representatives, and the IRB for each Study site.

10. BIBLIOGRAPHY

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11. SUPPLEMENTS/APPENDICES

To be completed upon final release.