



BTG

Interventional  
Pulmonology

PneumRx

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

## **Attachment 5: RENEW Clinical Protocol**

The table of contents can be found on page 5 of 62 or [click here](#).

**CLINICAL TRIAL PROTOCOL COVER SHEET**

**Device:** PneumRx® RePneu® Coil System

**Study Number & Rev.:** CLN0009.p. Rev F

**Study Title:** *Lung Volume **Reduction** Coil Treatment in Patients **with** Emphysema (RENEW) Study*

**Study Design:** Multicenter, randomized, assessor-blinded controlled study of safety and effectiveness of the PneumRx, Inc. RePneu Coil System

**Sponsor Name:** PneumRx, Inc.

**Sponsor Address:** 530 Logue Avenue  
Mountain View, California 94043  
USA

**Study Coordination and Data Analysis:** PneumRx, Inc.

**Projected Initiation Date:** September 2012

**Projected Completion Date:** September 2018

**STATEMENT OF CONFIDENTIALITY**

The information contained herein is confidential information that is the sole and exclusive property of PneumRx, Inc. and may not be divulged to any person (except as required by law) without the prior written consent of PneumRx, Inc.

<b>Revision History</b>			
<b>Revision</b>	<b>CCO</b>	<b>Effective Date</b>	<b>Originator</b>
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E	2680	02 Jul 14	Kara Andersen Reiter
F	3058	23 Jun 15	Stephanie Buech

**STUDY ACKNOWLEDGMENT**

**Investigator's Statement:**

I have read and understand Protocol No. CLN0009.p.F, *Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study*, and agree to conduct the study as outlined herein.

\_\_\_\_\_  
Investigator's Name (please print)

\_\_\_\_\_  
Investigator's Title

\_\_\_\_\_  
Investigator's Signature

\_\_\_\_\_  
Date

**Sponsor Signature, Protocol Approval:**

This study protocol, Protocol No. CLN0009.p.F, *Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study*, has been reviewed and approved by PneumRx, Inc., in accordance with Company policy and procedures and the US FDA, as warranted, under IDE requirements per 21 CFR part 812.

For: PneumRx, Inc.  
530 Logue Avenue  
Mountain View, CA 94043  
USA

Brett Bannan  
Name (please print)

  
Signature

Sr. Director, Clinical Operations  
Position/Title

07 July 2015  
Date

**STATEMENT OF COMPLIANCE**

The Trial (entitled *Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study*) will be conducted in compliance with this Protocol, and with local, State, and Federal requirements, including FDA Good Clinical Practices, my overseeing IRB requirements, patient privacy requirements, and all applicable regulatory requirements.

Protocol Title: *Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study*

Version: CLN0009.p.F  
Revision Date: June 23, 2015

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Investigator's Name (please print)

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Investigator's Title

---

Investigator's Signature

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Date

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- A. Investigator Agreement
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### List of Abbreviations

6MWT	6 Minute Walk Test
ABG	Arterial Blood Gas
AE	Adverse Event
BD	Bronchodilator
BL	Baseline
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed tomography
CXR	Chest X-ray
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
DMC	Data Monitoring Committee / Data Safety Monitoring Board
EC	Ethics Committee
EKG	Electrocardiogram
EDC	Electronic Data Collection
FEV <sub>1</sub>	Forced Expiratory Volume (in one second)
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRCT	High Resolution Computed Tomography (CT Scan)
IC	Inspiratory Capacity
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent-to-Treat population
LRTI	Lower Respiratory Tract Infection
LVRC	Lung Volume Reduction Coil
LVRD	Lung Volume Reduction Device
LVRS	Lung Volume Reduction Surgery
mMRC	Modified Medical Research Council
O <sub>2</sub>	Oxygen
OUS	Outside United States
PaO <sub>2</sub>	Partial Arterial Blood Gases Oxygen
PaCO <sub>2</sub>	Partial Arterial Blood Gases Carbon Dioxide
PI	Principal Investigator
PP	Per-Protocol
QOL	Quality of Life
RV	Residual Volume
RV/TLC	Residual Volume / Total Lung Capacity
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SpO <sub>2</sub>	Oxygen Saturation by pulse oximetry
SGRQ	St. George's Respiratory Questionnaire
TLC	Total Lung Capacity
UADE	Unanticipated Adverse Device Effect

## 1 Protocol Synopsis

<b>Study Number and Title:</b>	CLN0009.p. E Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study
<b>Clinical Phase:</b>	Pivotal, Phase III
<b>Study Device</b>	PneumRx® RePneu Coil System
<b>Study Objectives:</b>	<p><b>Primary: 6MWT</b> The primary effectiveness variable will be the mean absolute change from baseline at 12 months in the 6 Minute Walk Test (6MWT), comparing LVRC and Control groups (overall type I error one-sided, <math>\alpha = 0.025</math>).</p> <p><b>Secondary:</b> The following secondary endpoints will be tested for their statistical significance:</p> <ul style="list-style-type: none"> <li>• SGRQ: mean absolute difference in SGRQ results comparing BL to 12 months, LVRC vs. Control</li> <li>• 6MWT: responder analysis, comparing BL to 12 months, LVRC vs. Control, responders defined as those with an improvement of <math>\geq 25</math> meters</li> <li>• FEV<sub>1</sub>: mean percent change in FEV<sub>1</sub> results measured using spirometry comparing BL to 12 months, LVRC vs. Control</li> </ul> <p><b>Other Efficacy Endpoints:</b> The following other efficacy endpoints will be tested for their statistical significance:</p> <ul style="list-style-type: none"> <li>• SGRQ: responder analysis, comparing BL to 12 months, LVRC vs. Control, responders defined as those with a <math>\geq 4</math> point improvement</li> <li>• RV: mean absolute difference in RV results measured using plethysmography comparing BL to 12 months, LVRC vs. Control</li> <li>• RV/TLC: mean absolute difference in RV/TLC results comparing BL to 12 months, LVRC vs. Control</li> </ul> <p><b>Safety Endpoint:</b> The safety analysis will tabulate the difference between the Treatment and Control Groups in the proportion of subjects who experience one or more Major Complication(s) within 12 months post-baseline (and within defined blocks of time post-BL).</p> <p>Other data to assess changes in variables of interest and measures will be collected during the study. Such are described in Section 3.3 of the study protocol.</p>

<p><b>Study Design:</b></p>	<p>This will be a prospective, multicenter, randomized, controlled study comparing outcomes between the LVRC and Control Groups. Subjects will be block randomized in an LVRC (Treatment) to Control ratio of 1:1. The randomization will be stratified by homogeneous versus heterogeneous emphysema, to support a balance of patients with differing heterogeneity in both the LVRC and Control Groups per FDA's request.</p>
<p><b>Study Population:</b></p>	<p>The study population will include all subjects who have met the inclusion/exclusion study criteria.</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> <li>1. Subject <math>\geq 35</math> years of age.</li> <li>2. CT scan indicates bilateral emphysema, as determined by the Core Radiology Lab using the criteria presented in the "CT Scoring Plan for Core Radiology Lab".</li> <li>3. Subject has post-bronchodilator FEV<sub>1</sub> <math>\leq 45\%</math> predicted.</li> <li>4. Subject has Total Lung Capacity <math>&gt; 100\%</math> predicted.</li> <li>5. Subject has residual volume (RV) <math>\geq 175\%</math> predicted.</li> <li>6. Subject has marked dyspnea scoring <math>\geq 2</math> on mMRC scale of 0-4.</li> <li>7. Subject has stopped smoking for at least 8 weeks prior to entering the study, as confirmed by a Cotinine test or other appropriate diagnostic test.</li> <li>8. Subject has read, understood and signed the Informed Consent form.</li> <li>9. Subject has completed a pulmonary rehabilitation program within 6 months prior to treatment and/or is regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred more than 6 months prior to baseline testing.</li> <li>10. Subject has received Pneumococcal and Influenza vaccinations consistent with local recommendations and/or policy.</li> </ol> <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> <li>1. Subject has severe homogeneous emphysema as determined by the Core Radiology Lab using the criteria presented in the "CT Scoring Plan for Core Radiology Lab."</li> <li>2. Subject has co-morbidities that may significantly reduce subject's ability to improve exercise capacity (e.g. severe arthritis, planned knee surgery) or baseline limitation on 6MWT is not due to dyspnea.</li> <li>3. Subject has a change in FEV<sub>1</sub> <math>&gt; 20\%</math> (or, for subjects with pre-bronchodilator FEV<sub>1</sub> below 1 L, a change of <math>&gt; 200</math> mL) post-bronchodilator unless investigator can confirm by other means that subject does not have asthma.</li> </ol>

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|  | <ol style="list-style-type: none"> <li>4. Subject has DLCO &lt;20% of predicted.</li> <li>5. Subject has severe gas exchange abnormalities as defined by:<br/>PaCO<sub>2</sub> &gt;55 mm Hg<br/>PaO<sub>2</sub> &lt;45 mm Hg on room air (High altitude criterion: PaO<sub>2</sub> &lt;30 mm Hg)</li> <li>6. Subject has a history of recurrent clinically significant respiratory infections, defined as 3 hospitalizations for respiratory infection during the year prior to enrollment.</li> <li>7. Subject has severe pulmonary hypertension defined by right ventricular systolic pressure &gt;50 mm Hg via right heart catheterization and/or echocardiogram.</li> <li>8. Subject has an inability to walk &gt;140 meters (150 yards) in 6 minutes.</li> <li>9. Subject has evidence of other severe disease (such as, but not limited to, lung cancer or renal failure), which in the judgment of the investigator may compromise survival of the subject for the duration of the study.</li> <li>10. Subject is pregnant or lactating, or plans to become pregnant within the study timeframe.</li> <li>11. Subject has an inability to tolerate bronchoscopy under moderate sedation or general anesthesia.</li> <li>12. Subject has clinically significant bronchiectasis.</li> <li>13. Subject has giant bullae &gt;1/3 lung volume.</li> <li>14. Subject has had previous LVR surgery, lung transplantation, lobectomy, LVR devices or other devices to treat COPD in either lung.</li> <li>15. Subject has been involved in pulmonary drug or device studies within 30 days prior to this study.</li> <li>16. Subject is taking &gt;20 mg prednisone (or equivalent dose of a similar steroid) daily.</li> <li>17. Subject requires high level chronic immunomodulatory therapy to treat a moderate to severe chronic inflammatory autoimmune disorder.</li> <li>18. Subject is on an antiplatelet agent (such as Plavix) or anticoagulant therapy (such as heparin or Coumadin) which cannot be stopped for seven (7) days prior to procedure.</li> <li>19. Subject has a sensitivity or allergy to nitinol (nickel-titanium) or its constituent metals.</li> <li>20. Subject has a known sensitivity to drugs required to perform bronchoscopy.</li> <li>21. Subject has been diagnosed with alpha-1 antitrypsin deficiency (AATD).</li> <li>22. Subject has any other disease, condition(s) or habit(s) that would interfere with completion of study and follow-up assessments, would increase risks of bronchoscopy or assessments, or in the judgment of the investigator would potentially interfere with compliance to this study or would adversely affect study outcomes.</li> </ol> |
|--|--|

<p><b>Study Treatment:</b></p>	<p>Subjects randomized to the LVRC (Treatment) Group will undergo two bronchoscopy sessions under general anesthesia or moderate sedation, at the discretion of the bronchoscopist. During the procedure, subjects will be treated with Coils according to the Instructions for Use. Subjects will receive prophylactic drugs before the procedure. Following LVRC placement (Visit 2), the subject will remain in the hospital under observation per standard hospital practice. Following hospital discharge, the subject will be contacted by phone one week after Visit 2 and will be seen at the study site at one month after the procedure. After the one month visit following Visit 2, the subject will be scheduled for the second procedure in the contralateral lung to take place approximately 4 months after Visit 2. Only a single lung will be treated during any bronchoscopy.</p> <p>Subjects randomized to the Control Group will receive all the same standard medical treatment as the LVRC Group, except they will not undergo any bronchoscopies for Coil placement during the pivotal IDE study, they will not receive prophylactic antibiotics or steroids before and after the LVRC procedure, they will not have chest x-rays in connection with LVRC placement and they will not have a CT scan at Visit 10. Control Group subjects will be seen and/or contacted by the Study Doctor or designee at the same frequency and intervals as the LVRC Group through Visit 10 to support similar levels of attention and care for both groups.</p>
<p><b>Study Procedures and Assessments:</b></p>	<p>The following assessments are prescribed in the protocol through the study period for the LVRC Group. The Control Group will be assessed similarly except the Control Subjects will not go through the bronchoscopy procedures for Coil placement, including prophylactic antibiotics and steroids and chest x-rays, and Control Subjects will exit the study after Visit 10 (12 months post Visit 2), whereas LVRC Group subjects will continue to be followed annually for safety and effectiveness at 2, 3, 4 and 5 years post-Visit 2.</p> <p>Visit 1: Baseline evaluation after informed consent is signed.</p> <p>Visit 2: LVRC Placement #1 Prescribe a prophylactic regimen of antibiotics and steroids before and after Coil placement. Recommendations including drug class, dose, frequency and duration to use are provided in the Study Operational Instructions. Subject to remain in the hospital for monitoring per standard hospital practice.</p> <p>Visit 3: 1 Week Follow-Up Phone Call/interview to assess overall status. Review medications and O<sub>2</sub> use and record AEs.</p> <p>Visit 4: 1 Month Follow-Up</p>



	<p>Perform focused physical exam including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds, post-bronchodilator spirometry and plethysmography, Measure Diffusing Capacity, Review medications and O<sub>2</sub> use, Administer St. George's Respiratory Questionnaire, Administer mMRC Dyspnea Scale, Perform the 6 Minute Walk Test, Record AEs since last follow-up.</p> <p>Visit 5: LVRC Placement #2 (4 Months Post-Visit 2) Prescribe a prophylactic regimen of antibiotics and steroids before and after treatment. Recommendations including drug class, dose, frequency and duration to use are provided in the Study Operational Instructions. Subject to remain in the hospital for observation and monitoring per standard hospital practice.</p> <p>Visit 6: 1 Week post Visit 5 Follow-Up Phone Call/interview to assess subject overall status. Review medications and O<sub>2</sub> use and record AEs.</p> <p>Visit 7: 1 month post Visit 5, and Visit 8, 9 months post Visit 2</p> <p>Perform focused physical exam including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds, post-bronchodilator spirometry and plethysmography, Measure Diffusing Capacity, Review medications and O<sub>2</sub> use, Administer St. George's Respiratory Questionnaire, Administer mMRC Dyspnea Scale, Perform the 6 Minute Walk Test, Record AEs since last follow-up.</p> <p>Visit 9: 10.5 months post Visit 2 Follow-Up Phone Call to assess subject status. Review medications and O<sub>2</sub> use and record AEs.</p> <p>Visit 10: 12 months post Visit 2 Perform focused physical exam including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds, post-bronchodilator spirometry and plethysmography, Measure Diffusing Capacity, Review medications and O<sub>2</sub> use, Administer St. George's Respiratory Questionnaire, Administer mMRC Dyspnea Scale, Perform the 6 Minute Walk Test, Record AEs since last follow-up. Chest CT scan (for LVRC Group only).</p> <p>Visit 11 (LVRC Group subjects only): 24 months post Visit 2 Perform focused physical exam including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds, post-bronchodilator spirometry and plethysmography, Measure Diffusing Capacity, Review medications and O<sub>2</sub> use, Administer St. George's Respiratory Questionnaire, Administer mMRC Dyspnea Scale, Perform the 6 Minute Walk Test, Record AEs since last follow-up.</p>
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	<p>Visit 12 (LVRC Group subjects only): 36 months post Visit 2                  Perform focused physical exam including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds, post-bronchodilator spirometry and plethysmography, Measure Diffusing Capacity, Review medications and O<sub>2</sub> use, Administer St. George’s Respiratory Questionnaire, Administer mMRC Dyspnea Scale, Perform the 6 Minute Walk Test, Record AEs since last follow-up.</p> <p>Visit 13 (LVRC Group subjects only): 48 months post Visit 2                  Perform focused physical exam including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds, post-bronchodilator spirometry and plethysmography, Measure Diffusing Capacity, Review medications and O<sub>2</sub> use, Administer St. George’s Respiratory Questionnaire, Administer mMRC Dyspnea Scale, Perform the 6 Minute Walk Test, Record AEs since last follow-up.</p> <p>Visit 14 (LVRC Group subjects only): 60 months post Visit 2                  Perform focused physical exam including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds, post-bronchodilator spirometry and plethysmography, Measure Diffusing Capacity, Review medications and O<sub>2</sub> use, Administer St. George’s Respiratory Questionnaire, Administer mMRC Dyspnea Scale, Perform the 6 Minute Walk Test, Record AEs since last follow-up.</p>
<p><b>Management of Adverse Events</b></p>	<p>AE information will be collected throughout the study. Adverse events will be recorded on the AE eCRF by the investigator or authorized designee. Event, date of onset, severity, duration, and relationship to the procedure/device will be recorded. All adverse events will be followed until they are adequately resolved or stabilized or for 1 month following study completion or termination, whichever comes first.</p>
<p><b>Statistical Analyses:</b></p>	<p>There will be up to 315 subjects enrolled at up to 30 sites, not including "roll-in" subjects. Only non-roll-in subjects will be included in the endpoint statistical analyses. Roll-in subject data will be reported separately.</p> <p>All tests of superiority will be one-sided at a 0.025 alpha level of superiority. Other statistical tests will be 2-sided at a 0.05 alpha level of significance unless otherwise stated.</p>
<p><b>Crossover of Control Subjects</b></p>	<p>Upon completing their 12-month visit and exiting the study, control subjects will be offered a crossover opportunity. An independent DMC will determine, based upon the safety data from the study, whether subjects may be allowed to enroll in a separate cross-over study. Subjects desiring Coil treatment will be provided informed consent and evaluated for eligibility. If subjects meet the inclusion and exclusion requirements of this study, they will undergo LVRC placement and be followed</p>

	and monitored per the study protocol. This post-pivotal crossover study will be prospectively managed under a separate protocol approved by FDA under IDE G110066.
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## 2 Introduction

### 2.1 Background

The objective of this study is to demonstrate the safety and effectiveness of the PneumRx RePneu Coil System (RePneu Coil) in a population of patients with emphysema.

Physician-investigators who wish to participate in this study understand that the study will be conducted under all applicable regulatory requirements for the country where the study is being conducted. All participating investigators and co-investigators will be asked to sign a Study Acknowledgment (refer to page 3 of this protocol), a Statement of Compliance (refer to page 4 of this protocol) and a sponsor-generated Investigator Agreement (Attachment A), as well as any required country-specific Investigator Agreement.

This study is being conducted according to Good Clinical Practice (GCP), in compliance with the principles enunciated in the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2008), the US FDA regulations in accordance with 21 CFR, Parts 50, 56, and 812, applicable local regulations, and PneumRx, Inc. and its designee(s) Clinical Standard Operating Procedures (SOPs). Participating study centers in the EU and Canada are also subject to the clinical study investigation laws and regulations of those communities and their local Ethics Committees, in addition to those of the US FDA for this IDE study.

### 2.2 Clinical Need

Emphysema is a chronic respiratory disease with an estimated prevalence of 1.8% (Halbert, 2006). 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 (O'Donnell, 2006). 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. 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.

The PneumRx RePneu Coil System is designed to compress the areas of lung parenchyma most damaged by emphysema. This compression reduces air flow to treated portions of the lung allowing enhanced airflow to healthier untreated portions of the lung (Figure 1). The compression also reduces the volume of the hyperinflated emphysematous lung, resulting in lung volume reduction with improved diaphragmatic efficiency. Additionally, by gathering up the loose parenchyma of the most severely damaged segments, the Coil restores elasticity and recoil to the whole lung, improving expiratory flow rates, lessening small airway collapse with air trapping, and reducing dynamic hyperinflation. Because the Coil acts by a simple mechanical action these effects are achieved immediately in the presence or absence of collateral ventilation. This device is deployed using a minimally invasive approach using a simple catheter-based delivery system through a fiber-optic bronchoscope and requires no incision.

### 2.3 Description of the RePneu Coil System

The RePneu Coil System (formerly called the PneumRx LVRD) is an implantable device, delivered through a fiber-optic bronchoscope, designed specifically to treat patients suffering from emphysema. The Coil System is a two part system that consists of 1) sterile Coils and 2) a sterile, disposable, single-use (single-patient) Delivery System consisting of a Guidewire, Catheter, Cartridge, and Forceps.

The Coil is composed of nitinol (nickel-titanium), a biocompatible super-elastic material. The self-recovering Coil is delivered into the airway in a straight configuration and recovers to a non-straight, pre-determined shape upon deployment. The Coil is intended to compress the most damaged parenchyma and tension the surrounding tissue, which increases elastic recoil, reduces hyperinflation and redirects air to healthier portions of the lung for more effective ventilation. Since this therapy targets local diseased regions of the lung, more than one Coil may be necessary to achieve adequate effect. In previous clinical trials, the majority of cases involved 10 Coils per treated lung, with good safety

and effectiveness results. The Coil will effectively reduce the volume of damaged parenchyma, even in the presence of collateral ventilation.

The Coil derives its recovery ability from the super-elastic properties of the nitinol wire. The Coils are available in four lengths to accommodate anticipated anatomical variations – the lengths are 100mm, 125mm, 150mm, and 175mm (Figure 2). The trailing proximal end of the Coil (most proximal 10mm) has a smaller diameter than the rest of the Coil to reduce rigidity, lessen pressure of the Coil on the airway wall, and facilitate recapture, if necessary. The distal and proximal ends of the Coil terminate with a smooth atraumatic ball.

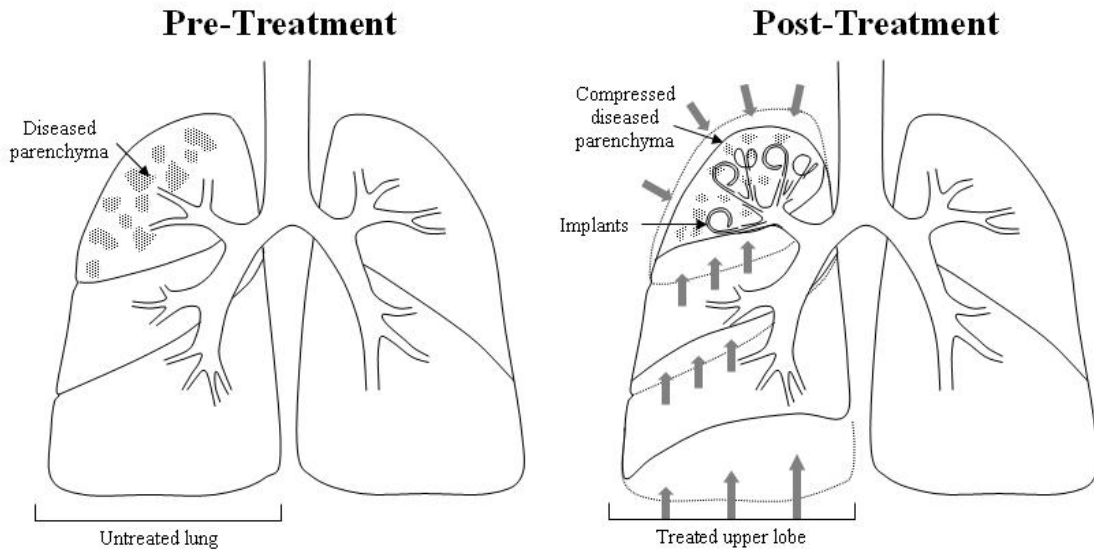
The Delivery System is used to safely deliver the Coils (Figure 3). The Guidewire serves as a specialized large and flexible guide for the Catheter, which enables the identification of suitable airways for treatment and supports the Catheter to help guide it to a delivery site. The Guidewire also facilitates the selection of the appropriate Coil length. The Catheter functions as a conduit to deliver the Coil from outside the patient to the targeted treatment area. It also can be used to reposition or remove the Coil. The Cartridge straightens the Coil, couples to the Catheter, and aids in the process of loading the Coil into the Catheter. The Forceps couples to the proximal end of the Coil and delivers it through the Catheter, enabling the clinician to control the placement and release of the device.

The Coil can be removed by reversing the deployment procedure. For additional information about repositioning or Coil removal, refer to Section 9.1 of the protocol and the “Coil Removal Instructions” section in the Instructions for Use.

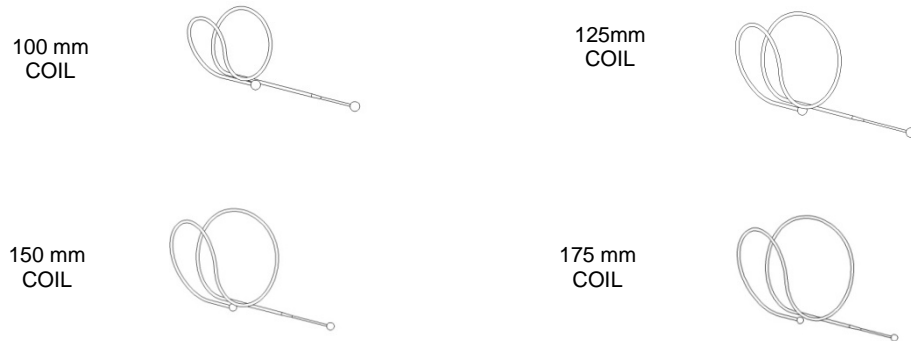
The procedure is designed to be performed using a therapeutic bronchoscope with a 2.8mm working channel (which accommodates the Delivery System) and fluoroscopy for visualization beyond the viewing range of the bronchoscope.

Each Coil is individually pouched in its own protective packaging shell and five Coils of the same size are packaged in a box. The Guidewire, Catheter, Cartridge, and Forceps are pouched together and packaged in a box. The LVRC Delivery System is sterilized by Ethylene Oxide (EO) and the Coils are sterilized by Electron Beam (E-Beam).

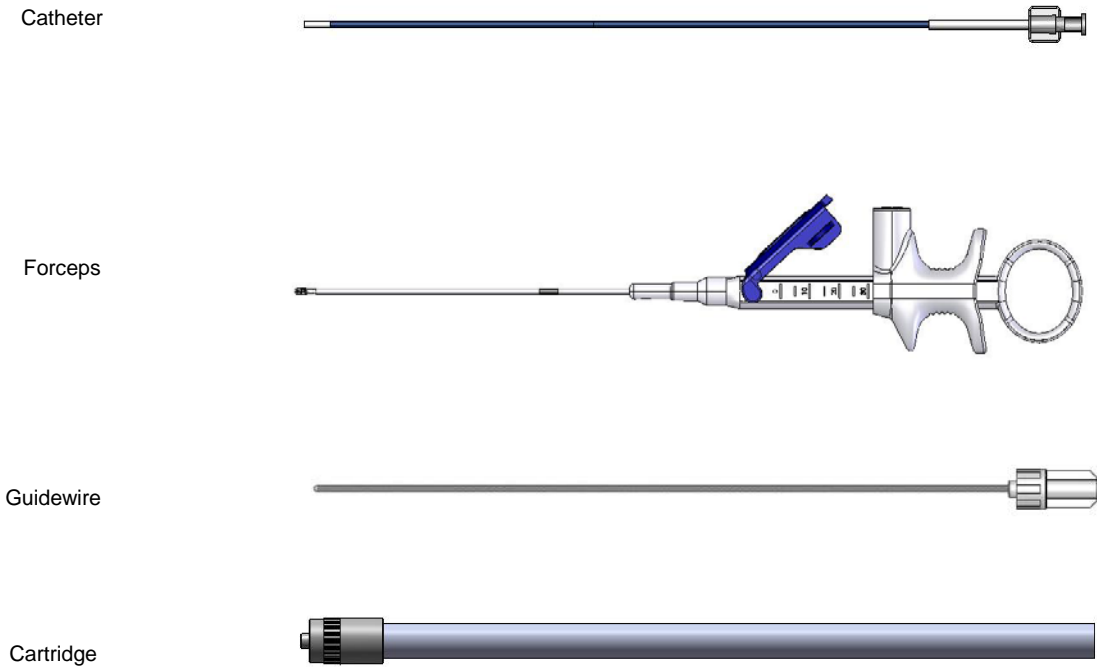
**Figure 1. Diagram of the Lung Volume Reduction Procedure Using Coils**



**Figure 2. Shapes and Sizes of Coils**



**Figure 3. Components of the Delivery System (Not drawn to scale)**



**2.4 Historical Data**

Prior to initiating this Study, PneumRx conducted and analyzed data from human clinical trials of the RePneu LVRC in Europe, performing over 250 LVRC procedures in 142 subjects. The data presented below are the accumulation of 3 OUS studies, each of which had inclusion/exclusion criteria virtually identical to those in the present study. The combined data from all OUS studies shows statistically significant improvements in pulmonary function, exercise capacity and quality of life at both 6-Months and 12-Months post treatment, as set forth below:

**Table 1. 6 Minute Walk Test (6MWT), Bilateral Subjects**

	<b>6 Months Post Baseline (180 Days)</b>	<b>p-value</b>	<b>12 Months Post Baseline (360 Days)</b>	<b>p-value</b>
<b>Change in Meters from Baseline</b>	+49.07 ± 8.26	<.0001	+61.94 ± 12.36	<.0001
<b>% Change from Baseline</b>	+19.53% ± 3.46%	<.0001	+22.58% ± 5.27%	0.0002

**Table 2. Residual Volume (RV), Bilateral Subjects**

	<b>6 Months Post Baseline (180 Days)</b>	<b>p-value</b>	<b>12 Months Post Baseline (360 Days)</b>	<b>p-value</b>
<b>Change in Liters from Baseline</b>	-0.67 ± 0.09	<.0001	-0.54 ± 0.11	<.0001
<b>% Change from Baseline</b>	-12.08% ± 1.51	<.0001	-9.97% ± 1.98%	<.0001

**Table 3. Forced Expiratory Volume in 1 Second (FEV<sub>1</sub>), Bilateral Subjects**

	<b>6 Months Post Baseline (180 Days)</b>	<b>p-value</b>	<b>12 Months Post Baseline (360 Days)</b>	<b>p-value</b>
<b>Change in Liters from Baseline</b>	+0.13 ± 0.02	<.0001	+0.10 ± 0.04	0.0178
<b>% Change from Baseline</b>	+17.30% ± 2.81%	<.0001	+12.37% ± 4.37%	0.0090

**Table 4. Saint George's Respiratory Questionnaire (SGRQ), Bilateral Subjects**

	<b>6 Months Post Baseline (180 Days)</b>	<b>p-value</b>	<b>12 Months Post Baseline (360 Days)</b>	<b>p-value</b>
<b>Change from Baseline (Points)</b>	-11.43 ± 1.41	<.0001	-12.29 ± 2.15	<.0001

**Table 5. Total Lung Capacity (TLC), Bilateral Subjects**

	<b>6 Months Post Baseline (180 Days)</b>	<b>p-value</b>	<b>12 Months Post Baseline (360 Days)</b>	<b>p-value</b>
<b>Change in Liters from Baseline</b>	-0.29 ± 0.07	<.0001	-0.24 ± 0.07	0.0028
<b>% Change from Baseline</b>	-3.33% ± 0.82%	0.0001	-2.81% ± 0.85%	0.0025

**Table 6. Residual Volume / Total Lung Capacity (RV/TLC), Bilateral Subjects**

	<b>6 Months Post Baseline (180 Days)</b>	<b>p-value</b>	<b>12 Months Post Baseline (360 Days)</b>	<b>p-value</b>
<b>Change from Baseline</b>	-11.43 ± 1.41	<.0001	-12.29 ± 2.15	<.0001
<b>% Change from Baseline</b>	-19.11% ± 2.56%	<.0001	-20.84% ± 3.95%	<.0001

With respect to safety, the Coil has been designed to be as safe as possible, which is supported by the fact that the Serious Adverse event profile of the device is comparable to that reported in the literature, specifically referenced in the control patient population in the EASE trial (Shah, 2011). Comparing the PneumRx OUS study results to the EASE sham control group, it appears that the risks associated with the LVRC System are largely attributable to the bronchoscopic procedure itself rather than to the device per se. Specifically, the rate of serious events of pneumothorax, hemoptysis, COPD exacerbation and



pneumonia are comparable between the LVRC treatment population and the EASE sham control group.

**Table 7. Comparison of 6-Month SAE Data Per Procedure - LVRC System vs. EASE Sham Control**

Reported SAE	PneumRx OUS studies (up to 6 Months)	EASE sham control (6 Months reported data)
Pneumothorax	4/246 procedures = 1.6%	1/107 procedures = 1%
Hemoptysis	2/246 procedures = 0.8%	0/107 procedures = 0%
COPD exacerbation/ pneumonia <sup>1</sup>	45/246 procedures = 18.3%	18/107 procedures = 17%

Based on these data, it appears that the LVRC device itself does not appreciably increase the risk of serious adverse events beyond the risk of undergoing a bronchoscopy procedure or simply having emphysema. Notably, a large proportion of the reported SAEs occur during the LVRC "treatment recovery period," i.e., within the first 30 days of treatment, and all resolved with standard medical treatment. Comparing these risks to the efficacy data to date, it appears that the benefit of the LVRC System far outweighs the risk.

The RePneu Coil is classified as a Class III device per FDA regulations. The device was approved for CE Mark (Class IIa [LVRC Delivery System] and IIb [LVR Coil] in accordance with the Medical Device Directive) in October 2011 and is used commercially in Europe.

### 3 Study Objectives

The primary objective of this study is to determine whether treatment with the RePneu Coil System results in improved exercise capacity and quality of life, as measured by improvements in the 6 Minute Walk Test (6MWT).

The 6MWT is well described in the literature as an important measure of integrated cardiopulmonary and musculoskeletal function (Criner, 2011a), and has been validated across several chronic pulmonary conditions including COPD (Wise, 2005; Holland, 2010). Administration of the test has been standardized (ATS Statement 2002).

From a feasibility standpoint, even advanced emphysema patients are able to complete a 6MWT, and to a greater degree than tests of maximum exercise capacity (Brown, 2008). In COPD, the 6MWT correlates with both maximum oxygen uptake (Ross, 2010) and health-related quality of life measures (Brown, 2008; Wise, 2005) and predicts survival (Palange, 2007). It has good reproducibility (Hernandes, 2011) and its learning curve can be managed via practice testing where appropriate (Hernandes, 2011; Criner, 2011a). The 6MWT has been used as an outcome measure in a broad range of clinical trials and has been shown to improve in COPD following both surgical and non-surgical lung volume reduction procedures, regardless of study design (Scirba, 2010; Criner, 2011b).

<sup>1</sup> While PneumRx reported on COPD exacerbations and pneumonias separately, the EASE trial reported a single data point for "COPD exacerbation or infection."

### 3.1 Primary Effectiveness Endpoint

The primary effectiveness variable will be the mean absolute change from baseline at 12 months in the 6 Minute Walk Test (6MWT), comparing LVRC and Control groups (overall type I error one-sided,  $\alpha = 0.025$ ).

### 3.2 Secondary Effectiveness Endpoints

The following secondary endpoints will be tested for their statistical significance:

- Six Minute Walk Test (6MWT): responder analysis, comparing BL to 12 months, LVRC vs. Control, responders defined as those with an improvement of  $\geq 25$  meters<sup>2</sup>
- Mean percent change in Forced Expiratory Volume in one second ( $FEV_1$ ), comparing BL to 12 months, LVRC vs. Control
- St. George's Respiratory Questionnaire (SGRQ): mean absolute difference in SGRQ results comparing BL to 12 months, LVRC vs. Control

The statistical tests used for the secondary analyses will be 2-sided at a 0.05 alpha level of significance.

Appropriate adjustments will be made to account for the impact on Type I error using methods described by Hochberg (1988).

### 3.3 Other Effectiveness Endpoints and Measures

Other effectiveness endpoints will be tested for their statistical significance:

- St. George's Respiratory Questionnaire (SGRQ): responder analysis comparing BL to 12 months, LVRC vs. Control, responders defined as those with an improvement of  $\geq 4$  points<sup>3</sup>
- Residual Volume (RV): mean absolute difference in RV results measured using plethysmography,<sup>4</sup> comparing BL to 12 months, LVRC vs. Control
- RV/Total Lung Capacity (RV/TLC), mean absolute difference in RV/TLC results measured using plethysmography, comparing BL to 12 months, LVRC vs. control

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<sup>2</sup> Holland, 2010. In this study, the MCID is determined based on within-subject changes over time. This is more relevant to an LVRC intervention than is an MCID based on between-subject differences at a given time point. Other recent publications support an MCID of 25 meters for 6MWT (Puhan, 2011).

<sup>3</sup> Schunemann, 2003.

<sup>4</sup> The impact of lung hyperinflation on patient health status is increasingly recognized in COPD. (O'Donnell, 2006; Singh, 2008). Indeed, "static lung volumes have better correlation with individually perceived symptoms and exercise capacity. Moreover, parameters of hyperinflation show better correlation with patient-centered health outcomes than does forced expiratory volume in one second ( $FEV_1$ )." (Tzani, 2011). As a result, clinicians are increasingly relying on lung volume measurements, such as RV, as evidence of meaningful improvements in COPD patients. (Celli, 2003; O'Donnell, 2004).

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The statistical tests used for the above secondary analyses will be 2-sided at a 0.05 alpha level of significance.

Descriptive statistics will be used to evaluate the following other measures of interest: Inspiratory Capacity (IC), mean change in FEV<sub>1</sub>, percentage change in 6MWT, percentage change in RV, reduced hospitalization, reduced O<sub>2</sub> usage, reduced drug usage for treatment of emphysema, reduced unanticipated doctor visits, reduced number of days missed from school/work, and reduced Emergency Room visits.

Primary endpoint analysis, secondary endpoints analyses and other effectiveness endpoints analyses will be conducted as described above and in the SAP. Other variables collected (listed above) will be analyzed using descriptive statistics; data range, mean, standard deviation, median and confidence intervals will be reported.

### 3.4 Safety Endpoint

The safety analysis will tabulate the difference between the LVRC and Control Groups in the proportion of subjects who experience one or more Major Complication(s) (See Section 3.5) within 12 months post-baseline. Major Complications will be determined/adjudicated by the Clinical Events Committee.

The proportion of subjects in each treatment group who experience one or more Major Complication(s) will be reported along with exact 95% confidence intervals. A statistical comparison between the proportions of subjects in each treatment group will be evaluated with the Fisher's Exact test.

Adverse Events will be categorized into clinically relevant groups (based on MedDRA codes). Complications occurring in the treatment arm will be further categorized as device-related, procedure-related, or neither, and by those occurring during procedure hospitalization and those occurring post-discharge. Summary tabulations will be presented by treatment arm.

Rehospitalization rates will be reported by treatment arm on a Per Subject basis and on a Per-Event basis. The Per-Subject rehospitalization rate is the proportion of subjects who were readmitted post-discharge. An individual subject will only be counted once in the Per-Subject no matter how many times they are readmitted during the follow-up period. The Per-Event rehospitalization rate is the proportion of hospital readmissions per treatment arm including multiple readmissions per individual subject. These data will be summarized by treatment arm.

### 3.5 Safety Analysis

All adverse events (AEs) reported will be listed, documenting course, outcome, severity, seriousness, and relationship to the procedure and to the study device. Verbatim terms reported on the electronic Case Report Forms (eCRFs)<sup>5</sup> will be mapped to standard Preferred Terms and System/Organ/Class using the MedDRA dictionary. The number and percent of Preferred Terms will be

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<sup>5</sup> NOTE: All Clinical trial data will be captured using an Electronic Data Capture system. For purposes of this protocol, the term CRF is used throughout.

summarized by the subject, the number of treatment procedures performed and the event. Further, the number and percent of subjects who withdrew or discontinued from the study due to an AE will be tabulated.

An AE that worsens in severity over time will be captured as multiple unique events, with the onset date of the new event corresponding to the date of worsening severity. For purposes of analysis, if the same AE is reported more than once for the same subject, that event will be counted only once for the most severe and most-related occurrence.

Each Major Complication type will also be analyzed separately. The proportion of subjects in each treatment group who experience each Major Complication will be reported along with exact 95% confidence intervals for each treatment arm as well as an exact 95% confidence interval for the difference in proportions between treatment groups. This type of analysis will allow the investigator (and the FDA) to weigh the significance of each type of Major Complication.

The standard definition of a Serious Adverse Event (SAE) per 21 CFR 812 and 803 will be followed. This definition of "serious" will apply to any untoward medical event that meets one or more of the criteria listed below (1-6).

1. results in death
2. is life-threatening
3. requires inpatient hospitalization or prolongation of existing hospitalization
4. results in persistent or significant disability/incapacity
5. is a congenital anomaly/birth defect, or
6. requires intervention to prevent permanent impairment or damage

In addition, there are potential AEs of interest known to occur following intervention with GOLD Stage III or IV COPD patients. The following are Major Complications (which will be adjudicated by the Clinical Events Committee based on AE/SAE documentation in the eCRFs).

Major Complications:

- Death;
- Pneumothorax that requires a chest drainage tube for more than 7 days (from time of chest drainage tube insertion to the time of chest drainage tube removal);
- Hemoptysis requiring blood transfusion(s), arterial embolization, or surgical/endoscopic procedure;
- COPD exacerbation that becomes life-threatening or disabling as a result of an increase in respiratory symptoms requiring in-patient hospitalization of >7 days with or without mechanical ventilation;
- Lower Respiratory Infections (including pneumonia) defined by new or increased clinical symptoms such as fever, chills, productive cough, chest pain, dyspnea and an infiltrate on plain chest x-ray and hospitalization for administration of intravenous antibiotics and/or steroids;
- Respiratory failure defined as a requirement for mechanical ventilatory support (whether via endotracheal tube or mask) for >24 hours; and

- An unanticipated bronchoscopy in order to remove one or more Coils due to a device-related AE. (Note: This definition does not include re-positioning, replacement or removal of the Coil(s) during the initial placement procedure.)

## 4 Study Design

### 4.1 Design Overview

This will be a prospective, multicenter, randomized, assessor-blinded controlled study comparing outcomes between the Treatment and Control Groups. Subjects will be block randomized (Section 6.2) in a Treatment (LVRC) to Control ratio of 1:1.

### 4.2 Number of Subjects

There will be up to 315 subjects enrolled at up to 30 sites, not including "roll-in" subjects (as described in Section 6.2.5). The null hypothesis and alternative hypothesis are presented below where the  $\Delta 6\text{MWT}$  equals the mean improvement in the absolute change between baseline and 12 months.

$H_0$ :  $\Delta 6\text{MWT}$  (Treatment) -  $\Delta 6\text{MWT}$  (Control)  $\leq 0$

$H_A$ :  $\Delta 6\text{MWT}$  (Treatment) -  $\Delta 6\text{MWT}$  (Control)  $> 0$

The estimates of the change due to LVRC treatment and standard deviation are based on data from the PneumRx pilot study, and the estimate of the change in the Control group is the reported change for the Control group of the Emphasys VENT study. The study is powered and designed to enroll at least 300 subjects to support hypothesis testing.

To allow for 5% subjects who may not be evaluable, we will therefore recruit a maximum of 315 subjects into the study specifically for statistical analysis. Missing data will be managed in accordance with the Statistical Analysis Plan, provided in Attachment B. Note that additional roll-in subjects are planned for this study, in addition to the study estimate of 315 subjects to be enrolled for hypothesis testing. Roll-in subject data will not be included in these analyses, but will be reported separately.

### 4.3 Control Group

Subjects in both the LVRC Treatment and Control Groups will be given Standard Medical Care for subjects with emphysema. Except for having no bronchoscopy or Coil placement, or prophylactic antibiotics or steroids or chest x-ray prior to and after Coil placement the Control Group will receive the same number of study visits and treatments through 12 months (Visit 10) as do subjects in the LVRC Group. At the end of Visit 10, Control Subjects will exit the study and may be evaluated for participation in a cross-over protocol, whereas LVRC group subjects will continue to have annual follow-up examinations for safety and effectiveness at 2, 3, 4 and 5 years post-Visit 2.

Standard Medical Care will be defined as proven optimal medical care for stable COPD as presented in the GOLD guidelines (Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, management, and

prevention of chronic obstructive pulmonary disease [Updated 2011]). Therapy for each subject in the Control Group is described in the following sub-sections.

#### 4.3.1 Pharmacological Treatment

As recommended by the GOLD guidelines, each subject will continue maintenance bronchodilator therapy, which will include an inhaled long-acting beta agonist, inhaled anticholinergic, or both. These drugs may also be combined with theophylline and/or inhaled corticosteroids at the discretion of the treating physician. The physician will be allowed to adjust the subject's pharmacological regimen as needed during the course of the study to deal with variations in the subject's condition (e.g., COPD exacerbations). However, the subject's medical regimen should be optimized at the pre-Treatment Visit, prior to completing the baseline Six Minute Walk Test and pulmonary function tests. From then on, changes to their medical regimen should be discouraged during the follow-up period. Changes in medications or dosages will be recorded in the eCRF.

All subjects enrolled in the study must have current influenza and pneumococcus vaccinations consistent with local recommendations and/or policy.

#### 4.3.2 Non-Pharmacological Treatment

Enrolled subjects will have completed a Pulmonary Rehabilitation program within 6 months prior to entering the Study and/or be regularly performing maintenance rehabilitation if the initial supervised therapy occurred more than 6 months prior to baseline testing.

#### 4.4 LVRC Group

Subjects in the LVRC Group will be given the same Standard Medical Care as described above for subjects in the Control Group. Each LVRC Group subject will undergo two bronchoscopies for Coil placement; separated by four months with a permitted window of time of -2 to +4 weeks for a second treatment. Subjects in the LVRC Group will continue to be monitored for 5 years, with annual follow-up examinations for safety and effectiveness at 2, 3, 4 and 5 years post-Visit 2.

#### 4.5 Population

The study population will include all subjects who have met the inclusion/exclusion study criteria defined in this protocol.

The Intent-to-Treat (ITT) population will include all subjects as randomized regardless of whether or not treatment was attempted.

The Per-Protocol (PP) study population will include those subjects who complete the study without noteworthy study protocol violations.

The safety population will include all ITT subjects who are randomized (for controls) or who enter the procedure room (for the LVRC treatment group assignment) regardless of whether or not device deployment was attempted.

Additional information regarding the study populations is provided in the Statistical Analysis Plan (SAP) (Attachment B).

#### 4.6 Demographic and Baseline Characteristics

Demographics and subject characteristics at baseline will be summarized to include age at enrollment, sex, and ethnic origin.

#### 4.7 Safety Evaluation

Safety will be evaluated by collection of AEs and SAEs from entry into the study (Visit 1) until Visit 10 (12 months Follow-up from Visit 2) for Control Group Subjects and until Visit 14 (60 months Follow-up from Visit 2) for LVRC Group Subjects or until the subject has completed or terminated from the study.

At each phone call or follow-up visit, subjects will be instructed to report to the investigator any adverse physical or mental changes they experienced since the previous visit/interview. All such AEs/SAEs reported by the subjects or observed by the investigators will be recorded.

Safety data from the various OUS studies that PneumRx has conducted to date have been collected and analyzed. A summary of the safety data is provided in Section 2.4, above.

#### 4.8 Brief Description of Study

The complete Study and its required visits, procedures, and assessments will be carefully discussed with the study subjects using an Institutional Review Board (IRB) or an Ethics Committee (EC) approved Informed Consent. The Informed Consent will contain all essential elements including a description of the research, expected duration and procedures, alternative treatments including lung volume reduction surgery, 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. The Informed Consent Form will include potential risks, discomforts or adverse effects, potential benefits, limits of confidentiality, incentive for participation, timely dissemination of any new information that becomes available and contact information of the research personnel. All patients will sign an Informed Consent prior to any procedure being performed to evaluate their eligibility for participation in the Study

Once the Informed Consent is signed, the subject will go through an initial screening evaluation. Subjects who have not completed a rehabilitation program as required by the inclusion criteria and are unable or unwilling to complete a rehabilitation program or unwilling to stop smoking will be excused from the study and recorded as screening failures. During the screening visit, demographic information, medical history, physical exam, smoking history and questionnaires will be collected to ensure the subject meets inclusion and exclusion criteria. If the subject does not meet the inclusion / exclusion criteria the subject will be excluded from the study.

If the subject has met the initial inclusion / exclusion criteria, the subject will continue the screening evaluation to ensure they meet the other inclusion / exclusion criteria. The investigator will perform other tests such as spirometry,

diffusing capacity, body plethysmography, CT scan, X-ray, 6 Minute Walk Test, echocardiogram, EKG, and blood tests.

Once the subject has completed the pre-treatment tests and meets all inclusion / exclusion criteria, the subject will be randomized to either the LVRC or the Control Group.

#### 4.8.1 LVRC Group

Subjects randomized to the LVRC Group will undergo bronchoscopy under general anesthesia or moderate sedation, at the discretion of the bronchoscopist. During the procedure, subjects will be treated with Coils according to the Instructions for Use. Subjects will receive prophylactic drugs as prescribed by the study doctor.

Following LVRC placement (Visit 2), the subject will remain in the hospital under observation per standard hospital practice. Following hospital discharge, the subject will be contacted by phone one week after Visit 2 and will be seen at the study site at one month after Visit 2. After the one month visit following Visit 2, the subject will be scheduled for the second LVRC placement in the contralateral lung to take place approximately 4 months after Visit 2. Only a single lung will be treated during any bronchoscopy.

After the subject's second LVRC placement procedure (Visit 5), the subject will remain in the hospital under observation per standard hospital practice. Following hospital discharge, the subject will be contacted by phone one week after Visit 5 and will be seen for the tests, procedures and follow-up described in Table 8. After the twelve month visit, LVRC Group subjects will be followed annually for safety and effectiveness out to a total of five years post-Visit 2 as part of post-market surveillance. Such subjects will remain under IDE G110066 and results reported under annual IDE reports, yet will transition out of the two-arm, controlled study (Visits 1-10) into a single arm part of the protocol (Visits 11-14). Note that Visits 1-10 of the study are designed for PMA application and approval purposes, and Visits 11-14 are designed for safety and efficacy monitoring for post-approval long term monitoring in accordance with the US IDE approval by FDA.

#### 4.8.2 Control Group

Subjects randomized to the Control Group will receive all the same standard medical treatment as the LVRC Group, except they will not undergo any bronchoscopies for Coil placement and they will not be given any prophylactic antibiotics or steroids or take chest x-rays associated with the LVRC procedures. Control Group subjects will exit the study after Visit 10, 12-months post-Visit 2).

Please refer to Table 9 for details regarding each Control Group Visit.



**Table 8. Visit Schedule LVRC Subjects**

Procedure / Assessment	Visit 1 Pre-Treatment (Screening) (may take place over several days)	Visit 2 LVRC Placement #1	Visit 3 1 Week post Visit 2* (Phone Call)	Visit 4 1 Month post Visit 2** (Office Visit)	Visit 5* LVRC Placement#2 (4 Month post Visit 2**)	Visit 6 1 Week post Visit 5* (Phone Call)	Visit 7 1 Month post Visit 5** (Office Visit)	Visit 8 9 Months post Visit 2** (Office Visit)	Visit 9 10.5 Mo post Visit 2** (Phone Call)	Visit 10 12 Months post Visit 2*** (Office Visit)	Visit 11 24 Months post Visit 2*** (Office Visit)	Visit 12 36 Months post Visit 2*** (Office Visit)	Visit 13 48 Months post Visit 2*** (Office Visit)	Visit 14 60 Months post Visit 2*** (Office Visit)
Informed Consent	X													
Inclusion/Exclusion	X													
Medical History/ Physical Exam	X													
Focused physical exam including vital Signs and SpO <sub>2</sub>	X	X		X	X		X	X		X	X	X	X	X
SGRQ	X			X			X	X		X	X	X	X	X
Spirometry	X			X			X	X		X	X	X	X	X
Lung Volumes & Diffusing capacity	X			X			X	X		X	X	X	X	X
Blood panel and ABG	X													
Cotinine or other appropriate diagnostic test	X													
EKG	X													
Echocardiogram*****	X													
Dyspnea Scale mMRC	X			X			X	X		X	X	X	X	X
6 Minute Walk Test	X			X			X	X		X	X	X	X	X
Concomitant Medication / O <sub>2</sub> Use	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing	X	X			X					X				
CT Scan	X									X				
Chest X-Ray	X	X****			X****									
Bronchoscopy / Coil Placement		X			X									
Take subject status*****			X	X	X	X	X	X	X	X	X	X	X	X
Exit Study														X

\* ±3 days

\*\* Minus 2 weeks to plus 4 weeks

\*\*\* ±4 weeks

\*\*\*\* For LVRC Group, chest x-ray #1 is done immediately post-procedure and chest x-ray #2 is done prior to discharge.

\*\*\*\*\* Includes a review of subject's medicines, O<sub>2</sub> use, and AE assessment

\*\*\*\*\* May use any echocardiogram taken within 6 months of Visit 1

**Table 9. Visit Schedule Control Subjects**

Procedure / Assessment	Visit 1 Pre-Treatment (Screening)	Visit 2 (Phone Call)	Visit 3 1 Week post Visit 2* (Phone Call)	Visit 4 1 Month post Visit 2** (Office Visit)	Visit 5* 4 Months post Visit 2** (Office Visit)	Visit 6 1 Week post Visit 5* (Phone Call)	Visit 7 1 Month post Visit 5** (Office Visit)	Visit 8 9 Months post Visit 2* (Office Visit)	Visit 9 10.5 Mo post Visit 2** (Phone Call)	Visit 10 12 Months post Visit 2*** (Office Visit)
Informed Consent	X									
Inclusion/Exclusion	X									
Medical History	X									
Vital Signs and/or Pulmonary assessment to include SpO <sub>2</sub>	X			X	X		X	X		X
SGRQ	X			X			X	X		X
Spirometry	X			X			X	X		X
Lung Volumes & Diffusing capacity	X			X			X	X		X
Blood panel and ABG	X									
Cotinine or other appropriate diagnostic test										
EKG	X									
Echocardiogram*****	X									
Dyspnea Scale mMRC	X			X			X	X		X
6 Minute Walk Test	X			X			X	X		X
Concomitant Medication/ O <sub>2</sub> Use	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing	X									
CT Scan	X									
Chest X-Ray	X									
Take subject status****			X	X	X	X	X	X	X	X
Exit Study										X

\* ± 3 days

\*\* Minus 2 weeks to plus 4 weeks

\*\*\* ± 4 weeks

\*\*\*\* Includes a review of subject's medicines, O<sub>2</sub> use, and AE assessment

\*\*\*\*\* May use any echocardiogram taken within 6 months of Visit 1

#### 4.9 Study Blind

The subject as well as the investigator performing the procedure will not be blind to the study. The investigator will however not assess the subjects for PFTs and 6MWT. The PFT and 6MWT assessor will be blinded to the treatment received by the subject.

#### 4.10 Statistical Analysis

Statistical analyses will be conducted in SAS version 9.3 or later. There will be up to 315 subjects planned for this study for hypothesis testing.

Demographic and baseline characteristics will be presented with summary statistics (sample size (N), mean, standard deviation (STD), median, minimum, and maximum) for continuous variables and frequency distributions for categorical variables. These characteristics will also be summarized by treatment group for the ITT population, safety population, and the PP population.

The primary effectiveness endpoint, change in 6MWT from Baseline (Pre-Treatment Visit) to the 12 month Follow-Up Visit, will be expressed as a mean absolute change in meters. The statistical testing will be based on an analysis of covariance (ANCOVA) with factors of treatment and investigational site and a covariate of baseline 6MWT and emphysema heterogeneity.

All tests of superiority will be one-sided at a 0.025 alpha level of superiority.

Other statistical tests will be 2-sided at a 0.05 level of significance unless otherwise stated.

The substitution of an analysis value for a missing 12 month value will be estimated by multiple imputation.

A similar procedure will be used for the analyses based on proportion of responders wherein the ANCOVA analysis is replaced with a logistic regression.

All adverse events occurring during the study for the safety population will be recorded and classified on the basis of MedDRA terminology. Descriptions of AEs will include the date of onset, the date the AE ended, resolved or stabilized, the severity of the AE, an assessment of the relationship to the device and/or procedure, and the outcome. All reported AEs will be summarized by treatment group

All information pertaining to AEs noted during the study will also be listed by subject. Details of the line listing by subject will include verbatim given by the Investigator, preferred term, system organ class, start date, stop date, severity, and device or procedure relatedness. The AE onset will also be shown relative (in number of days) to the day of the most recent procedure.

The proportion of subjects in each treatment group who experience one or more Major Complication(s) will be reported along with exact 95% confidence intervals. A statistical comparison between the proportion of subjects in each treatment group will be evaluated with the Fisher's Exact test.

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A detailed statistical analysis plan has been included in Attachment B.

## 5 Study Subject Recruitment

All study subjects will be patient volunteers who meet the inclusion / exclusion criteria including a willingness to read, understand, and sign the Informed Consent. Recruitment of study subjects will likely be from the pool of subjects attending clinics at the study site. Referrals may be sought from local physicians/general practitioners in the community who see and treat emphysema patients.

The duration of study recruitment period is expected to be between 12 and 18 months.

### 5.1 Inclusion Criteria

Subjects must meet **all** of the following inclusion criteria to be entered into the study:

1. Subject  $\geq 35$  years of age.
2. CT scan indicates bilateral emphysema, as determined by the Core Radiology Lab using the criteria presented in the "CT Scoring Plan for Core Radiology Lab".
3. Subject has post-bronchodilator  $FEV_1 \leq 45\%$  predicted.
4. Subject has Total Lung Capacity  $> 100\%$  predicted.
5. Subject has residual volume (RV)  $\geq 175\%$  predicted.
6. Subject has marked dyspnea scoring  $\geq 2$  on mMRC scale of 0-4.
7. Subject has stopped smoking for at least 8 weeks prior to entering the study, as confirmed by a Cotinine test or other appropriate diagnostic test.
8. Subject read, understood and signed the Informed Consent form.
9. Subject has completed a pulmonary rehabilitation program within 6 months prior to treatment and/or regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred more than 6 months prior to baseline testing.
10. Subject has received Pneumococcal and Influenza vaccinations consistent with local recommendations and/or policy.

### 5.2 Exclusion Criteria

Subjects will be excluded from the study if any of the following conditions apply:

1. Subject has severe homogeneous emphysema as determined by the Core Radiology Lab.
  2. Subject has co-morbidities that may significantly reduce subject's ability to improve exercise capacity (e.g. severe arthritis, planned knee surgery) or baseline limitation on 6MWT is not due to dyspnea.
  3. Subject has a change in  $FEV_1 > 20\%$  (or, for subjects with pre-bronchodilator  $FEV_1$  below 1 L, a change of  $> 200$  mL) post-bronchodilator unless investigator can confirm by other means that subject does not have asthma.
  4. Subject has DLCO  $< 20\%$  of predicted.
-

5. Subject has severe gas exchange abnormalities as defined by:
  - PaCO<sub>2</sub> >55 mm Hg
  - PaO<sub>2</sub> <45 mm Hg on room air (High altitude criterion: PaO<sub>2</sub> <30 mm Hg)
6. Subject has a history of recurrent clinically significant respiratory infections, defined as 3 hospitalizations for respiratory infection during the year prior to enrollment.
7. Subject has severe pulmonary hypertension defined by right ventricular systolic pressure >50 mm Hg via right heart catheterization and/or echocardiogram.
8. Subject has an inability to walk >140 meters (150 yards) in 6 minutes.
9. Subject has evidence of other severe disease (such as, but not limited to, lung cancer or renal failure), which in the judgment of the investigator may compromise survival of the subject for the duration of the study.
10. Subject is pregnant or lactating, or plans to become pregnant within the study timeframe.
11. Subject has an inability to tolerate bronchoscopy under moderate sedation or general anesthesia.
12. Subject has clinically significant bronchiectasis.
13. Subject has giant bullae >1/3 lung volume.
14. Subject has had previous LVR surgery, lung transplantation, lobectomy, LVR devices or other device to treat COPD in either lung.
15. Subject has been involved in pulmonary drug or device studies within 30 days prior to this study.
16. Subject is taking >20 mg prednisone (or equivalent dose of a similar steroid) daily.
17. Subject requires high level chronic immunomodulatory therapy to treat a moderate to severe chronic inflammatory autoimmune disorder.
18. Subject is on an antiplatelet (such as Plavix) or anticoagulant therapy (such as heparin or Coumadin) which cannot be stopped for seven (7) days prior to procedure.
19. Subject has a sensitivity or allergy to nitinol (nickel-titanium) or its constituent metals.
20. Subject has a known sensitivity to drugs required to perform bronchoscopy.
21. Subject has been diagnosed with alpha-1 antitrypsin deficiency (AATD).
22. Subject has any other disease, condition(s) or habit(s) that would interfere with completion of study and follow-up assessments, would increase risks of bronchoscopy or assessments, or in the judgment of the investigator would potentially interfere with compliance to this study or would adversely affect study outcomes.

## **6 Study Plan**

### **6.1 Investigator Training**

Investigators will be trained in the proper use and operation of the LVRC System before initiation of any treatment. Training will include hands-on use of the system and didactic sessions. In addition, on-site training will be provided to the investigator, co-investigators and other study support personnel before the first treatment at the study site. If necessary, additional training will be provided.

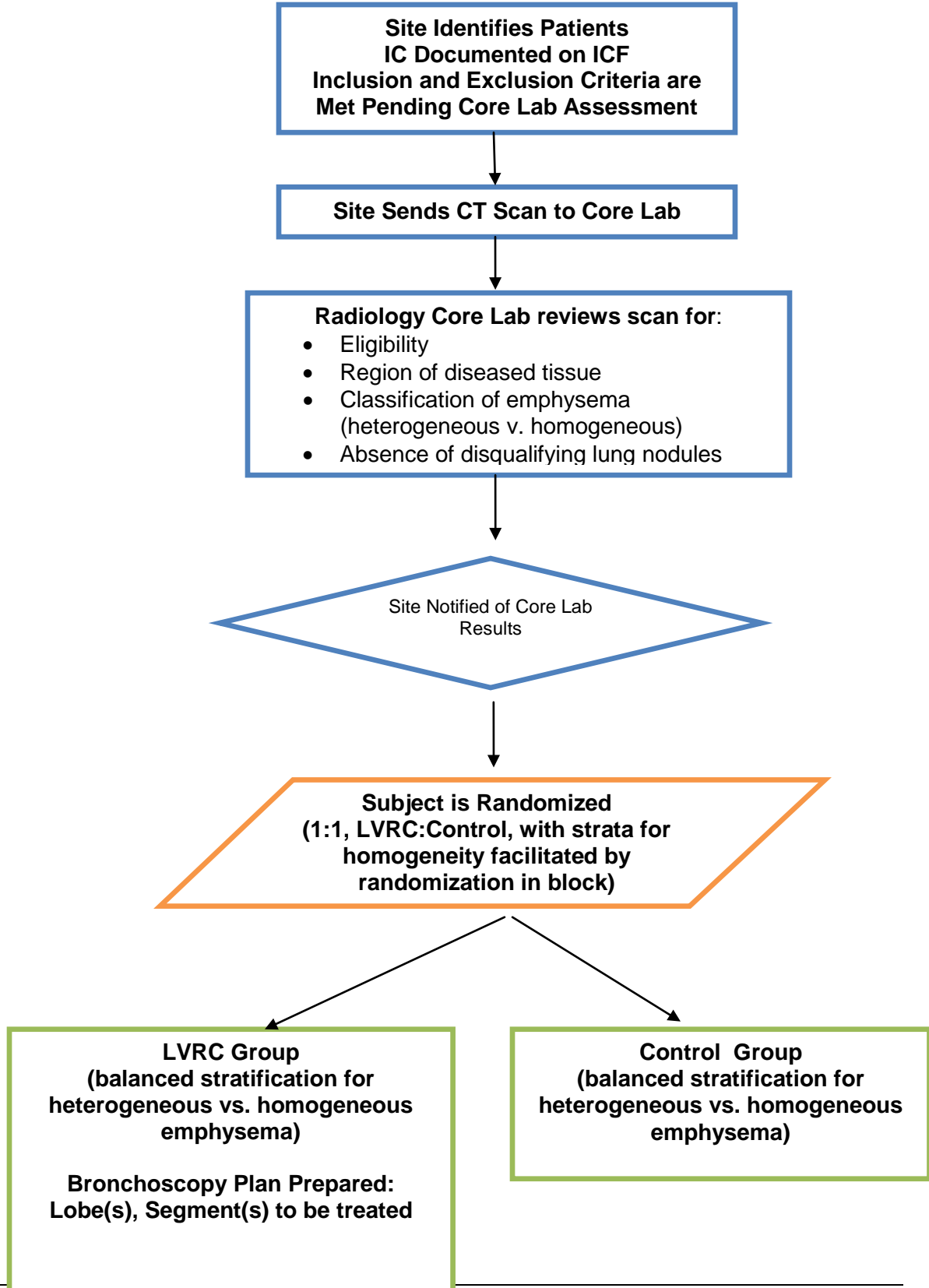
PneumRx personnel will be available to provide any additional technical support during treatment sessions until the investigator and his/her team feel comfortable with the use of the device.

Each site will be allowed up to 2 non-randomized roll-in subjects who will not be part of the study population intended for hypothesis testing. These subjects will be LVRC subjects meeting all study criteria and will be managed, treated and followed-up in the same way as subjects randomized to the LVRC Group.

### **6.2 Overview of Subject Randomization and Study Details**

Please see Figure 4 below for an overview of the randomization method and groups.

**Figure 4. Overview of Subject Randomization**



### 6.2.1 Informed Consent

- Provide information to the potential subject and review Informed Consent Form details. Obtain a signed Informed Consent from the subject as part of Pre-treatment/Baseline Screening (Visit 1).
- Provide the subject with a copy of the signed Informed Consent for their records.

### 6.2.2 Study Identification Number

- Assign the subject a unique study identification number (Study ID number) after signing of Informed Consent.

### 6.2.3 Pre-treatment/Screening Evaluations

**NOTE:** When possible, the same, blinded, authorized investigative site member should perform each subject's baseline and follow-up pulmonary function tests, including spirometry, plethysmography and the 6 Minute Walk Tests. These tests can be effort-dependent, and the ability of the authorized investigative site member to maximize subject effort may be a factor in test outcome. Study site personnel involved in assessment of subjects during pre-treatment, screening, inclusion/exclusion processes and study assessments will be blinded to the treatment allocation and trained to complete the assessments in accordance with ATS Guidelines and other standards as specified in the Study Operational Instructions.

Perform the following evaluations during the Pre-treatment Screening (Visit 1):

- Verify that the subject has completed a suitable pulmonary rehabilitation program within the last 6 months or be regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred more than 6 months prior to baseline testing.
- If the subject has not done so, refer the subject to a pulmonary rehabilitation program and make arrangements to see the subject at the conclusion of rehabilitation for reevaluation.
- Detailed medical history, to include the number of years the subject has been diagnosed with emphysema, other significant illnesses, current smoking status and history, medications, O<sub>2</sub> use, etc.
- Vital signs and pulmonary assessment, including SpO<sub>2</sub> and breath sounds.
- Resting Electrocardiogram (EKG).
- Echocardiogram, or review echocardiogram taken within the past 6 months.
- Blood panel to assess inclusion exclusion criteria and ability to undergo anesthesia (to 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.).
- Cotinine.
- Pregnancy test for females of child-bearing potential prior to radiographic procedures.



- Room air Arterial Blood Gasses (ABG).
- Pre- and Post-bronchodilator spirometry.
- Post-bronchodilator lung volume measurements by plethysmography.
- Diffusing Capacity (DLCO).
- Modified Medical Research Council mMRC dyspnea scale.
- 6 Minute Walk Test.
- St. George's Respiratory Questionnaire (SGRQ).
- Chest x-ray.
- CT Scan collected per guidelines provided by the Core (Radiology) Lab Protocol.

Note: Ensure notification from Core Radiology Lab approves Subject eligibility (study inclusion and exclusion criteria and Core Lab Protocol), defines heterogeneity for the subject, and provides input for bronchoscopy plan for lobe treatment with Coil. All other inclusion and exclusion criteria should be addressed prior to CT Scan and CT Scan assessment by the Core Lab.

#### 6.2.4 Randomization

- If the subject meets all entry criteria, the subject is assigned the next sequential Randomization Assignment, as provided by the sponsor. This assignment is computer generated and eCRFs will be identified by this number going forward. The subject and Medical Staff may be told of this assignment, with the exception of the endpoint variable assessor(s) (i.e. those working with the subject to collect data on the 6MWT, plethysmography measures, spirometry measures).
- Randomization assignment determines the next step.
- Subjects assigned to the Control Group will proceed directly to Step 6.3.
- Subjects assigned to the LVRC Treatment Group will proceed directly to Step 6.4.

#### 6.2.5 Subject Enrollment - Roll-in Phase

Each new investigational site will be allowed 2 roll-in patients prior to moving into randomization. All roll-in patients are to be implanted by the Principal Investigator. The Principal Investigator will be responsible for training all implanting co-investigators at their site. Roll-in is limited on a per site basis not per investigator. Once randomization of patients has started at a site, no further roll-in patients may be enrolled at that site. Roll-in patients will sign an Informed Consent Form and will be evaluated for full safety and effectiveness, identical to the LVRC Group subjects. Roll-in data, however, will be evaluated and reported on separately from the LVRC Group and Control Group subjects. After the 12-month visit, roll-in patients will be followed annually for safety and effectiveness out to a total of five years post-treatment as part of post-market surveillance, in the same fashion as that described for the study LVRC Group.

### 6.3 Control Group

#### 6.3.1 Control Visit 2 - Phone Call

- Contact Subject via telephone to assess overall status in lieu of LVRC placement procedure.
- Record AEs (See Section 7).
- Discuss maintenance rehabilitation activity plan.
- Encourage continuation in trial.

#### 6.3.2 Control Visit 3 - 1 Week Post Visit 2 Follow-Up Phone Call

- Contact Subject via telephone 1 week after Visit 2 to assess status.
- Review medications and O<sub>2</sub> use.
- Record AEs (See Section 7).
- Discuss maintenance rehabilitation activity plan.

#### 6.3.3 Control Visit 4 - 1 Month Post Visit 2 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform post-bronchodilator spirometry.
- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.
- Administer St. George's Respiratory Questionnaire.
- Administer mMRC Dyspnea Scale.
- Perform the 6 Minute Walk Test.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan.

#### 6.3.4 Control Visit 5 - 4 Months Post-Visit 2 Follow-Up - Control Group

- Record AEs (See Section 7).
- Discuss maintenance rehabilitation activity plan.

#### 6.3.5 Control Visit 6 - 1 Week Post Visit 5 Follow-Up Phone Call

- Contact Subject via telephone 1 week after Visit 5 to assess status.
- Review medications and O<sub>2</sub> use.
- Record AEs (See Section 7).
- Discuss maintenance rehabilitation activity plan.

### 6.3.6 Control Visit 7 - 1 Month Post Visit 5 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform post-bronchodilator spirometry.
- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.
- Administer St. George's Quality of Life Questionnaire.
- Administer mMRC Dyspnea Scale.
- Perform the 6 Minute Walk Test.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan.

### 6.3.7 Control Visit 8 - 9 Months Post Visit 2 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform post-bronchodilator spirometry.
- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.
- Administer St. George's Respiratory Questionnaire.
- Administer mMRC Dyspnea Scale.
- Perform the 6 Minute Walk Test.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan.

### 6.3.8 Control Visit 9 - 10.5 Months Post Visit 2 Follow-Up Phone Call

- Review medications and O<sub>2</sub> use.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan.

### 6.3.9 Control Visit 10 -12 Months Post Visit 2 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform post-bronchodilator spirometry.
- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.

- Administer St. George's Respiratory Questionnaire.
- Administer mMRC Dyspnea Scale.
- Perform the 6 Minute Walk Test.
- Record AEs since last follow-up (See Section 7).
- The subject can be exited from the study.

#### 6.3.10 Unscheduled Visits

It is expected that some subjects may present during the follow-up period with complaints (e.g., COPD exacerbation). These visits and the findings are to be recorded on the appropriate eCRFs. Notify the Sponsor should an unscheduled visit occur.

### 6.4 LVRC Group

#### 6.4.1 LVRC Visit 2 - LVRC Placement

- Perform pregnancy test for females of child bearing potential prior to radiographic procedures.
- Prepare subject for bronchoscopy per standard hospital practice.
- Prescribe a prophylactic regimen of antibiotics and steroids before and after treatment. Recommendations including drug class, dose, frequency and duration to use are provided in Study Operational Instructions.
- Administer general anesthesia or sedation to perform Coil placement. All local institutional policies relevant to general anesthesia and/or sedation should be observed.
- Insert the bronchoscope into the subject per the bronchoscope manufacturer's instructions.
- Navigate the bronchoscope and identify the airways leading to the diseased parenchyma via fluoroscopy.
- Insert the Catheter into the working channel of the bronchoscope and deliver the device per the RePneu LVRC Instructions for Use.
- Navigate the Catheter to the distal airways and verify the position via fluoroscopy.
- Deliver the Coil into the Catheter and deploy the Coil while monitoring the position via fluoroscopy in accordance with RePneu LVRC Instructions for Use.
- Only place the devices unilaterally. DO NOT place the devices in both the right and left lungs during one bronchoscopy session.
- Allow the subject to recover from anesthesia and monitor as per standard hospital practice.

#### 6.4.2 Post Bronchoscopy Monitoring and Evaluations - (LVRC Visit 2, continued)

- Subject will be monitored per standard hospital practice.
- Complete a chest x-ray post-procedure.
- Record AEs (See Section 7).

- Maintain subject in hospital for observation per standard hospital practice.
- Complete a second chest x-ray prior to discharge
- Discuss maintenance rehabilitation activity plan.

#### 6.4.3 LVRC Visit 3 - 1 Week Post Visit 2 Follow-Up Phone Call

- Contact Subject via telephone 1 week after Visit 2 to assess status.
- Review medications and O<sub>2</sub> use.
- Record AEs (See Section 6).
- Discuss maintenance rehabilitation activity plan.

#### 6.4.4 LVRC Visit 4 - 1 Month Post Visit 2 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform post-bronchodilator spirometry.
- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.
- Administer St. George's Respiratory Questionnaire.
- Administer mMRC Dyspnea Scale.
- Perform the 6 Minute Walk Test.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan.

#### 6.4.5 LVRC Visit 5 - 4 Months Post-Visit 2 LVRC Placement

- During Coil placement procedure #2, the investigator will treat the contra-lateral lung.
- Perform pregnancy test for females of child-bearing potential prior to radiographic procedures.
- Prescribe a prophylactic regimen of antibiotics and steroids before and after treatment. Recommendations including drug class, dose, frequency and duration to use are provided in Study Operational Instructions.
- Prepare subject for bronchoscopy per standard hospital practice.
- Administer general anesthesia or sedation to perform Coil placement. All local institutional policies relevant to general anesthesia and/or sedation should be observed.
- Insert the bronchoscope into the subject per manufacturer's instructions.
- Navigate the bronchoscope and identify the airways leading to the diseased parenchyma via fluoroscopy.
- Insert the Catheter into the working channel of the bronchoscope and deliver the device per the RePneu LVRC System Instructions for Use.

- Navigate the Catheter to the distal airways and verify the position via fluoroscopy.
- Deliver the Coil into the Catheter and deploy the Coil while monitoring the position via fluoroscopy.
- Only place the devices unilaterally. DO NOT place the devices in both the right and left lungs during one bronchoscopy session.
- Allow the subject to recover from anesthesia and monitor as per standard hospital practice.

#### 6.4.6 LVRC Visit 5, continued

- Subject will be monitored per standard hospital practice.
- Conduct chest x-ray.
- Record AEs (See Section 7).
- Maintain subject at the hospital for observation per standard hospital practice.
- Conduct another chest x-ray prior to discharge.
- Discuss maintenance rehabilitation activity plan.

#### 6.4.7 LVRC Visit 6 - 1 Week Post Visit 5 Phone Call

- Contact Subject via telephone 1 week after bronchoscopy session / LVRC procedure to assess status.
- Review medications and O<sub>2</sub> use.
- Record AEs (See Section 7).
- Discuss maintenance rehabilitation activity plan.

#### 6.4.8 LVRC Visit 7 - 1 Month Post Visit 5 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform post-bronchodilator spirometry.
- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.
- Administer St. George's Respiratory Questionnaire.
- Administer mMRC Dyspnea Scale.
- Perform the 6 Minute Walk Test.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan.

#### 6.4.9 LVRC Visit 8 - 9 Months Post Visit 2 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform post-bronchodilator spirometry.

- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.
- Administer St. George's Respiratory Questionnaire.
- Administer mMRC Dyspnea Scale.
- Perform the 6 Minute Walk Test.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan.

#### 6.4.10 LVRC Visit 9 - 10.5 Months Post Visit 2 Follow-Up Phone Call

- Review medications and O<sub>2</sub> use.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan.

#### 6.4.11 LVRC Visit 10 - 12 Months Post Visit 2 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform pregnancy test for females of child-bearing potential prior to radiographic procedures.
- Perform post-bronchodilator spirometry.
- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.
- Administer St. George's Respiratory Questionnaire.
- Administer mMRC Dyspnea Scale.
- Perform the 6 Minute Walk Test.
- Perform CT Scan per guidelines provided by the Core Radiology Lab.
- Record AEs since last follow-up (See Section 7).

#### 6.4.12 LVRC Visit 11 - 24 Months Post Visit 2 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform post-bronchodilator spirometry.
- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.
- Administer St. George's Respiratory Questionnaire.
- Administer mMRC Dyspnea Scale.

- Perform the 6 Minute Walk Test.
- Record AEs since last follow-up (See Section 7).

#### 6.4.13 LVRC Visit 12 - 36 Months Post Visit 2 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform post-bronchodilator spirometry.
- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.
- Administer St. George's Respiratory Questionnaire.
- Administer mMRC Dyspnea Scale.
- Perform the 6 Minute Walk Test.
- Record AEs since last follow-up (See Section 7).

#### 6.4.14 LVRC Visit 13 - 48 Months Post Visit 2 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform post-bronchodilator spirometry.
- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.
- Administer St. George's Respiratory Questionnaire.
- Administer mMRC Dyspnea Scale.
- Perform the 6 Minute Walk Test.
- Record AEs since last follow-up (See Section 7).

#### 6.4.15 LVRC Visit 14 - 60 Months Post Visit 2 Follow-Up

- Perform focused pulmonary assessment including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds.
- Perform post-bronchodilator spirometry.
- Perform post-bronchodilator lung volume measurements by plethysmography.
- Measure Diffusing Capacity.
- Review medications and O<sub>2</sub> use.
- Administer St. George's Respiratory Questionnaire.
- Administer mMRC Dyspnea Scale.
- Perform the 6 Minute Walk Test.
- Record AEs since last follow-up (See Section 7).
- The subject can be exited from the study.



#### 6.4.16 Unscheduled Visits

It is expected that some subjects may present during the follow-up period with complaints (e.g., COPD exacerbation). These visits and the findings should all be recorded on the appropriate eCRFs. Notify the Sponsor if an unscheduled visit occurs.

### 7 Management of Adverse Events (AEs) and Serious Adverse Events (SAEs)

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 adverse event has occurred. AE information will be collected throughout the study. Adverse events will be recorded on the eCRF by the investigator or authorized designee. Event, date of onset, severity, duration, and relationship to the procedure/device will be recorded. All adverse events will be followed until they are adequately resolved or stabilized, or for 1 month following study completion or termination, whichever comes first.

Safety data from the various OUS studies that PneumRx has conducted to date have been collected and analyzed. A summary of the safety data is provided in Section 2.4, above.

#### 7.1 Serious Adverse Events (SAE)

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

1. results in death,
2. is life-threatening,
3. requires inpatient hospitalization or prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacity,
5. is a congenital anomaly/birth defect, or
6. requires intervention to prevent permanent impairment or damage.

In addition, Major Complications, as defined below (which will be adjudicated by the Clinical Events Committee based on AE/SAE documentation in the eCRFs):

- Death;
- Pneumothorax that requires a chest drainage tube for more than 7 days (from time of chest drainage tube insertion to the time of chest drainage tube removal);
- Hemoptysis requiring an intervention (e.g., blood transfusion(s), arterial embolization, or surgical/endoscopic procedure);
- COPD exacerbation that becomes life-threatening or disabling as a result of an increase in respiratory symptoms requiring in-patient hospitalization of > 7 days with or without mechanical ventilation;
- Lower Respiratory Infections (including pneumonia) defined by new or increased clinical symptoms such as fever, chills, productive cough, chest

pain, dyspnea or an infiltrate on plain chest x-ray and hospitalization for administration of intravenous antibiotics and/or steroids;

- Respiratory failure defined as a requirement for mechanical ventilatory support (whether via endotracheal tube or mask) for >24 hours; and
- An unanticipated bronchoscopy in order to remove one or more Coils due to a device-related AE. (Note: This definition does not include re-positioning, replacement or removal of the Coil(s) during the procedure.)

**All SAEs must be reported to the PneumRx Clinical Affairs Group immediately (within one working day) using the Initial SAE eCRF.** To maintain subject confidentiality, the subject shall only be identified by the subject number used on the eCRFs. Further written reports through final resolution of the event, study completion or termination or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained shall be provided to PneumRx, Inc. Clinical Affairs via the eCRF.

## 7.2 Unanticipated Adverse Device Effect (UADE)

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

## 7.3 Severity of AEs and SAEs

The following general definitions for rating severity should be used for this study:

1. **Mild:** Awareness of signs or symptoms, but easily tolerated and transient; causing no loss of time from normal activities; symptoms would not require medication or a medical treatment; signs and symptoms are transient.
2. **Moderate:** Marked symptoms and discomfort severe enough to cause moderate interference with the subject's usual activities. Symptomatic treatment is possible.
3. **Severe:** Incapacitating with inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical intervention and/or treatment. Hospitalization may be required or prolonged.

## 7.4 Relationship of an Event

The relationship of an AE or SAE to the underlying disease or to the procedure will be attributed using the following definitions:

1. **Not Related:** There is no evidence that the event has a relationship to the procedure performed.

2. **Possibly Related:** The event has a timely relationship to the procedure performed. However, a potential alternative etiology may be responsible for the adverse event.
3. **Probably Related:** The event has a timely relationship to the study procedure performed and the causative relationship can clearly be established. No potential alternative etiology is apparent.

#### 7.5 Process for Assessment, Recording and Reporting of AEs

Subjects will be instructed at the beginning of the study to report to the investigator any adverse physical or mental changes they experience and they will be asked about adverse events at each visit, including those experienced at the baseline visit prior to, during, or immediately following treatment, as assigned per roll-in phase. All such adverse events reported by the subjects or observed by the investigators will be reported to the Sponsor.

As described in Section 7.0, if the event is deemed to be Serious, such events will be reported to the Sponsor via the completion of the Serious Adverse Event eCRF. The IRB/Ethics Committee(s) will be informed if the Serious or unexpected adverse event, in the opinion of the Investigator, or the DMC, is likely to affect the safety of the subjects or the conduct of the study.

An independent Data Monitoring Committee (DMC) will be established to provide independent benefit/risk oversight during the conduct of the study. The DMC or a subcommittee dedicated to review of Clinical Events will:

- Review and evaluate Serious Adverse Events on an “as needed” basis and **all** adverse events on a *quarterly basis or on an as needed basis, if the Sponsor requests an unscheduled review.*
- Recommend discontinuation of the study in the event of the occurrence of Serious or Unexpected Adverse Events that are determined by the DMC to pose a significant safety concern.

The Chairperson of the DMC will notify the Sponsor who will in turn notify the FDA or other regulatory bodies of safety outcome information from Committee meetings. This information will also be reported as part of required regulatory progress update reports.

#### 7.6 Data Monitoring Committee (DMC)

An independent DMC will be established prior to the enrollment of the first subject. The DMC will be comprised of at least four members, including but not limited to a pulmonary doctor with expertise in COPD, a statistician, a thoracic surgeon, and a Regulatory Affairs Advisor.

The DMC's role will be to review and evaluate safety events and monitor study safety data; and to recommend discontinuation of the study according to the Study Stopping Rules, in Section 8, below.

## **8 Administrative**

### **8.1 Premature Termination of Study**

The clinical study may be terminated at any time in the event of the occurrence of serious or unanticipated AEs that are determined by the Data Monitoring Committee (DMC) to pose a significant safety concern. In addition, the clinical study may be terminated at any time in the event that information indicates that the device will not be commercially viable, or in the event that the sponsor can no longer fund the study.

PneumRx will notify all investigators in the event of a premature withdrawal of IRB/Ethics Committee approval from any site. The investigators are responsible for informing their IRBs/Ethics Committees regarding premature trial termination. Subjects who experienced any SAEs that result in trial termination will be followed to resolution or stabilization.

#### **Study Stopping Rules:**

Treatment of new subjects will be suspended to allow time for analysis of the safety of the Coil and the LVRC procedure if any of the following are observed:

1. Two or more deaths, as deemed by the Investigator to be possibly or probably related to the Coil device or the LVRC procedure, that occur within 30 days following Coil treatment.
2. Any of the following during the immediate post-procedure period (3 days):
  - Hemoptysis >200 ml in 2 subjects at a single center.
  - Respiratory failure requiring mechanical ventilation for >24 hours in 2 subjects at a single center.
  - Pneumothorax requiring chest tube drainage for >7 days that occurs in 2 subjects at a single center, or greater than 4 of the first 20 subjects treated, regardless of center.

In the event that two or more deaths occur in the Control Group cohort during the term of the Study that are deemed by the Investigator to be possibly or probably related to the control treatment, an investigation into the deaths shall be initiated, but the trial will not be terminated.

PneumRx shall notify FDA within 24 hours of stopping the study based on the stopping rules.

### **8.2 Insurance Coverage**

If a device- or procedure-related incident occurs, the study Sponsor has purchased an insurance policy to cover damages within the legally prescribed scope.

## **9 Risks and Benefits**

### **9.1 Potential Risks to the Subject**

Participation in this clinical study may expose the subject to the following potential risks associated with the device and/or the procedure:

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- **Bronchoscopy**

With any bronchoscopic procedure, there is the possibility of exacerbation of emphysema symptoms, fever, bleeding, laryngospasm, bronchospasm, irregular heartbeat, shortness of breath, infection, transient infiltrates, pneumonia (Djukanovic, 1998), pneumothorax (Bleeker, 1992) or syncope. In the event that any of these were to occur, the subject will be treated for the condition. Some subjects may experience wheezing, coughing, or shortness of breath during the first few days following a bronchoscopy procedure.

- **Infection including Pneumonia**

There is a risk of developing pneumonia as a result of the LVRC being placed in the airway, excess mucus production, or impairment of the ability of the lung to clear mucus and/or microorganisms from the airways. There is also an increased risk of infection in patients with emphysema over those who do not have emphysema (Zalacain, 1999).

- **Hemoptysis**

Hemoptysis is defined as coughing up blood >5ml, which requires more than occasional blood-streaked sputum. There is also an increased risk of hemoptysis in patients with emphysema over those who do not have emphysema (Bidwell, 2005).

- **Moderate Sedation/Anesthesia**

There is a potential risk of developing side effects associated with the use of sedation and/or anesthesia. The risks of anesthesia depend on the agents and/or gases used. The risks of anesthesia include respiratory acidosis and possible respiratory failure, postoperative pain, nausea and vomiting, dizziness, drowsiness, shivering, liver toxicity, and/or cardiovascular events.

Trained professionals with extensive experience and expertise who routinely administer general anesthesia or local anesthesia with moderate sedation to subjects requiring multiple procedures will be responsible for the induction and associated monitoring required for this study. In addition, study subjects will be monitored throughout the recovery period as well after the recovery period, as indicated.

- **Coil Removal**

A Coil(s) may be removed up to 2 months following the treatment for medically indicated safety reasons (e.g., due to a persistent air leak or poor Coil location that may pose a safety risk). Other than during the LVRC treatment procedures (Study Visits 2 and 5), Coils should only be removed or repositioned for safety reasons, and Coils may not be replaced post-procedure. If the decision is made to remove a Coil(s), refer to the "Coil Removal Instructions" section in the Instructions for Use for details. The Investigator will notify the Sponsor of the need for removal prior to removing any Coil(s) and return the Coil(s) to PneumRx Quality Assurance for inspection.

In prior PneumRx OUS Feasibility Studies, numerous Coils have been bronchoscopically repositioned or removed during treatment procedures to

improve placement or to deploy a different size Coil. All attempts to remove or reposition Coils during the over 200 procedures performed in the OUS studies have been successful and easy to perform as determined by the Investigator. There have been no reported complications or adverse events associated with the bronchoscopic removal or repositioning of the Coils during the LVRC procedures.

Coil(s) can and may be repositioned, replaced or removed during the treatment procedure (Study Visits 2 and 5). Coils can be removed bronchoscopically up to 2 months after the LVRC procedure, but only if medically indicated. Such medically indicated post-procedure removal would be considered a Major Complication, and will be recorded in the eCRF AE page. Although Coils have been removed as late as 4 months post-procedure in animal studies, the need to remove Coils in human trials is not anticipated based on safety data from European clinical trials. Note that the Coil removal procedure has not been tested after time periods longer than 4 months post-procedure.

- **Pneumothorax**

Pneumothorax is defined as the presence of air within the pleural space, which may or may not require chest tube insertion. There is also an increased risk of pneumothorax in patients with emphysema over those who do not have emphysema (Guo, 2005).

- **Reaction**

Reaction to the study device, including allergic reaction, that could require emergency intervention to remove the study device.

The following are potential risks that are associated with the tests required as part of the study conduct:

- **Blood draws**

The risks of blood draws include temporary pain and discomfort from the needle stick, and/or tenderness, redness or bruising at the site, bleeding, fainting and lightheadedness. While rare, there is a possibility of infection or a local blood clot.

- **Pulmonary function tests**

Pulmonary function tests are low risk procedures. They may occasionally cause dizziness and/or slight chest discomfort due to muscle soreness, but these are self-limited. There is a risk of fainting during forced exhalation.

- **Chest X-rays, CT Scans and Fluoroscopy**

Study subjects will have radiation exposure as a result of the chest X-rays, CT scans and fluoroscopy required as part of the protocol.

The following risks are associated with the use of certain drugs that are required as part of the study conduct:

- **Medications required to perform bronchoscopy**

Drugs required for bronchoscopy could include lidocaine, atropine, narcotics, and one of the benzodiazepines. Although these drugs each have a number of potentially significant side effects, they are commonly used safely to perform bronchoscopy (Djukanovic, 1998).

Lidocaine toxicity has been described in association with bronchoscopy. At least one death has been reported in the literature as a result of lidocaine toxicity in a research Subject who underwent bronchoscopy (Clinical Trials Advisory Newsletter, 1996). Amounts of topical lidocaine given will be monitored and recorded and at all times will be less than 400 mg. Moderate sedation can be associated with respiratory suppression resulting in hypoxemia and the need for increased supplemental oxygen or the need for intubation with mechanical ventilation. In addition, moderate sedation can result in cardiovascular compromise with hypotension. To minimize these complications, sedation will be given in accordance with moderate sedation protocols applicable at the participating hospital and administered by trained professionals with experience in moderate sedation and ventilation.

Subjects with known sensitivity to drugs required to perform bronchoscopy are excluded from study participation. Should a subject experience a significant side effect for which there is concern, s/he will be managed as appropriate.

## 9.2 Potential Benefits to the Subject

It is possible that a study subject will not receive any benefits from treatment with the Coil.

Potential benefits of the Coil treatment that may be realized by study subjects include overall reduction in number or severity of symptoms related to emphysema and improved quality of life.

Another potential benefit to subjects participating in the study is the ability to learn more about their emphysema based on the assessments that will be performed throughout the course of the study.

For subjects with Medicare, Medicaid and/or third party insurance (private insurance) required to comply to the US Medicare Clinical Trial Policy rules for clinical trial coverage, most of the tests and procedures necessary for study completion will be billed to them. Tests and services required by the study that are not covered by the Medicare Clinical Trial Policy rules will be paid by PneumRx, Inc., the study sponsor.

The results of this study may help other emphysema subjects to gain access to a device that may improve their quality of life and general health.

## 10 Study Monitoring

PneumRx and its designee(s) for Data Management and Biostatistics will be responsible for coordinating and conducting the handling of clinical study data. Procedures will be described in detail in the Data Management Plan and the Statistical Analysis Plan (SAP).

Before acceptance of the clinical data, PneumRx and its assigned Clinical Monitor designee(s) will review the data entered on eCRFs (electronic case report forms) for completeness and adherence to the protocol based upon source documentation verification (SDV). Procedures to be followed and the data to be fully monitored to SDV will be described in detail in the Monitoring Plan. For example, all safety data and primary and secondary endpoint measures as defined by the protocol will be 100% monitored to SDV.

PneumRx and its designee(s) will qualify investigative study sites to review the adequacy of the subject population, facilities, equipment and resource needs of the study, and to familiarize the investigator with the study protocol.

At the time of enrollment, PneumRx and its designee(s) will meet with the investigator to ensure that subjects will be properly selected and enrolled, that the methods described in the study protocol are thoroughly understood and that the method(s) surrounding clinical data collection and capture are understood.

Assigned Clinical Monitors of PneumRx will visit the clinical site(s) periodically during the course of the study to perform SDV and perform device reconciliation. The Investigator and Institution must guarantee direct access to associated medical records by designated monitors and appropriate regulatory authorities.

The study may be subject to a quality assurance audit by either PneumRx or by appropriate regulatory authorities. It is important that the Investigator and the assigned authorized study personnel are available during monitoring visits and possible audits and that sufficient time is dedicated to the process.

## 11 Responsibilities of the Sponsor

The sponsor of this clinical trial is PneumRx, Inc. of Mountain View, CA, U.S.A. The sponsor is committed to:

- Conducting this clinical trial in compliance with Good Clinical Practice (GCP) Guidelines as required by United States Food and Drug Administration Code of Federal Regulations and the Declaration of Helsinki (2008), as well as with any local laws, regulations or requirements applicable to any particular study site.
- Protecting the rights, health, safety and welfare of study subjects; the sponsor is responsible for obtaining and reviewing copies of IRB/Research Ethics Board approvals and will verify that appropriate subject Informed Consent is obtained.



- Informing the clinical investigator of any new information about the study that may affect the health, safety or welfare of the subjects, or which may influence their decision to continue participating in the study.
- Providing the clinical investigator with the study protocol and the CRFs on which to document the study evaluation variables for each subject entered into the Study.
- Providing the data collection and management, statistical analysis and study report-writing resources necessary to complete reporting of the study results.
- Ensuring proper investigative site training and monitoring.
- Selecting qualified investigators with adequate facilities to conduct this clinical trial and establishing written Investigator Agreements.
- Maintaining copies of correspondence, records of shipment and disposition of devices, adverse device effects, records related to the signed investigator agreements, and other records related to the clinical study.
- Securing and maintaining US FDA IDE approval prior to treatment of any subjects.
- Provision of SAE reports to FDA as required per DMC determination of reportability and support of investigators as needed.

## 12 Responsibilities of the Principal Investigator

The Principal Investigator (PI) participating in this clinical trial must hold a current medical license as a physician in his/her country of employment for the full duration of the study. The investigator will affirm by his/her signature on the Investigator Agreement that he/she will fulfill his/her responsibilities relative to this clinical trial.

- **Subject Selection**

The investigator is responsible for ensuring that all subjects entering the study conform to the subject inclusion criteria and that no exclusion criteria apply.

- **IRB/Ethics Committee Approval**

The investigator is responsible for obtaining IRB/Ethics Committee approval from the institution at which he or she shall perform the procedure prior to consenting or enrolling any subjects in the study. The Informed Consent document to be used will also be submitted by the Investigator to the IRB/Ethics Committee for approval prior to initiation of the study. The investigator is also responsible for providing any other additional documentation relevant to the study as required by IRB/Ethics Committee for complete review of the study. Written assurance of IRB/Ethics Committee approval of the trial plan and the Informed Consent document must be provided to the sponsor prior to initiation of the study.

- **Informed Consent**

The investigator is responsible for fully discussing the nature of the study, the possible risks, and the alternative treatments (including lung volume reduction surgery) with prospective subjects prior to their enrollment in the study. The investigator is responsible for obtaining written Informed Consent from each subject prior to enrollment in the trial. The Informed Consent form to be used should be that version of the document approved by the IRB/Ethics Committee. The signed Informed Consent form will be maintained in the subject's medical record, and a copy of the signed Informed Consent form will become an integral part of each case report file retained by the Investigator. A copy of the signed Informed Consent form shall also be given to the subject who signed the form.

The approved Informed Consent Form specific to each responsible IRB/Ethics Committee will be used by the Investigator for this study.

- **Subject Evaluations and Data Reporting**

The investigator's designee is responsible for performing the subject evaluations as described in this trial plan. Regulations require that the study investigator maintain information in the study subject's medical records (i.e. source documentation) to corroborate data collected on the case report forms (CRFs).

All information generated by the subject evaluations is to be transferred from the source documentation and recorded using Electronic Data Collection (EDC) (or on CRFs provided by the sponsor). Paper CRFs should be completed in blue or black ink or should be typewritten. Any necessary corrections should be made by a single strikethrough in ink, initialed and dated by study site personnel. Correction fluid may not be used. The investigator will review, correct as needed, and sign off on the accuracy and completeness of the CRF data entered on the forms. Subject casebooks may be printed for review by authorized regulatory bodies. Original laboratory reports are to be retained by the Investigator, and the resulting data shall be entered onto the appropriate CRFs or electronically entered, as appropriate.

The sponsor will routinely monitor the subject data on an ongoing basis to support data quality and integrity. Source records will be reviewed as necessary to support assessment of data collected and reported using study CRFs.

The investigator is also responsible for submitting reports to PneumRx, Inc. and the reviewing IRB/Ethics Committee as specified in this protocol.

- **Protocol Deviations**

The study investigator should not deviate from this protocol unless the trial plan poses unacceptable risks to the health or welfare of the involved individual subject.

The investigator shall notify PneumRx Inc. and the reviewing IRB/Ethics Committee of any deviation from the protocol intended to protect the life or

physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than five working days after the emergency occurred. Except in such an emergency, prior approval of PneumRx Inc. is required for any deviation from the protocol. Approval from the IRB/Ethics Committee also is required if these changes or deviations are expected to affect the rights, safety or welfare of human subjects.

- **Record Retention**

The investigator shall maintain all original records as required by local regulation or law and at a minimum shall maintain documents until after FDA has approved the RePneu LVRC System.

- **Investigational Device Accountability**

The investigator must maintain accurate records of the receipt of all investigational devices shipped by the sponsor, including the date and lot numbers of devices received. In addition, accurate records must be kept regarding the date and quantities of investigational devices received, dispensed and returned. Information regarding the specific identification numbers for investigation devices used is to be recorded onto the appropriate device accountability log for each subject undergoing the treatment procedure throughout the course of the study. The investigator must assure that study supplies are dispensed only to subjects properly enrolled in the study and under the direct supervision of the investigator or co-investigators.

All used and unused investigational supplies, as well as all labeled containers, are to be returned to the sponsor as soon as practical upon request by the sponsor or designee or upon completion of the study. Investigational material accounting procedures must be completed before the study is considered terminated.

## 13 Good Clinical Practice & Regulatory Requirements

### **Informed Consent**

Written Informed Consent for the study must be obtained from all subjects who will participate in this clinical trial prior to their participation.

Individual institutions may revise the sponsor-provided Informed Consent form with information that would meaningfully add to the protection of the rights and welfare of subjects. Prior to submitting the revised Informed Consent form to the IRB/EC for review, the investigator is to receive authorization of the revisions by PneumRx Inc. Clinical Affairs staff. The IRB/EC at each clinical site will then review and approve the Informed Consent prior to study initiation. The investigator at each institution shall submit the approved Informed Consent to the sponsor who shall review it to ensure compliance with applicable regulations.

### **IRB/EC Approval**

This Study may not be initiated at any site until the IRB/EC has reviewed and approved the study protocol and the Informed Consent documents. Written committee approval is required prior to study initiation. The sponsor will review all documents and notify the site when screening and enrollment may begin.

**Subject Confidentiality**

Subject confidentiality shall be maintained at all times throughout the conduct of this trial, and all subject data shall be maintained secure against unauthorized access. The subject's records may be reviewed and/or photocopied by Regulatory Authorities and/or the study Sponsor (PneumRx Inc.) and its representatives. Copies (electronic or hard copy) of the subject's CT Scans will be collected as study data. In the event a subject's data are used for educational, presentation, and/or publication purposes, subject identity will be masked to protect the subject's confidentiality.

## 14 Citations and References

- American Thoracic Society. ATS Statement: Guidelines for the Six-Minute Walk Test. *Am J Respir Crit Care Med.* 2002. 166; 111-117.
- Bidwell JL, Pachner RW, Hemoptysis: Diagnosis and Management, *Am Fam Physician*, 2005 Oct 1;72(7) 1253-60.
- Bleeker ER, ER McFadden, et al. Editorial - Investigative bronchoscopy in subjects with asthma and other obstructive pulmonary diseases, whether and when. *Chest* 1992; 101(2): 297-298.
- Brown CD, et al. National Emphysema Treatment Trial Research Group. Exercise testing in severe emphysema: association with quality of life and lung function. *COPD.* 2008 Apr; 5(2): 117-24.
- Celli, B. et al; "Improvements in Resting Inspiratory Capacity and Hyperinflation with Tiotropium in COPD Patients with Increased Static Lung Volumes." *CHEST*; 124; 5; Nov. 2003; 1743-48.
- Clinical Trials Advisory Newsletter, Death of a healthy college student volunteer in a research study: special report. Naples, FL: Global Success Corporation, 1996.
- (a) Criner, G., 6-minute walk testing in COPD: is it reproducible? *Eur. Respir. J.* 2011 Aug; 38(2): 244-5.
- (b) Criner G, Cordova F, et al. The NETT: Part II - Lessons Learned about Lung Volume Reduction Surgery. *Am J. Respir Crit Care Med.* 2011 June 30 [Epub ahead of print], as doi:10.1164/rccm.201103-0455CI.
- Djukanovic R, R Dahl, et al. Safety of biopsies and bronchoalveolar lavage. *Eur Respir J* 1998; 11: Suppl 26: 39s-41s.
- Elashoff JD, Reedy TJ. Two-Stage Clinical Trial Stopping Rules. *Biometrics* 1984; 40: 791-795.
- GOLD guidelines (Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [Updated 2011]).
- Guo Y, Canmao XIE, et al. Factors related to recurrence of spontaneous pneumothorax. *Respirology.* 2005;10(3); 378-84.

Halbert, R, Natoli, J, et al. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006; 28(3): 523-532.

Hernandes, N.A. et al. Reproducibility of 6-minute walking test in patients with COPD. *Eur Respir J*. 2011 Aug; 382: 261-267.

Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2010; 91: 221-225.

Investigator's Brochure for the PneumRx RePneu Lung Volume Reduction Coil (RePneu LVRC) Trial for Treatment of Emphysema, CLN0009.p.

O'Donnell, DE et al, "Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in COPD/" *Eur. Respir. J* 2004; 23; 832-40.

O'Donnell, DE et al, "Effects of Fluticasone Propionate/Salmeterol on Lung Hyperinflation and Exercise Endurance in COPD;" *CHEST*; 130; 3; Sept. 2006; 647-56.

Palange P, Ward SA, et al. Recommendations on the use of exercise testing in clinical practice. ERS Task Force. *Eur Respir J*. 2007 Jan; 29(1):185-209.

Puhan MA, Chandra D, Mosenifar Z, Ries A, Make B, Hansel NN, Wise R, Scirba B for the National Emphysema Treatment Trial (NETT) Research Group, The minimal important difference of exercise tests in severe COPD, *Eur Respir J*. 2011; 27: 784-90.

*Respiratory Physiology, The Essentials*, JB West. Lippincott, Williams, Wilcons; Philadelphia, PA. 6th Edition, 2000.

Ross R, Jayasimha NM, et al. The six minute walk test accurately estimates mean peak oxygen uptake. *BMC Pulmonary Medicine*. 2010. 10:31.

Schunemann HJ, Griffith L, Jaeschke R, Goldstein R, Stubbing D, Guyatt GH. Evaluation of the minimal important difference for the feeling thermometer and the St. George's respiratory questionnaire in patients with chronic airflow obstruction. *J Clin Epidemiol* 2003;56:1170-1176.

Scirba, F.C. et al. VENT Study Research Group. A randomized study of endobronchial valves for advanced emphysema. *N Engl. J Med*. 2010 Sep 23; 363(13): 1233-44.

Shah, PL, Slebos, DJ et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial. *The Lancet* 2011; 378(9795) 997-1005.

Singh, D et al; "Superiority of 'triple' therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD;" Thorax; 2008;63; 592-8.

Site Coordinator Handbook for PneumRx RePneu Lung Volume Reduction Coil (RePneu LVRC) Trial for Treatment of Emphysema, CLN0009.p.

Tzani, P et al; "Effects of beclomethasone/formoterol fixed combination on lung hyperinflation and dyspnea in COPD patients;" Int'l J. of COPD; 2011;6; 503-09.

Wise RA and Brown, CD. Minimal Clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD. 2005 Mar;2(1):125-9.

World Medical Association Declaration of Helsinki, as most recently amended by the 59th Annual WMA General Assembly, Seoul, Korea, October 2008.

Zalacain R et al., Predisposing factors to bacterial colonization in chronic obstructive pulmonary disease. Eur. Respir J. 2009; 13:343-48.