



## CLINICAL TRIAL PROTOCOL COVER SHEET

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

**Study Number & Rev.:** CLN0016.p. Rev D

**Study Title:** LVRC IDE Crossover Study  
(Crossover from IDE Trial CLN0009,  
Lung Volume Reduction Coil Treatment  
in Patients with Emphysema (RENEW)  
Study, IDE G110066)

**Study Design:** Multicenter, single-arm, study 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:** December 2013

**Projected  
Completion Date:** September 2019

### 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.

Revision History			
Revision	DCO	Effective Date	Originator
A	2343	23 Sep 13	Kara Andersen Reiter
B	2373	09 Oct 13	Kara Andersen Reiter
C	3058	23 Jun 15	Stephanie Buech
D	3101	24 Aug 15	Stephanie Buech

**STUDY ACKNOWLEDGMENT**

**Investigator's Statement:**

I have read and understand Protocol No. CLN0016-FR.p.D, *LVRC IDE Crossover 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. CLN0016-FR.p.D, *LVRC IDE Crossover 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.  
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Brett Bannan  
\_\_\_\_\_  
Name (please print)

BB  
\_\_\_\_\_  
Signature

Sr. Director, clinical Operations  
\_\_\_\_\_  
Position/Title

24 AUG 2015  
\_\_\_\_\_  
Date

**STATEMENT OF COMPLIANCE**

The Trial (entitled *LVRC IDE Crossover 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: *LVRC IDE Crossover Study*

Version: CLN0016.p.D

Revision Date: 24 August 2015

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Investigator's Name (please print)

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Investigator's Title

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Investigator's Signature

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Date

## Table of Contents

<b>1</b>	<b>Protocol Synopsis .....</b>	<b>11</b>
<b>2</b>	<b>Introduction .....</b>	<b>16</b>
2.1	Background .....	16
2.2	Clinical Need .....	16
2.3	Description of the RePneu Coil System .....	17
2.4	Historical Data .....	19
<b>3</b>	<b>Study Objectives .....</b>	<b>22</b>
<b>4</b>	<b>Study Design .....</b>	<b>22</b>
4.1	Design Overview .....	22
4.2	Number of Subjects .....	22
4.2.1	Pharmacological Treatment.....	22
4.3	Population.....	22
4.4	Demographic and Baseline Characteristics.....	22
4.5	Safety Evaluation.....	23
4.6	Brief Description of Study .....	23
4.6.1	Treatment .....	24
<b>5</b>	<b>Study Subject Recruitment .....</b>	<b>26</b>
5.1	Inclusion Criteria.....	26
5.2	Exclusion Criteria.....	26
<b>6</b>	<b>Study Plan.....</b>	<b>27</b>
6.1	Investigator Training .....	27
6.1.1	Informed Consent .....	27
6.1.2	Study Identification Number.....	28
6.1.3	Pre-treatment/Screening Evaluations .....	28
6.2	Treatment .....	28
6.2.1	Visit 2 - LVRC Placement .....	28
6.2.2	Visit 2, cont: Post Bronchoscopy Monitoring and Evaluations .....	29
6.2.3	Visit 3 - 1 Week Post Visit 2 Follow Up Phone Call .....	29
6.2.4	Visit 4 - 1 Month Post Visit 2 Follow Up.....	29
6.2.5	Visit 5 - 2 Months Post-Visit 2 LVRC Placement #2 .....	30
6.2.6	Visit 5, cont: Post Bronchoscopy Monitoring and Evaluations .....	30
6.2.7	Visit 6 - 1 Week Post Visit 5 Phone Call .....	30
6.2.8	Visit 7 - 1 Month Post Visit 5 Follow Up.....	31
6.2.9	Visit 8 - 6 Months Post Visit 2 Follow Up .....	31

6.2.10	Visit 9 - 9 Months Post Visit 2 Phone Call .....	31
6.2.11	Visit 10 - 12 Months Post Visit 2 Follow Up .....	31
6.2.12	Visit 11 - 24 Months Post Visit 2 Follow Up .....	32
6.2.13	Visit 12 - 36 Months Post Visit 2 Follow Up .....	32
6.2.14	Visit 13 - 48 Months Post Visit 2 Follow Up .....	32
6.2.15	Visit 14 - 60 Months Post Visit 2 Follow Up .....	33
6.2.16	Unscheduled Visits .....	33
<b>7</b>	<b>Management of Adverse Events (AEs) and Serious Adverse Events (SAEs)</b>	<b>33</b>
7.1	Serious Adverse Events .....	34
7.2	Unanticipated Adverse Device Effect (UADE).....	34
7.3	Severity of AEs and SAEs .....	35
7.4	Relationship of an Event.....	35
7.5	Process for Assessment, Recording and Reporting of AEs .....	35
7.6	Data Monitoring Committee Composition and Role .....	36
<b>8</b>	<b>Administrative .....</b>	<b>36</b>
8.1	Premature Termination of Study.....	36
8.2	Insurance Coverage .....	37
<b>9</b>	<b>Risks and Benefits .....</b>	<b>37</b>
9.1	Potential Risks to the Subject.....	37
9.2	Potential Benefits to the Subject.....	39
<b>10</b>	<b>Study Monitoring.....</b>	<b>40</b>
<b>11</b>	<b>Responsibilities of the Sponsor .....</b>	<b>40</b>
<b>12</b>	<b>Responsibilities of the Principal Investigator .....</b>	<b>41</b>
<b>13</b>	<b>Good Clinical Practice &amp; Regulatory Requirements .....</b>	<b>43</b>
<b>14</b>	<b>Citations and References .....</b>	<b>45</b>

**Table of Tables**

Table 1. 6 Minute Walk Test (6MWT), Bilateral Subjects.....	20
Table 2. Residual Volume (RV), Bilateral Subjects.....	20
Table 3. Forced Expiratory Volume in 1 Second (FEV <sub>1</sub> ), Bilateral Subjects .....	20
Table 4. Saint George's Respiratory Questionnaire (SGRQ), Bilateral Subjects .....	20
Table 5. Comparison of 6-Month SAE Data Per Procedure - LVRC System vs. EASE Sham Control .....	21
Table 6. Visit Schedule .....	25

**Table of Figures**

Figure 1. Diagram of the Lung Volume Reduction Procedure Using Coils .....	18
Figure 2. Shapes and Sizes of Coils .....	19
Figure 3. Components of the Delivery System.....	19



## **Table of Attachments**

A. Investigator Agreement

### List of Abbreviations

6MWT	6 Minute Walk Test
ABG	Arterial Blood Gas
AE	Adverse Event
BD	Bronchodilator
BL	Baseline
CAO	Coil-Associated Opacity
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
PFT	Pulmonary Function Test
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>	CLN0016.p.D LVRC IDE Crossover Study
<b>Clinical Phase:</b>	Cross-over from Pivotal, Phase III
<b>Study Device</b>	PneumRx® RePneu Coil System (RePneu® Coil)
<b>Study Objectives:</b>	Provide LVRC procedure to qualifying subjects who were enrolled as Control Subjects in and completed the Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study, CLN0009, and obtain safety and effectiveness data on these patients.
<b>Study Design:</b>	This will be a prospective, multicenter, open label, single-arm study.
<b>Study Population:</b>	<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 was enrolled as a Control Subject in and completed all required study assessments through the 12 month visit for the Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study, CLN0009.</li> <li>2. Subject has post-bronchodilator FEV<sub>1</sub> ≤45% predicted.</li> <li>3. Subject has residual volume (RV) ≥175% predicted.</li> <li>4. 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>5. Subject has read, understood and signed the Informed Consent form.</li> <li>6. 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</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> &gt;20% (or, for subjects with pre-bronchodilator FEV<sub>1</sub> below 1 L, a change of &gt; 200 mL) post-bronchodilator unless investigator can confirm by other means that subject does not have asthma.</li> <li>4. Subject has DLCO &lt;20% of predicted.</li> </ol>

	<ol style="list-style-type: none"> <li>5. Subject has severe gas exchange abnormalities as defined by: PaCO<sub>2</sub> &gt;55 mm Hg 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. If pulmonary hypertension is present, "severe" is 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, with the exception of the RENEW 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</li> </ol>
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	study outcomes.
<b>Study Treatment:</b>	<p>Subjects 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 and after 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 2 months after Visit 2. Only a single lung will be treated during any bronchoscopy.</p>
<b>Study Procedures and Assessments:</b>	<p>The following assessments are prescribed in the protocol through the study period.</p> <p>Visit 1: Baseline evaluation after informed consent is signed. NOTE that SGRQ, mMRC and 6MWT, DLCO and other PFTs (excluding spirometry) results from the 12 month evaluation for RENEW will be used as baseline measures, provided that Visit 1 occurs within 6 weeks of the 12 month RENEW evaluation. Spirometry must be repeated. If Visit 1 occurs more than 6 weeks after the 12 month RENEW evaluation, all baseline measures will be taken and recorded at Visit 1.</p> <p>Visit 2: LVRC Placement #1 Prescribe a prophylactic regimen of antibiotics and steroids before and after Coil placement. 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 Perform focused physical exam including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds and 6MWT, administer SGRQ and mMRC. Review medications and O<sub>2</sub> use, Record AEs since last follow-up.</p> <p>Visit 5: LVRC Placement #2 (2 Months Post-Visit 2) Prescribe a prophylactic regimen of antibiotics and steroids before and after treatment. 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></p>

	<p>use and record AEs.</p> <p>Visit 7: 1 Month post Visit 5 Perform focused physical exam including Vital Signs (heart rate, blood pressure, temperature, respiratory rate, SpO<sub>2</sub>) and breath sounds and 6MWT, administer SGRQ and mMRC. Review medications and O<sub>2</sub> use, Record AEs since last follow-up.</p> <p>Visit 8: 6 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, lung volumes, DLCO and 6MWT; administer SGRQ and mMRC. Review medications and O<sub>2</sub> use, Record AEs since last follow-up.</p> <p>Visit 9: 9 Months post Visit 2 Follow Up Phone Call/interview to assess subject overall 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, lung volumes, DLCO and 6MWT; administer SGRQ and mMRC. Review medications and O<sub>2</sub> use, Record AEs since last follow-up. CT scan.</p> <p>Visit 11: 24 Months post Visit 2, Visit 12: 36 Months post Visit 2, and Visit 13: 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, lung volumes, DLCO and 6MWT, administer SGRQ and mMRC. Review medications and O<sub>2</sub> use, Record AEs since last follow-up.</p> <p>Visit 14: 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, lung volumes, DLCO and 6MWT; administer SGRQ and mMRC. Review medications and O<sub>2</sub> use, Record AEs since last follow-up. Exit study.</p>
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<b><i>Management of Adverse Events</i></b>	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.
<b><i>Statistical Analyses</i></b>	Descriptive statistics will be used to evaluate the data, including differences from Baseline to 12 months in 6MWT and SGRQ, and safety.

## **2 Introduction**

### **2.1 Background**

The objective of this study is to provide the LVRC procedure and safety and effectiveness follow up to qualifying subjects who were enrolled as Control Subjects in and completed the Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study, CLN0009. At the time of entry into the RENEW trial, patients who were randomized to the Control arm were told that they would have the opportunity to receive insertion of the Coil at the end of one year, if they still fulfilled the entry criteria, did not have any exclusion criteria, and if the Data Monitoring Committee (DMC) did not have any major safety concerns.

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 (RePneu Coil) 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 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.

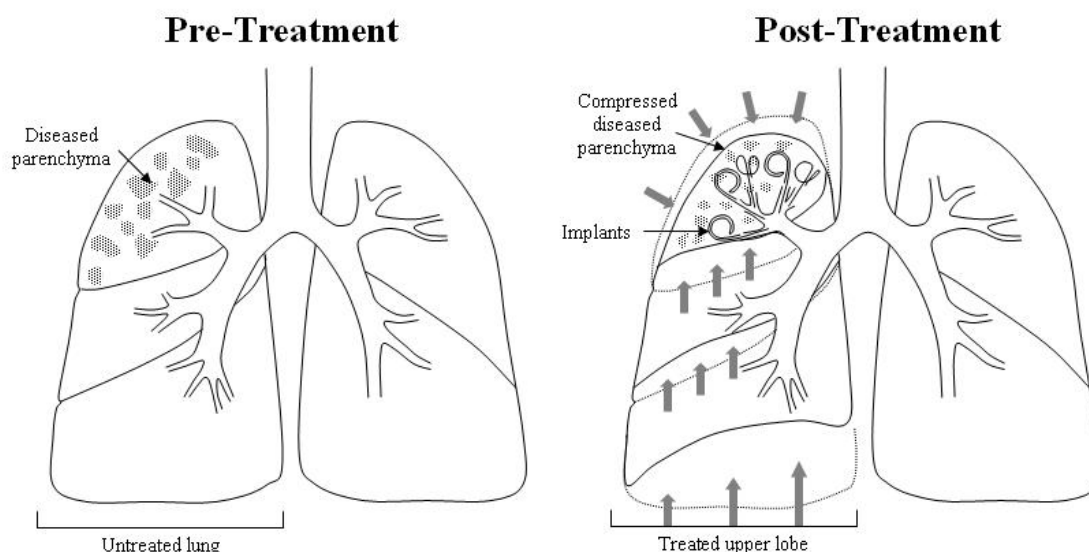
The Delivery System is used to safely deliver the Coils (Figure 3). The Guidewire serves as a specialized large and flexible guide for the Catheter, which enables the identification of suitable airways for treatment and supports the Catheter to help guide it to a delivery site. The Guidewire also facilitates 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.

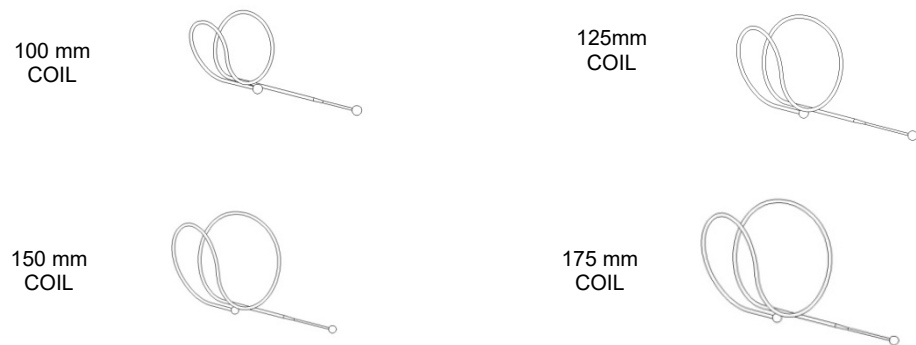
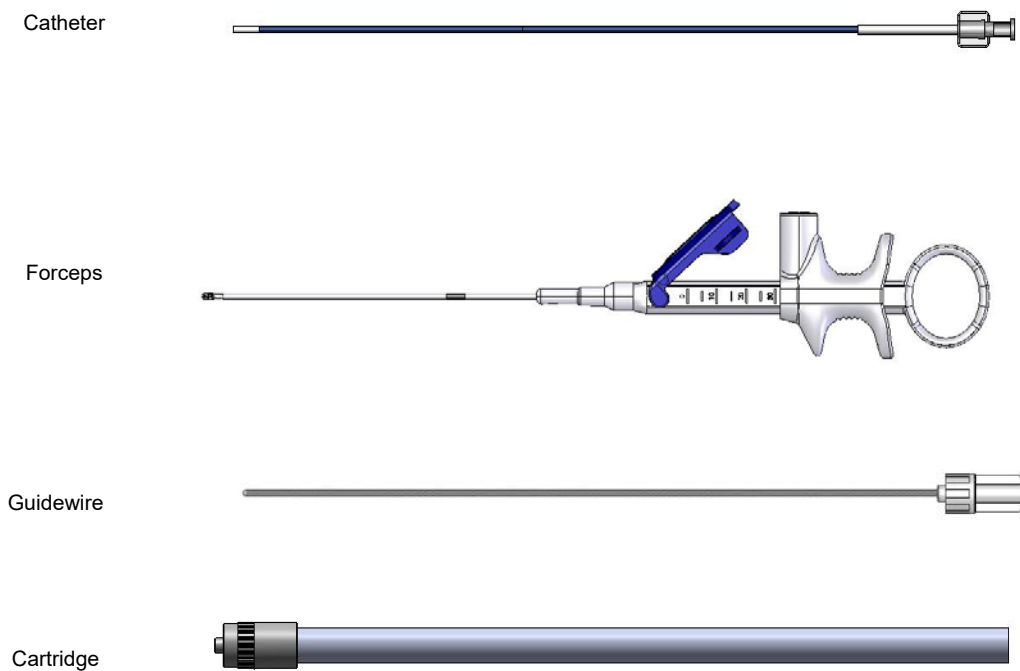
The Coil can be removed by reversing the deployment procedure. For additional information about repositioning or Coil removal, refer to Section 9.1 of the protocol and the “Coil Removal Instructions” section in the Instructions for Use.

The procedure is designed to be performed using a bronchoscope with a 2.8mm inner diameter 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**

## 2.4 Historical Data

PneumRx has conducted and analyzed data from human clinical trials of the RePneu Coil System 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 FDA-approved IDE study, as well as in the present study. The combined data from all OUS studies, as of May 31, 2013, show 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**

	N	6 Months Post Baseline (180 Days)	p-value	N	12 Months Post Baseline (360 Days)	p-value
<b>Change in Meters from Baseline</b>	110	+49.07 ± 8.26	<.0001	71	+61.94 ± 12.36	<.0001
<b>% Change from Baseline</b>	110	+19.53% ± 3.46%	<.0001	71	+22.58% ± 5.27%	0.0002

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

	N	6 Months Post Baseline (180 Days)	p-value	N	12 Months Post Baseline (360 Days)	p-value
<b>Change in Liters from Baseline</b>	112	-0.67 ± 0.09	<.0001	74	-0.54 ± 0.11	<.0001
<b>% Change from Baseline</b>	112	-12.08% ± 1.51	<.0001	74	-9.97% ± 1.98%	<.0001

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

	N	6 Months Post Baseline (180 Days)	p-value	N	12 Months Post Baseline (360 Days)	p-value
<b>Change in Liters from Baseline</b>	106	+0.13 ± 0.02	<.0001	73	+0.10 ± 0.04	0.0178
<b>% Change from Baseline</b>	106	+17.30% ± 2.81%	<.0001	73	+12.37% ± 4.37%	0.0090

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

	N	6 Months Post Baseline (180 Days)	p-value	N	12 Months Post Baseline (360 Days)	p-value
<b>Change from Baseline (Points)</b>	111	-11.43 ± 1.41	<.0001	74	-12.29 ± 2.15	<.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 for bronchoscopy alone in a sham procedure, specifically, referenced in the control patient population in the EASE trial (Shah, 2011), which observed 107 individuals for 6 months. Comparing the PneumRx OUS study results to the EASE sham control group, it appears that the risks associated with the Coil 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 5. Comparison of 6-Month SAE Data Per Procedure - LVRC System vs. EASE Sham Control**

<b>Reported SAE</b>	<b>PneumRx OUS studies (up to 6 Months)</b>	<b>EASE sham control (6 Months reported data)</b>
<b>Pneumothorax</b>	14/238 procedures = 5.9%	1/107 procedures = 0.9%
<b>Hemoptysis</b>	1/238 procedures = 0.4%	0/107 procedures = 0%
<b>Respiratory Failure</b>	0/238 procedures = 0%	0/107 procedures = 0%
<b>COPD exacerbation/ pneumonia<sup>1</sup></b>	41/238 procedures = 17.2%	18/107 procedures = 16.8%
<b>Death</b>	1*/238 procedures = 0.4%	4/107 procedures = 3.7%

\* Not related to device or procedure

With regard to a risk/benefit analysis, it is important to note that, in evaluating the clinical data presented in PneumRx's original IDE submission seeking approval for the IDE trial, the FDA determined that the risk/benefit ratio was acceptable to proceed with a pivotal clinical trial. As part of the approved IDE pivotal protocol, FDA acknowledged that "Upon completing their 12-month visit and exiting the [IDE] 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." PneumRx has submitted this crossover protocol to the independent DMC and, based upon their review of the safety data as of the date of their review, has concluded that the risk profile since FDA's approval of the pivotal trial is similar to the risk profile before the RENEW study, other than one intra-operative death and the recognition of local tissue reaction in the region of the coil observed on imaging studies and termed coil-associated opacity (CAO). As such the DMC felt that it was reasonable for subjects to be offered insertion of Coils, as part of the cross-over study, as long as they were informed of the possible risks. The DMC will continue to monitor the safety data from the IDE trial and will make recommendations regarding the continuation of this trial accordingly.

The RePneu Coil System 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 2010 and is used commercially in Europe.

A US IDE approval was granted for studying the LVRC further under the RENEW Study, protocol CLN0009, IDE G110066. This study protocol continues the research initiated under protocol CLN0009 by allowing the completed study Control subjects to have the opportunity to receive the LVRC under a controlled clinical study protocol (i.e. via crossover study design).

This crossover study requires approval by the RENEW Study Data Monitoring Committee and the FDA.

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<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 Study Objectives**

The primary objective of this study is to provide the LVRC procedure and safety and effectiveness follow up to qualifying subjects who were enrolled as Control Subjects in and completed the 12 month visit of the Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study.

Descriptive statistics will be used to evaluate the data, including differences from Baseline to 12 months in 6MWT and SGRQ, and safety.

### **4 Study Design**

#### **4.1 Design Overview**

This will be a prospective, multicenter, single-arm study.

#### **4.2 Number of Subjects**

The number of subjects in this study will be limited by the number of subjects who were randomized to the Control Group in the Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study, who completed the RENEW Study, and wish to participate in this crossover study, who provide written informed consent for this study, and who meet the inclusion and exclusion criteria of this study.

##### **4.2.1 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 Population**

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

#### **4.4 Demographic and Baseline Characteristics**

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

#### 4.5 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) or until the subject has completed or terminated from the study.

Prior to discharge after treatments and 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.

#### 4.6 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 Form (ICF). The ICF 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 ICF will also include potential risks, discomforts or adverse effects, potential benefits, limits of confidentiality, reimbursement of certain expenses for participation, timely dissemination of any new information that becomes available, and contact information of the research personnel. All patients will sign an ICF prior to any additional procedures being performed to evaluate their eligibility for participation in the Study.

End of study data from the 12 Month Visit of the RENEW Study will be obtained to complete RENEW participation. At the end of the 12 Month Visit, RENEW participants who meet inclusion and exclusion criteria for this study will be offered participation that begins with signing a new ICF. Medical history, physical exam, and smoking history will be collected to ensure the subject meets inclusion and exclusion criteria. Spirometry must be repeated after the RENEW Study 12 Month visit as both pre- and post-bronchodilator data must be collected at Baseline for the Crossover Study. Only post-bronchodilator spirometry is collected at the 12 Month visit for the RENEW Study. However, the PFT excluding spirometry, DLCO, 6MWT, mMRC, and SGRQ data collected for the 12 Month Visit of the RENEW Study will be reviewed and used as Baseline data for this Study, unless the 12 Month RENEW data was taken more than 6 weeks previously, in which case such tests/questionnaires are performed again, and data collected. If the subject does not meet the inclusion / exclusion criteria the subject will be excluded from the study.

If the subject has met the inclusion / exclusion criteria for this study, the subject will continue the screening evaluation to ensure they meet the remaining inclusion / exclusion criteria. The investigator will perform other tests such as spirometry, CT scan, X-ray, echocardiogram, EKG, and blood tests.

Once the subject has completed the pre-treatment tests and meets all inclusion / exclusion criteria, the subject will proceed to treatment.

#### 4.6.1 Treatment

For each treatment, subjects will undergo bronchoscopy under general anesthesia or moderate sedation, at the discretion of the bronchoscopist. During both procedures, subjects will be treated with Coils according to the Instructions for Use. Subjects will receive prophylactic drugs pre-procedure and post-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 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 2 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 6. Subjects will be followed up annually for 5 years. After the 5 year visit, the subject will exit the study.



Table 6. Visit Schedule

Procedure / Assessment	Visit 1 Pre-Treatment (Screening)	Visit 2 LVRC Placement #1	Visit 3 1 Week post Visit 2 <sup>a</sup> (Phone Call)	Visit 4 1 Month post Visit 2 <sup>b</sup> (Office Visit)	Visit 5 LVRC Placement#2 (2 Month post Visit 2)	Visit 6 1 Week post Visit 5 <sup>a</sup> (Phone Call)	Visit 7 1 Month post Visit 5 <sup>b</sup> (Office Visit)	Visit 8 6 Months post Visit 2 <sup>c</sup> (Office Visit)	Visit 9 9 Months post Visit 2 <sup>a</sup> (Phone Call)	Visit 10 12 Months post Visit 2 <sup>c</sup> (Office Visit)	Visit 11 24 Months post Visit 2 <sup>c</sup> (Office Visit)	Visit 12 36 Months post Visit 2 <sup>c</sup> (Office Visit)	Visit 13 48 Months post Visit 2 <sup>c</sup> (Office Visit)	Visit 14 60 Months post Visit 2 <sup>c</sup> (Office Visit)
Informed Consent	X													
Inclusion/ Exclusion	X													
Focused physical exam including vital Signs andSpO <sub>2</sub>	X	X		X	X		X	X		X	X	X	X	X
Record the following measures from the 12 Month RENEW Visit in the eCRF as baseline measurements: Spirometry, Lung Volumes and Diffusing Capacity, 6MWT, SGRQ, mMRC*	X													
Spirometry	X							X		X	X	X	X	X
Lung Volumes and Diffusing Capacity	X*							X		X	X	X	X	X
6MWT	X*			X			X	X		X	X	X	X	X
SGRQ	X*			X			X	X		X	X	X	X	X
mMRC	X*			X			X	X		X	X	X	X	X
Blood panel and ABG	X													
EKG	X													
Echocardiogram‡	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 <sup>d</sup>			X	X	X	X	X	X	X	X	X	X	X	X
Exit Study														X

<sup>a</sup> ±3 days  
<sup>b</sup> Minus 2 weeks to plus 4 weeks  
<sup>c</sup> ±4 weeks  
\* If 12 Month RENEW Visit occurred within 6 weeks of Visit 1, use 12 Month RENEW values for lung volumes, diffusing capacity, SGRQ, 6MWT, and mMRC as baseline measurements. If 12 Month RENEW Visit occurred more than 6 weeks before Visit 1, perform these tests and record results as baseline measurements.  
† Chest x-ray #1 is done immediately post-procedure and chest x-ray #2 is done prior to discharge.  
<sup>d</sup> 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

## 5 Study Subject Recruitment

All study subjects will be patient volunteers who completed the Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study as Control Subjects and who meet the inclusion / exclusion criteria including a willingness to read, understand, and sign the Informed Consent.

### 5.1 Inclusion Criteria

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

1. Subject was enrolled as a Control Subject in and completed all required study assessments through the 12 Month visit for the Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Trial, CLN0009.
2. Subject has post-bronchodilator FEV<sub>1</sub>  $\leq$ 45% predicted.
3. Subject has residual volume (RV)  $\geq$ 175% predicted.
4. 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.
5. Subject read, understood and signed the Informed Consent form.
6. 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<sub>1</sub>  $>$ 20% (or, for subjects with pre-bronchodilator FEV<sub>1</sub> 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. If pulmonary hypertension is present, "severe" is 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, with the exception of the RENEW 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 have been trained in the proper use and operation of the Coil System and may have performed Coil procedures as part of the Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study before initiation of any treatment. 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.

NOTE: All assessments by investigators or other healthcare professionals will be performed to the same standards (ATS Guidelines) as those in the pivotal protocol as detailed in the Study Operational Instructions.

#### **6.1.1 Informed Consent**

- Provide information to the potential subject and review Informed Consent Form details. Obtain Informed Consent in writing from the subject as part of Pre-treatment/Baseline Screening (Visit 1).

- Provide the subject with a copy of the signed Informed Consent Form for their records.

6.1.2 Study Identification Number

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

6.1.3 Pre-treatment/Screening Evaluations

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

- 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 or other appropriate diagnostic test
- Pregnancy test for females of child-bearing potential prior to radiographic procedures.
- Room air Arterial Blood Gasses (ABG).
- Chest x-ray.
- CT Scan collected per guidelines provided by the Core (Radiology) Lab Protocol.
- Pre- and post-bronchodilator spirometry

If screening performed more than 6 weeks after subject's 12 Month Visit in the RENEW study, also perform the following:

- 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)

6.2 Treatment

6.2.1 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.
-

- Unless contraindicated, prescribe a prophylactic regimen of antibiotics to be taken for at least seven (7) days after the procedure and steroids to be taken two (2) days before and at least seven (7) days after the procedure.
- 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 per the manufacturer's instructions.
- If not already documented, perform bronchoalveolar lavage and send sample for culture and Gram stain to document any host pathogens.
- Navigate the bronchoscope and identify the airways in one of the lobes identified by the CT Core Lab as a lobe to be treated.
- Deliver the Coils in accordance with RePneu Coil System 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.

6.2.2 Visit 2, cont: Post Bronchoscopy Monitoring and Evaluations

- 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 with subject.
- Provide detailed instructions to Subject on expected effects of Coil procedure and instruct the Subject to contact the Site and Principal Investigator immediately should any of the effects be experienced.

6.2.3 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.

6.2.4 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 6MWT
- Administer SGRQ
- Administer mMRC
- Review medications and O<sub>2</sub> use.

- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan.

6.2.5 Visit 5 - 2 Months Post-Visit 2 LVRC Placement #2

- 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.
- Unless contraindicated, prescribe a prophylactic regimen of antibiotics to be taken for at least seven (7) days post-procedure and steroids to be taken two (2) days before and at least seven (7) days after treatment.
- 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 per manufacturer's instructions.
- Navigate the bronchoscope and identify the airways in one of the lobes identified by the CT Core Lab as a lobe to be treated
- Deliver the Coils in accordance with the RePneu Coil System Instructions for Use.
- Only place the Coils 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.

6.2.6 Visit 5, cont: Post Bronchoscopy Monitoring and Evaluations

- 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 with Subject.
- Provide detailed instructions to Subject on expected effects of Coil procedure and instruct the Subject to contact the Site and Principal Investigator immediately should any of the effects be experienced.

6.2.7 Visit 6 - 1 Week Post Visit 5 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 with Subject.

6.2.8 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 6MWT
- Administer SGRQ
- Administer mMRC
- Review medications and O<sub>2</sub> use.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan with Subject.

6.2.9 Visit 8 - 6 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 Lung Volumes and DLCO
- Perform 6MWT
- Administer SGRQ
- Administer mMRC
- Review medications and O<sub>2</sub> use.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan with Subject.

6.2.10 Visit 9 - 9 Months Post Visit 2 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 with Subject.

6.2.11 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 Lung Volumes and DLCO
- Perform 6MWT
- Administer SGRQ
- Administer mMRC

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

6.2.12 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 Lung Volumes and DLCO
- Perform 6MWT
- Administer SGRQ
- Administer mMRC
- Review medications and O<sub>2</sub> use.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan with Subject.

6.2.13 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 Lung Volumes and DLCO
- Perform 6MWT
- Administer SGRQ
- Administer mMRC
- Review medications and O<sub>2</sub> use.
- Record AEs since last follow-up (See Section 7).
- Discuss maintenance rehabilitation activity plan with Subject.

6.2.14 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 Lung Volumes and DLCO
- Perform 6MWT
- Administer SGRQ
- Administer mMRC
- Review medications and O<sub>2</sub> use.
- Record AEs since last follow-up (See Section 7).



- Discuss maintenance rehabilitation activity plan with Subject.

#### 6.2.15 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 pregnancy test for females of child-bearing potential prior to radiographic procedures.
- Perform post-bronchodilator spirometry.
- Perform Lung Volumes and DLCO
- Perform 6MWT
- Perform SGRQ
- Perform mMRC
- Review medications and O<sub>2</sub> use.
- Record AEs since last follow-up (See Section 7).
- The subject can be exited from the study.

#### 6.2.16 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 that an AE 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/diagnosis, date of onset, severity, duration, and relationship to the procedure/device will be recorded, as well as a detailed description of the Event. All AEs will be followed until they are adequately resolved or stabilized, or for 1 month following study completion or termination, whichever comes first.

Due to the similarity in reported symptoms between an infectious pneumonia and the occurrence of post-Coil implant response (the localized tissue reaction sometimes referred to as “tension induced opacity” and hereafter as Coil Associated Opacity or CAO), the DMC has recommended that Subjects be instructed to immediately contact the PI or authorized designee if the Subject experiences any chest or pleuritic pain/discomfort, fatigue, or increased dyspnea/shortness of breath within approximately two (2) months following each Coil treatment. These symptoms may or may not be accompanied by fever, chills and/or night sweats. Recommendations on diagnosis, treatment and follow-up of these events are provided in the Study Operational Instructions.

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

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 Medical Monitor 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 immediately (within one working day) using the AE 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 may 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. 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 Adverse Event eCRF. The IRB/EC(s) will be informed if the Serious or unexpected adverse event, in the opinion of the Investigator, or the Medical Monitor, is likely to affect the safety of the subjects or the conduct of the study.

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

#### 7.6 Data Monitoring Committee Composition and Role

An independent DMC will be engaged 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 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/EC approval from any site. The investigators are responsible for informing their IRBs/ECs 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 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, 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.

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 a products liability 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:

- **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), death 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. Of over 1300 LVRC procedures performed to date, there has been one reported death that was deemed related to the device or the 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 (1) an allergic reaction to the metal (nickel-titanium) that may require removal of the study device, and (2) an opacity on chest x-ray that may be difficult to differentiate from infectious pneumonia.

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.

- **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 with the US Medicare Clinical Trial Policy rules for clinical trial coverage, many 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.

Before acceptance of the clinical data, PneumRx and its assigned Clinical Monitor designee(s) will review the data entered on eCRFs 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.

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 eCRFs 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's 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 PI 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/EC Approval**

The investigator is responsible for obtaining IRB/EC 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/EC 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/EC for complete review of the study. Written assurance of IRB/EC 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 ICF to be used should be the version of the document approved by the IRB/EC. The signed ICF will be maintained in the subject's medical record, and a copy of the signed ICF will become an integral part of each case report file retained by the Investigator. A copy of the signed ICF shall also be given to the subject who signed the form.

The approved ICF specific to each responsible IRB/EC 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 eCRFs.

All information generated by the subject evaluations is to be transferred from the source documentation and recorded using EDC. Paper source documents 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 data entered on the eCRFs. 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 eCRFs.

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 eCRFs.

The investigator is also responsible for submitting reports to PneumRx, Inc. and the reviewing IRB/EC 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/EC 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/EC 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 Coil 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 ICF with information that would meaningfully add to the protection of the rights and welfare of subjects. Prior to submitting the revised ICF 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 ICF prior to study initiation. The investigator at each institution shall submit the approved ICF 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**

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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.

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