NCT #: NCT02499380

CLINICAL TRIAL PROTOCOL COVER SHEET

Device:	PneumRx® RePneu® Coil System
Study Number & Rev.:	CLN0017.p. Rev A
Study Title:	**Changes in lung physiology and cardiac performance in patients with emphysema post bilateral RePneu Coil Treatment**
Study Design:	Post-market, multicenter, single-arm, study of the CE Marked PneumRx, Inc. RePneu Coil System whithin intended use
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 2014
Projected Completion Date:	December 2016

Revision History			
Revision	**DCO**	**Effective Date**	**Originator**
A	2699	19 Aug 14	[redacted]

STUDY ACKNOWLEDGMENT

Investigator's Statement:

I have read and understand Protocol No. CLN0017.p.A 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. CLN0017.p.A, has been reviewed and approved by PneumRx, Inc., in accordance with Company policy and procedures and the national laws.

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

_____
Name (please print)

_____
Signature

_____
Position/Title

_____
Date

STATEMENT OF COMPLIANCE

The Trial will be conducted in compliance with this Protocol, and with local, and national requirements, including Good Clinical Practices, my overseeing ethics committee requirements, patient privacy requirements, and all applicable regulatory requirements.

Protocol Title: **Changes in lung physiology and cardiac performance in patients with emphysema post bilateral RePneu Coil Treatment**

Version: CLN0017.p.A
Revision Date: July 29, 2014

_____
Investigator's Name (please print)

_____
Investigator's Title

_____
Investigator's Signature

_____
Date

Table of Contents

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
EC	Ethics Committee
EKG	Electrocardiogram
EDC	Electronic Data Collection
FEV_1	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
IFU	Instructions for Use
ITT	Intent-to-Treat population
LRTI	Lower Respiratory Tract Infection
LVRS	Lung Volume Reduction Surgery
mMRC	Modified Medical Research Council
O_2	Oxygen
PaO_2	Partial Arterial Blood Gases Oxygen
$PaCO_2$	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_2	Oxygen Saturation by pulse oximetry
SGRQ	St. George's Respiratory Questionnaire
TLC	Total Lung Capacity
UADE	Unanticipated Adverse Device Effect

1 Protocol Synopsis

Study Number and Title:	CLN0017.p.A **Changes in lung physiology and cardiac performance in patients with emphysema post bilateral RePneu Coil Treatment**
Clinical Phase:	Post-market study with CE Marked device within intended use
Study Device	PneumRx RePneu® Coil
Study Objectives:	The objective of this post-marketing study is to advance the understanding of mechanism of action of the CE marked RePneu Coil by observing changes in lung physiology and cardiac performance in patients with emphysema treated with the RePneu Coils, when used as intended.
Study Design:	This will be a prospective, multicenter, open label, single-arm study.
Study Population:	The study population will include all subjects who have met the inclusion/exclusion study criteria. **Inclusion Criteria**: 1. Adult subjects diagnosed with emphysematous type of COPD. 2. CT scan indicates bilateral emphysema, with sufficient lung parenchyma for coil deployment (based on PneumRx CT scoring criteria). 3. Subject has post-bronchodilator FEV1 ≤45% predicted. 4. Subject has Total Lung Capacity >100% predicted. 5. Subject has residual volume (RV) ≥175% predicted. 6. Subject has marked dyspnea scoring ≥2 on mMRC scale of 0-4. 7. Subject read, understood and signed the Informed Consent form. 8. Subject has received Pneumococcal and Influenza vaccinations consistent with local recommendations and/or policy.

	Exclusion Criteria: 1. 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 not due to dyspnea. 2. 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. 3. Subject has severe gas exchange abnormalities as defined by: • $PaCO_2$ >55 mm Hg • PaO_2 <45 mm Hg on room air (High altitude criterion: PaO_2 <30 mm Hg) 4. Subject has severe pulmonary hypertension defined by right ventricular systolic pressure >50 mm Hg via right heart catheterization and/or echocardiogram. 5. 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. 6. Subject is pregnant or lactating, or plans to become pregnant within the study timeframe. 7. Subject has an inability to tolerate bronchoscopy under moderate sedation or general anesthesia. 8. Subject has clinically significant bronchiectasis. 9. Subject has had previous LVR surgery, lung transplantation, lobectomy or other BLVR treatment in either lung. 10. Subject has participated in studies to treat COPD using high dose radiation 11. Subject has been involved in pulmonary drug or device studies within 30 days prior to this study. 12. Subject is chronically taking >20 mg prednisone (or equivalent dose of a similar steroid) daily. 13. Subject requires high level chronic immunomodulatory therapy to treat a moderate to severe chronic

	inflammatory autoimmune disorder. 14. Subject is on any type of antiplatelet or anticoagulant therapy which cannot be stopped for seven (7) days prior to procedure. 15. Subject has a sensitivity or allergy to Nickel. 16. Subject has a known sensitivity to drugs required to perform bronchoscopy. 17. Subject has been diagnosed with alpha-1 antitrypsin deficiency (AATD). 18. 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.
Study Treatment:	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 treatment. Following RePneu Coil placement, the subject will remain in the hospital under observation per standard hospital practice. Following hospital discharge, the subject will be will be seen at the study site one month following the procedure. After the one month post-procedure visit the subject will be scheduled for the second procedure in the contralateral lung to take place within the following 4 weeks. Following hospital discharge, the subject will be seen at the study site one month following second procedure. If, at the discretion of the treating investigator, the patient did not respond to the bilateral treatment due to low coil dose, an optional 3rd procedure may be scheduled. If a patient is unable to complete these treatments for any reason, that patient's data will be collected and analyzed separately.
Study Procedures and Assessments:	**Baseline Visit:** Participant agrees to be a part of the study and signs the informed consent. Baseline tests for all primary and secondary endpoints will be performed. **Participant is evaluated and selected for RePneu procedure and has met inclusion/exclusion criteria**. **First and Second Procedure visit: Participant undergoes the RePneu Procedure** in accordance with manufacturer

	Instructions for Use. Procedure data will be collected. ***Third Optional Procedure*:** Patient will receive an additional 1-3 coils in each treated lobe, at the discretion of the treating investigator if the initial coil dose did not bring the expected benefit. The procedures shall be performed no closer together than 4 weeks and if possible no longer than 8 weeks apart. **Follow up Visit (s):** The follow up visits shall be performed 1 month post each procedure and then 4 months post final treatment. The final study follow up visit shall be performed 1 year post first treatment. Follow-up visits will occur at the hospital in which the coil implantation procedure was performed.
Management of Adverse Events	AE information will be collected throughout the study. Adverse events will be recorded on the AE CRF 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.
Statistical Analyses	The endpoints will be analyzed with a paired t-test, which will compare baseline to 4-month post final treatment and 12-months post first treatment follow-up values. A p-value of <0.05 will be considered statistically significant. Parametric descriptive statistics will be used to summarize data for secondary effectiveness variables. Adverse events will be categorized into medically relevant categories and presented as frequency counts and percentages. Intention to Treat (ITT) and Per-protocol analyses will be performed as well as a site-specific subgroup analysis. Other subgroup analyses will include: - upper vs. lower lobe treatments multi-variate analysis of baseline characteristics, adverse events, and various CT and other imaging characteristics

2 Introduction

2.1 Background and Clinical Need

Emphysema is a chronic respiratory disease with an estimated prevalence of 1.8% [1]. Emphysema is characterized by gradual destruction and disappearance of alveolar walls. This results in reduction in the elasticity and recoil pressure of the lungs, and allows the smaller airways to collapse prematurely during exhalation, resulting in hyperinflation, air trapping, and diaphragmatic flattening with decreased diaphragmatic efficiency. This hyperinflation worsens with rapid breathing associated with exercise. These effects are believed to be a primary contributor to the dyspnea experienced by emphysema patients [2]. The alveolar wall damage also creates large nonfunctional air pockets or bullae that become physiologic dead space in the thorax, preventing healthier portions of the lung from expanding and contracting normally. Patients with advanced emphysema also frequently demonstrate collateral ventilation both within the affected lobes and even across lobar fissures. As the disease progresses, the emphysema patient eventually becomes hypoxemic due to progressive loss of alveolar capillary membrane surface area. Hypoxemia and deconditioning contribute to muscle weakness and fatigue. The crippling effects of end-stage emphysema include severe dyspnea, severe limitation of activities, recurrent lung infections, and ultimately respiratory failure, which can result in death.

There are several treatments available for emphysema including smoking cessation, medications, physical therapy, supplemental oxygen, and surgery. 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 seldomly 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 but none of them are indicated for use in homogeneous type of emphysema.

The PneumRx 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.

2.2 Description of the RePneu Coil System

The RePneu System is approved for CE Mark (Class IIa [Delivery System] and IIb [RePneu Coil] in accordance with the Medical Device Directive) since October 2010 and is used commercially in Europe.

The RePneu Coil is an implantable device, delivered through a fiber-optic bronchoscope, designed specifically to treat patients suffering from emphysema. It 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, 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 three lengths to accommodate anticipated anatomical variations – the lengths are 100mm, 125mm, and 150mm (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 rounded 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 procedure is designed to be performed using a 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 Delivery System is sterilized by Ethylene Oxide (EO) and the RePneu Coils are sterilized by Electron Beam (E-Beam).

Figure 1. Diagram of the Endoscopic Emphysema Treatment Procedure Using Coils

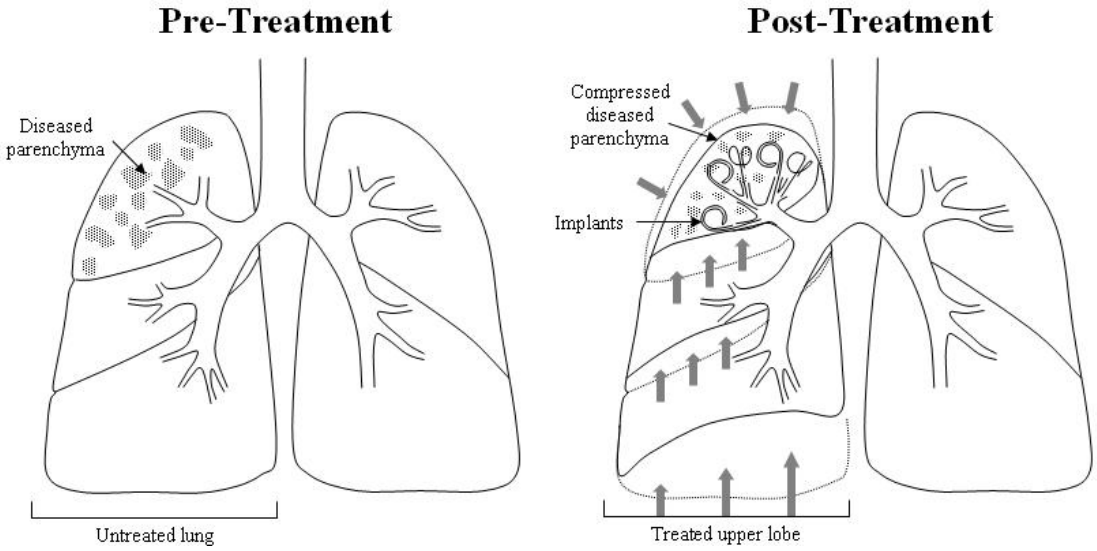


Figure 2. Shapes and Sizes of Coils

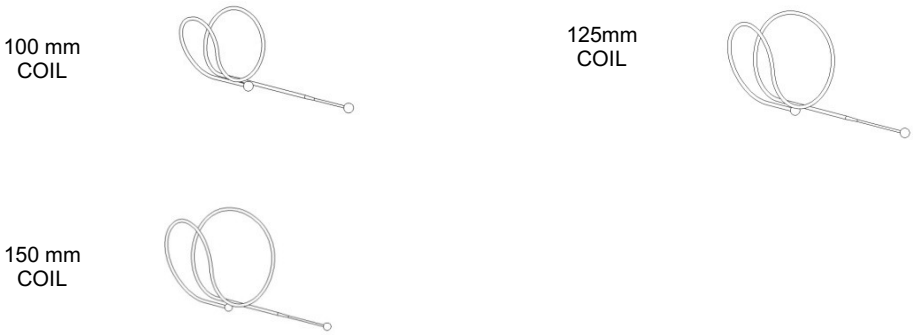
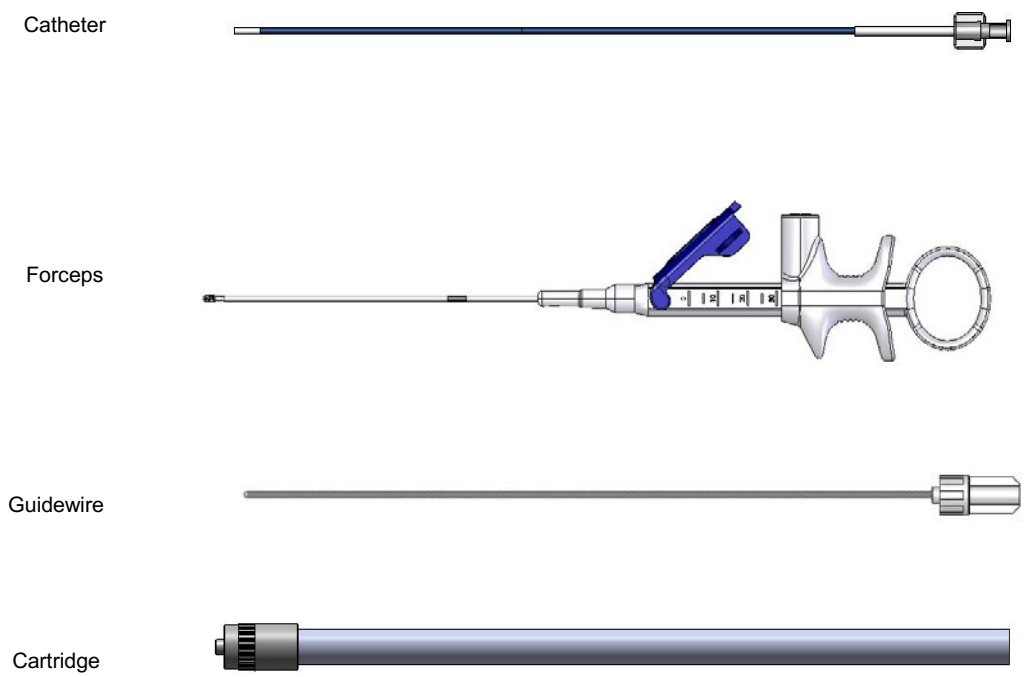


Figure 3. Components of the Delivery System



2.3 Historical Data

PneumRx has conducted and analyzed data from human clinical trials of the RePneu Coil in Europe. The data presented below are the accumulation of 4 completed studies[3-7], each of which had inclusion/exclusion criteria virtually identical to each other as well as to the present study . The results are presented in the summary below:

Table 1. Effectiveness summary of completed studies

Study #	*Publication*	*Treated patients*	*3 Months*				*6 Months*				*12 Months*			
			FEV1 % or L	RV % or L	6MWT m	SGRQ pts	FEV1 % or L	RV % or L	6MWT m	SGRQ pts	FEV1 % or L	RV % or L	6MWT m	SGRQ pts
CLN0006	Herth, 2010	11	-5.0%	+ 3.3 %	+5.6 %	-6.1								
	Slebos, 2012	16					+14.9 %	-11.4 %	+84.4	-14.9				
CLN0008 (RESET)	Shah, 2013	23	+14.29 %	-0.51 L	+51.2	-8.11								
	Submitted May 2014	45					+0.07 L	-0.34 L	+54.6	-7.3	+0.06 L	-0.32 L	+34.1	-6.1
CLN0011	Deslee 2014,	60					+0.11 L	-0.65 L	+29.7	-12.1	+0.11L	-0.71 L	+51.4	-11.1
CLN0012	Klooster 2014	10					+0.11 L	-0.6 L	+61	-15				

With respect to safety, the RePneu Coils have shown an excellent safety profile to date. 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 [8], which observed 107 individuals for 6 months. Comparing the RePneu Coil combined study results to the EASE sham control group, it appears that the risks associated with the RePneu System are largely attributable to the bronchoscopic procedure itself rather than to the device per se. Specifically, the rate of serious events of hemoptysis, COPD exacerbation and pneumonia are comparable between the RePneu Coil treatment population and the EASE sham control group (Table 2).

Table 2. Comparison of 6-Month SAE Data per Procedure – RePneu System vs. EASE Sham Control

Reported SAE	PneumRx studies (up to 6 Months)	EASE sham control (6 Months reported data)
Pneumothorax	14/238 procedures = 5.9%	1/107 procedures = 0.9%
Hemoptysis	1/238 procedures = 0.4%	0/107 procedures = 0%
Respiratory Failure	0/238 procedures = 0%	0/107 procedures = 0%
COPD exacerbation/ pneumonia[1]	41/238 procedures = 17.2%	18/107 procedures = 16.8%
Death	2*/238 procedures = 0.8%	4/107 procedures = 3.7%

* Not related to device or procedure

[1] 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 objective of this post-marketing study is to advance the understanding of the mechanism of action of the CE marked RePneu Coil by observing changes in lung physiology and cardiac performance in patients with emphysema treated with the RePneu Coils, when used as intended.

Primary Endpoint:

Changes at 4 months post final treatment and 12 months post first treatment in:

- 6 Minute Walk Distance (6MWD)

Secondary Endpoints:

Changes prior and post procedure at Tx1, Tx2 and optional Tx3 in:

- Geometry (roundness) of major lung airways as defined by the ratio of major versus minor diameter measured from 3 bronchoscopic still images prior and post procedure taken in the lobar airway of the carina leading to segmental airways or while in any segmental airways of the same lobe of the carina leading to sub-segmental airways)
- Static and dynamic pulmonary compliance measurement prior to and post treatment including closing volumes, closing capacity and small airways function

Changes at 4 months post final bilateral treatment and 12 months post first treatment in:

- Physical activity and energy expenditure measured over a period of a week using multi-axial accelerometer.
- Forced expiratory volume in one second (FEV1)
- St. George's respiratory questionnaire (SGRQ)
- Residual volume (RV)
- Residual volume/total lung capacity (RV/TLC)
- Diffusion capacity (DLCO)
- mMRC dyspnea scale
- Cardiovascular parameters such as heart rate, heart ejection fraction, systemic blood pressure
- Body composition including BMI, fat per mass

Changes at 12 months post first treament in:

- Ventilation and perfusion single photon emission tomography (V/P SPECT) or Quantitative lung perfusion scintigraphy (LPS)
- Diaphragm position during exhalation (Comparison of diaphragm apex to rib landmarks using frontal HRCT)
- Lung density distribution (post CT image data processing and reconstruction)

4 Study Design

4.1 Design Overview

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

4.2 Number of Subjects

Thirty subjects will be enrolled into the study from each participating site. Subjects who completed only a unilateral treatment, for any reason will be replaced and not considered in the ITT analysis. Two sites will be recruiting subjects resulting in at least 60 enrolled and bilaterally treated subjects.

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

Subject demographics and baseline characteristics will be summarized including 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 through the 12 months follow-up visit, or until the subject has terminated participation in the study. 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.

4.6 Statistical analysis

The endpoints will be analyzed with a paired t-test, which will compare baseline to 4-month post final treatment and 12-monhts post first treatment follow-up values. A p-value of <0.05 will be considered statistically significant. Parametric descriptive statistics will be used to summarize data for secondary effectiveness variables. Adverse events will be categorized into medically relevant categories and presented as frequency counts and percentages.

Intention to Treat (ITT) and Per-protocol analyses will be performed as well as a site-specific subgroup analysis.

Other subgroup analyses will include:

- upper vs. lower lobe treatments
- multi-variate analysis of baseline characteristics, adverse events, and various CT and other imaging characteristics

4.7 Brief Description of Study

The details of this post-market study and its required visits, procedures, and assessments will be carefully discussed with the study patients using 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 patient's right to decline to participate or to withdraw from the study at any time and for any reason without fear of retribution. It will be clearly stated that the patient will be eligible for treatment with RePneu Coils without agreeing to participate in this post-market study and will receive the same medical attention. The Informed Consent Form will include potential risks, discomforts or adverse effects, potential benefits, limits of confidentiality, incentive for participation, and 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.

Subjects who agree to participate in the study will sign a new Informed Consent and then will be evaluated to determine whether they meet inclusion and exclusion criteria for this study. Medical history, physical exam, and smoking history 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 exited from the study.

Once the subject meets all inclusion / exclusion criteria and completes the baseline tests the subject will be scheduled for treatment.

4.7.1 CT Based Patient Selection and Treatment Planning

CT based visual assessments and the PneumRx lobar damage scoring method will be used to select patients and plan the coil treatment. A character score (0-5) is assigned for each of the 4 main lobes (UL, UR, LL, and LR) that best matches the damage seen in the CT image. This is the method employed for CT-based patient selection and treatment planning in the FDA-pivotal RENEW trial.

Background

The RePneu Coil technology causes local airway distortion that restores tension (recoil properties) in the lung. Coils provide distortion of the airway path which produces the same effect as if the airway is shortened. The coils work best in lobes with continuous structure so tension can be maintained over a large volume. Lungs with preserved continuous tissue structure present better patient outcomes. An example of non-continuous structure would be patients with a giant bulla. In this case, a coil may successfully distort tissue adjacent to the bulla but the tension may never be developed throughout the lobe or lung because the bulla can simply expand. In this case, the tension is not maintained across the volume.

Lobe Scores

Lobe score will be determined by visual evaluation of the lobe to identify the single axial slice with the greatest severity of damage (largest total area of tissue defects). The average damage observed in the slice (not the single largest defect in the slice) will be compared to the provided visual standards of lung damage to assign a score for the lobe. This method characterizes the slice with the greatest combination of tissue defects that can possibly interrupt the transmission of tension across the lobe of interest. Each lobe should be examined individually.

This method is not based on densitometry or other analytical metrics that have been found to be overly sensitive to diffuse patterns of low damage (diffuse damage sometimes looks like total destruction when there is still substantial preserved structure).

Scores 0-5 are patterns of damage that should be scored using the average (>50% of the area) of the **most severely damaged axial CT slice** in the lobe. Additionally, the apical and basilar 10mm of each lobe should be excluded from consideration while scoring each lobe.

The following are general descriptions of the patterns of damage that relate to each character score; however, comparisons with the provided visual standard images should be used as the predominant means to assign a score:

#0 score – The majority of the slice presents with low attenuation lung that may present visually as normal tissue or having damage limited to **scattered small** centrilobular emphysematous **holes**. The tissue presents as relatively healthy and the majority of the **parenchyma appears normal** and fully connected throughout the lobe.

If **any single bulla** is present that **exceeds 8cm in length** or any single **paraseptal defect** is present (a defect that is completely without internal structure or septi) that **exceeds 10cm in length within the axial plane, the patient should be excluded from the study.**

We have seen this pattern in emphysema patients who still present with post-bronchodilator residual volumes in excess of 250% predicted. Some patients present with large amounts of air trapping even when only low levels of tissue destruction can be visualized on the CT images. These patients have relatively preserved structure and still benefit very much from the treatment.

#1 score – The majority of the slice presents with more obvious centrilobular disease. **Many small** (approximately 1-3mm diameter) lung parenchyma **tissue defects** are present but the **parenchyma is still extensively connected** and preserved. If **any single bulla** is present that **exceeds 8cm in length** or any single **paraseptal defect** is present (a defect that is completely without internal structure or septi) that **exceeds 10cm in length within the axial plane, the patient should be excluded from the study**.

#2 score – The majority of the slice presents with more advanced centrilobular emphysema. **Defects** (approximately 3-10mm diameter) can be seen **making up the majority of the damage** however the periphery of secondary pulmonary lobule and the **interstitium remain intact**. If **any single bulla** is present that **exceeds 8cm in length** or any single **paraseptal defect** is present (a defect that is completely without internal structure or septi) that **exceeds 10cm in length within the axial plane, the patient should be excluded from the study.**

#3 score – The majority of the slice presents with **mostly** non-coalescent bullous centriobular emphysema with **2-3cm parenchymal defects**. The lung tissue is still globally connected (the interstitium and boundary of the secondary pulmonary lobule can still be seen. This will look similar to the #2 score but with larger defects. If **any single bulla** is present that **exceeds 8cm in length** or any single **paraseptal defect** is present (a defect that is completely without internal structure or septi) that **exceeds 10cm in length within the axial plane, the patient should be excluded from the study.**

#4 score – The majority of the slice presents with panlobular emphysema or coalescent emphysema with parenchyma **defects 3-5cm** in size **and complete loss of secondary pulmonary lobular structure**. **If any single bulla is present that exceeds 8cm** in length or any single **paraseptal defect** is present (a defect that is completely without internal structure or septi) that **exceeds 10cm in length within the axial plane, the patient should be excluded from the study.**

#5 score – The majority of the slice presents with **confluent defects** that are **larger than 5cm** or the slice presents with more than one **paraseptal defect longer than 7.5cm** along the perimeter of the lobe. If **any single bulla** is present that **exceeds 8cm in length** or any single **paraseptal defect** is present (a defect that is completely without internal structure or septi) that **exceeds 10cm in length within the axial plane, the patient should be excluded from the study.**

4.7.2 Treatment with RePneu Coils

Subjects 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, according to CE Mark intended use. Subjects will receive prophylactic drugs as prescribed by the protocol.

Following RePneu Coil placement at Treatment 1 (Tx1) and Treatment 2 (Tx2), the subject will remain in the hospital under observation per standard hospital practice. Following hospital discharge, the subject will be seen at the study site at one month after Tx1. After the one month visit following Tx1, the subject will complete the Tx2. Only a single lung will be treated during either of the first 2 bronchoscopies.

After Tx2, the subject will remain in the hospital under observation per standard hospital practice. Following hospital discharge, the subject will be seen at the study site at one month post Tx2.

If, at the discretion of the treating investigator and in consulation with the patient, the patient did not respond to the bilateral treatment possibly due to low coil dose determined at Visit 3 (1 month post Tx2), an optional Tx3 may be scheduled to place an additional 1-3 coils bilaterally. The investigator will determine wheather the patient anatomy (large lung, large lobe, diffuse large volume damage) warrants an additional 1-2 coils in each upper lobe or 1-3 additional coils in each lower lobe. The exact number of addition coils is at the discretion of the investigator.

The procedures shall be performed no closer together than 4 weeks and if possible no longer than 8 weeks apart.

The follow up visits should be performed at 4 months post final treatment and1 year post treatment 1.

Follow-up visits will occur at the hospital which performed the coil implantation procedure.

Treatment Planning Chart

		Upper Lobe Character Score					
Lower Lobes Character Score		0	1	2	3	4	5
	0	U	U	U	U	U	NT
	1	L	U	U	U	U	NT
	2	L	L	U	U	U	NT
	3	L	L	L	U	NT	NT
	4	L	L	L	NT	NT	NT
	5	NT	NT	NT	NT	NT	NT

U – Upper lobe treatment with approximately 10 coils per lobe
L – Lower lobe treatment generally between 11 and 14 coil per lobe
NT – Patient not eligible, do not treat

A) Evaluate the CT independent data to diagnose COPD and possibly exclude the patient from safe use of the coil technology.

B) Review the patient's CT for indicators of disease that may exclude the patient from treatment **(study site responsibility)** such as:
   a. Clear visible bronchiectasis in the treatment lobe
   b. Scarring/ fibrosis in the treatment lobe
   c. Unstable or suspicious nodule in any lobe
   d. Severe bullous disease

Steps C-E will be performed by PneumRx and by the treating site. Decisions related to treatment planning will be by agreement between the site investigator and PneumRx.

C) Review the patient's CT and assign a character score for each lobe. The right upper, left upper, right lower and left lower lobe should be evaluated and a character score should be recorded for each lobe. The score should be based on a review of all the slices that comprise the lobe. The score should characterize the average damage of the most severe slice within each lobe as detailed above (not an average of the entire lobe).

D) Interpret the character score to recommend a treatment plan or to exclude the patient using the following guideline:

   a. If the any of the 4 major lobes receive a score of 5, the patient should be excluded from the study.
   b. If either lung presents with a score of 4 and 4 or a combination of 3 and 4, the lung is in a severely damaged homogeneous condition and the patient should be excluded.
   c. The treatment planning chart should be reviewed to determine a treatment plan for each lung. Treatments should be upper or lower lobes, or opposite upper/lower lobe pairs (i.e. left-upper and right-lower lobes) but not both lobes in a single lung, except for the optional Tx3. The treatment plan should recommend treatment in the lobe with the highest character score in each lung as indicated by the treatment planning chart.

E) Heterogeneous or Homogeneous?

   Patients will be classified as heterogeneous or homogeneous by comparing the character score of the evaluable lobes in each lung. A character score difference between the upper versus lower lobe greater than 1 (2 and above) indicates heterogeneous damage in that lung. A lung with character scores that match or are different by 1 point is considered homogeneous. A patient that presents both lungs as homogenous is considered homogeneous. All other patients are considered heterogeneous (a patient with both types is considered heterogeneous).

4.7.3 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. Medically necessary changes in medications or dosages will be recorded in the CRF. Supplemental oxygen utilization should be recorded and monitored throughout the Study.

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

Prophylactic anti-inflammatory treatment with steroids 50mg/day shall be given 1 day prior, during and after each treatment for up to 15 days. Prophylactic treatment with antibiotics can be considered for at lease 5 days if some bleeding occurs during the implantation and there are infiltrations on chest x-ray post Tx or patient has an excess secretion or sputum culture shows pathologic concentration. Pseudomonades effective antibotics are needed only in case of positive culture in sputum.

Table 3. Visit Schedule

Procedure / Assessment	Visit 1 Baseline Screening (at least 7 days prior to Tx1)	Tx1 RePneu Placement	Visit 2 1 month post Tx1	Tx2 RePneu Placement (4-8 weeks post Tx1)	Visit 3 1 month post Tx2	Optional Tx3 RePneu Placement (4-8 weeks post Tx2)	Visit 3 4 months post final Tx	Visit 4 12 months post Tx1
Informed Consent	X							
Inclusion/ Exclusion	X							
Focused physical exam including vital Signs and SpO_2	X	X	X	X	X	X	X	X
Spirometry	X						X	X
Lung volumes	X						X	X
6MWT	X						X	X
SGRQ	X						X	X
mMRC	X						X	X
Concomitant medication / O_2 Use	X	X	X	X	X	X	X	X
Pregnancy testing	X	X		X		X		
Physical activity and energy expenditure for 6-8 days	X						X	X
Bronchoscopic still images		X		X		X		
Static and dynamic pulmonary compliance prior and post Tx		X		X		X		
Echocardiogram	X						X	X
Body composition	X						X	X
V/P SPECT or Lung perfusion scintigraphy	X							X
High Resolution CT	X							X
Chest X-Ray	X	X		X		X		
Bronchoscopy / Coil Placement		X		X		X		
Adverse Events	X	X	X	X	X	X	X	X

5 Study Subject Recruitment

All study subjects will be patient volunteers who are diagnosed with emphysema 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. Adult subjects diagnosed with emphysematous type of COPD.
2. CT scan indicates bilateral emphysema, with sufficient lung parenchyma for coil deployment (based on PneumRx CT scoring) criteria.
3. Subject has post-bronchodilator FEV1 ≤45% predicted.
4. Subject has Total Lung Capacity >100% predicted.
5. Subject has residual volume (RV) ≥175% predicted.
6. Subject has marked dyspnea scoring ≥2 on mMRC scale of 0-4.
7. Subject read, understood and signed the Informed Consent form.
8. 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 co-morbidities that may significantly reduce subject's ability to improve exercise capacity (e.g. severe arthritis, planned knee surgery) or baseline limitation not due to dyspnea.
2. Subject has a change in FEV1 >20% (or, for subjects with pre-bronchodilator FEV1 below 1 L, a change of > 200 mL) post-bronchodilator unless investigator can confirm by other means that subject does not have asthma.
3. Subject has severe gas exchange abnormalities as defined by:
    a. PaCO2 >55 mm Hg
    b. PaO2 <45 mm Hg on room air (High altitude criterion: PaO2 <30 mm Hg)
4. Subject has severe pulmonary hypertension defined by right ventricular systolic pressure >50 mm Hg via right heart catheterization and/or echocardiogram.
5. 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.
6. Subject is pregnant or lactating, or plans to become pregnant within the study timeframe.
7. Subject has an inability to tolerate bronchoscopy under moderate sedation or general anesthesia.
8. Subject has clinically significant bronchiectasis.

9. Subject has had previous LVR surgery, lung transplantation, lobectomy or other BLVR treatment in either lung.
10. Subject has participated in studies to treat COPD using high dose radiation.
11. Subject has been involved in pulmonary drug or device studies within 30 days prior to this study.
12. Subject is chronically taking >20 mg prednisone (or equivalent dose of a similar steroid) daily.
13. Subject requires high level chronic immunomodulatory therapy to treat a moderate to severe chronic inflammatory autoimmune disorder.
14. Subject is on any type of antiplatelet or anticoagulant therapy which cannot be stopped for seven (7) days prior to procedure.
15. Subject has a sensitivity or allergy to Nickel.
16. Subject has a known sensitivity to drugs required to perform bronchoscopy.
17. Subject has been diagnosed with alpha-1 antitrypsin deficiency (AATD).
18. 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 and/or re-trained in the proper use and operation of the RePneu System, and will have performed several commercial procedures prior to initiation of any treatment.

PneumRx personnel will be present at the first five treatments for each implanter to provide any additional technical support during treatment sessions, and/or 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/ERS Guidelines) as those in the pivotal protocol as detailed in the Study Operational Instructions.

6.2 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.

6.3 Study Identification Number

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

6.4 Screening / Baseline Evaluations

- Perform all screening and baseline assessments according to the schedule.

6.5 Treatment Tx1, Tx2 and optional Tx3

- 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.
- 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 Coil 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 Coils Instructions for Use.
- Only place the devices unilaterally. DO NOT place the devices in both the right and left lungs during one bronchoscopy session (except for Tx3).
- Allow the subject to recover from anesthesia and monitor as per standard hospital practice.

6.6 Post Bronchoscopy Monitoring and Evaluations

- 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.

6.7 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 CRFs. 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 adverse event has occurred. AE information will be collected throughout the study. Adverse events will be recorded on the CRF 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.

7.1 Serious Adverse Events (SAE)

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.

All SAEs must be reported to the PneumRx Clinical Affairs Group within two working days using the SAE CRF form. To maintain subject confidentiality, the subject shall only be identified by the subject number used on the CRFs. 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 CRF.

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. 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 CRF. The Ethics Committee(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.

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 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 Ethics Committee approval from any site. The investigators are responsible for informing their Ethics Committees regarding premature trial termination. Subjects who experienced any SAEs that result in trial termination will be followed to resolution or stabilization.

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 [9], pneumothorax [10], 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.

- **Infection including Pneumonia**
  There is a risk of developing pneumonia (confirmed by positive culture) as a result of the RePneu Coils 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 [11].

- **Hemoptysis**
  Hemoptysis is defined as coughing up blood > 5ml, which results in 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 [12].

- **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 RePneu Coil treatment procedures 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 Studies, numerous Coils have been bronchoscopically repositioned or removed during treatment procedures to improve placement or to deploy a different size Coil. There have been no reported complications or adverse events associated with the bronchoscopic removal or repositioning of the Coils during the procedures.

  Coil(s) can and may be repositioned, replaced or removed during the treatment procedure. Coils can be removed bronchoscopically up to 2 months after the procedure, but only if medically indicated. Such medically indicated post-procedure removal would be considered a Major Complication, and will be recorded in the CRF 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 [13].

- **Reaction**
  Reaction to the study device 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:

- **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 [9].

  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.

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 CRFs (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 (2013), 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 Ethics Committee 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'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.

- Provision of SAE reports to National Health Authorities as required per reportability and support of investigators as needed.

- Review CTs for treatment reccomendation and give feedback to the Investigator within 24 hours of receipt.

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's 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.
    - The Investigator will send CTs to PneumRx for treatment recommendation and wait for the feedback before proceeding with the treatment.
- **Ethics Committee Approval**
  The investigator is responsible for obtaining 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 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 Ethics Committee for complete review of the study. Written assurance of 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 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 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 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 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 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 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.

- **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 EC for review, the investigator is to receive authorization of the revisions by PneumRx Inc. Clinical Affairs staff. The 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.

EC Approval
This Study may not be initiated at any site until the 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

1. Halbert, R.J., et al., *Global burden of COPD: systematic review and meta-analysis.* Eur Respir J, 2006. **28**(3): p. 523-32.
2. O'Donnell, D.E., et al., *Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD.* Chest, 2006. **130**(3): p. 647-56.
3. Herth, F.J., et al., *Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study.* Ther Adv Respir Dis, 2010. **4**(4): p. 225-31.
4. Slebos, D.J., et al., *Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema.* Chest, 2012. **142**(3): p. 574-82.
5. Shah, P.L., et al., *Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial.* The Lancet Respiratory Medicine, 2013. **1**(3): p. 233-240.
6. Klooster, K., et al., *Lung Volume Reduction Coil Treatment in Chronic Obstructive Pulmonary Disease Patients with Homogeneous Emphysema: A Prospective Feasibility Trial.* Respiration, 2014.
7. Deslee, G., et al., *Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial.* Thorax, 2014.
8. Shah, P.L., et al., *Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial.* Lancet, 2011. **378**(9795): p. 997-1005.
9. Djukanovic, R., et al., *Safety of biopsies and bronchoalveolar lavage.* Eur Respir J Suppl, 1998. **26**: p. 39S-41S.
10. Bleecker, E.R., et al., *Investigative bronchoscopy in subjects with asthma and other obstructive pulmonary diseases. Whether and when.* Chest, 1992. **101**(2): p. 297-8.
11. Zalacain, R., et al., *Predisposing factors to bacterial colonization in chronic obstructive pulmonary disease.* Eur Respir J, 1999. **13**(2): p. 343-8.
12. Bidwell, J.L. and R.W. Pachner, *Hemoptysis: diagnosis and management.* Am Fam Physician, 2005. **72**(7): p. 1253-60.
13. Guo, Y., et al., *Factors related to recurrence of spontaneous pneumothorax.* Respirology, 2005. **10**(3): p. 378-84.