A Randomiz**E**d Contro**L**ed Study of Pn**E**umRx Endobronchial Coil System **V**ersus Standard-of-Care Medical M**A**nagement in the **T**reatment of Subjects with Severe **E**mphysema (**ELEVATE**)

NCT03360396

Effective Date of Initial Version: 10 January 2018

Effective Date of Final Version: 04 September 2020

Protocol Number:	BTG-004517-01-FR
Protocol Name:	A Randomiz**E**d Control**L**ed Study of Pn**E**umRx Endobronchial Coil System **V**ersus Standard-of-Care Medical M**A**nagement in the **T**reatment of Subjects with Severe **E**mphysema (**ELEVATE**)
Global Sponsor:	Boston Scientific Corporation 300 Boston Scientific Way, Marlborough, MA 01752, USA
Global Principal Investigator(s):	Felix Herth, M.D. Professor of Medicine Head, Department of Internal Medicine, Pulmonary and Critical Care Medicine Thoraxklinik at Heidelberg University Hospital Amalienstr. 5 69126 Heidelberg Arschang Valipour, M.D.; FCCP; PhD; Assistant Professor Head, Department of Respiratory and Critical Care Medicine Krankenhaus Nord-Klinik Floridsdorf Brünner Straße 68 1210 Vienna, Austria
Sponsor Medical Expert	Thomas Bowman, M.D. 300 Boston Scientific Way Marlborough, MA 01752, USA +1 (508) 683-6580
Study Device	PneumRx Endobronchial Coil System With CE Mark
Protocol ver.7.0 Approval Date:	See Header
Protocol Amendment ver. Approval Date:	N/A

TABLE 1: Protocol Revision History

VERSION NUMBER	AMENDMENT APPROVAL DATE	BRIEF DESCRIPTION OF CHANGES
Ver. 1	10-Jan-2018	Original Release
Ver. 2	26-Apr-2018	Changes and clarifications as per ANSM feedback
Ver. 3	09-May-2018	Addition of mandatory Pregnancy Test as per ANSM request
Ver. 4	29-May-2018	Adaptations according to new IFU Version J
Ver. 5	05-Mar-2020	Reduced scope as per ANSM alignment
Ver. 6	4Aug2020	• Change in sponsorship to Boston Scientific Corporation (BSC) • Updates to Safety Section 7 to align with the ISO 14155 & MEDDEV 27.3 Event Definitions and BSC Event Reporting Requirements
Ver. 7	See Header	• Updates per ANSM Feedback

PROTOCOL APPROVAL & RELEASE SIGNATURE PAGE

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Protocol Version:	Ver. 7
Protocol Approval Date:	See Header

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

Approver	Printed Name	Signature	Date (DD/MMM/YYYY)
Principal Investigator			
Sponsor: Senior Manager Clinical Development			
Sponsor: Statistician			

GLOBAL PRINCIPAL INVESTIGATOR SIGNATURE

Protocol Number:	BTG-004517-01-FR
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Protocol Version:	Ver. 7
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The Global Principal Investigator (undersigned) hereby declares that he/she has read this protocol and agrees to its contents.

The undersigned confirms that the trial will be conducted and documented in accordance with the Declaration of Helsinki, the protocol, standards ISO 14155:2011 E, Clinical investigation of medical devices for human subjects – Good Clinical Practice, applicable laws and regulatory requirements specified in the protocol, and the stipulations of the clinical trial agreement.

Investigator Name (please print): _____

Investigator Signature: _____

Date (DD/MMM/YYYY): _____

COUNTRY COORDINATING INVESTIGATOR SIGNATURE

Protocol Number:	BTG-004517-01-FR
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Investigator Name (please print): _____

Investigator Signature: _____

Date (DD/MMM/YYYY): _____

INVESTIGATOR PROTOCOL REVIEW STATEMENT

Protocol Number:	BTG-004517-01-FR
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Protocol Version:	Ver. 7
Protocol Approval Date:	See Header

The site Principal Investigator (undersigned) hereby declares that he/she has read this protocol and agrees to its contents.
The undersigned confirms that the trial will be conducted and documented in accordance with the Declaration of Helsinki, the protocol, ISO 14155:2011 E, Clinical investigation of medical devices for human subjects – Good Clinical Practice, applicable laws and regulatory requirements specified in the protocol, and the stipulations of the clinical trial agreement.
By written consent to this protocol, the investigator agrees to the above and to fully co-operate with all monitoring and audits in relation to this trial by allowing direct access to all documentation, including source data, by authorized individuals representing Boston Scientific Corporation, IEC/IRBs and/or by regulatory authorities.

Investigator Name (please print): _____

Investigator Signature: _____

Date (DD/MMM/YYYY): _____

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TABLE 2: TERMS, ACRONYMS, ABBREVIATIONS

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

6MWD	6 Minute Walk Distance
6MWT	6 Minute Walk Test
ABG	Arterial Blood Gases
AE	Adverse Event
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
ATS	American Thoracic Society
BG	Blood Gas
BMI	Body Mass Index
BP	Blood Pressure
CAIRS	Coil Associated Inflammatory Response Syndrome
CAO	Coil Associated Opacity
CAT	COPD Assessment Test
CI	Confidence Interval
CO_2	Carbon Dioxide
CoHB	Carboxyhemoglobin
COPD	Chronic Obstructive Pulmonary Disease
CPP	Comité de Protection des Personnes
CT	Computed Tomography
CV	Curriculum Vitae
DLCO	Diffusion Capacity for the Lungs for Carbon Monoxide
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D	EuroQol-5 Dimensions quality of life questionnaire
ERC	Eligibility Review Committee
ERS	European Respiratory Society
eTMF	Electronic Trial Master File
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second

GCP	Good Clinical Practice
Hg(mm Hg)	Mercury (millimeters of Mercury)
HR	Heart Rate
HRCT	High Resolution Computed Tomography
HU	Hounsfield Unit
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent-to-Treat
LAA	Low Attenuation Area
$LoVR_{exp}$	Mean Expiratory Lobar Volume
LVEF	Left Ventricular Ejection Fraction
LVR	Lung Volume Reduction
LVRS	Lung Volume Reduction Surgery
MCID	Minimum Clinical Important Difference
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mMRC	Modified Medical Research Council
OUS	Outside United States
PA	Posterior anterior
PaCO2	Partial Pressure of Carbon Dioxide in Arterial Blood
PaO2	Partial Pressure of Oxygen in Arterial Blood
PFT	Pulmonary Function Testing
PHT	Pulmonary Hypertension
PI	Principal Investigator
PP	Per Protocol
QCT	Quantitative Computed Tomography
QOL	Quality of Life
RV	Residual Volume
RVSP	Right Ventricular Systolic Pressure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SDV	Source Data Verification
SGRQ	Saint George's Respiratory Questionnaire
SoC	Standard of Care
SOC	System Organ Class
SOI	Study Operations Instructions
SOP	Standard Operating Procedure
SD	Standard Deviation
T	Temperature
TLC	Total Lung Capacity
Tx	Treatment
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VC	Vital Capacity

PROTOCOL SYNOPSIS

Reference	BTG-004517-01-FR
Title:	A RandomizEd ControlLed Study of PnEumRx Endobronchial Coil System Versus Standard-of-Care Medical MAnagement in the Treatment of Subjects with Severe Emphysema (**ELEVATE**)
Sponsor:	Boston Scientific Corporation 300 Boston Scientific Way, Marlborough, MA 01752, USA
Timelines and duration:	Study Duration: All Subjects randomized to Treatment will be followed for 36 months post initial treatment. Subjects randomized to Control will be eligible to crossover and receive treatment as soon as possible. Crossover subjects will then be followed for 36 months post initial treatment. Control subjects who choose not to crossover will exit the study immediately. Expected Enrollment Start: Early 2018 Estimated Study Completion: First half 2023
METHOD	
Design:	Prospective, multicenter, open label, randomized (2:1), controlled study comparing outcomes in subjects treated with the PneumRx Endobronchial Coil System (Coil) to a medically-managed control group. The medically-managed control group will be eligible to crossover after 6 months.
Population:	The population studied included severe emphysema patients indicated for Coil treatment per the approved, CE marked Instructions for Use (IFU), who met the following inclusion criteria and did not meet any of the exclusion criteria. Inclusion Criteria: 1. Read, understood and signed the Informed Consent form 2. Meets indications for use per the IFU 3. Bilateral heterogeneous and/or homogeneous emphysema 4. 15% predicted ≤ Post bronchodilator Forced Expiratory Volume in 1 second (FEV_1) ≤ 45% predicted 5. Post bronchodilator Residual Volume (RV) ≥ 200% predicted 6. Post bronchodilator Total Lung Capacity (TLC) >100% pred. 7. Post bronchodilator RV/TLC >55% 8. Dyspnea related to hyperinflation scored ≥ 2 on modified Medical Research Council (mMRC) dyspnea scale despite optimal medical management 9. Receiving optimal drug therapy and medical management according to clinical practice. 10. Performing regular physical activity, at least 2 times per week [1]

[1] The World Health Organization defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure – including activities undertaken while working, playing, carrying out household chores,

	11. Stopped smoking as confirmed by carboxyhemoglobin (CoHB) 12. 100m ≤ 6 minute walk distance (6MWD) ≤ 450m 13. Deemed eligible per Eligibility Review Committee (ERC) 14. If treated in France, Subject must be entitled to French social security. Exclusion Criteria: 1. Known sensitivity to drugs required for performing bronchoscopy or in whom bronchoscopic procedures are contraindicated 2. Evidence of active infection in the lungs 3. Hypersensitivity or allergy to nitinol (nickel-titanium) or its constituent metals 4. Clinically significant pulmonary fibrosis 5. Clinically significant, generalized bronchiectasis 6. Clinically significant bleeding disorders 7. Patient taking immunosuppressive drugs other than steroids (e.g., for the treatment of cancer, rheumatoid arthritis, autoimmune disease, or prevention of tissue or organ rejection). 8. Primary diagnosis of asthma 9. Two (2) or more COPD exacerbations in the prior year, or 1 or more COPD exacerbations in the prior 3 months with indication for hospitalization assessment, according to GOLD 2017 recommendations[2]. 10. Predominant small airways disease defined as significant bronchiectasis with sputum production (> 2 tablespoons daily) or significant bronchial wall thickening per High Resolution Computed Tomography (HRCT) 11. Percent Low Attenuation Area (%LAA) < 20% in the most damaged lobe of either lung. 12. Computed Tomography (CT) Imaging consistent with active pulmonary infection, significant interstitial disease or pleural disease 13. Severe bullous disease (defined by bulla > 1/3 of lung volume, or single bullous defect > 8cm) or significant paraseptal emphysema [defined by numerous large (>1cm) paraseptal defects in the target lobe comprising >5% of total lung volume]. Lung pathology of nodule not proven stable or benign 14. Radiographic confirmation of atelectasis or other scarring/fibrosis in areas of intended Coil implant 15. Use of more than 20 mg/day prednisone (or equivalent dosage of a similar steroid) daily 16. Severe pulmonary hypertension (Right Ventricular Systolic Pressure (RVSP) > 50 mm Hg (preferably measured by right heart catheterization) or other signs of Pulmonary Hypertension (PHT) with

travelling, and engaging in recreational pursuits. For those with limited mobility, this should be done at least 2 days per week.

[2] Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017

	right ventricular dysfunction) 17. Severe hypercapnia (PaCO2 > 55 mmHg on room air) and/or severe hypoxemia (PaO_2 < 45mm Hg on room air, High altitude criterion: PaO_2 < 30 mm Hg) 18. Previous Lung Volume Reduction (LVR) surgery, lung transplantation, lobectomy, LVR devices or other device to treat COPD in either lung. 19. Diagnosed with alpha-1 antitrypsin deficiency 20. Diffusion Capacity of the Lungs for Carbon Monoxide (DLCO)< 20 % 21. Significant, recent or unstable cardiac disease defined as severe heart failure (Left Ventricular Ejection Fraction (LVEF) < 45% despite optimal medical management), unstable cardiac arrhythmia or coronary artery disease (angina on activity), or ischemic event in the past 6 months. 22. Body Mass Index (BMI) > 30 23. Participation in any other clinical study. 24. Subject is pregnant or lactating, or plan to become pregnant within the study timeframe. 25. If treated in France, Subject is a "personne vulnerable" as defined by French regulation
Eligibility Review Committee:	Final eligibility was be confirmed by an expert panel of experienced interventionalists, the Eligibility Review Committee (ERC), prior to randomization.
Participating sites:	Up to 30 centers across Europe were invited to participate. Sites were selected based on their experience with the Coil System, expertise in interventional bronchoscopy and operational and multidisciplinary resource availability.
Visits and Assessments:	Baseline Visit: After obtaining Subject consent, the Subject's eligibility for Treatment was evaluated. Relevant medical history, medications, comorbidities, previous treatments of emphysema, physical activity / rehabilitation status, and baseline characteristics were collected and entered into the Electronic Data Capture (EDC) system. Pulmonary Function Test (PFT), pregnancy test, imaging (HRCT scan inspiratory and expiratory,), exercise testing (6 Minute Walk Test – 6MWT), dyspnea assessment (mMRC), quality of life (QoL) assessment (St Georges Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), EuroQol-5 Dimensions QoL questionnaire (EQ-5D), and blood gases (BG) were collected. Eligibility was reviewed by the ERC, and if deemed eligible, subject was randomized. Procedure Visits: Subjects will undergo the Coil treatment. One lung will be treated per procedure, with procedures separated by approximately 2 months. Lobar targeting will be based on quantitative CT (QCT) densitometry analysis and Coils will be placed in the lobe with the higher LAA as measured in Hounsfield units (HU) at a -950 HU threshold.

Procedure data, chest X-ray data, adverse event data, pregnancy test, and medications will be collected and entered into the EDC system.

Each center's principal investigator (PI), or one primary implanter, will perform all coil treatments in ELEVATE. If necessary, a secondary implanter will also be trained as a back-up.

Follow-up Visits:

Follow-up visits should be conducted per the schedule below. Study specific follow-up visits should take place during exacerbation free periods defined as 30 days with symptoms within normal day-to-day variability.

12- and 36-month study follow-up visits will include:

- PFT
- AE review
- Medications
- Inspiratory and expiratory HRCT

Definition of visit windows:

Patients should have visits scheduled during exacerbation-free periods, defined as 30 days with symptoms within normal day to day variability.

Treatment/Control Group Subjects:

Visit:	Visit Window:
Baseline	Eligibility, Inclusion
Randomization	
Treatment 1	
Treatment 2	2 months +/- 4 weeks post 1st treatment
12 months post Treatment 1	12 months +/- 4 weeks post 1st treatment
36 months post Treatment 1	36 months +/- 4 weeks post 1st treatment

Device:	PneumRx Endobronchial Coil System (Coil)
Treatment:	The Coil System is a CE-marked implantable device that is indicated for use in patients with homogeneous and/or heterogeneous severe emphysema to improve quality of life, lung function, and exercise capacity. The Coil System consists of sterile Endobronchial Coils which come in 3 different sizes (100 mm, 125 mm, and 150mm) and a sterile, disposable, single-procedure Delivery System consisting of a Cartridge, Catheter, Guidewire and Forceps. The Coil System is designed for bilateral treatment using a therapeutic bronchoscope with a 2.8 mm working channel and fluoroscopy for visualization beyond the bronchoscope. Post-treatment pulmonary rehabilitation or exercise program is strongly encouraged.
Primary Objectives:	The objective of the study is to prospectively confirm the safety and effectiveness profile of Coil treatment in consideration of the findings of previous Randomized Controlled Trials. <u>Co-Primary Effectiveness Endpoints</u>: • Percent change in FEV_1 from baseline to 6 months and • Change in SGRQ from baseline to 6 months
Management of Adverse Events	Safety information will be collected on an ongoing basis throughout the study as participating centers become aware that an adverse event has occurred. Serious Adverse Events (SAE) and specific respiratory Adverse Events (AE) of interest will be recorded on the AE form in the EDC system by the investigator or authorized designee. Event, date of onset, severity, seriousness, duration, and relationship to the procedure/device will be recorded. All AEs will be followed until they are adequately resolved or stabilized or study completion/ termination, whichever comes first. An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

	Death, Led to serious deterioration in the health of the subject that either resulted in A life threatening illness or injury, or A permanent impairment of a body structure or a body function, or In-patient or prolonged hospitalization, or Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function Led to fetal distress, fetal death or a congenital anomaly/birth defect. Information on Specific Respiratory Events of interest will be collected and analyzed via event specific case report forms. These events of interest include: • COPD exacerbation • Hemoptysis • Pneumothorax • Lower Respiratory Tract Infection/Pneumonia • Tissue Reaction, Localized (a.k.a. Coil Associated Inflammatory Response Syndrome (CAIRS), also called Coil Associated Opacity (CAO) in the IFU)
Statistical Analyses:	The co-primary effectiveness endpoint will be analyzed on the intent-to-treat (ITT) population through the 6-month visit, using descriptive statistics to summarize results separately for treatment and control groups. No comparative inferential statistics will be conducted.

	Safety analyses will be conducted on the safety population defined as those subjects who enter the bronchoscopy suit for the initial Coil

	procedure. AE and SAEs will be summarized by Treatment group based on MedDRA codes. Incidence rates through 6 months will be summarized for treatment and control groups. Events will also be summarized by relevant, discrete time periods including the Treatment recovery period (30 days from either treatment). Descriptive statistics will summarize percent change in FEV_1 as well as AEs and SAEs at 12 and 36 months follow-up for all coil treated subjects.
RESULTS	
Number of subjects to be analyzed	A total of 120 Subjects were randomized in a 2:1 ratio of Treatment to Control, respectively (80 Treatment group subjects, 40 Control group subjects).

Duration of the follow-up	Subjects will continue in the study through 36 months from first Coil implant. If Control subjects don't participate to crossover, they will exit the study immediately.

The trial will be conducted and documented in accordance with the Declaration of Helsinki, the protocol, ISO 14155:2011 E, Clinical investigation of medical devices for human subjects – Good Clinical Practice, applicable laws and regulatory requirements specified in the protocol, and the stipulations of the clinical trial agreement.

1 SCHEDULE OF VISITS

Treatment/Control Group Subjects:

Procedure / Assessment	Baseline	Randomization	Treatment (Tx) 1*	Treatment (Tx) 2+++	12 Month post initial treatment Follow-Up Visit***	36 Months post initial treatment Follow-Up Visit***
Informed Consent	X					
Baseline Assessment[1]	X					
Randomization	X	X				
Procedure Treatment	X		X	X		
Medications	X		X	X	X	X
AEs			X	X	X	X
PFTs including Lung volumes and Spirometry	X				X	X
6MWT	X					
QOL (SGRQ, mMRC, CAT, EQ5D)	X					
HRCT (inspiratory and Expiratory)	X				X	X
Chest X-Ray	X		X[2]	X[2]		
Pregnancy test	X		X	X		

[1]Includes demographics, medical history, physical exam, vitals, echocardiogram, and additional pre -treatment evaluations (e.g. blood panel, blood gas).
[2]At procedure visits, a Chest X-Ray or a still fluoroscopic image will be performed immediately post procedure. A second chest X-Ray should be done before discharge, a minimum of 4 hours following the first chest X-Ray.
*No more than 45 days post baseline visit
+++ 2 months ±4 weeks post initial coil treatment
*** ±4 week

2 BACKGROUND

2.1 Disease Background

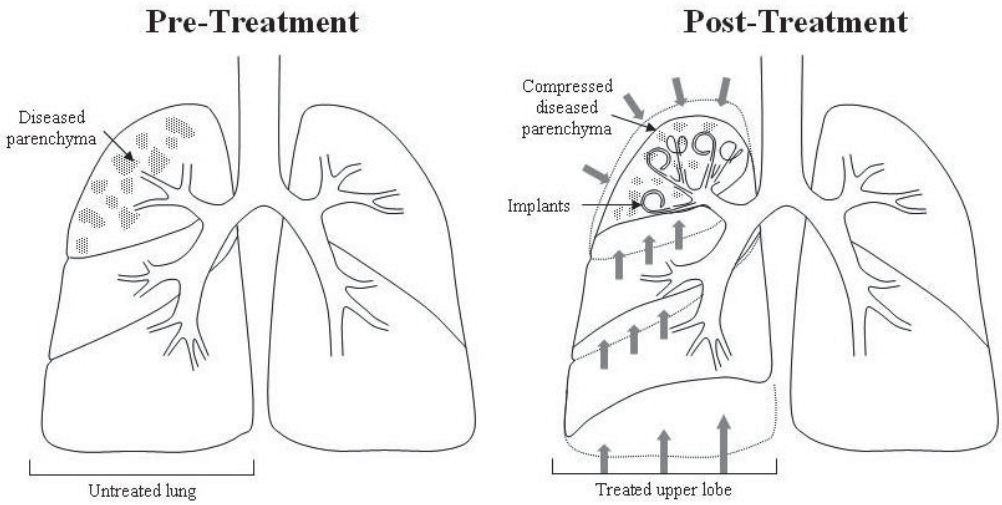
Emphysema is a chronic respiratory disease with an estimated global prevalence of 1.8% (Halbert, 2006). Emphysema is characterized by gradual destruction and disappearance of alveolar walls. This results in reduction in the elastic recoil pressure of the lungs, and allows the smaller airways to collapse 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, emphysema patients develop progressive increases in Residual Volume (RV) and Total Lung Capacity (TLC) which lead to dyspnea. Eventually patients also develop 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 medications, physical therapy, supplemental oxygen, endobronchial valve procedure, and surgery. Smoking cessation is important in the treatment of emphysema to limit the rate of progression of the disease. Emphysema can also 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. LVRS is major surgery that carries the risk of morbidity and mortality. Recently, less invasive bronchoscopic approaches have been developed and several approaches are being actively investigated in human clinical trials in Europe and the US.

2.2 General Description of Investigative Agent(s)/Device

The Coil System is designed to compress the areas of lung parenchyma most damaged by emphysema to allow more normal tissue to expand (**Figure 1**).

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



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

Because the Coil acts by a simple mechanical action of tissue tensioning and compression, the desired effects are achieved without collateral ventilation interfering with treatment outcome. The Coil is deployed using a minimally invasive approach through a bronchoscope and requires no incision. The Coil is designed to treat emphysema patients regardless of their disease distribution; it is suitable for patients with homogeneous and/or heterogeneous (either upper lobe predominant disease or lower lobe predominant) emphysema.
The Coil System has been shown to improve QoL, exercise capacity, and pulmonary function in patients with emphysema (Sciurba et al., 2016; Slebos et al., 2015; Deslée et al., 2016; Shah et al., 2013).

2.3 Summary of Prior Clinical Experience with the Coil System

The Coil System received the CE mark on October 8, 2010 and has been commercially available in select European countries since that time. Over 7,000 Coil procedures have been completed in Europe and other markets where the Coil System is commercially available. Additionally, the Coil System has been studied in over 2,000 subjects across 8 clinical studies in the EU and North America, including a US pivotal randomized controlled study conducted to support future FDA approval.

3 TRIAL OBJECTIVE(S)

3.1 Trial Objectives

3.1.1 Primary Objectives

The primary objective of the ELEVATE study is to prospectively confirm the safety and effectiveness profile of Coils for the treatment of severe emphysema in consideration of the findings of previous randomized controlled trials.

3.1.2 Secondary Objectives

Secondary objectives are determination of responder rates to clinical endpoints and mean change in physiologic endpoints.

3.2 Trial Design

This is a prospective, multicenter, open label, randomized (2:1), controlled study comparing outcomes in subjects treated with the Coil System (Treatment) to a medically-managed control group (Control). Control group patients will be eligible for treatment with Coils (Crossover) 6 months after entry into the study.

The study is anticipated to begin enrollment early 2018. All subjects randomized to Treatment will be followed for 36 months post initial treatment. Subjects randomized to Control will be eligible for crossover as soon as possible. Crossover subjects will then be followed for 36 months post initial treatment. The anticipated last patient visit is expected in first half of 2023. If Control subjects choose not to crossover to treatment, they will exit the study immediately.

The data in this study, including Subject characteristics, outcome measures (e.g., health-related QOL, pulmonary function, exercise capacity), and safety (SAEs and specific respiratory AEs of interest), will be collected via the use of an electronic data capture (EDC) system on electronic Case Report Forms (eCRFs).

No biological samples will be taken other than blood draws taken at screening, and no biological samples will be stored for the study.

3.3 Randomization

A total of 120 subjects were randomized in a 2:1 ratio of Treatment to Control respectively (80 Treatment group subjects, 40 Control group subjects) across up to 30 sites.

3.4 Primary Endpoint (s)

The Co-Primary Effectiveness Endpoint for the study is:

- Percent change in FEV_1 from baseline to 6 months
- Change in St. George's Respiratory Questionnaire (SGRQ) from baseline to 6 months.

4 SUBJECT SELECTION

4.1 Patient Population

Severe emphysema patients indicated for Coil System treatment per the approved, CE marked IFU who meet the study inclusion and exclusion criteria, will be eligible to participate in the study.

4.2 Subject Selection

Recruitment will come from centers across Europe experienced in Coil System treatment and interventional bronchoscopy procedures that have affiliated physicians who have successfully completed the PneumRx Training program. The Coil procedure will be performed only at hospitals that have met the site qualification requirements for use of the Coil System as defined in the Coil training program and the study protocol. Additional qualification requirements include the ability to conduct the study per the approved protocol and demonstrated conduct of PFT, 6MWT, SGRQ, mMRC Dyspnea Scale testing in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) standards.

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

Each center's PI, or a primary implanter, will perform all Coil treatments in the study if possible. If necessary, a secondary implanter will be trained as a back-up for situations in which the primary implanter is unavailable.

Pregnancy test need to be performed for females of child-bearing potential prior to radiographic procedures at baseline and implant procedures.

4.2.1 Inclusion Criteria

The study population will include all subjects who have met the inclusion criteria:

1. Read, understood and signed the Informed Consent form
2. Meets indications for use per the IFU
3. Bilateral heterogeneous and/or homogeneous emphysema
4. 15% predicted ≤ Post bronchodilator Forced Expiratory Volume in 1 second (FEV1) ≤ 45% predicted
5. Post bronchodilator Residual Volume (RV) ≥ 200% predicted
6. Post bronchodilator Total Lung Capacity (TLC) >100% predicted
7. Post bronchodilator RV/TLC > 55%
8. Dyspnea ≥ 2 on modified Medical Research Council (mMRC) dyspnea scale despite optimal medical management
9. Receiving optimal drug therapy and medical management according to clinical practice.
10. Performing regular physical activity, at least 2 times per week [3]
11. Stopped smoking as confirmed by carboxyhemoglobin (CoHB)
12. 100m ≤ 6 minute walk distance (6MWD) ≤ 450m
13. Deemed eligible per Eligibility Review Committee (ERC)
14. If treated in France, Subject must be entitled to French social security

4.2.2 Exclusion Criteria

The study population will not include any subjects who have met any of the exclusion criteria.

1. Known sensitivity to drugs required for performing bronchoscopy or in whom bronchoscopic procedures are contraindicated
2. Evidence of active infection in the lungs
3. Hypersensitivity or allergy to nitinol (nickel-titanium) or its constituent metals
4. Clinically significant pulmonary fibrosis
5. Clinically significant, generalized bronchiectasis
6. Clinically significant bleeding disorders
7. Patient taking immunosuppressive drugs other than steroids (e.g., for the treatment of cancer, rheumatic arthritis, autoimmune disease, or prevention of tissue or organ rejection).
8. Primary diagnosis of asthma
9. Two (2) or more COPD exacerbations in the prior year, or 1 or more COPD exacerbations in the prior 3 months with indication for hospitalization assessment, according to GOLD 2017 recommendations[45].

[3] The World Health Organization defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure – including activities undertaken while working, playing, carrying out household chores, travelling, and engaging in recreational pursuits. For those with limited mobility, this should be done at least 2 days per week.

[4] Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018

10. Predominant small airways disease defined as significant bronchiectasis with sputum production (> 2 tablespoons daily) or significant bronchial wall thickening per High Resolution Computed Tomography (HRCT)
11. Percent Low Attenuation Area (%LAA) < 20% in the most damaged lobe of either lung.
12. Computed Tomography (CT) Imaging consistent with active pulmonary infection, significant interstitial disease or pleural disease
13. Severe bullous disease (defined by bulla > 1/3 of lung volume, or single bullous defect > 8cm) or significant paraseptal emphysema [defined by numerous large (>1cm) paraseptal defects in the target lobe comprising >5% of total lung volume].
14. , or Lung pathology of nodule not proven stable or benign Radiographic confirmation of atelectasis or other scarring/fibrosis in areas of intended Coil implant
15. Use of more than 20 mg/day prednisone (or equivalent dosage of a similar steroid) daily
16. Severe pulmonary hypertension (Right Ventricular Systolic Pressure (RVSP) > 50 mm Hg (preferably measured by right heart catheterization) or other signs of Pulmonary Hypertension (PHT) with right ventricular dysfunction)
17. Severe hypercapnia (PaCO2 > 55 mmHg on room air) and/or severe hypoxemia (PaO_2 < 45mm Hg on room air, High altitude criterion: PaO_2 < 30 mm Hg)
18. Previous Lung Volume Reduction (LVR) surgery, lung transplantation, lobectomy, LVR devices or other device to treat COPD in either lung.
19. Diagnosed with alpha-1 antitrypsin deficiency
20. Diffusion Capacity of the Lungs for Carbon Monoxide (DLCO) < 20 %
21. Significant, recent or unstable cardiac disease defined as severe heart failure (Left Ventricular Ejection Fraction (LVEF) < 45% despite optimal medical management), unstable cardiac arrhythmia or coronary artery disease (angina on activity), or ischemic event in the past 6 months
22. Body Mass Index (BMI) > 30.
23. Participation in any other clinical study.
24. Subject is pregnant or lactating, or plan to become pregnant within the study timeframe.
25. If treated in France, Subject is a “personne vulnerable” as defined by French regulation.

4.3 Subject Crossover

Control group Subjects will be eligible for crossover to Treatment as soon as possible. Control subjects will be eligible for crossover if they still meet all inclusion and exclusion criteria, and if the patient is deemed to benefit from the Coil treatment by the investigator, based on best medical judgment. Crossover subjects will continue in the study through 36 months from first Coil implant. If Control subjects do not crossover to treatment, they will exit the study immediately.

4.4 Subject Withdrawal

Subjects are free to withdraw from the study at any time and will be withdrawn if they inform their PI that they no longer wish to participate or if they become lost to follow-up. The investigator may withdraw a subject at any time for safety or non-compliance with the protocol. Subject’s Withdrawal will be recorded in the EDC system along with the relevant reason(s) for study exit (lost to follow-up, withdrawn by investigator, or withdrawn by subject). Data collected prior to the subject’s withdrawal will remain part of the study record, unless country specific data protection regulations prohibit it.

5 TREATMENT OF SUBJECTS

5.1 Coil System

5.1.1 Pre-implant Patient Care

Procedural planning should be performed in accordance with the IFU. Prior to the first treatment, HRCT for assessment of the degree of emphysematous lung tissue should be used to identify the lung lobes most appropriate for treatment.

5.1.2 Implant Procedure

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

1) Sterile implants (3 sizes: 100 mm, 125 mm, and 150 mm)
2) Sterile, disposable, single-use (single-patient) Delivery System consisting of a Cartridge, a Catheter, a Guidewire and Forceps.

Each Coil implantation procedure must be performed under fluoroscopy in accordance with the IFU. Use of general anesthesia or conscious sedation is at the discretion of the bronchoscopist and anesthesiologist. A complete treatment includes two treatments: the first side (upper or lower lobe Coil implantation) followed by treatment of the contralateral side. Procedures must be staggered (contralateral procedure should be scheduled approximately 2 months after first treatment), such that both lungs are not treated during a single procedure. Lobar targeting for Coil implantation will be based on quantitative CT (QCT) densitometry analysis provided by PneumRx, per the PneumRx QCT Service.

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

Each center's PI, or a primary implanter, will perform all Coil treatments in the study if possible. If necessary, a secondary implanter will be trained as a back-up if primary implanter is unavailable.

5.1.3 Post-implant Management

Prophylactic regimen of medications should be administered according to the IFU and standard of care (SoC).

Per the IFU, a chest X-ray or still fluoroscopy image should be done post-procedure to verify Coil placement and to ensure there is no pneumothorax. A second, confirmatory chest X-ray should be done before discharge a minimum of 4 hours following the first chest X-ray. The second, confirmatory X-ray must be two views, posterior anterior (PA) and Lateral.

The Subject will be counseled on expected side-effects of the Coil procedure, including the potential AEs listed in Section 7.7. The Subject will be instructed to contact the treating physician immediately should any of the potential AEs be experienced. It is particularly important that Subjects be instructed at discharge to contact their implanting physician if they experience symptoms that may be indicative of pneumonia or CAIRS/CAO, to ensure that appropriate treatment is delivered.
Follow-up visits should be conducted per the schedule below. Study specific follow -up visits should take place during exacerbation free periods defined as 30 days with symptoms within normal day to day variability.

Treatment Group Subjects:

Visit	Visit window
Baseline visit	Eligibility, inclusion
Randomization	
First coil treatment	No more than 45 days post baseline visit
Second coil treatment	2 months +/- 4 weeks post first procedure
12-month follow-up	12 months +/- 4 weeks post first procedure
36-month follow-up	36 months +/- 4 weeks post first procedure

Control Group Subjects:

Visit	Visit window
Baseline visit	Eligibility, inclusion
Randomization	
First coil treatment	
Second coil treatment	2 months +/- 4 weeks post first procedure
12-month follow-up	12 months +/- 4 weeks post first procedure
36-month follow-up	36 months +/- 4 weeks post first procedure

5.1.4 Duration of Treatment and Follow up

All Subjects randomized to Treatment will be followed for 36 months post initial treatment. Subjects randomized to Control will be allowed immediate treatment and will be followed for 36 months post initial treatment. If Control Subjects do not crossover to treatment, they will exit the study immediately.

5.1.5 Concomitant Therapies or Interventions

Both Treatment and Control Subjects will be given SoC treatment for subjects with GOLD III or IV emphysema, defined as proven optimal medical care for stable COPD, either as presented in the GOLD guidelines (Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [Updated 2017])[7] or per national or local standards.

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 manage 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 6MWT and PFTs. Changes in medications or dosages will be recorded in the eCRF.

Pulmonary rehabilitation and maintenance therapy is recommended by the GOLD guidelines. Subjects may participate in pulmonary rehabilitation and maintenance therapy throughout their participation in the study. Post treatment pulmonary rehabilitation or a regular exercise program is strongly encouraged.

6 MEASUREMENTS AND EVALUATIONS

6.1 Treatment Group Assignment

A total of 120 Subjects were randomized in a 2:1 Treatment to Control ratio (80 Treatment group Subjects, 40 Control group Subjects).

Randomization will occur after ERC review of Subject data entered into the EDC. Site will be notified when randomization can occur after ERC review.

6.2 Pulmonary Function Central Laboratory

A PFT Core lab will provide oversight of PFT tests. This will include training of sites, certification of assessors and review of Baseline and 6 month PFT data to ensure valid measurements meeting the standards defined by ATS/ERS (Miller et al., 2005; Wagner et al., 2005; McIntyre et al., 2005, Miller et al., 2005).

6.3 Central Imaging Review

Quantitative assessment of baseline CT imaging will follow the PneumRx QCT process. Minimum scan criteria should be met as defined by the PneumRx QCT service. Sites will upload or send CD or other digital media of HRCT scan to PneumRx QCT service. PneumRx will provide site with a lung densitometry report that will report on the heterogeneity of emphysema, lobar volumes, and the degree of destruction (%LAA) for each lobe which should be used to determine the lobe of each lung to treat with Coils.

6.4 Time and Event Schedule

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

6.4.1 Baseline Visit

After the Subject provides informed consent, the Subject will be evaluated to ensure they are appropriate candidates for use of the Coil System. Eligibility to enroll in the study is assessed as described in Section 4.2.

The following evaluations will be performed as part of the Baseline visit.

- Informed Consent
- Demographic Information
- Medical history information, including comorbidities, smoking status, previous treatments of emphysema and baseline characteristics, physical activity, rehabilitation status
- Medications
- Pulmonary Function Test (PFT)
- Six Minute Walk Test (6MWT)
- Modified Medical Research Council mMRC dyspnea scale will be completed.
- QoL assessments: SGRQ, CAT, and EQ5D will be completed
- Blood gas, including CoHB for smoking cessation confirmation
- Blood test including cardiac panel with BNP test and other biomarker, if available
- Pregnancy test for females of child-bearing potential prior to radiographic procedures
- Echocardiogram
- Vital signs
- Inspiratory and expiratory HRCT (Note: a HRCT scan (inspiratory and expiratory) performed within 6 months prior to baseline may be used if it was acquired per the PneumRx QCT service protocol.)
- Chest X-Ray.

6.4.2 Procedure/Implant Visit

Enrolled Subjects randomized to the either arm will undergo the Coil Treatment in accordance with the approved (CE Mark) IFU. Procedure visits will include 2 sessions: treatment procedure for one lung, followed by treatment procedure for the contralateral side lung, which should be scheduled approximately 2 months following the initial procedure.

The following evaluations will be performed for each procedure visit:

- Pregnancy test for females of child bearing-potential prior to radiographic procedures
- Treatment date
- Duration of bronchoscopy procedure
- Duration of fluoroscopy
- Duration of hospital stay
- Lung lobe and location treated
- Number and size of implanted Coils
- Procedural SAEs (see Section 7)
- Device malfunctions
- Prophylactic medications (antibiotics, steroids – including dosage and start/stop dates)
- Fluoroscopy image immediately post procedure – should be captured in eCRF
- Chest X-ray (PA and Lateral) before discharge at least 4 hours following the fluoroscopy image

6.4.3 Follow-Up Visits

Follow-up office visits will be conducted at 12, and 36 months post first Endobronchial Coil treatment for both Treatment group subjects and Crossover subjects..

Follow-up visits should be conducted per the schedule below. Study specific follow-up visits should take place during exacerbation free periods defined as 30 days with symptoms within normal day to day variability.

12- and 36-month study follow-up visits will include:

- PFT
- AE review
- Medications
- Inspiratory and expiratory HRCT

6.4.4 Patient completion or early withdrawal

Subjects who receive the Treatment procedure complete the study 36 months after the initial implant procedure or when they choose to withdraw from the study, if earlier than 36 months post-procedure. In the event of a continuing SAE related to the Coil system, the subject will be asked to return for follow-up until the SAE has resolved or is deemed to be continuing indefinitely. Control subjects who do not crossover to treatment will exit the study immediately.

6.4.5 Data Collection

Informed consent, baseline assessments, procedure data, adverse event data, medications, and effectiveness measures will be collected and entered into the EDC system. The eCRFs will be completed by the PI (or an authorized member of the investigator's staff) at the participating site and entered into the EDC database. All entries into the EDC system will be in English.

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

6.5 Trial Evaluations and Procedures

6.5.1 Informed ConsentProcess

All Subjects must sign an ICF approved by the relevant IEC to be enrolled in the study.
The PI or delegate will review the treatment plans with the Subject, and the Subject will have an opportunity ask questions about trial procedures, the required visit schedule, risks and benefits of the study treatments, and alternative treatment options prior to signature. The Subject will receive a copy of the signed ICF to keep for their records.

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

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

6.5.2 Demographics

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

6.5.3 Medical History

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

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

Smoking status and physical activity will be captured.

6.5.4 Vital Signs, Blood panel and Echocardiogram

Assessments of blood panel at baseline will follow routine standards (Haemoglobin, Hematocrit (HCT), White Blood Cells, Platelet count, Prothrombin time, Eosinophil leucocytes, INR, Sodium, Potassium, Chloride,

Glucose, Total Protein, Albumin, Blood Urea Nitrogen, Creatinine, Cardiac panel including BNP-test and other biomarker if available).
Assessment of pulmonary hypertension and left ventricular ejection fraction will be performed at baseline and

documented in the CRF.

Pregnancy test need to be performed for females of child-bearing potential prior to radiographic procedures at baseline and implant procedures.

6.5.5 Pulmonary Function Test

PFT will include post bronchodilator Spirometry, Lung plethysmography, and $DLCO_{sb}$ at Baseline and Follow- up Visits. Baseline Visit should also include pre bronchodilator spirometry to assess bronchodilator reversibility. Tests should be conducted per ATS/ERS standards and will be assessed by an independent, 3rd party vendor for adherence to these standards to ensure consistency and quality of data collection at baseline.

6.5.6 Six Minute Walk Test

6MWT will be conducted by a qualified individual according to ATS/ERS Guidelines as specified in the schedule of visits.

6.5.7 Medication and Prior Treatment History

The use of concurrent respiratory, cardiac, anticoagulant, antibiotic, and steroid medications (medications taken within 30 days of screening and during the conduct of the trial) will be recorded and entered in to the EDC.

6.5.8 Eligibility Review Committee

Data from subjects who have signed the ICF and are considered by the treating physician to be eligible to receive the Coil treatment as part of the trial, should be submitted to the ERC for final assessment of eligibility for the study. The ERC will review the data in accordance with the procedures agreed to in the ERC Charter.

The ERC will consist of a minimum of 5 interventionalists. The purpose of the ERC is to provide peer-review from interventionalists who are extremely knowledgeable in the procedure and patient selection to confirm eligibility and suitability of subjects selected for participation in the ELEVATE trial. The ERC shall provide the final decision with regard to enrollment.

Data that will be provided to the ERC for review include PFT, medical history, and HRCT with QCT data. Two (2) of the 5 ERC members will be selected via random number generation. A member may decline to evaluate a subject file; in this case another member will be randomly selected. If 2 members agree to either approve or deny enrollment, that decision will be final. If the 2 members disagree, then a third, randomly selected member will independently review the case to determine eligibility. ERC members will document the reason for denial if the subject is not deemed not eligible for the study. The process will be blinded, such that a member receiving a request for review will not know how others have voted. An ERC member cannot review his /her own subject, in which case another ERC member will be randomly selected to review the data.

The determination of study eligibility will be recorded on the relevant eCRF.

6.5.9 Expert Radiology Review

All baseline CT scans will be reviewed by expert Radiologists in accordance with the ELEVATE Radiology Review Manual. An eCRF providing a detailed pulmonary radiologic assessment will be completed by one of 3 independent radiologists for each subject. The report from the expert Radiologist will be reviewed by the ERC as part of the subject eligibility assessment.

6.5.10 Randomization/Enrollment Event

If a Subject is deemed eligible to participate in the trial, the Subject is assigned the next sequential Randomization Assignment via the study EDC. Randomization will be determined using assignment by a computer-generated

randomization scheme. Upon randomization/enrollment, each Subject will be assigned a unique numeric Subject identity code.

A total of 120 Subjects were randomized in a 2:1 ratio Treatment to Control respectively (80 Treatment group subjects, 40 Control group subjects).

6.5.11 Implant Procedure Record

Details on the Coil treatment procedures performed on study Subjects will be recorded in the relevant eCRF. Procedure data collected and entered into the EDC system will include:

- Treatment date
- Duration of bronchoscopy procedure
- Duration of fluoroscopy
- Duration of hospital stay
- Lung lobe and location treated
- Number and size of implanted Coils
- Procedural SAEs (see Section 7)
- Device malfunctions
- Prophylactic medications (antibiotics, steroids – including dosage and start/stop dates)

6.5.12 Coil Removal

Coil removal following implantation (defined as removal of a Coil after termination of the Coil implantation procedure) must be medically indicated and performed in accordance with the IFU. Each occurrence of post - procedure Coil removal will be recorded as an SAE in the appropriate eCRF. Recommendations regarding Coil removal will be provided to the study site as part of the Study Operational Instructions (SOI). To perform bronchoscopic Coil removal subsequent to the implantation procedure, you must have a therapeutic bronchoscope with a minimum 2.0mm inner diameter working channel and a 65cm maximum working length.

6.5.13 Quality of Life

QoL instruments suitable for Subjects being treated for emphysema (i.e., SGRQ, CAT, EQ5D, and mMRC) will be administered at study visits as specified in the schedule of visits.

6.5.14 Imaging

Chest X-rays (PA and lateral) will be performed at Baseline and post-procedure in accordance with the IFU. These will be documented in the appropriate eCRF, subject-identifying information redacted, and submitted to Boston Scientific Corporation upon request.

HRCT will be performed at the Baseline Visit and 12 and 36 month Follow-up Visits. HRCT will include both inspiratory and expiratory scans completed per the recommendations provided as part of the PneumRx QCT service.

7 ADVERSE EVENTS

7.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a study subject, user or other persons whether or not related to the investigational medical device.

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

7.1.1 Definitions of SAE/SADE/USADE/Device Deficiency

Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:

- results in death;
- Led to serious deterioration in the health of the subject , that either resulted in
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - In-patient or prolonged hospitalization, or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Led to fetal distress, fetal death or a congenital anomaly/birth defect.

Serious Adverse Device Effect (SADE)

An SADE is an adverse effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)

A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling.

A device malfunction is the failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use.

:

SAE information will be collected throughout the study. SAEs will be recorded on the eCRF by the investigator or authorized designee. Event, date of onset, duration, serious/non-serious, anticipated/not anticipated, severity, relationship to the procedure/device, outcome, and action taken will be recorded. Additional information on specific events may be requested in the eCRFs. All events must be recorded in English. Any source documentation required to investigate SAEs for reporting must be translated to English.

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

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

All SAEs that are determined to be related to the device or procedure will be evaluated for reportability in accordance with MEDDEV 2.7/3 revision 3. The investigator will be responsible for submitting source documentation to PneumRx in order to document the investigation for the event.

7.2 Recording Adverse Events (AE)

Subjects will be required to report AEs of interest. At each study visit, site staff will ask general, open-ended, non-directed questions to obtain information about AEs. If the subject is unable to attend a trial visit, AEs can be collected by telephone contact. At any time during the study, the Subject may volunteer information that meets the definition of an AE.

The investigator should record all SAEs and specific Respiratory AEs of interest in the eCRFs. Below is a list of specific Respiratory AEs of interest that should be recorded:

- COPD Exacerbation
- Hemoptysis
- Pneumothorax
- Lower Respiratory Tract Infection/Pneumonia
- Tissue Reaction, Localized (a.k.a. Coil Associated Inflammatory response syndrome (CAIRs), also called Coil Associated Opacity (CAO) in the IFU)

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

For each SAE and specific respiratory AEs of interest, the following information will be recorded at a minimum:

- AE term
- Serious/non-serious
- Severity
- Action taken
- Relationship to Coil System
- Expected/Unexpected
- Date and time of onset
- Date and time of resolution

Was the subject withdrawn from the study due to the AE

Any SAE experienced by a subject will be followed until the SAE has resolved to the PI's or sub-investigator's satisfaction or is considered stable. If a problem still exists, then the PI or sub-investigator at his/her discretion will ask the subject to come back to the clinic for further evaluation. SAEs should be managed as discussed in Section 7.5.

7.3 Recording and Reporting Device Deficiencies

All device deficiencies must be reported to BSC within 24 hours of becoming aware of the event. The report should be submitted in English with all available information. Devices should be returned to Boston Scientific Corporation via the standard commercial method.

7.4 Device and Procedure Causality Assessment

The PI or sub-investigator must indicate whether he/she believes the SAE is unrelated, possibly related (reasonable possibility that the investigational device and/or procedure caused the SAE) or probably related to the medical device or procedure.

7.5 Submitting Expedited Safety Reports

All SAEs and UADEs (defined above) must be reported to the sponsor via EDC within 24 hours of learning of the event. Any supporting source documents required to investigate the SAE or USADE must be provided as soon as possible to PneumRx.

The sponsor must promptly inform the Independent Ethics Committee (IEC), both CPP and ANSM in France, of all USADEs and SAEs as required per site IEC requirements. These events will be reported by the sponsor, as appropriate, to the regulatory authorities according to relevant jurisdictional m edical device regulations. As the Coil System is a CE marked and commercially available device in the EU, Medical Device Vigilance System reporting requirements are applicable to adverse incidents reported through this study.

7.6 Periodic Safety Reporting

Periodic annual safety reports will be submitted to the ANSM and will be communicated across all study centers.

7.7 Expected Adverse Events

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

- Allergic Reaction
- Aspiration
- Bleeding or Hemorrhage
- Bronchial Blood Clot
- Bronchial Ulceration
- Emphysema, Subcutaneous
- Hemoptysis, including Severe Hemoptysis
- Hoarseness
- Hypertension
- Hypotension
- Pneumonia*
- Pneumonitis
- Pneumothorax
- Procedure-Related Complication (e.g., fever, spasm)
- Pulmonary Embolism

- Bronchospasm
- Cardiac Arrhythmias
- COPD Exacerbation
- Cough
- Death
- Device Dislocation
- Dyspnea
- Infection
- Inflammation
- Lung Abscess
- Pain
- Painful Respiration
- Pleural Effusion
- Pleural Fistula
- Respiratory Distress
- Respiratory Failure
- Respiratory Tract Infection
- Sedation – Related Complications (e.g., nausea, vomiting, headache)
- Sepsis
- Tissue Reaction, Localized (a.k.a CAIRs/CAO)
- Tissue Trauma, Procedural (e.g., tissue perforation, dissection)

*A recognized, non-infectious localized tissue reaction, also termed Coil Associated Inflammatory response syndrome (CAIRs), also called Coil Associated Opacity (CAO) in the IFU, may occur in the area of implanted coils and is typically diagnosed on imaging (chest X-ray or CT scan). This is believed to be an inflammatory response that presents with pneumonia-like symptoms, including chest or pleuritic pain/discomfort, increased dyspnea, fatigue, and/or haze or infiltrates on chest X-ray, and may be difficult to distinguish from pneumonia. While some degree of CAIRs/CAO has been observed in clinical trials up to 2 months following the Coil procedure, many of these events are asymptomatic or symptomatically mild, resolve with limited intervention, and do not develop into serious adverse events (SAEs). However, CAIRs/CAO can become severe and require prompt and specific intervention. Thus, subjects are advised to contact their treating physician immediately for follow-up if they experience pneumonia-like symptoms.

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

8 STATISTICAL CONSIDERATIONS

8.1 Trial Design and Determination of Sample Size

A total of 120 Subjects were randomized in a 2:1 ratio of Treatment to Control respectively (80 treatment group subjects, 40 Control group subjects).

8.2 Statistical Analysis

The statistical analysis plan (SAP) will be a separate document and will be updated as required, in association with any protocol amendments. The plan will include detailed descriptions of analysis methods, tables, listings and figures and will describe statistical programming considerations.

8.3 Analysis Populations and Sub-Groups

Intent to Treat Population (ITT) – All randomized Subjects, regardless of whether or not treatment was attempted.

Per Protocol Population (PP) - All randomized Subjects without major protocol deviations (see Section 10.9).

Safety Population - All randomized Subjects who enter the bronchoscopy suite for the initial Coil procedure.

8.4 Baseline and Demographic Characteristics

Descriptive statistics will be used to summarize Subject demographics and baseline characteristics.

8.5 Efficacy Analyses

All effectiveness analyses will be analyzed on the ITT population through the 6-month visit, using descriptive statistics to summarize results separately for treatment and control groups. No comparative inferential statistics will be conducted. In addition, descriptive statistics will summarize percent change in FEV_1 from baseline to 12 and 36 months for all coil treated subjects. Baseline will be defined as the last measurement taken prior to coil treatment.

Descriptive statistics will summarize effectiveness endpoints at 12, 24 and 36 months follow-up.

8.6 Safety Analyses

Safety analyses will be conducted on the safety population defined as those Subjects who enter the bronchoscopy suite for the initial Coil procedure. AE and SAEs will be summarized by treatment group based on MedDRA codes. Incidence rates through 6 months will be summarized for treatment and control groups. For coil treated subjects, events will also be summarized by relevant, discrete time periods including the Treatment recovery period (30 days from either treatment), as well as through the 12- and 36-month follow-up periods.

9 DATA MANAGEMENT

Data from the study will be collected via EDC. Clinical data will be sent in a secured validated format to Boston Scientific Corporation on an ongoing basis.

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

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

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

AEs will be coded according to the version of MedDRA agreed upon by Boston Scientific Corporation.

Electronic data checks for accuracy will be built into the EDC system. Data analyses will be performed and reviewed in an aggregate and de-identified fashion. These reviews will aid in continued refinement of the data collection process and analysis. Access to de-identified data will be provided to Boston Scientific Corporation .

10 LEGAL//ETHICS AND ADMINISTRATIVE PROCEDURES

10.1 Good Clinical Practice/Regulatory Compliance

The procedures set out in the this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigators abide by ISO 14155:2011 E, Clinical investigation of medical devices for human subjects – Good Clinical Practice, applicable state and local regulations; and the standard operating procedures (SOPs) of Boston Scientific Corporation, and its designee(s).

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

10.2 Trial Site and Investigator Qualification

This study will be performed by qualified investigators at up to 30 sites across Europe.

All participating study sites will be reviewed by the study sponsor to verify that they are able to meet the requirements of the study. Each participating institution must have an established IRB/IEC and clinical protocol review process that is compliant with ISO I4155, ensuring the clinical protocol can be adequately evaluated and approved at the institutional level.

10.2.1 Investigator CV

The investigator will provide the sponsor or designee with his/her signed Curriculum Vitae (CV), as well as those of any sub-investigator or staff personnel with significant study responsibilities.

10.2.2 Statement of Investigator

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

10.2.3 Financial disclosure

Financial disclosure statements will be completed for the investigator and all sub-investigators to disclose potential conflicts of interest (ISO 14155). The investigator is responsible for ensuring completed and signed financial disclosure forms are submitted to the sponsor or designee. A copy of the form(s) will be given to the investigator for their files. Financial disclosure information will be collected by the sponsor before the s tart of the study and maintained for one year after study completion.

10.2.4 Investigator Recruitment

All investigators will be specialists in interventional bronchoscopy or will be experienced thoracic surgeons who are experienced with the Coil procedure. Potential investigators will be recruited and approved by Boston Scientific Corporation. Once the investigator is approved, the investigators will obtain approval from their IEC.

One physician at each site will agree to act as the PI. Each center's PI, or one primary implanter, will perform all coil treatments in the study. Additional physicians at each site may also participate as sub-investigators; however, coil implantations for ELEVATE (treatment and crossover) will be performed by one primary implanter if possible. If necessary, a secondary implanter will be trained as a back-up should scheduling or logistical issues arise.

10.2.5 Investigator Training

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

10.2.6 Responsibilities

10.2.6.1 Sponsor Responsibilities

The sponsor of this study is Boston Scientific Corporation. The sponsor is committed to:

- Protecting the rights, health, safety and welfare of study Subjects by the review of IEC approvals and verification of the Subject informed consent process.
- Informing the clinical investigator of any new information that may affect the health, safety or welfare of the Subjects, or which may influence their decision to continue participating in the study.
- Periodically reviewing the data to ensure that the investigator is in compliance with the protocol and the investigator's agreement.
- Providing the investigator with the study protocol and access to the EDC system and trial eCRFs.
- Selection and approval of investigators to participate in this trial.
- Maintaining a system of study documentation associated with the trial and corresponding sites and investigators.
- Providing training on key elements of the protocol, including Subject inclusion/exclusion criteria, EDC system, and what constitutes Follow-up.
- Oversight of the Eligibility Review Committee
- Review eCRFs to ensure completeness and accuracy of study data. Sites will be asked to resolve discrepancies via the EDC system.
- Acting as a resource for questions after training for the duration of the trial.

10.2.6.2 Responsibilities of the Principal Investigator

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

- Ensuring that all Subjects entering the study conform to the Subject inclusion criteria and that no exclusion criteria apply.
- Obtaining IEC approval from the respective institution to perform the procedure, prior to enrolling any Subjects in the study. The informed consent document to be used will also be submitted by the investigator to the IEC for approval prior to initiation of the investigator's participation in the study. The PI is also responsible for providing any other additional documentation relevant to the study as required by the IEC for their complete review. Written assurance of IEC approval of the study plan and the informed consent document must be provided to Boston Scientific Corporation, Inc. prior to initiation of the study at the site.
- Obtaining written Informed Consent from each Subject prior to enrollment and verifying that the correct and approved IEC version is used. The signed ICF will be maintained in the Subject's medical record, and a copy of the signed ICF will become an integral part of each case report file retained by the investigator. A copy of the signed ICF shall be given to the Subject who signed the ICF.

- The investigator will review, correct as needed, and sign off on the accuracy and completeness of the data entered in the EDC system. Original laboratory reports, procedure notes, etc. are to be retained by the investigator, and the resulting data shall be entered onto the appropriate eCRFs.
- The investigator will report all SAEs, USADEs, and device deficiencies to the sponsor via EDC within 24 hours of learning of the event.

10.2.7 Site qualifications

The Institution must have appropriately qualified investigators and clinical / administrative support staff in place to adequately conduct the study in compliance with the relevant guidelines and regulations (see Section 10.1) and to treat emphysema with Coils.

10.3 Institutional Review Board (IRB)/Independent Ethics Committees (IEC)

10.3.1 Institutional approval of the protocol

It is the responsibility of the PI to submit this protocol, the informed consent document (approved by the sponsor or designee), relevant supporting information and all types of Subject recruitment information to the IEC for review and approval prior to site initiation. A copy of the written approval of the protocol and ICF must be received by the sponsor or designee prior to the recruitment of Subjects at the site.

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

The investigator, will be responsible for keeping the IEC apprised of the progress of the trial, any changes to the protocol, deviations from the protocol and SAES or USADEs.

10.4 Informed Consent – Ethical Compliance

It is the responsibility of the investigator to obtain written Informed Consent from Subjects prior to the conduct of any trial procedures. All consent documentation must in accordance with applicable regulations and GCP. Each Subject or the subject's legally authorized representative is requested to sign the ICF after the subject has received and read the written information and received an explanation of the study, including but not limited to: the objectives, treatment plan, potential benefits and risk, inconveniences, alternative treatment options and the Subject's rights and responsibilities. The Subject has the right to decline participation or withdraw from the study at any time for any reason without fear of retribution. A copy of the informed consent documentation (Consent Form or Subject Information and Consent Form, as applicable) must be given to the Subject or the Subject's legally authorized representative. If applicable, it will be provided in a certified translation of the Subject's local language.

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

Each investigator will provide the sponsor with a copy of the IEC approved consent forms and a copy of the IRB/IEC written approval, prior to the start of the trial. Additionally, if the IEC required modification of the sample Subject Information and Consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

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

10.5 Subject Privacy and Confidentiality

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

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

As part of required content of the informed consent, the Subject must be informed that his/her records will be reviewed by the sponsor, sponsor representative and/or a representative of the appropriate regulatory agency. The informed consent or related document will also state that patient privacy will be maintained pursuant to both European and local regulation.

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

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

10.6 Trial Monitoring

Monitoring of the study will be detailed in the study monitoring plan and will be performed by qualified personnel from the sponsor or sponsor designee. This trial will be Risk-Based Monitored. Monitoring will consist of centralized monitoring with an escalation to remote or on-site monitoring if needed.

Centralized monitoring will be conducted to look for timely entry of data into EDC, completion of trial visits within windows and valid endpoint measurements. Monitoring can be escalated per the Monitoring Plan.

Remote monitoring can be conducted over the phone or by webcast and will concentrate on correcting issues found during centralized monitoring or to request additional details. Monitoring can be escalated to on-site visits per the monitoring plan.

During on-site monitoring visits, the progress of the study will be discussed with the investigator or his/her representative. The ICFs will be reviewed for signatures and the eCRFs checked for completeness and accuracy. Subject source data must be available for review. The investigator and his/her staff are expected to cooperate with the study monitor and be available during at least a portion of the monitoring visit to review the eCRFs and any queries/resolutions, answer questions, and provide any missing information.

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

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

10.7 Modification of the Protocol

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

10.8 Suspension or Termination of Trial

BSC reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/IECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination. Possible reasons for premature study termination include, but are not limited to, the following:

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.

10.9 Departure from Protocol

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

Protocol deviations will be tracked in the EDC, and categorized as follows:

- Major protocol deviations
- Minor protocol deviations

Major protocol deviations are defined as:

- Enrollment eligibility criteria deviations
- Informed consent process was not followed
- Endpoint assessments not performed to standards
- Endpoint testing not performed
- Procedure not performed in accordance with the IFU
- SAE not reported per protocol
- Randomization errors

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

10.10 Potential Risks to Subjects

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

10.11 Potential Benefits to Subjects and Society

In the future, patients may benefit from results that lead to a better understanding of the safety and effectiveness of the Coil System in the broader context of other options for treating emphysema. In previous studies of the LVRC, many subjects have experienced improvements in lung function, exercise capacity, and quality of life.

The health care system may benefit from a better overall understanding of safety, effectiveness and costs of this procedure.

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

10.12 Financial Considerations

10.12.1 Subject Compensation:

Subjects will not be compensated for their participation in the study. Subject reimbursement for travel may be considered.

10.12.2 Physician Compensation:

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

10.13 Recording, Access to and Retention of Source Data

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

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

All key data must be recorded in the Subject's source documents including the informed consent acquisition.

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

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

As described in the ICH GCP Guidelines, 'essential documents', including eCRFs, source documents, consent forms, laboratory test results, device inventory records, should be retained by the investigator until at least two years after the last approval of a marketing application in an ICH region or at least two years have elapsed since the formal discontinuation of a clinical development of the IP. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. The investigator must obtain written permission from the sponsor prior to destruction of any trial document.

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

10.14 Electronic Case Report Forms

The investigator is responsible for maintaining adequate and accurate source documents from which accurate information will be transcribed in to eCRFs that have been designed to capture all observations and other data pertinent to the clinical investigation. eCRFs should be completed by the investigator or delegate as stated on the Delegation of Authority Log.

Overwriting of information or use of liquid correcting fluid is not allowed in source documentation.

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

10.15 Publications

All manuscripts, abstracts or other modes of presentation arising from the results of the trial must be reviewed and approved in writing by the sponsor, in advance of submission. The review is intended to protect sponsor proprietary information existing either at the date of commencement of the trial or generated during the trial. No individual investigator may publish results from his/her site until after publication of the primary manuscript describing the full trial population.

The detailed obligations regarding the publication of any data, material results or other information that is generated or created in relation to the trial shall be set out in the agreement between the investigator and sponsor, in accordance with the Boston Scientific Corporation Publication Policy.

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

10.16 Audit/Inspections

To ensure compliance with relevant regulations, data generated by this trial must be available for inspection upon request by representatives of the regulatory authorities, the sponsor and its representatives, and the IEC for each trial site.

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