



**Lung Function Improvement after Bronchoscopic Lung Volume
Reduction with Pulmonx Endobronchial Valves used in Treatment of
Emphysema
(LIBERATE STUDY)**

U.S. Investigational Device Exemption (IDE) Clinical Investigational Plan

#630-0012_H

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Executive Summary

Study Device and Intended Use	The Pulmonx Zephyr Endobronchial Valve (EBV) is an implantable bronchial valve intended to decrease volume in targeted regions of the lung. It is indicated for the treatment of patients with hyperinflation associated with severe heterogeneous emphysema in regions of the lung that have little or no collateral ventilation as assessed by the Chartis System.
Study Purpose	The purpose of this study is to assess the safety and effectiveness of bronchoscopic lung volume reduction (BLVR) using the Pulmonx Endobronchial Valve (EBV) in treated study participants compared to control participants to support a premarket approval application to FDA.
Study Design	This will be a multi-center, prospective, randomized, controlled study with EBV treatment statistically evaluated using Intent-to-Treat (ITT) analyses. A maximum of 183 study participants, who meet study entry criteria, consisting of screening eligibility criteria, baseline eligibility criteria, and procedure eligibility criteria, will be enrolled. Safety and effectiveness of BLVR using the Pulmonx EBV will be evaluated at 1 year. For study participants who have been treated with EBV, a secondary valve intervention such as valve removal, replacement, or adjustment may be considered during the study follow-up. Long-term data will be collected annually for EBV-treated study participants through 5 years. Per the regulatory plan agreed to with FDA, 1 year of follow-up is required pre-approval and the remaining 4 years of follow-up will be conducted post-approval.
Study Population	The study population will be comprised of 183 study participants with severe heterogeneous emphysema as defined by the study eligibility criteria. The study participants will be randomly assigned at a 2:1 ratio to the study treatment along with optimal medical therapy or to optimal medical therapy alone.
Study Objective	The objective of the study will be to evaluate lung function changes and adverse events after BLVR using the Pulmonx EBV.
Primary Effectiveness Endpoint	The percentage of study participants in the EBV treatment arm meeting the clinically significant threshold of $\geq 15\%$ improved forced expiratory volume in one second (FEV ₁), obtained immediately following bronchodilator therapy, as compared to the percentage in the control arm at 1 year post-procedure.

Safety Endpoint

Evaluation of the short- and long-term adverse events profile of the EBV treatment arm during the treatment period, defined as the day of the study procedure until 45 days after the study procedure (short), and in the post-treatment period, defined as 46 days after the study procedure until the 1-year follow-up visit (long).

Treatment Lobe Volume Reduction (TLVR) for the Treatment Arm

- TLVR, measured as the 'absolute change from baseline' for treated lobe volume as seen via HRCT (high resolution computed tomography), will be evaluated at 45 days and 1 year.
- TLVR, measured as the 'percentage change from baseline' for treated lobe volume as seen via HRCT, will be evaluated at 45 days and 1 year.

St. George's Respiratory Questionnaire (SGRQ)

- Difference between study arms in 'absolute change from baseline' for SGRQ score at 1 year.

Secondary Effectiveness Measures

FEV₁

- Persistence of treatment effect will be evaluated by determining the difference between study arms for 'absolute change from baseline' for FEV₁ at 45 days, 6 months, and 1 year.
- Persistence of treatment effect will be evaluated by determining the difference between study arms for 'percentage change from baseline' for FEV₁ at 45 days, 6 months, and 1 year.

6-Minute Walk Distance (6MWD)

- Difference between study arms in 'absolute change from baseline' for 6MWD at 1 year.
 - Difference between study arms in 'percentage change from baseline' for 6MWD at 1 year.
-

Additional Measures

Mean changes and/or changes measured using responder analyses for:

- Spirometry, including FEV₁, forced vital capacity (FVC) and the ratio of FEV₁/FVC
- Body plethysmography, including residual volume (RV), inspiratory capacity (IC), functional residual capacity (FRC), total lung capacity (TLC), and the ratios of RV/TLC and IC/TLC
- SGRQ global and domain (i.e. 'symptoms', 'activity', and 'impacts on daily life') scores

- Modified Medical Research Council (mMRC) dyspnea scale score
 - BODE Index
 - Transitional Dyspnea Index (TDI) from Baseline Dyspnea Index (BDI)
 - COPD Assessment Test (CAT)
 - SF-36 Health Survey
 - EQ-5D Health Survey
 - Health Care Utilization Questionnaire
 - 6 minute walk distance
 - Borg scale dyspnea scores before and after 6MWD test
 - Change in use of 'maintenance' medications, including bronchodilators, corticosteroids, antibiotics, and anti-inflammatories
 - Daily diary (EXACT-PRO, pulmonary rehabilitation compliance, health status changes)
 - Carbon Monoxide Diffusing Capacity (DL_{CO})
 - Lung radiographic features
 - Blood chemistry measures
-

Crossover of Control Study Participants

After completing the 1 year visit, if a control study participant continues to qualify for the study treatment, (s)he will be permitted to crossover to the study treatment.

Interim Data Analysis

An interim data analysis designed to evaluate effectiveness for continuing crossover of control arm study participants after the 1-year follow-up visit to EBV treatment will be performed when 74 study participants have completed the 1-year follow-up. If crossover of control arm study participants is found to be justified by the interim analysis then crossover of control arm study participants after (s)he has reached the 1-year time point may be continued. The results of the interim analysis will be reviewed by the DSMB and FDA. If the DSMB recommends not continuing crossing control arm participants to EBV treatment then those control arm patients who have not crossed over will exit from the study per protocol after the 1-year visit.

Long-Term Follow-Up

Data will be collected annually through 5 years for study participants receiving the study treatment. Per the regulatory plan agreed to with FDA, 1 year of follow-up is required pre-approval and the remaining 4 years of follow-up will be conducted post-approval. The annual 2-, 3-, 4-, and 5-year data will consist of FEV₁ and adverse events.

CLINICAL INVESTIGATION PLAN AGREEMENT FORM

I agree to the terms of this clinical investigation plan. I will conduct the investigation according to the procedures specified herein.

Site No.:

Principal Clinical Investigator

Name:

Signature: _____

Date: _____

1.0 BACKGROUND

1.1 Pathophysiology of Emphysema

Emphysema is a debilitating and progressive disease that presents a major health problem globally. It is characterized by gradual, irreversible destruction of lung tissue and loss of elastic recoil within the lungs, causing loss of ability to expel air and efficiently absorb oxygen. Emphysema dramatically reduces a person's expiratory function, leading to dyspnea (breathlessness), lessened capacity for performing daily living activities, and reduced quality of life.

Breathlessness in emphysema is thought to result from three primary problems: 1) loss of parenchymal tissue for gas exchange, 2) gas trapping which limits expiration, and 3) altered breathing mechanics of the chest wall and diaphragm as a result of hyperinflation. Breathlessness during exercise worsens as patients must breathe at even higher lung volumes to exchange sufficient air (dynamic hyperinflation). As emphysema progresses, the diseased, hyperinflated areas of the lung eventually fill the chest cavity, leaving less room for functioning lung tissue and preventing adequate diaphragmatic and chest wall function.

1.2 Management of Emphysema: Lung Volume Reduction Surgery (LVRS)

The goals of therapy for emphysema are to slow the progressive decline in lung function, prevent and shorten exacerbations of the disease, improve exercise capacity and quality of life, and prolong survival [1]. Medical treatment for palliating symptoms associated with emphysema is well established and widely used but is of limited efficacy [2,3].

Lung volume reduction surgery (LVRS) has been shown to offer relief to patients suffering from emphysema when other treatment options fail [4-10]. The physiologic basis of LVRS is directly tied to the pathophysiology of emphysema. With LVRS, the physician aims to reduce hyperinflation by removing the most hyperinflated portions of the lung, leaving the remaining lung room to expand and therefore function more efficiently and allow improved breathing mechanics. The National Emphysema Treatment Trial (NETT) compared LVRS to optimal medical management in 1,218 patients with advanced emphysema of various morphologies [10]. Clear clinical benefits were observed with LVRS over optimal medical management.

After LVRS, improvement in dyspnea and increases in exercise tolerance correlate best with reduced hyperinflation and increased transdiaphragmatic pressure resulting from repositioning of the diaphragm and recruitment of inspiratory respiratory muscles [11,12]. An additional mechanism is increased elastic recoil of the lung, probably because the most severely hyperinflated part of the lung is resected. These changes often result in marked improvement of lung function, commonly reported using forced expiratory volume in one second (FEV₁). Moreover, LVRS has also been found to lengthen survival in patients with heterogeneous emphysema [13,14]. Nevertheless, the reported risks of procedure-related morbidity and mortality with LVRS are of substantial concern [15].

1.3 Bronchoscopic Lung Volume Reduction (BLVR)

A less invasive approach to LVRS using the bronchoscope has long been sought. The goal of bronchoscopic lung volume reduction (BLVR) is to obtain similar physiologic benefits as LVRS, without the risk of chest surgery. The aim in BLVR procedures is to

reduce or eliminate the impact of hyperinflated lung tissue on adjoining higher functioning lung tissue.

1.4 BLVR with the Pulmonx Endobronchial Valve (EBV)

Pulmonx has developed a one-way valve that can be implanted during bronchoscopy, where the aim is to block inspiratory airflow into targeted, hyperinflated regions of the lung, while permitting exhaled gas to escape. When an endobronchial valve is placed in a bronchial lumen and is performing as intended, air is restricted from going through or around the valve during inspiration and gas is allowed to vent during expiration. The Pulmonx Zephyr valve has been previously studied in a large multi-center, prospective, randomized trial [16,17]. At that time, the Zephyr valve was manufactured by Emphasys Medical Inc. (Redwood City, CA).

1.5 Pivotal Investigation of the EBV: The VENT Study (IDE#G020230)

The Endobronchial Valve for Emphysema Palliation Trial (VENT study) was a prospective, randomized, controlled study conducted in the United States to evaluate the Zephyr EBV in comparison with optimal medical treatment in patients with heterogeneous emphysema. The Zephyr EBV is a silicone covered stent-like device with a built-in one-way valve that lets air out of, but not into, targeted regions of the lung. The valve was placed bronchoscopically into the target lobar bronchus.

The VENT study results were reviewed by FDA as part of PMA P070025 and were presented at a meeting of the Anesthesiology and Respiratory Therapy Devices Advisory Panel in December 2008. While the effectiveness outcomes for the EBV-treated study group were significantly improved over the control group, and the results of the study successfully met the pre-determined primary endpoints, the Advisory Panel and FDA concluded that the mean results did not reach minimally important clinical difference. However, it was recognized that outcomes with EBV appeared to be clinically meaningful in a discrete subgroup of patients.

1.6 Learnings from the VENT Study

As presented to FDA during the PMA review of the Zephyr endobronchial valve, analyses of VENT study participant subgroups indicated that the Zephyr EBV had higher effectiveness in study participants who had certain lung radiographic features. Key findings of the VENT study data indicated that EBV therapy was optimized in patients who had high resolution computed tomography (HRCT) findings suggestive of a complete fissure between the EBV-treated lobe and the adjacent lobe [16,17].

Complete fissure, as determined via qualitative assessment of HRCT scans, is thought to correspond to lack of inter-lobar collateral ventilation (CV) [18]. Researchers in the clinical community have theorized that presence of lobar CV is likely to mitigate clinical response to EBV treatment [19,20].

1.7 Collateral Ventilation Impacts Lung Volume Reduction

During the 1930's, Van Allen and Lindsog [21] were the first to demonstrate experimentally that presence of CV allows inter-lobar communication of air. As the use of surgical treatments for emphysema grew and direct observation of the *in vivo* tissue condition was possible, collateral air flow was found to be linked to the regional over-distention and air trapping known to exist with emphysema [22]. Collateral channels were

found to occur more frequently in emphysema patients than in normal subjects and the channels were wider and less resistant during exhalation [23].

Understanding CV pathways in endobronchial lung volume reduction candidates and having the ability to selectively target treatment effectively has become an important clinical goal. It has been hypothesized by researchers in the clinical community that CV was likely to be a primary reason for the infrequency of observing clinically significant lung volume reduction in patients participating in the VENT study. Assessment of inter-lobar CV, as described below, will be performed in the proposed trial as a means to select study participants who are likely to experience significant lung volume reduction with the Pulmonx Zephyr EBV.

1.8 Measurement of Collateral Ventilation

In 2005, Pulmonx, Inc. developed an integrated system for CV assessment now known as the Chartis[®] Catheter and Chartis[®] Console. The Chartis System is a catheter-based device that allows sealing of a lung compartment and measurement of air pressure and flow from the sealed compartment (K111522 for Chartis Catheter and K111764 for Chartis Console¹). Based on these measurements, CV within a lobe targeted for endobronchial treatment can be identified.

Safety and feasibility of obtaining measurements predictive of atelectasis after EBV treatment using the Chartis system has been previously reported [24] (NCT00684892). Gompelmann and colleagues observed that in 18/20 (90%) of the EBV treated cases, post-procedure atelectasis response, as visualized using chest X-ray, matched the Chartis system prediction of presence or absence of collateral ventilation. No adverse events associated with use of the Chartis system were observed.

In a later, larger, prospective multi-center study conducted in Germany, the Netherlands, and Sweden, the Chartis System was used successfully as a tool to identify emphysema patients who would achieve clinically significant lung volume reduction after EBV treatment [25] (NCT01101958). Patients were prospectively classified using the Chartis System during the bronchoscopy procedure—prior to EBV placement—as having or not having CV in the targeted treatment lobe. The patients who were classified as having little or no lobar CV had significant target lobe volume reduction and significantly improved respiratory function, exercise performance, and quality of life measures after EBV treatment whereas those who were identified as having CV did not.

The secondary objective of the Chartis multicenter study was to compare the accuracy of the Chartis System and visual assessment of HRCT fissure completeness for assessing CV status by evaluating their relationship with volumetric reduction of the treated lobe after EBV placement. Diagnostic accuracy of the Chartis System for prospectively classifying presence or absence of CV in a lobe targeted for EBV treatment, when compared to the observed response to the EBV procedure as measured using volumetric reduction seen with HRCT, was found to be similar to HRCT fissure analysis.

¹ Cleared indications for use: The Chartis System is indicated for use by bronchoscopists during a diagnostic bronchoscopy in adult patients in a bronchoscopy suite. The system, composed of the Chartis Catheter and Chartis Console, is designed to measure pressure and flow in order to calculate resistance to airflow and quantify collateral ventilation in isolated lung compartments. The Chartis Catheter is used through the working channel of a bronchoscope and connects to the Chartis Console. The Chartis Console is a re-usable piece of capital equipment that displays the patient information.

1.9 Conclusion from the Prior Studies

The evidence from the prior investigations suggest that BLVR performed using the Pulmonx Zephyr EBV may induce regional lung volume reduction associated with improved clinical condition in patients identified as having little or no CV.

2.0 STUDY DEVICE AND INTENDED USE

The Pulmonx Zephyr Endobronchial Valve (EBV) is an implantable bronchial valve intended to decrease volume in targeted regions of the lung. It is indicated for the treatment of patients with hyperinflation associated with severe heterogeneous emphysema in regions of the lung that have little or no collateral ventilation as assessed by the Chartis System.

3.0 STUDY DEVICE / TECHNOLOGY DESCRIPTION

The Pulmonx Zephyr Endobronchial Valve (EBV) is a device that incorporates a one-way valve that is implanted in a bronchial lumen. A stent-like self-expanding retainer that secures the implanted EBV in place supports the one-way valve. The implanted EBV is designed to allow air to be vented from the isolated lung segment while preventing air from refilling the isolated lung during inhalation. It is not anticipated that the study device will require modification during execution of the study.

3.1 Endobronchial Valve

The EBV is assembled from two distinct components: a one-way valve and a retainer.

3.1.1 One-Way Valve

A one-way polymer valve is mounted inside the retainer. The valve vents during exhalation and closes when flow is reversed (inhalation).

3.1.2 Retainer

The retainer is a self-expanding tubular mesh structure that is laser cut from Nitinol tubing. The retainer is covered with silicone in order to create a seal between the implant and the bronchial wall. When the EBV is delivered into the target lumen, the retainer expands to contact the walls of the bronchial lumen.

3.2 Delivery Catheter

The flexible delivery catheter facilitates placement of the EBV in a targeted bronchial lumen. The delivery catheter is very similar to currently marketed tracheobronchial stent delivery catheters and will be familiar to physicians trained in the placement of airway stents. The EBV is compressed into the retractable distal housing. The EBV is deployed by actuating the deployment handle, which retracts the distal housing and releases the EBV to expand inside the target lumen. The delivery catheter can then be retracted from the EBV and removed from the patient.

4.0 STUDY PURPOSE

The purpose of this study is to assess the safety and effectiveness of BLVR using the Pulmonx Endobronchial Valve (EBV) in treated study participants compared to control participants to support a premarket approval application to FDA.

5.0 STUDY DESIGN

This will be a multi-center prospective, randomized, controlled study with EBV treatment statistically evaluated using Intent-to-Treat (ITT) analyses. Random assignment will be conducted using an allocation ratio of 2:1; two study participants will be randomized to the EBV Treatment arm for every one participant randomized to the Control arm. A maximum of 183 patients with severe heterogeneous emphysema, who meet study entry criteria, consisting of screening eligibility criteria, baseline eligibility criteria, and procedure eligibility criteria, will be enrolled. Safety and effectiveness of BLVR using the Pulmonx EBV will be evaluated at 1 year. For study participants who have been treated with EBV, a secondary intervention such as valve removal, replacement, or adjustment, as described in this protocol, may be considered during the study follow-up. Long-term data will be collected annually through 5 years. Per the regulatory plan agreed to with FDA, 1 year of follow-up is required pre-approval and the remaining 4 years of follow-up will be conducted post-approval. The flow of study participants through the study protocol is shown in **Appendix 1**.

6.0 STUDY POPULATION

The study population will be comprised of 183 study participants with severe heterogeneous emphysema as defined by the study eligibility criteria. The study participants will be randomly assigned to the study treatment along with optimal medical therapy or optimal medical therapy alone.

6.1 Optimal Medical Therapy

All study participants will receive optimal medical therapy, defined for the purposes of this protocol as maximal medical treatment for stable COPD as indicated by the 2011 NIH/WHO GOLD guidelines [26]. The optimal medical therapy will be initiated, if not begun previously, upon a study candidate's enrollment into the study. The GOLD recommendations for optimal medical therapy consist of smoking cessation support, oxygen supplementation, pharmacological treatments, and pulmonary rehabilitation. All enrolled study participants will be provided access to a smoking cessation support program and will receive oxygen supplementation as medically indicated during their participation in the study. Pharmacological treatments and pulmonary rehabilitation therapy are described in detail in Section 9.0 and Section 10.0, respectively. All study participants will meet the study eligibility criteria for having current Pneumococcus and Influenza vaccinations.

7.0 STUDY OBJECTIVE

The objective of the study will be to evaluate lung function changes and adverse events after BLVR using the Pulmonx EBV.

7.1 Primary Effectiveness Endpoint

The percentage of EBV Treatment arm study participants meeting the threshold of $\geq 15\%$ improved forced expiratory volume in one second (FEV_1), obtained immediately following

bronchodilator therapy, as compared to the percentage in the Control arm at 1 year post-procedure.

7.2 Safety Endpoint

Evaluation of the short- and long-term adverse events profile of the EBV Treatment arm during the treatment period, defined as the day of the study procedure until 45 days after the study procedure (short), and in the post-treatment period, defined as 46 days after the study procedure until the 1-year follow-up visit (long).

7.3 Secondary Effectiveness Measures

Secondary effectiveness measures will consist of the following:

- 1) Treatment Lobe Volume Reduction (TLVR) for the EBV Treatment Arm
 - i. TLVR, measured as the 'absolute change from baseline' for treated lobe volume as seen via HRCT, will be evaluated at 45 days and 1 year.
 - ii. TLVR, measured as the 'percentage change from baseline' for treated lobe volume as seen via HRCT, will be evaluated at 45 days and 1 year.
- 2) St. George's Respiratory Questionnaire (SGRQ)
 - i. Difference between study arms in 'absolute change from baseline' for SGRQ score at 1 year.
- 3) FEV₁
 - i. Persistence of treatment effect will be evaluated by determining the difference between study arms for 'absolute change from baseline' for FEV₁ at 45 days, 6 months, and 1 year.
 - ii. Persistence of treatment effect will be evaluated by determining the difference between study arms for 'percentage change from baseline' for FEV₁ at 45 days, 6 months, and 1 year.
- 4) 6-Minute Walk Distance
 - i. Difference between study arms in 'absolute change from baseline' for 6MWD at 1 year.
 - ii. Difference between study arms in 'percentage change from baseline' for 6MWD at 1 year.

7.4 Additional Measures

Mean changes and/or changes measured using responder analyses for:

- Spirometry, including FEV₁, forced vital capacity (FVC) and the ratio of FEV₁/FVC
- Body plethysmography, including residual volume (RV), inspiratory capacity (IC), functional residual capacity (FRC), total lung capacity (TLC), and the ratios of RV/TLC and IC/TLC
- SGRQ global and domain (i.e. 'symptoms', 'activity' and 'impacts on daily life') score
- Modified Medical Research Council (mMRC) dyspnea scale score
- BODE Index
- Transitional Dyspnea Index (TDI) from Baseline Dyspnea Index (BDI)

- COPD Assessment Test (CAT)
- SF-36 Health Survey
- EQ-5D Health Survey
- Health Care Utilization Questionnaire
- 6 minute walk distance
- Borg scale dyspnea scores before and after 6MWD test
- Change in use of 'maintenance' medications, including bronchodilators, corticosteroids, antibiotics, and anti-inflammatories
- Daily diary (EXACT-PRO, pulmonary rehabilitation compliance, health status changes)
- Carbon Monoxide Diffusing Capacity (DL_{CO})
- Lung radiographic features
- Blood chemistry measures

7.5 Crossover of Control Study Participants

After completing the 1-year visit, a control arm participant may be permitted to crossover to the study treatment if (s)he continues to qualify for the study treatment. In order to qualify for crossover, a control arm participant must have been followed up successfully through 1 year and demonstrate lack of a clinically important response. The crossover procedure must be scheduled to occur within the 60 days after the 1 year visit. After treatment, the follow-up visits and testing at each visit will be identical to the study schedule for treatment arm participants.

Note: Per Revision H of this protocol, the requirement of a heterogeneity score of 15% between lobes is not applicable for any remaining crossover subjects. The most diseased target can be treated regardless of heterogeneity, provided that the target lobe is collateral ventilation negative (CV-).

Patients treated after approval of this Amendment will fall outside of the original 60 day window from the 1-year visit date. This delay will not be marked as a deviation from the protocol.

7.6 Interim Analysis

An interim data analysis designed to evaluate effectiveness for continuing crossover of Control arm study participants after the 1 year follow-up visit to EBV treatment will be performed when 74 (50% of the required minimum of 147) study participants have completed the 1 year follow-up. If crossover of Control arm study participants is found to be justified by the interim analysis then crossover of Control arm study participants after (s)he has reached the 1-year time point may be continued. The results of the interim analysis will be reviewed by the DSMB and FDA. If the DSMB recommends not continuing crossing control arm participants to EBV treatment, then those control arm participants who have not crossed over will exit from the study protocol after the 1-year visit.

7.7 Long-Term Follow-Up

Data will be collected annually through 5 years for study participants receiving the study treatment. Per the regulatory plan agreed to with FDA, 1 year of follow-up is required pre-approval and the remaining 4 years of follow-up will be conducted post-approval. The annual 2-, 3-, 4-, and 5-year follow-up data will consist of FEV₁ and adverse events.

8.0 STUDY PARTICIPANT MANAGEMENT

8.1 Clinical Site Study Team

The Principal Investigator at each clinical site will be responsible for identifying and providing oversight of the study team at the clinical site. The clinical site study team will be responsible for executing all study-related activities.

8.2 Clinical Study Site Training

Prior to enrolling any study participants, the site Principal Investigator(s) and the Study Coordinator(s) will complete the Pulmonx Clinical Study Training Program. An overview of the training program is provided in Section 18.0.

8.3 Study Candidate Recruiting

After obtaining approval from the Institutional Review Board (IRB) overseeing their site, patients at the site may be approached by clinical site staff as candidates for the study. Clinical sites will be encouraged to advertise for local recruitment and web-links to study information may be provided to relevant organizations. Additionally, study investigators will be provided with written and electronic study-related materials that they may provide to referring care providers in their regions.

8.4 Study Candidate Selection

Any clinic patient may be considered for study candidacy while receiving routine care for emphysema. The screening flow for study candidates, with timing of study participant enrollment, is shown in **Appendix 2**.

Prior to initiating any study screening-related activities with individual patients, all study candidates will sign a Screening Informed Consent Form (**Appendix 3**), or similar, to acknowledge their willingness to participate in study screening activities. A screening log that shows all screened patients who sign the Informed Consent will be maintained. The intent of the screening log (**Appendix 4**) is to capture the reasons that chronic obstructive pulmonary disease (COPD) patients who are interested in the study are not eligible to participate.

8.4.1 Informed Consent and HIPAA Authorization

The informed consent process will be conducted in accordance with the Declaration of Helsinki, International Congress of Harmonization (ICH) Good Clinical Practice guidelines (to the extent that they are consistent with U.S. Federal regulations), and the U.S. Federal Code of Regulations, Section 21, Part 50. The Principal Investigator or a member of his/her staff should approach study candidates who meet study eligibility criteria to obtain informed consent. The

Investigator or his/her designee will explain the purpose of the study and the anticipated benefits and associated risks of study participation.

The study candidate will be given an Informed Consent Form. This form(s) (or modifications) must have prior approval of the study site's Institutional Review Board (IRB) before use. The study candidate will be given adequate time to review the Informed Consent Form. Study candidates may not be consented after receiving any medication (e.g. sedatives, narcotics, etc.) that might alter their ability to comprehend the informed consent. After the study candidate has had the opportunity to read the form and discuss the study information with study site personnel, they will be asked to make a decision regarding participation in the study.

All study candidates who choose to participate in the study will sign the Informed Consent Form prior to commencement of any study-specific testing. Failure to provide informed consent renders the study candidate ineligible for the study. The signed Informed Consent Form will be retained at the investigational site, and copies will be provided to the study participant. Study participants may voluntarily withdraw from the study at any time following enrollment into the study.

The HIPAA Authorization (Health Insurance Portability and Accountability Act) adds to protections already provided by the informed consent. These additions state that the study participant must be informed that they can withdraw authorization to use data or samples not already submitted to the study sponsor and that the request must be in writing. If the study participant allows samples to be used after withdrawal from the study, this permission may be withdrawn at a later date. The HIPAA authorization specifies who may review confidential medical information, to whom test results will be submitted, and that test results obtained solely for research will not be part of the study participant's medical record. A copy of the study participant's information, including the signed consent form and HIPAA Authorization, must be provided to the study participant.

8.5 Screening Eligibility Criteria

All study candidates will have signed a study Screening or Study Procedure Informed Consent form prior to undergoing any testing to determine study eligibility. The screening eligibility criteria are given in **Appendix 5**. It is recommended that screening eligibility criteria testing be conducted sequentially in the order shown here: medical history collection and physical examination, an echocardiogram, volumetric high resolution computed tomography (CT) (see Section 8.5.1 below), electrocardiography (ECG), spirometry, body plethysmography, diffusing capacity (DL_{CO}), 6MWD, arterial blood gases (ABGs), complete blood count (CBC), alpha 1-antitrypsin deficiency detection, plasma cotinine level (or arterial carboxyhemoglobin if using nicotine products) and serum fibrinogen.

If the study candidate has had a CT within the last three months prior to signing the screening consent and the images were obtained in accordance with the CT scan protocol then a repeat CT scan will not be necessary. Of note, screening of CT scan records of clinic patients seen previously for medical care at the study site is permitted.

8.5.1 CT Screening Eligibility Criteria

Acquisition of CT scans will be standardized across clinical sites by training sites and using an imaging procedures core manual. The protocol will include volume acquisition thin section obtained at suspended breath hold at full inspiration (TLC) and full expiration (RV). Images will be reconstructed using a smooth or standard filter; the protocol is detailed in **Appendix 6**. The radiology technologists at the clinical sites will be trained to the HRCT data collection protocol.

The clinical site will evaluate HRCT images to determine screening eligibility of the study candidate. The grading system used by the clinical sites to evaluate HRCT scans will be standardized and site personnel will be trained to use it. The HRCT eligibility criteria will be assessed by determining parenchymal destruction and emphysema heterogeneity scores using the total lung capacity (TLC) scan and the definitions below (Sections 8.5.1.1 and 8.5.1.2). The site will use FDA cleared software, which may include VCAR (GE Medical Systems, Milwaukee, WI), Apollo (VIDA, Coralville, IA), syngo Lung Care CT (Siemens Healthcare Solutions, Deerfield, IL), MeVis Visia CT Lung System (MeVis Medical Solutions, Milwaukee, WI), Myrian (Intrasense, Montpellier, France), or other 510k cleared software to measure lung density to determine parenchymal destruction.

The site reader will use the parenchymal destruction scores provided by the software to calculate emphysema heterogeneity using a provided worksheet. The CT study must exhibit sufficient landmarking to be evaluated using the software as it is intended for delineating lobar parenchymal destruction.

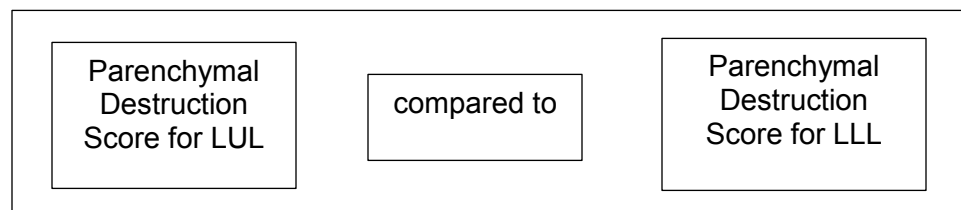
8.5.1.1 *Definition of Parenchymal Destruction Score*

Lobar parenchymal destruction scores will be determined, on thin section volumetric series, using specialized software to calculate the proportion of image voxels within a lobe that fall below a pre-defined Hounsfield unit threshold. These scores will be reported as a parenchymal destruction score for each lung lobe. For example, a parenchymal destruction score of 50% means that 50% of the volume of that lobe meeting the Hounsfield threshold and will be considered destroyed by emphysema.

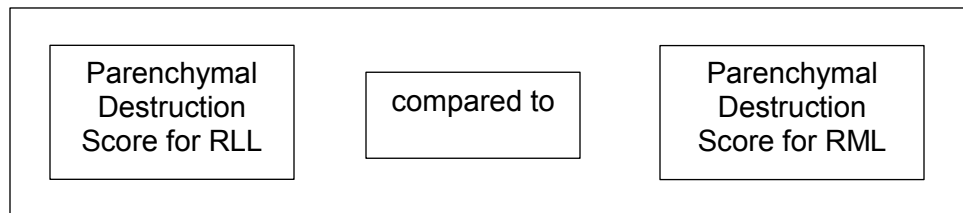
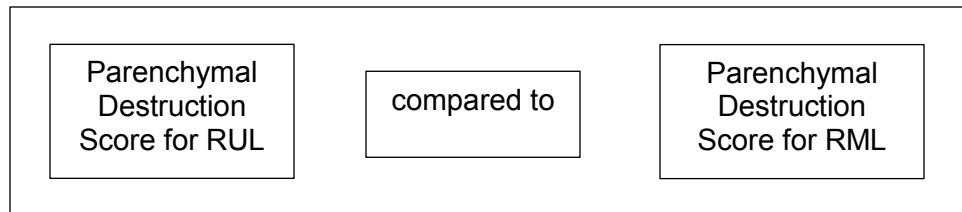
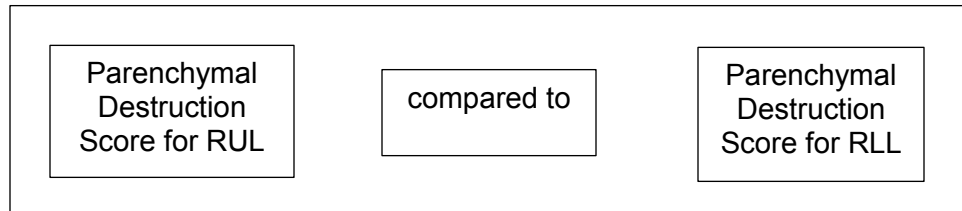
8.5.1.2 *Definition of Emphysema Heterogeneity Score*

Emphysema heterogeneity score will be defined as the difference (in percent) between the parenchymal destruction scores of the target lobe and the ipsilateral non-target lobe(s).

For the left lung, emphysema heterogeneity will be quantified by calculating the difference between the target treatment lobe (left upper lobe [LUL] or left lower lobe [LLL]) parenchymal destruction score and the ipsilateral non-target lobe parenchymal destruction score.



For the right lung, emphysema heterogeneity will be quantified by calculating the difference between the parenchymal destruction scores for all three lobes separately (right upper lobe [RUL], right middle lobe [RML], and right lower lobe [RLL]).



The Study Bronchoscopy Plan described in Section 8.7 below will be utilized to determine if a study candidate meets the emphysema heterogeneity criterion and qualifies to proceed with study screening.

8.5.2 Supervised Pulmonary Rehabilitation Program Required to Establish Baseline Eligibility

A study candidate who has completed a supervised pulmonary rehabilitation program within the last six months prior to the baseline eligibility screening visit, or who is regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred more than six months prior, may proceed to baseline testing provided that the pulmonary rehabilitation program is documented and meets the criteria specified by this study protocol. The pulmonary rehabilitation program will include at least two visits to the rehabilitation center per week. Minimum attendance of eight visits will be required to fulfill the study enrollment pulmonary rehabilitation program requirement. Any study candidate who has not completed at least eight visits will not be eligible to enter the study.

8.6 Baseline Eligibility Criteria

Any study candidate who meets the screening eligibility criteria and has successfully completed a supervised pulmonary rehabilitation program may have clinical testing to support assessment of the baseline eligibility criteria (**Appendix 7**). The baseline eligibility determination must be made \leq 120 days following the screening eligibility determination. It is recommended that baseline eligibility testing be conducted sequentially in the order listed in Section 14.0. Study candidates who meet the screening and baseline eligibility criteria may be considered for study enrollment.

Study candidates meeting the screening and baseline eligibility criteria will be required to have signed the Study Informed Consent Form (**Appendix 8**) or similar prior to undergoing the bronchoscopy procedure to assess study procedure eligibility. Study candidates who have met the screening and baseline eligibility criteria but who are no longer interested in participating in the study or who do not sign the Study Informed Consent Form will be recorded on the screening log.

Study-related testing should not be conducted if the study participant is having an active COPD exacerbation at the time of baseline testing. If a study participant has a COPD exacerbation, the baseline testing should be postponed until the exacerbation is resolved as determined by the site principal investigator.

8.7 Bronchoscopy Plan for CV Assessment and Determining Study Eligibility

A bronchoscopy procedure plan will be created by the Study Investigator for each study candidate. The goal of bronchoscopy planning is to determine whether the study candidate meets the emphysema heterogeneity eligibility criterion and to pre-identify the lobe(s) most appropriate for study treatment (EBV placement). The bronchoscopy plan will be developed using the CT scan collected during the study participant's eligibility screening (see Section 8.5.1). The pre-identified lobe(s) will be assessed for CV using the Chartis System during the bronchoscopy procedure. The bronchoscopy plan will be documented using the appropriate Case Report Form.

8.7.1 Algorithm for Radiologic Determination of Emphysema Heterogeneity and Identification of Target Treatment Lobe(s)

The bronchoscopy plan will be completed using the flowchart algorithm provided in **Appendix 9**. Lobes in both lungs may be eligible to undergo treatment but only one lung will be treated.

Note: Per Revision H of this protocol, the requirement of a heterogeneity score of 15% between lobes is not applicable for any remaining crossover subjects. The most diseased target can be treated regardless of heterogeneity, provided that the target lobe is collateral ventilation negative (CV-).

8.8 Study Procedure Eligibility Criteria

The final study procedure eligibility criteria will be assessed during the bronchoscopy procedure (**Appendix 10**). The bronchoscopy procedure should occur \leq 60 days after the baseline assessment visit. Those study participants who are found to be eligible to

participate in the study will be enrolled into the study and randomly assigned to treatment (or control) at that time. If randomly assigned to the study treatment arm, the study participant will undergo the study-directed treatment during the same session unless this is contraindicated by the length of time the study participant has been under anesthesia; if the time remaining for safe administration of anesthesia is considered to be insufficient for completing the study procedure, it will be deferred to another session.

To meet the study procedure eligibility criteria, the study participant must have at least one pre-identified target lobe (upper or lower lobe), as delineated in the bronchoscopy procedure plan, which is found to have little or no CV as measured by the Chartis System (see Section 11.2). A flow chart showing the key decision-points during the bronchoscopy procedure is provided in **Appendix 11**. Every effort will be made to have Pulmonx technical staff at all bronchoscopy procedures to provide support.

8.9 Study Participant Enrollment

A study candidate will be enrolled into the study after meeting all screening and baseline eligibility criteria, providing informed consent for study participation, and meeting the study procedure eligibility criteria. Enrollment of a study candidate as a study participant will be documented using the appropriate Case Report Form.

8.9.1 Randomization Assignment and Study Treatment

A study participant will be randomly assigned to treatment or control after determining he/she meets the study procedure eligibility criteria during the bronchoscopy procedure (see Section 11.2). If the study participant does not meet the study procedure eligibility criteria, he/she will not be randomly assigned to treatment nor receive any study-related treatment. If the study candidate is found to meet the study procedure eligibility criteria, then (s)he will be randomly assigned to study treatment during the bronchoscopy procedure.

Random assignment will be conducted using an allocation ratio of 2:1; two study participants will be randomized to the EBV Treatment arm for every one participant randomized to the Control arm. Random assignment will be conducted using a stratified permuted block design generated separately for each clinical site, with assignment stratified by anatomical site of the planned treatment (e.g. right lung or left lung). Mixed block sizes will be used. The goal of stratification will be to ensure a 2:1 randomization mix within each stratum.

8.10 Follow-Up Visits

8.10.1 Study Schedule

The required study schedule for study participants is shown in Section 14.0 and **Appendix 12**.

8.10.1.1 *Study Participants Treated with EBV*

Any study participant receiving EBV treatment will be followed-up annually through 5 years.

8.10.2 Visit Windows

The study follow-up visits required by the study protocol are shown in the Table below. The study follow-up visits should be scheduled within the ranges

(windows) specified in the Table. These windows have been established to allow for maximum data collection in a study population known to have a high risk of missing clinic visits due to confounding clinical circumstances. It is recommended that all efforts be made to schedule follow-up visits as early as possible within the visit window in case the visit may need to be rescheduled. Utilization of these visit windows will aid in avoiding imputation of data during statistical analysis.

Study-related testing should not be conducted if the study participant is having an active COPD exacerbation at the time of a study follow-up visit. If a study participant has a COPD exacerbation, the study visit should be cancelled and rescheduled to be conducted at 14 days, or as early as possible after 14 days, following the initiation of treatment for the exacerbation. The clinical study site will document in the study participant's medical record all incidents in which a scheduled study visit is cancelled and rescheduled due to occurrence of a COPD exacerbation.

When the study participant informs the site of the COPD exacerbation, the investigator may request the study participant to come in for evaluation. This evaluation may include a physical examination and review of medications and will be classified as an interim visit.

If the rescheduled study follow-up visit falls outside of the study follow-up visit window, it will be recorded as an out of window protocol deviation. If the study participant fails to make the rescheduled study follow-up visit it will be captured as a missed visit and protocol deviation.

Table. Study Follow-Visits and Windows for Scheduling the Visits

	Visit	Range
1	24-Hour [‡]	+/- 8 hours
2	Daily phone call for 10 days following discharge [‡]	by 11:59 pm local time
3	7 days after discharge [‡] (phone call not required on this day)	+ 1 business day
4	30-day [‡]	+/-5 days
5	45-day	+/- 10 days
6	3-Month	+/- 14 days
7	6-Month	+/- 21 days
8	9-Month	+/- 21 days
9	1-Year	+/- 45 days
10-13	2, 3, 4, 5 Years [‡]	+/- 60 days
[‡] EBV-treated study participants only; *Procedure day = Day 0		

8.11 Retention of Study Participants

Every effort should be made by clinical site staff to retain study participants for the duration of the study. Study participants failing to return for follow-up, or failing to return contact attempts by site staff for follow-up visits, shall be contacted a minimum of three times by the Study Coordinator or Investigator, with the last attempt by certified mail, before exiting the study participant as lost to follow-up. All contact attempts of study participants who do not return for follow-up should be documented in the study participant's medical record.

8.11.1 Participant Withdrawal

Study participants may choose to withdraw from the study at any time without penalty or loss of benefits to which they are otherwise entitled. If a study participant provides a reason(s) for early withdrawal, the reason(s) shall be documented on the appropriate Case Report Form and in the study participant's medical record. If possible, a final medical exam, along with spirometry assessment, shall be performed prior to their withdrawal.

9.0 PHARMACOLOGIC TREATMENTS FOR STUDY PARTICIPANTS

9.1 Optimization of Medications

Study participants will be carefully monitored at each study visit to confirm that pharmacological treatment is optimized. Optimization of pharmacological treatment will also be assessed immediately prior to the bronchoscopy procedure; if there is any reason to believe that the study participant is not receiving optimized medical therapy, the bronchoscopy procedure may be postponed.

9.2 Bronchodilators

Study participants may receive maintenance bronchodilator therapy, which may include an inhaled long acting beta-agonist, an inhaled anticholinergic, or both. These may be administered by metered dose inhaler, dry powder inhaler or drug aerosol. These agents may also be combined with theophylline at the discretion of the treating physician. A standardized regimen of treatment will not be required since study participants may have variable responses to bronchodilator treatment or need individualized treatment depending on their condition.

9.3 Corticosteroids

Study participants may receive corticosteroid(s) for mitigation of COPD exacerbations. The treating physician will determine medication regimen and instruct study participants on appropriate use.

9.4 Other Pharmacologic Agents

Other pharmacologic treatments such as mycolytic agents, antibiotics, anti-inflammatories, and other medications such as antioxidant agents, immunoregulators, antitussives, and vasodilators may be prescribed at any time they are medically indicated.

10.0 POST-BRONCHOSCOPY PULMONARY REHABILITATION

The pulmonary rehabilitation program should include the elements recommended by the American Thoracic Society and European Respiratory Society Statement on Pulmonary Rehabilitation [27]. In general, the post-bronchoscopy program should consist of a supervised 'in clinic' pulmonary rehabilitation component and a 'home-based'

maintenance pulmonary rehabilitation component. The active 'in clinic' pulmonary rehabilitation program should be initiated for all study participants within the first 30 days following the bronchoscopy procedure. For study participants in the treatment arm, initiation of the program must be cleared by the investigator. For the active 'in clinic' component of the program, the ATS/ERS practice guidelines recommend a minimum of 20 sessions be given at least three times per week although twice-weekly supervised plus one unsupervised home session may also be acceptable. For the maintenance component, study participants will be advised to adhere to a program consisting of at least 3 home-based sessions per week.

10.1 Pulmonary Rehabilitation Program

A Pulmonary Rehabilitation Manual for the study, an example of which is provided in **Appendix 13**, will be provided to each study site. This manual will contain details regarding administration of the pulmonary rehabilitation program including definitions of responsibilities and requirements for identification and qualification of the pulmonary rehabilitation facility.

10.1.1 Pulmonary Rehabilitation Program Elements

The pulmonary rehabilitation program should consist of lower limb endurance training, upper limb endurance training, and lower and upper limb strength training. A list of suggested exercises is provided in the Pulmonary Rehabilitation Manual. If deemed necessary by the therapist, oxygen saturation may be monitored during exercise. The home rehabilitation program will be developed for individual patients by the pulmonary rehabilitation center at each clinical site. The therapist will suggest appropriate exercises.

- Lower limb endurance training
Lower limb endurance training should consist of walking, either done on a treadmill, or ambulating freely indoors or outdoors, for ≥ 20 minutes in a session.
- Upper limb endurance training
Upper limb endurance training consists of a group of exercises involving some form and level of resistance for each hand (e.g. dumbbells or Therabands).
- Lower and upper limb strength training
Lower and upper limb strength training consists of a group of exercise involving some form and level of resistance (e.g. dumbbells or Therabands).

11.0 BRONCHOSCOPY PROCEDURE

Every effort will be made for a Pulmonx representative to be in attendance at a study participant's bronchoscopy procedure. The bronchoscopy procedure should be recorded on video, CD ROM, or DVD and a copy maintained in the study participant's files. Alternatively, photographs of valve placement may be obtained. Prior to the procedure, identify and document site personnel responsible for managing any pneumothorax. During the bronchoscopy procedure, all study candidates will undergo assessment of study eligibility using

the Chartis System. All study candidates found to be eligible to undergo the study procedure will be enrolled into the study and will be randomly assigned at that time. All enrolled study participants will be treated as randomly assigned. See **Appendix 11** for an overview of the events occurring during bronchoscopy procedure.

11.1 Procedure Medications

In addition to the medications described in Pharmacologic Treatments (Section 9), the peri-procedural medication regimen shown in the Table below is **recommended**.

Table. Summary of Procedure Medications (or equivalent)

Medication	Before Procedure	During Procedure	Post-Procedure
Cease use of anti-coagulants 5-7 days before	X		
Cease use of aspirin at least 3 days before, if indicated per physician discretion	X		
Inhaled bronchodilator 20 minutes before	X		
Initiate prophylactic antibiotic (e.g. Cephalosporin or Quinolone)	X		
Anesthetic		X	
Oral course of prophylactic antibiotics (5-7 days)			X
Bronchodilator therapy			X

11.1.1 Medications administered prior to the bronchoscopy

Study candidates will be asked to cease using anti-coagulant medications (if applicable) 5-7 days before the procedure and to refrain from taking aspirin for at least three days before the procedure if indicated per physician discretion. At the preference of the treating physician, prophylactic antibiotics and/or corticosteroids may be administered one or two days prior to the procedure. Approximately 20 minutes before the procedure, study candidates may be treated using an inhaled bronchodilator. Just prior to the procedure, intravenous first or second generation antibiotics such as cephalosporin or quinolone (e.g. Ancef, Kefzol, Cefaclor) should be administered.

11.1.2 Medications administered during the bronchoscopy

The procedure anesthetic will be administered according to standard local protocols used for bronchoscopy. Assessment of collateral ventilation using the Chartis System will be performed under conscious sedation with unassisted breathing. The study procedure (EBV placement) may be performed under conscious sedation with unassisted breathing or under general anesthesia with the patient on a ventilator.

11.1.3 Medications administered following the bronchoscopy

For the 24 hours after the procedure, intravenous first or second generation cephalosporin or quinolone (e.g. Ancef, Kefzol, Cefaclor) should be administered. A standard-of-care corticosteroid regimen may also be initiated at this time.

Beginning at 24 hours after the procedure, study participants will receive, or continue to receive if initiated previously, a five to seven day prophylactic course of oral cephalosporin, quinolone, or macrolide antibiotics.

11.2 Assessment of Study Procedure Eligibility Criteria

Study procedure eligibility will be determined by assessing CV of the pre-identified target treatment lobe(s), as documented in the bronchoscopy plan (Section 8.8), using the Chartis System. All potential target treatment lobes identified in the bronchoscopy plan will be assessed during the bronchoscopy session. The Chartis System will be used as described in the Instructions for Use. The CV assessment(s) will be performed under conscious sedation with unassisted breathing. The procedure for assessing CV, along with case examples, is provided in **Appendix 14**.

11.2.1 Study Participant Meets Study Procedure Eligibility Criteria

If the study participant meets the study eligibility criteria, (s)he will be randomly assigned to study treatment or control.

11.2.1.1 *Randomization Assignment*

A study participant will be randomly assigned to treatment using the method required by the study sponsor. Study staff will conduct random assignment of study participants by either telephoning or electronically accessing a centralized location from the bronchoscopy suite to learn the study participant's random assignment. Random assignment will be documented using the appropriate Case Report Form.

11.2.2 Study Participant Does NOT Meet Study Procedure Eligibility Criteria

If the study candidate does not meet the study procedure eligibility criteria, the bronchoscopy procedure will be terminated using the standard practice guidelines at the clinical site. The study candidate will be permitted to recover from anesthesia by following the clinical site hospital's standard protocol.

11.3 Assignment to Control Arm

If the study participant is randomly assigned to the Control arm, the bronchoscopy procedure will be terminated using the standard practice guidelines at the clinical site and the study participant will be followed up as described in Section 8.10 and Appendix 12.

11.4 Assignment to Study Treatment Arm

If the study participant is randomly assigned to the EBV treatment arm, (s)he should immediately undergo the study procedure (see Section 11.5). However, in any case in which there may be insufficient time to complete the study procedure because the time to safely administer the anesthesia is running out, the study procedure may be deferred. The study participant will be followed up as described in Section 8.10 and Appendix 12.

11.5 Execution of the Study Procedure

The study treatment will be considered to be initiated immediately upon introduction of the EBV delivery catheter into the bronchoscope. The study procedure may be performed with the study participant under conscious sedation with unassisted breathing or under general anesthesia on a ventilator. For study participants who are not on a ventilator, a bite block may be used to facilitate access. For general anesthesia procedures, a rigid bronchoscope in conjunction with a flexible bronchoscope or a flexible bronchoscope alone through an endotracheal tube may be used for valve placement. The study device will be placed in accordance with the study protocol requirements and the Instructions for Use. The target treatment lobe(s) will consist of only one of the following: LUL, LLL, RUL, RLL, or RUL+RML.

11.5.1 Lobar Occlusion with EBV

The target lobe is intended to be completely occluded with EBV placement, meaning that all airways feeding the lobe are to be blocked with a valve. Lobar occlusion is required as the segmental boundaries are often largely destroyed in cases of advanced emphysema. If valves do not occlude the entire lobe, gas may freely travel from a non-valved segment to a valved segment, reducing the potential benefit. Valves may be placed at the lobar, segmental, or sub-segmental levels, in this order of preference, depending on the anatomy of the study participant. Whenever possible, valves should be placed in an earlier generation bronchus (e.g. if a large valve will fit in the left upper lobe bronchus, that should be the target instead of a valve placed in each of the segmental bronchi). Potential targets at the segmental bronchi level are shown in **Appendix 15**.

Success for achieving lobar occlusion must be verified, via bronchoscopy, immediately following valve placement and recorded on the appropriate CRF. If a valve appears to be misplaced or misaligned, it will be removed and replaced. If it is not possible to place or align the valve correctly then the valve will be removed and the reason for not placing the valve will be recorded on the appropriate CRF.

11.6 Post-Bronchoscopy Recovery Period Procedures for Study Treatment Arm

Study participants who receive the study treatment will be required to stay in the hospital for at least 5 nights. During the hospital stay, chest X-rays will be obtained daily, including a chest X-ray at Day 0, Day 1, Day 2, Day 3, Day 4, and Day 5. If a study participant is being treated for a pneumothorax during the study procedure hospital stay, collection of chest X-rays beyond Day 5 will be at the discretion of the study physician, with a protocol mandated chest X-ray on the day of discharge. An overview of the post-procedure hospital stay for study participants who receive the study treatment is shown below.

Post-Study Procedure Checklist For Coordinators

Day 0-Post-Study Procedure

_____ Ensure that patient is transferred to appropriate recovery area as per local hospital's standard protocol.

- _____ Ensure that chest x-ray is obtained and reviewed by treating physician within 1 hour (\pm 30 minutes) of procedure for assessment of volume reduction and pneumothorax.
- _____ Ensure that patient receives antibiotics, corticosteroids, bronchodilators, or any other medications as needed.
- _____ Ensure that vital signs and pulse oximetry are recorded and assessed during the 24 hours following the procedure.
- _____ Ensure that patient is assessed for any adverse events.

Day 1-Hospital Stay

- _____ Ensure that chest x-ray is obtained and reviewed by treating physician for assessment of volume reduction and pneumothorax.
- _____ Ensure that ABG and serum fibrinogen samples have been collected.
- _____ Ensure that patient completes Daily Diary.
- _____ Ensure that patient is assessed for any adverse events.

Day 2-Hospital Stay

- _____ Ensure that chest x-ray is obtained and reviewed by treating physician for assessment of volume reduction and pneumothorax.
- _____ Ensure that patient completes Daily Diary.
- _____ Ensure that patient is assessed for any adverse events.

Day 3-Hospital Stay

- _____ Ensure that chest x-ray is obtained and reviewed by treating physician for assessment of volume reduction and pneumothorax.
- _____ Ensure that patient completes Daily Diary.
- _____ Ensure that patient is assessed for any adverse events.

Day 4-Hospital Stay

- _____ Ensure that chest x-ray is obtained and reviewed by treating physician for assessment of volume reduction and pneumothorax.
- _____ Ensure that patient completes Daily Diary.

_____ Ensure that patient is assessed for any adverse events.

Day 5-Hospital Discharge

_____ Ensure that treating physician completes a physical examination.

_____ Ensure that chest x-ray is obtained and reviewed by treating physician for assessment of volume reduction and pneumothorax.

_____ Ensure that patient completes Daily Diary.

_____ Ensure that patient is assessed for any adverse events.

_____ Ensure that treating physician has cleared the patient for discharge.

_____ Ensure that patient receives antibiotics, corticosteroids, bronchodilators, or any other medications as needed.

_____ Ensure that patient receives Medical Alert Card, Treated Study Participant Bracelet, Transferring Instructions if Late Pneumothorax, and Post-Discharge Instructions. Ensure that you have discussed these items with the study participant and caregivers and that they have been given opportunity to ask/have answered any questions.

_____ Ensure that you have explained to the patient that he/she will be called every day for the next 10 days to follow up on how he/she is doing and whether he/she has experienced any adverse events. If there is a specific time of day that works best for the patient, ensure that this is documented (Time of Call).

11.7 Procedures Prior to Discharge

The Study Coordinator should schedule the appropriate study follow-up visits with the study participant prior to their discharge from the hospital. See Section 14.0 for the detailed procedures. Prior to discharge, all study participants should receive post-operative bronchodilator inhalers and be prescribed a prophylactic course of antibiotics if this was not previously done.

For the study treatment arm, a Medical Alert Card containing emergency contact information, which will be completed by the research staff, and post-discharge instructions will be provided to study participants that received the study treatment. An example of the Medical Alert Card and the Post-Discharge Instructions are provided as **Appendix 16** and **Appendix 17**, respectively. The Treated Study Participant Bracelet and Transferring Instructions if Late Pneumothorax should also be given to the study participant.

12.0 SECONDARY VALVE PROCEDURES

Any study participant who receives EBV treatment may undergo valve removal, replacement, or adjustment while participating in the study. In the case of a secondary valve procedure(s), the follow-up schedule will be calculated from the date of the initial treatment. These procedures and the conditions in which they may be considered are described below.

12.1 Valve Removal

Study investigators may consider removing valves due to occurrence of an adverse event (see Section 15.0). Valves may be removed according to the Manufacturer's Instructions for Use.

12.2 Valve Replacement

Study investigators may consider replacing valves for study participants who expectorate a valve(s) or in cases where the valve(s) was removed due to an adverse event (See Section 14.0) which has since been resolved. Up through the 1-year follow-up time point, valves may be replaced up to a maximum of two times. The treating physician will determine the timing of a valve replacement on a per-patient basis. Valves may be replaced according to the Manufacturer's Instructions for Use.

12.3 Valve Adjustment

It is anticipated that there may be a few cases in which a valve may not have been initially placed to occlude the treated lobe. In any case where clinical evidence exists that a valve was not placed to block the airway leading into the target lobe, adjustment of the valve may be considered by the investigator. Valve adjustment will be considered to be part of the study procedure since clinical effect with the Pulmonx EBV is thought to be associated with placing valves to achieve lobar occlusion.

Valve adjustment may be performed only once for a study participant and should be performed within 75 days of the study procedure. In any case in which it is necessary to re-schedule a valve adjustment due to a study participant's illness (e.g. COPD exacerbation), the valve adjustment may be conducted up to 90 days post-procedure.

The investigator may consider valve adjustment if both of the following are observed:

- 1) The 45-day HRCT scan, as read by the core radiology reading laboratory and measured using FDA cleared software designed to evaluate HRCT changes, shows less than 50% volumetric reduction in the EBV-treated lobe.
- 2) The 45-day HRCT scan, as read by the core radiology reading laboratory, demonstrates signs indicative of incomplete occlusion, including no valve in a segmental airway, anatomic variation resulting in the valve not occluding accessory branches, leakage around the valve, and incorrect placement.

The post-procedure flow and follow-up testing schedule for study participants having valve adjustment is shown in **Appendix 1** and **Appendix 12**. The bronchoscopy procedure for the valve adjustment will be conducted as described in Section 11.

13.0 CLINICAL EFFECTIVENESS OUTCOMES

13.1 Spirometry

Spirometry testing will be performed using the guidelines outlined in the ATS/ERS Task Force ‘Standardisation of Lung Function Testing’ [28,29]. **Spirometry testing will be conducted both before and after bronchodilator use.** For each of these conditions, the maneuver should be repeated until at least three good efforts are captured to ensure that spirometry results are acceptable and reproducible. All three good efforts will be recorded. Spirometric reference values from the third National Health and Nutrition Examination Survey (NHANES III) [30] should be used for this study.

13.2 Patient-Reported Health Status Measures

The study participant should complete the health status questionnaires themselves but the Clinical Coordinator or designee should be available to give advice if it is required. The opinions of family, friends or members of staff should not influence the study participant’s responses. These questionnaires are designed to elicit the patient’s opinion of his/her health, **not** someone else’s opinion of it. If the spouse or partner has accompanied the patient, then they should be asked to wait in a separate area while the study participant completes the questionnaires. Similarly, the study participant should not be allowed to take the questionnaires home.

The questionnaires should be completed in a quiet area free from distraction and, ideally, the study participant should be able to sit at a desk or table. The Study Coordinator or designee should explain to the study participant why they are completing these questionnaires, and how important it is for the researchers to understand how they feel about their illness and the effect it has on their daily life. The study participant should be asked to complete the questionnaires as honestly as possible and it should be stressed that there are no right or wrong answers; the study participants should be instructed to provide the answer that the study participant feels best applies to them. It should be explained that they must answer every question and that study staff will be available to answer any questions.

Once the study participant has finished completing the questionnaires, the study Coordinator or designee should review **ALL** questionnaires to confirm that a response has been given to every question. If there are missed items, the affected questionnaire(s) should be returned to the study participant before they leave the clinic so that they can complete the missed items.

13.2.1 St. George’s Respiratory Questionnaire (SGRQ)

The St. George’s Respiratory Questionnaire (SGRQ) is designed to measure and quantify disease-specific health status in patients with chronic airflow limitation. The SGRQ was developed in Britain and has been used extensively worldwide. It has been evaluated for reliability and validity in numerous studies of patients with COPD and has been validated for clinical use in the United States [31].

The SGRQ instrument consists of three discrete component scales (symptoms, activity, and impacts on daily life). The first part (“Symptoms”) evaluates symptomatology, including frequency of cough, sputum production, wheeze, and breathlessness. The second part includes questions to address two components: “Activity” and “Impacts”. The “Activity” component includes questions that

address activities that cause breathlessness or are limited due to breathlessness. The “Impacts” section includes questions that explore the effects of the patient’s health status on factors such as employment, being in control of health, panic, stigmatization, the need for medication, side effects of prescribed therapies, health expectations, and disturbances of daily life. A total score is calculated from all three components. The scoring range for the components and total score is 0-100, with a lower score indicating relatively higher wellness and a higher score representing higher disability.

13.2.2 Modified Medical Research Council (mMRC) Dyspnea Scale

The modified Medical Research Council Dyspnea Scale was developed and validated as a simple measure that could be used to quantify the effect of breathlessness on daily activities [32]. It consists of five statements designed to collect information about perceived breathlessness. The statements are: Grade 1, “I only get breathless with strenuous exercise”; Grade 2, “I get short of breath when hurrying on level or up a slight hill”; Grade 3, “I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level”; Grade 4, “I stop for breath after walking 100 yards or after a few minutes on the level”; Grade 5, “I am too breathless to leave the house”.

13.2.3 Baseline/Transitional Dyspnea Index (BDI/TDI)

The BDI/TDI is used to quantify dyspnea and its validity has been reported [33]. The BDI will be collected at the baseline visit and the TDI should be collected at the 3-month, 6-month, 9-month, and 1-year follow-up visits. The assessment measures three domains: 1) functional impairment, which determines the impact of breathlessness on the ability to carry out activities; 2) magnitude of task, which determines the type of task that causes breathlessness; and 3) magnitude of effort, which establishes the level of effort that results in breathlessness. The score ranges from -3 (major deterioration) to +3 (major improvement) for each domain. The sum of all domains is the total score. A change of at least 1 unit is thought to represent a clinically meaningful effect.

13.2.4 COPD Assessment Test (CAT)

The COPD Assessment Test consists of eight items, all of which are self-assessed by patient to have a score ranging from 0 to 5 and it has been validated [34]. The eight items are designed to quantify magnitude of symptoms related to cough, phlegm, chest tightness, breathlessness, daily activities limitation, self-confidence, quality of sleep, and energy level.

13.2.5 Short Form (SF)-36

The SF-36 is a validated, subject-based health status assessment survey designed to assess the impact of a disease state on an individual’s general sense of wellbeing [35]. It has been used extensively across many medical specialties to assess general health-related status and is commonly used in health economic studies.

13.2.6 EuroQol (EQ-5D)

The EQ-5D is a standardized instrument that is used as a measure of health outcome [36]. It is applicable to a wide range of health conditions and treatments. The questionnaire is comprised of questions that provide a descriptive state of health in the areas of mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Every question contains three response

categories: level 1 – ‘no problems’, level 2 – ‘some problems’ and level 3 – ‘inability or extreme problems’.

13.2.7 Health Care Utilization Questionnaire

The study participant will self-report health care utilization data such as physician office visits, emergency room visits, hospitalizations for respiratory symptoms, and use of home health care.

13.3 Body Plethysmography Testing

Body plethysmography will be used to determine the volume of thoracic gas (VTG) per the American Association of Respiratory Care (AARC) Clinical Practice Guideline “Body Plethysmography: 2001 Revision and Update” [37]. The reported VTG should be averaged from a minimum of 3-5 separate, acceptable panting maneuvers; should be calculated using values that agree within 5% of the mean (widely varying values should be averaged, and reported as variable); should indicate whether the thoracic volume was at functional residual capacity (FRC) or at some other level; should be compared with other lung volume determinations (He dilution, N₂ washout) if such are being performed.

Lung volumes including the slow vital capacity (VC) maneuver and its subdivisions inspiratory capacity (IC) and expiratory reserve volume (ERV) should be performed during the same testing session. The ERV, IC, and VC should be measured in conjunction with each VTG trial before disconnecting from the measuring system. Tracing should be added to illustrate correct performance. The largest volume of VC or forced vital capacity (FVC) obtained should be used for calculation of derived lung volumes. The mean values should be reported for IC and ERV from acceptable VTG maneuvers. Total lung capacity (TLC) = mean FRC + mean IC (mean IC should be close to the largest IC) and RV = TLC – largest VC.

Airways resistance and specific airways conductance maneuvers should be conducted such that the open-shutter panting maneuver shows a relatively closed loop. The panting frequency for within-testing session comparisons (i.e. pre- and post-bronchodilator testing) and for serial testing in a given study participant should be kept constant to aid in interpretation. Consensus of the group suggests a range of 60-90 cycles per minute.

A linked, rather than unlinked, maneuver should be performed; this means that following shutter closure at FRC, an expiratory maneuver to RV is performed, followed by an inspiratory VC maneuver to TLC.

Body plethysmography values recorded on the CRF will be post-bronchodilator. Body plethysmography reference values from the ATS statement on ‘Lung Function Testing: Selection of Reference Values and Interpretative Strategies’ [38] should be used for this study.

13.4 Diffusing Capacity Testing

Diffusing capacity will be corrected for hemoglobin.

Diffusing capacity testing will be measured using the single-breath carbon monoxide methods. The test will be conducted per the ATS document “Standardisation of the Single-Breath Determination of Carbon-Monoxide Uptake in the Lung” [39]. Acceptable test criteria include the use of proper quality controlled equipment, inspired volume of 85% of vital capacity in less than 4 seconds, a stable breath-hold for 8 to 12 seconds, no

evidence of leaks or Valsalva or Muller maneuvers, expiration in less than 4 seconds with appropriate clearance of dead space and proper sampling/analysis of alveolar gas.

If clinically acceptable, the study participant should not breathe supplemental oxygen for 10 minutes prior to the test. There should be at least two acceptable tests that meet the reproducibility requirement of being within +/- 10% or 3 ml CO of the average DL_{CO}. The average of at least two acceptable tests that meet this reproducibility requirement should be reported.

13.5 Medication Use

Medication use is expected to fall within the guidelines established for treating COPD [40]. Study participants will be asked to provide information regarding their use of four classes of medications, including bronchodilators (beta-agonists, anticholinergics, methylxanthines), corticosteroids, antibiotics, and anti-inflammatories (e.g. statins, roflumilast). Addition of new medications in these classes or alterations in dose over the course of the study will be tracked. Study participants will be requested to bring all medication containers with them to each follow-up visit.

13.6 Daily Diary

The daily diary (hard-copy form) will be given to the study candidate at the baseline visit and collected at the bronchoscopy procedure visit and then electronically at the 45-day, 3-month, 6-month, 9-month, and 1-year follow-up visits.

Study participants will be asked to maintain a daily diary in which they will note compliance to the pulmonary rehabilitation program, complete the EXACT-PRO questionnaire, and note health status changes. They will be asked to complete the diary immediately before going to bed at night. Completion of the daily diary will begin on the first day after the bronchoscopy procedure and will be completed through the 1 year follow-up visit. Every effort will be made to ensure that study participants complete all diary entries, although failure to do so will not be considered a protocol deviation.

13.6.1 Pulmonary Rehabilitation Program Compliance

Study participants will be asked to self-report the number of exercises performed that day and the amount of time (minutes) spent doing them.

13.6.2 EXACT-PRO Questionnaire

The EXACT-PRO was developed to serve as a standardized outcome measure to evaluate COPD exacerbations [41]. Respondents are asked to self-report symptoms such as cough, mucous discharge, chest discomfort, and breathlessness. The questionnaire consists of 14 items, in which the patient grades the symptom as experienced by selecting one of five different responses (e.g. 'not at all', 'rarely', 'occasionally', 'frequently', 'almost constantly').

13.6.3 Health Status Changes

Health status changes data will consist of asking the study participant to self-report changes in maintenance medications, presence of emphysema symptoms, and whether or not they may have been deterred from their normal daily activities due to their emphysema symptoms.

13.7 Six-Minute Walk Distance (6MWD) Test

Six-minute walk distance testing will be performed according to the “ATS Statement” Guidelines for the Six-Minute Walk Test – March 2002” [42]. The test should be performed indoors, along a flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 30 meters in length. The length of the corridor should be marked every 3 meters. The turnaround points should be marked with a cone. A starting line, which marks the beginning and the end of each 60-meter lap, should be marked on the floor. The study participant should rate their baseline dyspnea and overall fatigue before the test and rate their dyspnea and overall fatigue after the test using the Borg scale. Required equipment, patient preparation, and measurements are specified in the ATS guidelines.

13.7.1 Dyspnea Assessment

Dyspnea and overall fatigue will be measured in all study participants using the Borg Scale [43,44] immediately prior to and immediately after performing the 6MWD test.

13.8 Blood Work

Blood chemistry variables collected during for the study will include arterial blood gases (ABGs), complete blood counts (CBCs), serum (or plasma) fibrinogen, plasma cotinine and/or arterial carboxyhemoglobin, and alpha-1 anti-trypsin deficiency.

13.8.1 Arterial Blood Gases (ABGs)

Blood gases should be collected with the study participant breathing room air. If the study participant is receiving supplemental oxygen at the time arterial blood gases are intended to be sampled, the supplemental oxygen should be discontinued for 10 minutes prior to sampling. If during this 10-minute period oxygen saturation falls below 80%, supplemental oxygen should be provided and increased in one liter/minute increments every three minutes until the minimum flow necessary to achieve 90% oxygen saturation is reached. Blood gases should then be sampled at this point. Subsequent blood gas samples should be taken under the same supplemental oxygen flow rate conditions.

13.8.2 Complete Blood Counts (CBCs)

Complete blood counts will be collected to characterize general health status.

13.8.3 Serum Fibrinogen

Blood fibrinogen is a measure of systemic inflammation. Increased levels have been shown to be associated with increased risk of COPD exacerbations [45].

13.8.4 Plasma Cotinine and/or Arterial Carboxyhemoglobin

Plasma cotinine and/or arterial carboxyhemoglobin counts will be collected to monitor nicotine use.

13.8.5 Alpha-1 Antitrypsin Protease Inhibitor Counts

Alpha-1 antitrypsin protease inhibitor counts will be used to assess screening eligibility criteria.

13.9 Chest X-Ray

Chest X-ray will be collected as specified in Section 14.0 and at any other time in which it may be considered medically necessary following the bronchoscopy procedure to screen for signs of volume reduction and pneumothorax.

13.10 Physical Exam

A routine medical examination will be performed as specified in Section 14.0.

13.11 High Resolution Computed Tomography

All attempts will be made to acquire volumetric high resolution computed tomography (HRCT) images using standardized methods across clinical sites at all times of acquisition. The CT scans should be obtained using the study CT acquisition protocol (see Appendix 6).

The screening CT study, collected for all study participants as part of the study screening process, will be considered the baseline CT for statistical analysis. Study investigators, in conjunction with the site-based radiologist(s) if desired, will evaluate CT images collected for study candidates during screening using an FDA approved software package to determine whether study candidates meet study eligibility criteria.

For study participants who receive the study treatment, post-bronchoscopy follow-up CT studies will be collected at the 45-day and 1-year visits. For study participants who receive the study treatment and undergo valve adjustment, an additional HRCT scan will be collected at the 3-month visit.

Clinical site personnel will transmit the CT studies in original DICOM format to a core reading laboratory who will assess the image quality of the studies and review and analyze the images. The CT images will be analyzed quantitatively using automated 510k cleared software and qualitatively, depending on the variable of interest, by the core reading laboratory.

The core reading laboratory will assess all HRCT scans to determine whether study participants who received the study treatment may be candidates for valve adjustment. This will be conducted by 1) determining volumetric change between the screening HRCT scan and post-procedure 45-day HRCT scans in the treated lobe and 2) evaluating valve placement in the target airways. For study participants who undergo a valve adjustment procedure, the 3-month CT scan will be assessed for volumetric change in the treated lobe; valve placement will also be evaluated. The 1-year HRCT scans will be assessed to determine target lobe volume reduction. In addition, the 1-year HRCT scans may be examined to assess valve placement for lobar occlusion and other radiographic features.

13.12 BODE Index

The BODE index is a multidimensional measure that has been reported to be predictive of risk of death from any cause and from respiratory causes [46,47]. It combines four measures frequently used in COPD studies as a composite score: body-mass index (BMI), obstruction (FEV_1 % predicted), dyspnea, usually characterized using the mMRC

survey score, and exercise capacity, as determined using the 6MWD test. Each component is graded and a score of 0 to 10 is obtained as indicated in the table below. The BODE Index will be calculated and reported in the final study report.

Table. Determination of the BODE Index Score.

	Points for BODE Index Score			
	0	1	2	3
BMI (kg.m ⁻²)	>21	≤21		
FEV1 % predicted	≥65	50-64	36-49	≤35
MMRC	0-1	2	3	4
6MWD (m)	≥350	250-349	150-249	≤149

14.0 SEQUENCE FOR TESTING

14.1 Screening Assessment – within 6 months prior to randomization

- Informed Consent
- Inclusion and Exclusion Criteria
- Medical History
- Vital Signs/Physical Exam
- Lung Function Testing (Study Protocol Section 13.0)
 - Spirometry (collected using your clinic’s normal care regime)
 - Body Plethysmography
 - Diffusing Capacity (DL_{co})
- HRCT Scan (Study Protocol Section 8.5.1, Appendix 6 and core lab Protocol)
 - In order for the study candidate to be found to meet the HRCT emphysema lobar destruction score criterion and the emphysema heterogeneity score criterion, the CT scan must be collected using the HRCT scan acquisition protocol
 - Full inspiratory scan (TLC)
 - Full expiratory scan (RV)
 - Forward CT scans to core lab of all candidates meeting the HRCT scan screening eligibility criteria
 - Forward the first 5 Myrian analyses (both (in)eligible candidates) to core lab to confirm proficiency for using the CT scan screening software
 - NOTE: A pre-existing CT scan that the study candidate provides to you or that is found during the chart screening may be “pre-screened” using the CT scan screening software.
- ECG
- 6-Minute Walk Distance (Study Protocol Section 13.7)
- Echocardiogram
- Blood Work (Study Protocol Section 13.8)
 - Arterial Blood Gases (ABGs)
 - Complete Blood Counts (CBCs)
 - Alpha-1 Antitrypsin Deficiency Test
 - Plasma Cotinine

- use Arterial Carboxyhemoglobin if candidate uses nicotine products)
- Serum Fibrinogen

If the Study Screening Eligibility Criteria are met by the Candidate, ask the Candidate to begin the Study Eligibility Pulmonary Rehabilitation Program (if the Study Candidate has already met the Pulmonary Rehabilitation Criterion you may proceed with the Baseline Visit)

14.2 Baseline Assessment - Conduct ≤ 120 days following screening eligibility

- Sign Participation Informed Consent (if only Screening Informed Consent was collected previously)
- Pulmonary Rehabilitation Eligibility Criterion Completed
 - At least 8 sessions (4 weeks with 2 sessions per week; Study Protocol Section 10.1)
- Spirometry
- 6-Minute Walk Distance (Study Protocol Section 13.7)

After confirmation of Baseline Eligibility:

- Vital Signs/Physical Exam
- Medication Use
- Vaccinations, if necessary (Pneumococcal, Influenza)
- Self-Reported Health Status Measures
 - SGRQ
 - SF-36
 - EQ-5D
 - BDI
 - mMRC
 - CAT
 - Health Care Utilization
- Daily Diary
 - Send paper diary home with study candidate to complete daily for 7 days prior to the scheduled bronchoscopy procedure
- Create Bronchoscopy Procedure Plan
- Contact Pulmonx and schedule Procedure date

14.3 Bronchoscopy Procedure – Should occur ≤ 60 days after baseline assessment visit

- **Pre-Procedure Orders and Preparation**
 - Female – pregnancy test, if applicable to informed consent
 - Ensure study personnel are identified for pneumothorax management

Recommended:

- Prophylactic antibiotic regimen may be initiated 2 days prior to procedure if desired by study investigator
- Corticosteroids may be initiated 2 days prior to procedure if desired by investigator

- Inhaled bronchodilator may be given 20 min prior to procedure
- Prior to the procedure, IV first or second generation antibiotics should be administered
- Record or collect photos of EBV placement

- **Bronchoscopy**
 - Anesthesia = conscious sedation with study candidate breathing spontaneously
 - Chartis System: assessment of target lobe collateral ventilation
 - After confirmation of study device eligibility criterion (finding of little or no collateral ventilation in targeted treatment lobe) proceed with randomization

- **Study Device Placement**
 - May convert study participant to general anesthesia
 - Record device lot numbers and valve placement location on worksheet

14.4 Post Procedure

- Study Treatment Arm:
 - Perform chest x-ray within 1 hour (\pm 30 minutes)
 - Monitor vital signs and pulse oximetry for first 24 hours
 - Collect ABGs and serum fibrinogen at 24 hours
 - Antibiotics
 - Bronchodilator Therapy
 - Perform chest X-rays daily x 5 days during hospital stay

- Control Arm:
 - Monitor vital signs and pulse oximetry until discharge
 - Collect ABGs and serum fibrinogen before discharge

14.5 Prior to Discharge

- Study Treatment Arm
 - Perform pre-discharge chest X-ray and physical examination
 - Schedule follow-up visits, including daily contact through 10 days
 - Bronchodilator inhaler, course of antibiotics, corticosteroids
 - Disburse Daily Diary
 - Provide Medical Alert Card, Treated Study Participant Bracelet, Transferring Instructions if Late Pneumothorax, and Post-Procedure Instructions
 - Adverse Event Assessment

- Control Arm
 - Schedule follow-up visits
 - Bronchodilator inhaler, course of antibiotics, corticosteroids
 - Disburse Daily Diary

14.6 Daily Follow Up Phone Call for 10 Days after Discharge (up to 11:59 pm)

- Study Treatment Arm
 - Symptom Checklist
 - Follow up may occur in hospital if subject is still hospitalized

14.7 Day 7 after Discharge Visit (+ 1 business day)

Study Treatment Arm Only

- Vital Signs/Physical Exam
- Chest X-ray
- Symptom Checklist
- Investigator to assess for return to regular activity and initiation of the protocol required pulmonary rehabilitation program
 - Assessment should show lack of evidence of pneumothorax, infection, or exacerbation, tolerance of light activities, and physical condition at least similar to or better than at the baseline visit
- Adverse Events assessment
- Symptom Checklist may be conducted during visit

14.8 Day 30 Visit (+/- 5 days)

Study Treatment Arm Only

- Vital Signs/Physical Exam
- Chest X-ray
- Adverse Events assessment

14.9 Day 45 Visit (+/- 5 days)

- Vital Signs/Physical Exam
- Medication Use
- Daily Diary Collection
- Spirometry
- Body Plethysmography
- DLco
- Collect mMRC Survey
- 6-Minute Walk Distance
- Adverse Event Assessment
- Study Treatment Arm
 - Chest X-ray
 - HRCT Scan (may be completed in a separate visit)
 - Forward CT scan to core lab

14.10 3 Month Visit (+/- 14 days)

- Vital Signs/Physical Exam

- Medication Use
- Daily Diary Collection
- Collect SGRQ Survey
- Collect Health Care Utilization Survey
- Collect TDI Survey
- Collect CAT Survey
- Study Treatment Arm
 - Only EBV treated participants who undergo valve adjustment -- may be completed in a separate visit
 - HRCT, forward CT scan to core lab
 - Chest X-ray
 - Body Plethysmography

14.11 6 Month Visit (+/- 21 days)

- Vital Signs/Physical Exam
- Medication Use
- Daily Diary Collection
- Spirometry
- Collect SGRQ Survey
- Collect Health Care Utilization Survey
- Collect mMRC Survey
- Collect TDI Survey
- Collect CAT Survey
- 6-Minute Walk Distance
- Adverse Event Assessment

14.12 9 Month Visit (+/- 21 days)

- Medication Use
- Daily Diary Collection
- Collect TDI Survey
- Collect CAT Survey
- Collect Health Care Utilization Survey

14.13 1 Year Visit (+/- 45 days)

- Vital Signs/Physical Exam
- Medication Use
- Daily Diary Collection
- Spirometry
- Collect SGRQ Survey
- Collect Health Care Utilization Survey
- Collect SF-36 Survey
- Collect EQ-5D Survey
- Body Plethysmography
- DL_{co}

- Collect TDI Survey
- Collect CAT Survey
- Collect mMRC Survey
- 6-Minute Walk Distance

The following may be completed in a separate visit or in order as scheduling permits after all other testing

- ECG
- Blood Work (ABGs, CBCs, plasma cotinine, serum fibrinogen)
- Adverse Event Assessment
- Study Treatment Arm
 - HRCT Scan for EBV treated participants
 - Forward CT scan to core lab
- Control Arm
 - After completing the 1-year visit testing, assess suitability for crossing over to study treatment.
 - The study investigator must document the participant's suitability for crossing over to study treatment; to qualify for crossover, a control arm participant must have been followed up successfully through 1 year and demonstrate lack of a clinically important response
 - The crossover procedure must be scheduled to occur within the next 60 days following the 1-year visit
 - After receiving the study treatment, the follow-up visits and testing at each visit will be identical to the schedule for treatment arm participants

14.14 Annual Visits (+/- 60) only for Study Participants treated with EBV

- Spirometry
- Adverse Event Assessment

15.0 SAFETY ELEMENTS

15.1 Adverse Events

Previous studies of emphysema patients who were followed longitudinally and treated using medical management [10,16,17], diagnostic or interventional bronchoscopy [448,49], or endobronchial valves [16,17] indicate that a moderate risk of adverse events may be anticipated during this study. Adverse events will be graded by defining their severity and relatedness to the study device.

It is anticipated that the rates for adverse events will be higher for the study treatment arm than control arm during the treatment period ('short', or day of the study procedure to 45 days) but that the rates for these occurrences will be similar for both study arms during the post-treatment period ('long', or 46 days to 1 year).

Adverse events that may be observed include:

- ❖ Cardiovascular events such as:
 - New onset cardiac arrhythmia
 - New diagnosis of congestive heart failure, which may be indicated by ≥ 1 -point increase in NYHA functional classification score
 - Acute myocardial infarct requiring medical care
 - New diagnosis transient ischemia attack (TIA) or stroke
 - New diagnosis deep vein thrombosis
 - Pulmonary embolism, which may be indicated by direct clinical evidence or V/Q evidence of segmental or larger perfusion defects

- ❖ COPD and Emphysema events such as:
 - COPD exacerbation requiring treatment with antibiotics and/or oral steroids
 - AECOPD requiring emergency room visit or hospitalization
 - Respiratory failure requiring re-intubation at any time during follow-up and/or invasive mechanical ventilation >24 hours after the bronchoscopy procedure
 - Pneumonia requiring treatment with antibiotics, indicated by consolidation on X-ray or CT scan and clinical characteristics of active infection (fever, leukocytosis, hypotension)

- ❖ Pulmonary / Thoracic events such as:
 - Hemoptysis requiring new evaluation or intervention
 - Pneumothorax indicated by clinical symptoms and/or X-ray
 - Pneumothorax requiring intervention
 - Empyema requiring new evaluation or intervention
 - Non-cardiac chest pain driving the study participant to seek medical care
 - Pleural effusion noted radiologically
 - Lung mass / cancer noted radiologically
 - Fractured rib noted radiologically
 - Laryngospasm driving the study participant to seek medical care
 - Dysphonia driving the study participant to seek medical care
 - Hypoxemia requiring increased or new oxygen use
 - Adverse tracheobronchial observations such as bronchial granulation tissue, bronchial ulceration, bronchial trauma

- ❖ Other events such as:
 - Death, any cause
 - Septicemia as evidenced by constitutional signs and symptoms consistent with bloodstream infection (with at least two separate blood cultures positive for the same pathogen(s), requiring systemic antimicrobial therapy)
 - Non-pulmonary infection requiring medical care
 - Fever > 99.5 °C for > 24 hours

- ❖ Endobronchial Valve events such as:
 - Valve expectoration, as reported by the study participant
 - Valve migration, as indicated by clinical and/or radiological evidence that a valve has left the target airway
 - Pneumonia distal to implanted valves, indicated by consolidation on X-ray or CT scan and clinical characteristics of active infection (fever, leukocytosis, hypotension)

15.2 Serious Adverse Events

An adverse event is considered serious if it meets the definition of a serious adverse event (SAE) as defined in Section 21.2. Serious adverse events may occur at any time during the study and will be reported as serious regardless of when they occur, provided they meet the definition of a serious adverse event.

15.3 Management of Selected Anticipated Adverse Events

15.3.1 Pneumothorax

Pneumothorax is an expected and anticipated event in patients undergoing a lung volume reduction procedure. With lung volume reduction surgery (LVRS), pneumothorax occurs in all (100%) cases and all patients leave the operating room with a chest tube(s) to manage air leaks. After EBV treatment, it is anticipated that the collapsed lung in the target lobe or expanding lung in adjacent lobe(s) may develop an air leak(s). With lung volume reduction procedures, achieving a higher success rate may be associated with having a higher risk of pneumothorax.

In the VENT study, pneumothorax was seen in 15%-20% of EBV-treated study participants who were thought to have little or no lobar CV (i.e. had HRCT suggestive of complete fissure) along with HRCT evidence of lobar occlusion with valve treatment. Therefore, it is anticipated in this study that approximately one in five of EBV-treated study participants may experience a post-procedure pneumothorax.

Study participants who received the study treatment will be provided with a Medical Alert Card, Treated Study Participant Bracelet, Transferring Instructions if Late Pneumothorax, and Post-Procedure Instructions prior to hospital discharge. Study participants who received the study treatment will be contacted during the 10 days after discharge and asked about increased chest pain, nausea, and new, worsening shortness of breath, which are all potential indicators of pneumothorax.

A suggested treatment plan for managing any suspected pneumothorax is provided in **Appendix 18**. Any study participant who has a persistent pneumothorax requiring care beyond a chest tube should be transferred to the treating hospital and attended to by the treating physician and his or her study team.

15.3.2 Pneumonia

Pneumonia-like symptoms, including low-grade fever, increased sputum, and radiographic abnormalities, are anticipated consequences of bronchoscopy. In this study, pneumonia will be defined as: 1) fever (≥ 99 °F) persisting for ≥ 48 hours and 2) white blood count $>15,000$ cells/mcL. Any study participant having clinical and radiological signs of pneumonia or pneumonia-like symptoms will be medically treated.

15.3.2.1 *Pneumonia Distal to Valve(s)*

Any study participant observed to have consolidation on X-ray or CT scan and clinical characteristics of active infection (fever,

leukocytosis, and hypotension) will be considered to have pneumonia distal to valve(s).

15.3.3 COPD Exacerbation

Any study participant reporting or admitted to the hospital for suspected COPD exacerbation will undergo immediate clinical evaluation and a treatment plan will be formulated. An exacerbation will be defined as a worsening of the study participant's symptoms from his or her usual stable state that is beyond normal day-to-day variations, and is acute in onset, and requires modification of the study participant's medication regimen. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production, and change in sputum color.

15.3.4 Hemoptysis

Any study participant experiencing hemoptysis will be immediately evaluated and a treatment plan will be formulated. Generally, only minimal hemoptysis after the procedure is observed. Larger amounts of bleeding may require imaging or endoscopy as dictated clinically at the discretion of the study investigator. Massive hemoptysis is defined as > 200 ml blood loss in less than 24 hours.

15.3.5 Respiratory Failure

Any study participant experiencing respiratory failure requiring re-intubation will undergo immediate clinical evaluation and management as dictated by the underlying etiology.

15.4 Events Anticipated to Precipitate Valve Removal

In the U.S. VENT study, 31 (14.5%) patients underwent valve removal after the procedure. Therefore, it is anticipated that valve removal attributed to the following conditions may occur.

15.4.1 Valve Migration

In any case in which a valve migration, as defined in Section 15, is observed, removal of the valve is required.

15.4.2 Pneumonia and Pneumonia Distal to Valve(s)

If the pneumonia does not resolve normally with medical therapy then valve removal may be considered.

15.4.3 Respiratory Failure

Valve removal may be considered if the device placement itself is felt to be the causative factor.

15.4.4 Hemoptysis

In cases where hemoptysis is observed, valve removal may be considered.

15.4.5 Granulation

In cases where granulation is observed, valve removal may be considered.

15.4.6 Continuing COPD exacerbations

In cases where a study participant has recurrent COPD exacerbations, valve removal may be considered.

15.4.7 Increased Dyspnea

In cases where severely increased dyspnea is observed, valve removal may be considered.

15.4.8 Request by Study Participant

A study participant may request that the valves be removed for any reason.

16.0 RISK - BENEFIT EVALAUATION

16.1 Potential Benefits

Potential benefits include improvement in the study participant's lung function and other improvements that may be associated with improved lung function.

16.2 Potential Risks

The primary risks associated with use of the Pulmonx EBV, as proposed in this study protocol (see Adverse Events section), are similar to other bronchoscopic and surgical procedures used to treat emphysema.

16.3 Risk Minimization

Risk mitigation measures include the following:

- a) The use of standard medical grade materials that have been thoroughly characterized and tested to assure biocompatibility,
- b) Extensive pre-clinical evaluation including *in vitro* bench testing and animal study,
- c) Prior human clinical trial experience including four hundred ninety two (492) patients followed for one year.
- d) The well-established, standard nature of the bronchoscopic procedure and technique (i.e., used in placement of bronchial stents),
- e) The ability to abort the procedure at any time. The physician may elect to discontinue the use of the Pulmonx Endobronchial Valve at any time in favor of alternative medical or surgical procedures, and
- f) Reversibility, as the Pulmonx Endobronchial Valves may be removed.

17.0 PROTECTION OF HUMAN PARTICIPANTS

17.1 Institutional Review Board (IRB) Approval

The Investigator will obtain IRB approval prior to asking participants to sign the Informed Consent Form and complete any study-specific procedures. The IRB approval must be maintained for the duration of the study. If IRB approval is withdrawn, the Investigator must immediately discontinue any study related activities that will not adversely affect the health and welfare of the study participant. The investigator must notify the study Sponsor of such withdrawal in writing within 5 working days.

17.2 Confidentiality

All information and data concerning participants or their participation in this trial will be considered confidential, and handled in compliance with the Declaration of Helsinki, ICH guidelines (to the extent that they are consistent with U.S. federal regulations), CFR section 21, and HIPAA requirements. Only authorized personnel, the study Sponsor or

its designees, and FDA will have access to these confidential files. All data used in analysis, reporting, and publication of this clinical trial will be maintained without identifiable reference to the participant.

17.3 Ethical Considerations

This study will be performed in accordance with the principles in the Declaration of Helsinki. These principles suggest that biomedical research involving human subjects should:

- Conform to generally accepted scientific principles.
- Be conducted only under the supervision and direction of scientifically or medically qualified persons.
- Be preceded by careful assessment of risks in comparison with benefits to the participant or to others.
- Be more concerned with the interest of the participant than those of science and society.
- Respect the privacy of the participant.
- Preserve the accuracy of the results in publication.
- Inform each potential participant of the aims, methods, anticipated benefits and potential hazards of the study, the discomfort it may entail, and alternatives to study participation.
- Never interfere with the physician-patient relationship.

17.4 Methods to Eliminate Bias

Steps will be taken to minimize the effects of any bias that might occur when conducting a clinical trial of this nature. All candidates presenting to the clinic that meet the eligibility criteria will be invited to participate in the study. No other criteria, apart from the eligibility criteria listed in this protocol, will be used to consider candidates for enrollment in the study. Participant selection criteria will be closely followed and the demographics and the condition of each participant will be documented prior to treatment. Additionally, a standardized arm-specific treatment protocol will be followed for each participant and it will be clearly documented. Finally, both the investigative site staff and the study participants will be instructed to complete the data forms in a consistent manner. Any significant deviations from the procedures described in this protocol will be documented.

17.5 Early Termination of the Clinical Investigation

If the investigation is terminated prematurely or suspended, the Sponsor will promptly inform the Clinical Investigators/investigation sites of the termination or suspension and the reason(s) for this. The Independent Ethics Committee (IEC) will also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Clinical Investigator/investigation sites.

18.0 CLINICAL SITE TRAINING

18.1 Clinical Study Staff Training

The site Principal Investigator will be responsible for the supervision of the trial and will provide direction to all other research staff as necessary. The Study Sponsor will train

the Principal Investigator and clinical study staff through conference calls, face-to-face meetings, and site visits.

18.2 Procedure and Training Videos

All site Investigators participating in the study will attend a presentation designed to convey the technical aspects of the study device and procedure.

18.3 Physician Hands-on Training: Endobronchial Valve

All site Investigators will be trained on an anatomical bronchial model that simulates the clinical experience of using the EBV. After instruction from a qualified Pulmonx trainer and passing the training program evaluation, the physician will demonstrate successful placements as well as successful removals of valves using the bronchial model.

18.3.1 Valve Placement

A minimum of four consecutive successful placements must be demonstrated in different anatomical locations to achieve lobar occlusion. A successful placement has been achieved when the trainer verifies appropriate placement.

- At least two large valves shall be successfully placed. One (1) in the right upper and one (1) in the left upper bronchus.
- At least two small valves shall be successfully placed. One (1) in the right apical bronchus and one (1) in the left apicoposterior bronchus.

18.3.2 Valve Removal

A minimum of two successful removals must be demonstrated. A successful removal has been achieved when the trainer verifies that all elements of the device have been retrieved from the bronchial model.

18.4 Physician Hands-on Training: Chartis Assessment System

All site Investigators will be trained on the Chartis Assessment System using an anatomical bronchial model that simulates the clinical experience of using the Chartis System. After instruction from a qualified Pulmonx trainer, the physician will demonstrate successful catheter placements to simulate isolation of the discrete lung lobes.

The Investigator will also be trained to determine CV status for a series of sample assessments to demonstrate accurate interpretation.

18.5 Study Coordinator Training

The Study Coordinator(s) with primary responsibility for managing the study at each site will be provided with comprehensive training on the study device, study procedure, post-procedure study participant management, study protocol, and duties and responsibilities of the Study Coordinator. They will be provided with detailed information on important logistical and administrative tasks with regards to reporting requirements, CRF management, and product tracking. Each site coordinator will receive a study binder containing, at a minimum, the study protocol, case report forms (CRFs), sample informed consent document, and study contact information.

18.6 Protocol Training

Prior to enrollment of study participants, the site Principal Investigator(s), Sub-Investigators, and the Study Coordinator(s) will meet with Pulmonx personnel to discuss the protocol and to ensure that all study eligibility criteria and study protocol details are well understood. Staff will be trained to encourage all study participants to continue full adherence to the study protocol activities and follow-up schedule. A training record will be maintained for each site Investigator and Study Coordinator and shall be used to document completion of successful training.

18.7 Assistant Physicians, Scrub Nurses, and Technicians

The site Principal Investigator (or designee) will be responsible for providing oversight of all allied health personnel who will be assisting with execution of study-related activities in order to ensure compliance with clinical trial requirements.

18.8 Valve Loader Training

Each site will designate at least one person who will be trained in the loading of the valves into the delivery systems during the procedure. These designees will undergo training in loading techniques by qualified Pulmonx personnel. They will then demonstrate three successful valves loadings, as verified by the trainer.

18.9 Nursing Staff In-service

The Principal Investigator will provide oversight of all nursing staff responsible for post-procedure care in order to ensure compliance with clinical trial requirements.

19.0 STUDY OVERSIGHT

19.1 Data and Safety Monitoring Board (DSMB)

A data safety monitoring board (DSMB) will be utilized to review data to evaluate safety of study participants during their participation in the study and to review the interim data analysis. The DSMB will consist of a statistician, a pulmonologist, and a thoracic surgeon with LVRS experience who have no scientific, financial, or other conflict of interest related to the investigation. Members will not have any direct affiliation with the study Sponsor or the Investigational Sites that would create a conflict of interest impacting their ability to serve objectively on the DSMB.

The DSMB will be responsible for making recommendations to the Operations Committee regarding the primary endpoint at the interim analysis and monitoring for any potential problems at any time during the study. DSMB responsibilities, membership, meeting frequency and procedures will be documented in a committee charter but the DSMB may call a meeting at any time if there is reason to suspect that safety is an issue. The DSMB will be provided access to all study safety data including all adverse event reports. Interaction on the part of DSMB members with clinicians, nurses, technicians and other protocol participants will be strongly discouraged in order to avoid any potential bias. The DSMB will function in accordance with applicable regulatory guidelines.

The DSMB will be expected to review all adverse events and other safety outcomes for the duration of the study. Meetings are anticipated to be conducted on a quarterly basis.

The DSMB will also have the responsibility to review the interim analysis. During the course of the trial, the DSMB will review accumulating safety data to monitor for incidence of trends that would warrant modification or termination of the trial. Any DSMB recommendations for study modification or termination because of concerns of subject safety or issues relating to data monitoring or quality control will be submitted in writing to Pulmonx for consideration.

19.2 Clinical Events Committee

The Clinical Events Committee (CEC) will consist of board-certified physicians who may be specialists in pulmonology, thoracic surgery, interventional pulmonology, or thoracic radiology who are not otherwise participating in the study (Note: The CEC members will be not be DSMB participants). The CEC will regularly review and adjudicate all serious and/or potentially device-related Adverse Events through at least the 1 year follow-up visit and may also conduct an annual review at 2, 3, 4, and 5 years.

19.3 Operations Committee

This committee will be responsible for the day-to-day administrative management of the trial. This committee will meet as needed by conference or teleconference to monitor study participant enrollment, clinical site progress, and protocol compliance. It will also be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications.

19.4 Core Radiology Laboratory

The core radiology laboratory will be responsible for training clinical sites to the HRCT acquisition protocol, monitoring their adherence to the HRCT protocol, and assessing study participant HRCT scans.

19.5 Core Spirometry Laboratory

The core spirometry laboratory will be responsible for training and monitoring clinical sites for adherence to the spirometry acquisition protocol, and conducting quality assurance of spirometry collection during the study.

19.6 Daily Diary Data Acquisition

Core laboratory equipment and processes will direct the Daily Diary data acquisition.

20.0 DATA ANALYSIS OVERVIEW

20.1 Populations for Effectiveness and Additional Measures

The primary analysis population will be made up of study participants enrolled as ITT study participants. The ITT study population will consist of all study participants who have been randomly assigned to study treatment or control, regardless of whether or not they undergo the assigned treatment.

Statistical analyses will also be performed on a Completed Cases (CC) basis and Per-Protocol (PP) basis. The CC population is defined as all randomized and eligible patients who received study-directed treatment and had 1 year of follow-up. The PP population is

defined as all randomized study participants who meet study eligibility criteria, who were treated as randomly assigned, and had follow-up for the endpoints.

If applicable, statistical analyses will also be conducted after sorting patients by the actual treatment received regardless of their randomization assignment.

20.2 Safety Analysis Population

Both the ITT analysis population and 'As Treated' (AT) analysis population will be used to assess the safety data. For the AT analysis, study participants will be analyzed based on the treatment they actually received.

20.3 Primary Effectiveness Endpoint

Achievement of the primary effectiveness endpoint will be determined by assessing the percentage of study participants in the EBV Treatment arm who meet the threshold of $\geq 15\%$ improved forced expiratory volume in one second (FEV_1), collected post-bronchodilator, as compared to the Control arm at 1 year post-procedure.

FEV_1 is the volume of air exhaled during the first second of a forced expiratory maneuver and is commonly used to measure airway obstruction. It is a well-accepted parameter for both staging of COPD and assessment of lung function improvement after treatment. Increased expiratory flow resistance, manifested as a decreased FEV_1 , is one of the hallmarks of emphysema. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) reports that FEV_1 is the gold standard for measuring airflow limitation in COPD (44). In addition, FEV_1 is used to classify COPD into severity stages. One of the most important predictors of survival in COPD is the degree of airway obstruction as measured by post-bronchodilator FEV_1 (45-47). Decline of FEV_1 is associated with adverse health consequences such as increased COPD exacerbations and reduced quality of life (48).

20.3.1 Sample Size Rationale

The results of two prospective studies were used to inform the sample size estimation. The Endobronchial Valve for Emphysema Palliation Trial ("VENT Pivotal Trial", IDE#G020230, NCT00129584) was a multi-center, prospective, randomized, controlled study conducted at sites in both the United States and Europe to assess the safety and effectiveness of using the Zephyr EBV device for palliating symptoms associated with severe heterogeneous emphysema. Four hundred ninety two (492) participants were enrolled into the study and randomized to Zephyr EBV Treatment or medical management (control) [16,17]. The Chartis Pulmonary Assessment System study is a recently completed prospective post-market study that was conducted in Germany, The Netherlands, and Sweden. The primary objective of the study was to quantify the accuracy of the Chartis System when used to identify targeted treatment lobes as having or not having inter-lobar CV in patients with emphysema who were to be treated using endobronchial valves (26). The results of both the VENT Study and the Chartis System study showed that treatment effect with the endobronchial valve is correlated with lack of inter-lobar CV [16,17,25].

Patients in the VENT Study and in the Chartis Study who were considered to have little or no inter-lobar CV contributed the information used for the sample size estimate. Patients who have little or no lobar CV in the targeted treatment lobe are expected to be good responders to endobronchial valve treatment. For the sample

size estimate, a 'responder' was considered to be a study participant who had $\geq 15\%$ improved FEV₁ after EBV treatment.

Based on the results of these studies, the responder rate in the EBV Study Treatment Group is expected to be approximately 35% at 1 year. The responder rate for the control group is not expected to exceed 10% at 1 year. Assuming a two-sided 0.05 alpha level, study power of 90%, and 2:1 allocation random assignment, a sample size of 147 will be adequate to test for superiority.

The study sample size will be increased to 183 in order to allow for 20% lost to follow-up and incomplete data. Each study site will be allowed to enroll a maximum of 25 study participants.

20.4 Safety Endpoint

Safety will be determined by evaluating the adverse events profile for the EBV Treatment Group for 1) the shorter-term treatment period, defined as the day of the study procedure until 45 days after the study procedure ('short') and 2) the longer-term post-treatment period, defined as 46 days after the study procedure until the 1 year follow-up visit ('long').

20.5 Secondary Effectiveness Measures

The following will be assessed for the EBV treatment arm:

- 1) Treatment Lobe Volume Reduction (TLVR) for the EBV Treatment Arm
 - a. TLVR, measured as the 'absolute change from baseline' for treated lobe volume as seen via HRCT (high resolution computed tomography), will be evaluated at 45 days and 1 year.
 - b. TLVR, measured as the 'percentage change from baseline' for treated lobe volume as seen via HRCT will be evaluated at 45 days and 1 year.

The study participants in the EBV treatment arm will be compared to the control arm at 1 year to assess:

- 2) St. George's Respiratory Questionnaire
 - a. Difference between study arms in 'absolute change from baseline' for SGRQ score at 1 year.
- 3) FEV₁
 - a. Persistence of treatment effect will be evaluated by determining the difference between study arms for 'absolute change from baseline' for FEV₁ at 45 days, 6 months, and 1 year.
 - b. Persistence of treatment effect will be evaluated by determining the difference between study arms for 'percentage change from baseline' for FEV₁ at 45 days, 6 months, and 1 year.
- 4) 6-Minute Walk Distance
 - a. Difference between study arms in 'absolute change from baseline' for 6-minute walk distance at one year.
 - b. Difference between study arms in 'percentage change from baseline' for 6-minute walk distance at one year.

20.6 Additional Measures

Mean changes and/or changes measured using responder analyses for:

- Spirometry including FEV₁, forced vital capacity (FVC and, the ratio of FEV₁/FVC
- Body plethysmography including residual volume (RV), inspiratory capacity (IC), functional residual capacity (FRC), total lung capacity (TLC), and the ratios of RV/TLC and IC/TLC
- SGRQ global and domain (i.e. 'symptoms', 'activity' and 'impacts on daily life' scores
- Modified Medical Research Council (mMRC) Dyspnea Scale Score
- BODE Index
- Transitional Dyspnea Index (TDI) from Baseline Dyspnea Index (BDI)
- COPD Assessment Test (CAT)
- SF-36 Health Survey score
- EQ-5D Health Survey score
- Health Care Utilization Questionnaire
- 6 minute walk distance
- Borg scale dyspnea scores before and after 6MWD test
- Change in use of 'maintenance' medications, including bronchodilators, corticosteroids, antibiotics, and anti-inflammatories
- Daily diary (EXACT-PRO, pulmonary rehabilitation compliance, health status changes)
- Carbon Monoxide Diffusing Capacity (DL_{CO})
- Lung radiographic features
- Blood chemistry measures

20.7 Interim Analysis

An interim analysis designed to evaluate effectiveness for continuing crossover of control arm study participants after the 1 year follow-up visit to EBV treatment will be performed when 74 (50% of the required minimum of 147) study participants have completed the 1 year follow-up. If crossover of control arm study participants is found to be justified by the interim analysis then crossover of a control arm study participant after (s)/he has reached the 1 year follow-up time point may be continued. The results of the interim analysis will be reviewed by the DSMB and FDA. If the DSMB recommends not continuing crossing control arm participants to EBV treatment then those control arm participants who have not crossed over will exit from the study per protocol after the 1-year visit.

20.8 Long-Term Follow-up

Data will be collected annually through 5 years for study participants receiving the study treatment. Per the regulatory plan agreed to with FDA, 1 year of follow-up is required pre-approval and the remaining 4 years of follow-up will be conducted post-approval. The annual 2-, 3-, 4-, and 5-year data will consist of FEV₁ scores and adverse events.

20.9 Time Points for Data Analysis

20.9.1 Length of Follow-up for PMA Study Data Analysis

Safety and effectiveness will be evaluated at the Interim Analysis and at 1 year.

20.9.2 Length of Follow-up for Durability Data Analysis

Long-term data will be collected annually through 5 years.

20.10 Statistical Analysis Plan

The details for the Statistical Analysis Plan are provided in **Appendix 19**.

21.0 REGULATORY AND REPORTING REQUIREMENTS

21.1 Adverse Events and Reporting

An adverse event (AE) is an untoward medical occurrence in a patient or clinical investigation participant receiving a procedure using a medical device and that does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical device, whether or not related to the medical device. Generally, a condition is an adverse event if it is undesirable and was not present before the participant underwent the procedure or is more severe than before the participant underwent the procedure, and/or is more frequent than before the participant underwent the procedure.

Adverse event information will be collected over the entire duration of the study. Collection of adverse event data will commence upon random assignment of a study participant. The following information will be recorded on the appropriate case report form:

- Event diagnosis or syndrome
- Date of onset
- Duration
- Severity (mild, moderate, or severe)
- Relationship to the device (not related, possibly related, probably related, related, or unknown)
- Relationship to the procedure (not related, possibly related, probably related, related, or unknown)
- Action taken, and
- Outcome (not resolved, resolved with sequelae, or resolved).

If the diagnosis or syndrome is not known, the unfavorable or unintended sign or symptom experienced by the participant should be recorded on the CRF. Adverse events will be determined by the study investigator treating the study subject. Adverse events will be monitored and treated as appropriate until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Adverse events will be followed until resolution or until the end of the study. In addition, all IRB and FDA reporting requirements will be followed.

21.2 Serious Adverse Events and Reporting

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or congenital

anomaly/birth defect.

All serious adverse events should be reported immediately (within 24 hours of knowledge of the event) to the study sponsor. All IRB and FDA reporting requirements will be followed.

21.3 Unanticipated Adverse Device Effects (UADE) and Reporting

Unanticipated adverse device effects (UADE) are defined as: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with the study device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, Investigator's Brochure, or package insert, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. All unanticipated adverse device effects must be reported immediately (within 24 hours of knowledge of the event) to the study Sponsor. The Investigator must submit to the sponsor and to the reviewing IRB a written report as soon as possible, but in no event later than 5 working days after the Investigator first learns of the event.

A sponsor who conducts an evaluation of a UADE under CFR 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

A sponsor who determines that a UADE presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect.

21.4 Informed Consent Violation Reporting

If the Investigator uses an investigational device prior to obtaining informed consent from an intended study participant, the Investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the event occurs.

21.5 Protocol Deviation Reporting

The Investigator must notify the sponsor and the reviewing IRB of any deviation from the Investigational plan to protect the life or physical well-being of a study participant in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. All other deviations from the protocol will be reported on the appropriate case report form and reported to the IRB, if required.

21.6 Investigator Reporting

The Investigator must, upon request by the reviewing IRB/EC, FDA, or study sponsor, provide accurate, complete, and current information, or a summary report, about any aspect of the investigation.

22.0 STUDY DATA REPORTING AND PROCESSING

22.1 Study Data Collection

The Case Report Form set is designed to accommodate the specific features of the trial design. Modification of the CRFs may be done to ensure all required data is appropriately recorded. Significant modifications will be reviewed and approved by the Operations Committee.

22.2 Site Data Monitoring and Quality Control

Study coordinators or investigators at each clinical site will perform primary data collection based on source-documented hospital chart reviews. Case Report Forms will be submitted to data management in an expedited fashion.

To ensure proper tracking of Case Report Forms and test reports obtained from the individual clinical sites, a master tracking system will be utilized. Deficiencies identified by the master tracking system and any other specific clinical sites needs will be communicated regularly. In addition, regularly scheduled teleconferences between the Study Coordinator(s) for each site and the sponsor may occur.

All clinical sites will be monitored periodically by the sponsor's personnel, or sponsor's designee, for protocol adherence, accuracy of CRF completion, and compliance to applicable regulations. Ongoing and/or serious non-compliance with respect to these standards will be evaluated and appropriate corrective/preventive actions required will be determined. If corrective/preventive actions are not subsequently undertaken, the clinical sites will be asked withdraw from the study.

22.3 Communication

During execution of the study protocol, the sponsor will coordinate and host teleconference calls between the sponsor monitor, data management, and / or each clinical site, as necessary, to resolve any problems concerning the protocol and / or data collection. Every effort will be made to ensure compliance with the protocol. In addition, sponsor representative(s) will maintain personal contact with the Investigator and staff throughout the study by phone, mail, email and on-site visits. If problems cannot be resolved immediately, an appropriate expert(s) will be consulted.

22.4 Recruitment Tracking

A weekly recruitment status report generated by the master tracking system will be used regularly to identify variations in recruitment frequency among sites. For any well-balanced trial, a normal distribution in recruitment is expected; however, outliers will be investigated for trial compliance.

22.5 Data Processing and Quality Control

Data gathered during the course of the study will be reported on the study CRFs via a secure web-based database. The sponsor will evaluate all CRFs upon receipt. Missing, incomplete, or inconsistent data will be requested from the Investigator and corrections will be made. All efforts will be made to avoid loss of data. All changes will be appropriately documented. Passwords will be issued to appropriate personnel to ensure

confidentiality and protection of the data by allowing variable levels of access to the computer system.

22.6 Monitoring, Audits and Inspections

During the investigation, the monitor will have regular contacts with the investigative site. These contacts will include visits to confirm that the facilities remain adequate to specified standards and that the investigative team is carrying out the procedure stated in the investigational plan. All data must be accurately recorded in the Case Report Forms. Source data verification (a comparison of data in the CRF with the subject's medical records and other records at the investigation site) with access to records will also be performed. The monitor or other sponsor personnel will be available between visits if the Investigator or other staff at the site needs information and/or advice. Authorized representatives of the study sponsor, and FDA, may visit the site to perform audits / inspections, including source data verification.

22.7 Investigator Access to the Data and Publication Policies

At the conclusion of the trial, a multi-center abstract reporting the primary results will be prepared and presented at a major medical meeting. A multi-center publication will also be prepared for publication in a reputable medical journal. The publication of results from any single center experience within the trial will not be allowed until the aggregate study results have been published, unless there is written consent from the study sponsor. The analysis of other pre-specified and non-pre-specified endpoints will be performed by the sponsor. Such analyses as well as other proposed investigations will require the approval of the Operations Committee. It is anticipated that many secondary manuscripts with principal authorship drawn from members of the Steering Committee. For purposes of timely abstract presentation and publication, such secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data will require the approval of the Operations Committee.

23.0 ADDITIONAL STUDY AND ADMINISTRATIVE ELEMENTS

23.1 Duration of Investigation

It is anticipated that some of the study participants will take part in this clinical study for up to 7 years. Given an accrual rate of approximately 15 patients per month, it is anticipated that time for recruitment will be 12 months for the enrollment of 183 study participants to yield an estimated final completed study group total of 147 study participants.

23.2 Participant Accountability

23.2.1 Missed Follow-up Visits

Study participants that miss a scheduled visit will be contacted to reschedule as soon as possible. Study participants failing to return for follow-up, or failing to return to contact attempts by site staff for follow-up visits, shall be contacted a minimum of three times by the Study Coordinator or Investigator, with the last attempt by certified mail, before exiting the study participant as lost to follow-up.

23.2.2 Participant Withdrawal

Study participants will be advised that they may voluntarily withdraw from the study at any time and they will be instructed to notify the Investigator immediately, should they choose to withdraw. Study participants may withdraw for any reason and are not obligated to reveal their reasons for withdrawal.

23.3 Documentation Requirements

All study information beginning at the screening assessment continuing through the final follow-up will be recorded on source documents such as initial history and physical noting eligibility, outside medical records, written records of all research procedures, including questionnaires, diaries, follow-up documentation, lab work, pathology reports, ECGs, X-ray reports, and any other diagnostic information, record of medications dispensed or devices used, clinic charts or hospital records. Data will be transcribed onto participant case report forms (CRFs) or recorded on eCRFs (electronic CRFs) in a database supplied by the sponsor.

23.4 Study Monitoring

Monitoring of the study will be conducted by the sponsor or its designee following 21CFR 50, 54, 56, and 812 and the guidelines established by the Declaration of Helsinki and ICH GCP (to the extent that they are consistent with U.S. federal regulations). A site initiation meeting will be held and periodic site visits will be performed. The monitor will maintain oral and written communications with the Investigators and study personnel. Case report forms will be reviewed with source records and compliance with the protocol will be documented.

23.5 Data Management

Study data will be maintained in a password-protected electronic database created by the Sponsor specifically for this research study. Study participants will be identified only by an anonymous study identification number.

23.6 Registration of the Clinical Trial

The clinical trial will be registered and maintained on the publicly available clinical trials website (www.clinicaltrials.gov) by the study sponsor within 21 days of the first study enrollment.

23.7 Amendments to the Clinical Investigational Plan

Any change to the approved investigational plan must be documented in a written and numbered CIP amendment with a justification for the amendment. Changes to the investigational plan will only be effected following IRB and FDA approval as applicable.

23.8 Device Accountability

All of the valves and valve delivery catheters used in the study will be maintained in a secure location at the investigational site until used or returned to the sponsor. Study devices will only be used under the Investigator's supervision in study participants. The Investigator will not supply the study device to any person not authorized under this protocol to receive it. The Investigator shall maintain accurate device accounting records including quantity and date of receipt, person in receipt, lot number, use or disposition,

participant identification associated with device, date of expiration (if applicable) and quantity and date of any devices returned to the Sponsor.

23.9 Deviations from the Clinical Investigation Plan

Except in an emergency, prior approval by the study Sponsor is required for changes in or deviations from the investigational plan. If the changes or deviations may affect the scientific soundness of the study or the rights, safety, or welfare of participants, FDA and IRB approval is required. Every effort should be made to comply with the requirements of the protocol. Deviations will be recorded with an explanation for the change. The study Sponsor is responsible for analyzing the deviations and assessing their significance. Corrective action will be implemented to avoid repeat deviations.

24.0 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for ensuring that this investigation is conducted according to all signed agreements, the study protocol, and the applicable code of Federal Regulations. This section describes these responsibilities at his/her site.

24.1 Study Administration

The Investigator must read and acknowledge his/her understanding of the study protocol and ensure adequate training of staff for executing the study has occurred. Specifically, he/she must: Sign the Protocol Signature Page, Clinical Trial Agreement, Non-Disclosure Agreement and Financial Disclosure and provide a copy of each to the Pulmonx Clinical Research Department or designee.

- Provide current copies of each Investigator's, Sub-Investigator's, and Coordinator's Curriculum Vitae (CV) to the Pulmonx Clinical Research Department.
- Provide current copies of each Investigator's, and Sub-Investigator's Medical License as required throughout the course of the study.
- Provide documentation of GCP training for all study staff.
- Complete training using the Pulmonx Chartis Assessment System prior to treating enrolled subjects.
- Complete training using the Pulmonx Endobronchial Valve System prior to treating enrolled subjects.
- Delegate appropriate and qualified staff as indicated on the Site Delegation of Authority Log.
- Complete all required study procedures and documentation at all visits.

24.2 Institutional Review Board (IRB) Approval

The Investigator must submit the study protocol to his/her IRB and obtain their written approval before being allowed to participate in the study. Specific responsibilities include:

- Submit proposed protocol amendments and informed consent revisions to the IRB/IEC and await approval.

- Inform sponsor and IRB of any unanticipated device-related events (UADEs) within 24 hours of knowledge.
- Submit all required reports to IRB/IEC and sponsor within specified timeframes.

24.3 Conduct the Informed Consent Process

Part of the IRB approval must include approval of an Informed Consent Form specific to the study. The Investigator or his/her designee must administer these approved Informed Consent text to each prospective study candidate and obtain the study candidate's signature on the text, prior to conducting any study-specific tests and enrollment into the study, respectively. The study sponsor will provide Sample Informed Consent text for the Informed Consent forms to the Investigator. This text may be modified to suit the requirements of the individual site. A copy of the informed consent form that has been approved by the reviewing IRB will be provided to the study sponsor. Specifically, the Investigator must:

- Explain all study procedures to the study candidates and obtain written informed consent.
- Ensure HIPAA Authorization is obtained from each study participant and on file.

24.4 Study Coordinator

To assure proper execution of the study protocol, each investigator must identify a Study Coordinator for the site. Working with and under the authority of the Investigator, the Study Coordinator assures that all study requirements are fulfilled, and is the contact person at the site for all aspects of study administration.

24.5 Investigator Records

Each Investigator must maintain the following accurate, complete, and current records relating to the conduct of the investigation. The data for some of these reports may be available in computerized form from the sponsor but the final responsibility for maintenance remains with the Investigator. Study-related documents must be retained for a minimum of two years after study completion and access must be permitted to the study sponsor monitor to inspect facilities and records. Specific examples of records maintenance include:

24.5.1 Correspondence

The study site will maintain records of all correspondence with another Investigator, an IRB, a Core Laboratory, the Study Sponsor, a monitor, or FDA, including required reports.

24.5.2 Study Devices

Records of receipt, use, or disposition of the study device, including receipt dates, serial and lot numbers, names of all persons who received or used the device, why and how many devices were returned to the study Sponsor or otherwise disposed of.

24.5.3 Study Participant Records

Records of each study participant's case history, including study-required Case Report Forms, evidence of informed consent, all relevant observations of adverse device effects, the condition of each study participant upon entering and

during the course of the investigation, relevant medical history, the results of all diagnostic testing, and the date of each study treatment.

24.5.4 Protocol and Deviations

The protocol, along with any documentation showing the dates and reasons for any protocol deviations, will be maintained by the study site.

24.5.5 Investigator Reports

The reports for which the Investigator has responsibility to generate are shown in the table below. The table also shows who should be the recipient of the report and timeframe for submitting it. While some of these reports will be developed by or with the assistance of Pulmonx, the final responsibility for them rest with the Investigator.

Type of Report	Prepared by Investigator For:	Time Constraints of Notification
Unanticipated Adverse Effect	Sponsor	As soon as possible but no later than 10 working days after knowledge of the event.
Withdrawal of IRB Approval	Sponsor	Within 5 working days.
Progress Report	Sponsor / IRB	Submitted at least annually.
Protocol Deviations to protect the life or physical well-being of the subject in an emergency	Sponsor / IRB	Within 5 working days.
Informed Consent Not Obtained prior to device use	Sponsor / IRB	Within 5 working days.
Final Summary Report	Sponsor / IRB	Within 3 months of study completion/termination.

25.0 SPONSOR RESPONSIBILITIES

25.1 Clinical Site Selection and Training

- Submit the IDE application to FDA and obtain approval from FDA to initiate the study.
- Ensure that IRB approval and continuing review are obtained.
- Select the clinical Investigators and study sites, and other consultants who participate in the study.
- Ensure that the Investigator is an appropriately qualified practitioner legally entitled to practice.
- Ensure that the Investigator is trained and experienced in the field of application of the device under consideration.
- Ensure that the Investigator has sufficient background and meets the requirements for conducting a clinical investigation.
- Ensure that the appropriate information and training are provided to the Investigator in the use of the device to be used in the study in accordance with the clinical investigation plan.

- Obtain from each participating Investigator a signed agreement which includes: 1) Investigator's CV, statement of the investigator's relevant experience and/or information regarding other research activities, including instances where the research activity was terminated.
- Provide financial support to each study site and the core laboratories per individual contracts with each site.
- Provide the study device to participating study sites, in quantities sufficient to support study activities, per agreements executed with the study sites.
- Provide training to Principal Investigator(s) and Study Coordinator(s).

25.2 Good Clinical Practice

- Ensure that the study is conducted according to ICH Good Clinical Practice Guidelines (to the extent that they are consistent with U.S. federal regulations), and all applicable regulatory standards per federal regulations for clinical study sites, core laboratories, and other participants, and perform regular site monitoring to assure compliance with them.
- Perform site monitoring of clinical data at clinical study sites.
- Provide the Investigator with sufficient clinical study material and help the Investigator to carry out the clinical investigation in compliance with the approved protocol.
- Evaluate (together with the Investigator) all serious adverse events (SAE) and unanticipated adverse device effects (UADE) without delay and take all necessary steps to protect the study participant. The appropriate authorities will be notified of all SAEs and UADEs in accordance with the legal requirements.
- The Sponsor will inform the Investigator(s) when the prescribed period for retaining clinical study documents has elapsed.

25.3 Clinical Site Management

The sponsor reserves the right to:

- Demand the exclusion of a study participant from the clinical investigation in the case of ineligibility.
- Exclude/Terminate Investigator(s) from the clinical investigation because of severe protocol deviations or because of fraud and misconduct.
- Terminate the study investigation prematurely. If this should become necessary, the Sponsor and the Investigator will conclude the proceedings after consideration and consultation, taking into account the protection of the study participants' interests.

25.4 Study Sponsor Monitoring on Site

The study Sponsor personnel or their designee will perform study site monitoring. Each site will be monitored according to 21 CFR 812 and Pulmonx Inc. (or designee's) internal monitoring SOPs. This will be done to ensure that the study is conducted in full compliance with all applicable regulations, and with the study protocol. A pre-investigation meeting will occur with each potential study site in order to orient the prospective Investigator and staff to the clinical trial protocol, applicable regulations and requirements, and expectations of the study, including the numbers and time frame for

study participant enrollment, study participant selection, informed consent, randomization, required clinical data and record keeping. The prospective study site will be evaluated to ensure that it has an adequate patient base and can provide sufficient staff and documentation support to conduct the study properly.

No study site may receive shipment of the study device components until Pulmonx receives the following documents:

1. Written IRB approval for conduct of the study
2. Review of the site's approved written study-specific informed consent document.
3. Executed Clinical Trial Agreement

25.5 Sponsor Records

25.5.1 Correspondence

Records of all correspondence with Investigators, IRB, Core Laboratories, Clinical Research Organizations (CRO), study monitors, or FDA, including required reports, will be maintained.

25.5.2 Study Devices

Records of study device shipments and disposition shall be maintained. Records of shipments shall include the name and address of the consignee, type and quantity of devices shipped. Records of disposition shall describe the batch numbers of any devices returned to the Sponsor, repaired, or disposed of in other ways by the Investigator or another person, and the reasons for and method of disposal.

25.5.3 Research Agreements and Financial Disclosure

The sponsor shall maintain signed copies of clinical site and investigator agreements, including the financial disclosure information.

25.5.4 Study Participant Records

The sponsor shall maintain records concerning adverse device effects.

25.6 Sponsor Reports

25.6.1 Unanticipated Adverse Device Effects

The sponsor shall report the result of such evaluations to FDA and to all reviewing IRB's and participating Investigators within 10 working days after the sponsor first receives notice of the effect.

25.6.2 Withdrawal of IRB Approval

The sponsor shall notify FDA and all reviewing IRB's and participating Investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

25.6.3 Withdrawal of FDA Approval

The sponsor shall notify all reviewing IRB's and participating Investigators of any withdrawal of approval of an investigation or a part of an investigation by FDA within 5 working days after receipt of the withdrawal of approval.

25.7 Investigator List

The sponsor shall maintain and update as necessary a current of the names and addresses of all Investigators participating the investigation.

25.8 Progress Reports

The sponsor shall submit annual progress reports to all reviewing IRB's and FDA.

25.9 Recall and Device Disposition

The sponsor shall notify FDA and all reviewing IRB's of any request that an Investigator return, report, or otherwise dispose of any study devices.

25.10 Final Reports

The sponsor shall submit to FDA and all reviewing IRB's a final report upon completion or termination of the study.

26.0 GLOSSARY OF TERMS

6MWD Test – The six-minute walk distance test is a cardiopulmonary function test that measures a patient's exercise capacity by the distance that he or she can walk in six minutes.

AE – An Adverse Event is any pulmonary complication whether considered major or minor and whether or not associated directly with the Pulmonx Endobronchial Valve procedure. Anticipated AE's are listed as endpoints, but unanticipated events are documented as well.

Atelectasis – Lung collapse.

Body Plethysmography – a box-like device in which the patient sits that measures pressure and volume changes in the lung to determine functional residual capacity and other lung volumes.

COPD – Chronic obstructive pulmonary disease is a condition in which the lungs are limited by airway narrowing and air trapping.

CRF – Case report forms are used to collect data for this study.

CV – Collateral ventilation; inter-lobar communication of air

HRCT Scan – a high-resolution computed tomography scan used to generate a cross-sectional image of the lungs and other thoracic organs and tissues.

Diffusing Capacity – Measures the rate of carbon monoxide gas transfer across the alveolar-capillary blood-gas membrane (DLCO).

DLCO – a measure of diffusing capacity (see above)

Dyspnea – Shortness of breath.

EBV – Pulmonx Endobronchial Valve

ECG – Electrocardiogram; a recording of the heart's electrical activity.

EBV – Pulmonx Endobronchial Valve (EBV) Procedure – a bronchoscopic method of delivering and deploying a valve to prevent inspiratory airflow into a targeted lung segment while allowing for expiratory airflow.

ERV – Expiratory reserve volume – the maximal amount of gas that can be exhaled from the resting end-expiratory level.

FEV₁ – Forced expiratory volume in one second is the minimum volume of gas that can be forcefully exhaled in one second after a maximal inspiration.

FRC – Functional residual capacity: the volume in the lungs at the end-expiratory position.

FVC – Forced vital capacity is the total volume forcefully exhaled after a maximal inspiration.

Heterogeneous – A term used to describe non-uniform distribution of diseased, emphysematous areas in the lung.

Homogeneous – A term used to describe uniform distribution of diseased, emphysematous areas in the lung.

IC – Inspiratory capacity is the volume of gas that can be inhaled during maximal forced inhalation after normal expiration.

LVRS – acronym for lung volume reduction surgery.

mmHg – Millimeters of mercury is a unit of measure for pressure.

NETT – acronym for National Emphysema Treatment Trial

PaCO₂ – Partial pressure of carbon dioxide in arterial blood.

PaO₂ – Partial pressure of oxygen in arterial blood.

RV – Residual volume: the volume of air remaining in the lungs after a maximal exhalation.

SAT – Blood saturation is the percentage of hemoglobin sites occupied by oxygen molecules.

SGRQ – St. George's Respiratory Questionnaire: a standardized quality of life measurement used to assess patients with obstructive pulmonary diseases.

Spirometry – a method of measuring lung volumes and flows.

TLC – Total lung capacity is the total volume of gas that is held within the lungs at maximal inspiration.

VC – Vital capacity: the volume equal to TLC – RV.

VTG – Volume of thoracic gas: the absolute volume of gas in the thorax at any point in time and any level of alveolar pressure.

V/Q Scan – Ventilation/perfusion scan is used to assess regional lung function. Note: Xenon gas will be used at some centers to identify areas of poor ventilation in the lung.

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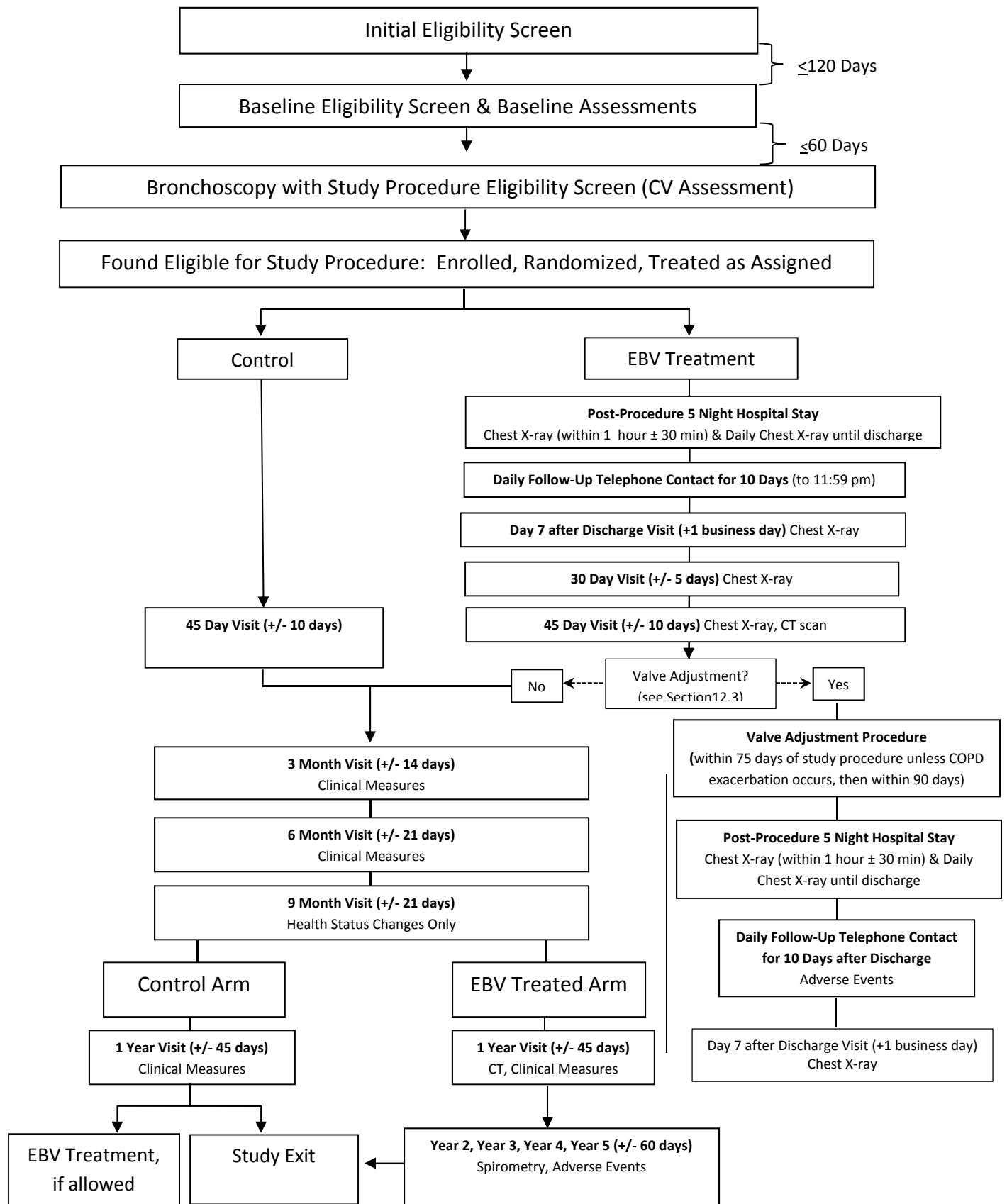
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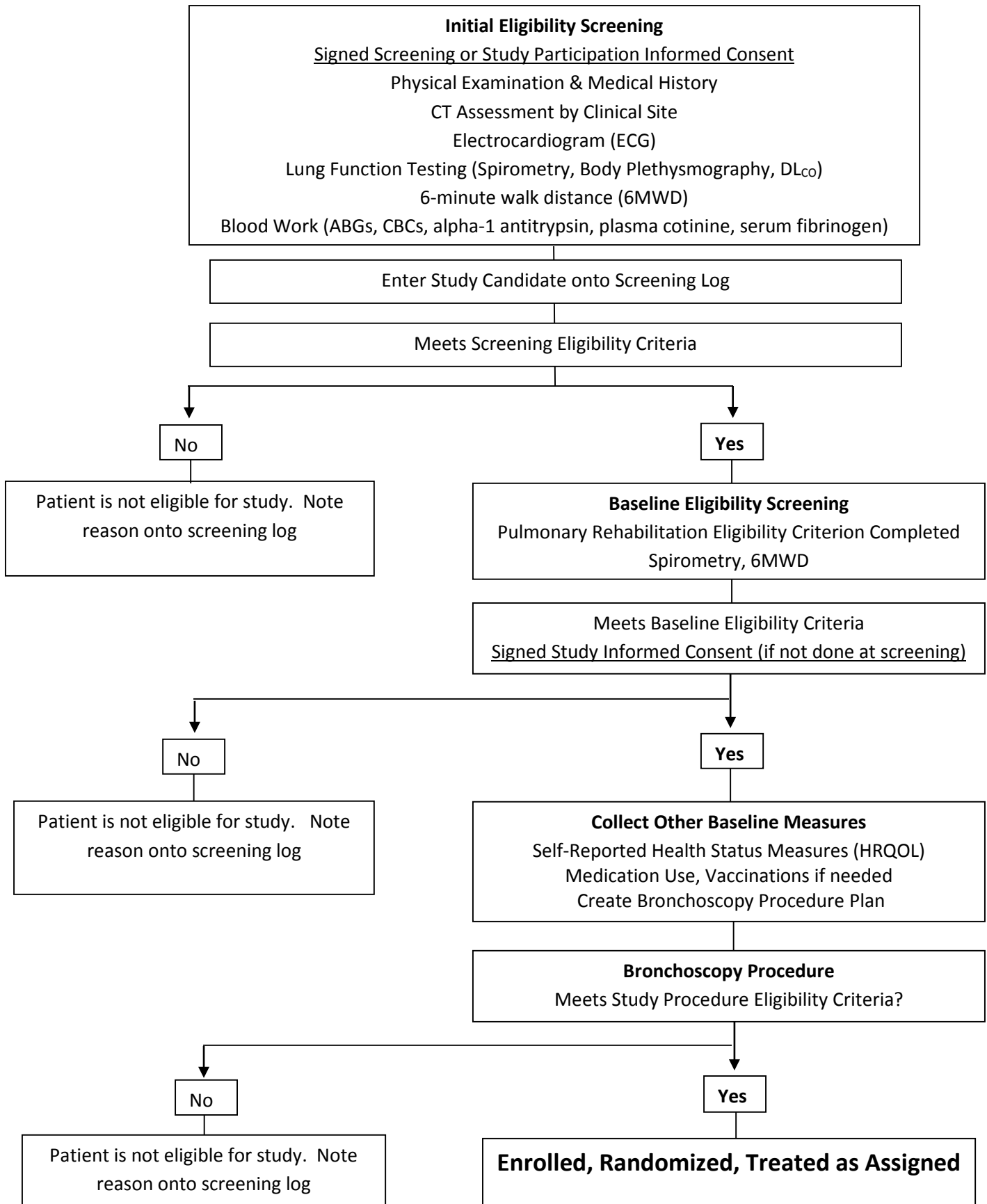
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LIBERATE Study
Clinical Investigational Plan #630-0012-H
Appendix 2. Study Participant Screening and Enrollment Flowchart



Investigator Name: _____ Site ID# _____
Institution: _____ Participant ID: _____

Telephone: _____

Dear Patient:

You are being invited to be screened for a clinical study involving research. This Informed Consent Letter describes the study and the screening tests that must be done to find out if you would be a candidate for the study. If you choose to be screened for the study you must read this form carefully. You are urged to discuss any questions you have with your physician and / or the hospital's research staff.

Purpose of the Research Study

Since you are being asked to consider undergoing screening to find out if you may be a candidate for this study, you have probably suffered an impaired lifestyle as a result of emphysema. Emphysema is a serious disease that afflicts more than four million people worldwide. It is one form of Chronic Obstructive Pulmonary Disease, or COPD. Emphysema causes the lungs to lose the ability to move air in and out normally and to efficiently absorb oxygen, making breathing more difficult.

The purpose of this research is to study a medical device that is designed to be placed by a doctor in a diseased section of the lungs. This device is called the Pulmonx Endobronchial Valve (EBV). The EBV is a one-way valve that blocks off the diseased lung section to inhaled air but lets the trapped air already inside the area escape. With placement of the EBV, the diseased part of the lung collapses; this allows the healthier parts of the lung to expand. The aim of the EBV treatment is to help someone with emphysema breathe more easily by allowing the healthier parts of the lung to work better. This research study is designed to investigate the safety and effectiveness of the Pulmonx EBV for treating emphysema symptoms. The EBV is considered experimental. This means that it has not yet been approved by the U.S. FDA (Food and Drug Administration) for commercial use in the United States.

Number of Patients in the Study

Approximately two hundred (200) patients will be enrolled into this study. In order to qualify for enrollment into this study, you must undergo a bronchoscopy procedure. During the bronchoscopy procedure, your doctor will measure some of the airways in your lungs using a device that measures airflow to find out if you meet the study criteria for having the EBV treatment. There is a chance that after measuring some of airways in your lungs you will not be eligible to take part in this study.

During the bronchoscopy procedure, one hundred and eighty-three (183) patients will be found to qualify for the study. The 183 patients who qualify for the study will be randomly assigned to the study treatment. Approximately two-thirds will be randomly assigned to the EBV treatment group and have EBV implanted in their lungs and approximately one-third will be randomly assigned to the control group and not have EBV implanted in their lungs. This means that during the bronchoscopy procedure if you are found to be eligible to participate in the study, you will have a 2 in 3 chance of receiving EBV and a 1 in 3 chance of not receiving EBV.

The results of the study will be evaluated after all of the study participants have made the 1-year visit. For study participants who have EBV, they will be expected to continue coming to the research clinic once a year through 5 years.

Tests and Evaluations

If you agree to undergo the screening for this study, the following tests and assessments will be performed. If you should feel dizzy, chest pain, palpitations, nausea, severe difficulty breathing or wheezing, during any of the testing, please let your healthcare professional know immediately.

Chest X-ray

During this test, a simple X-ray will be made of your chest.

HRCT (High Resolution Computed Tomography) of Chest

You will be asked to lie down on your back on an x-ray table that will slide into a large, tunnel-shaped machine. You must not move during the test and will be asked to relax and breathe normally. The technician will also ask you to do some breathing maneuvers such as take a deep breath in or out.

Echocardiogram

An echocardiogram will be done to assess your heart's function. An echocardiogram is a test that uses sound waves to create a moving picture of the heart. The picture is much more detailed than a plain x-ray image and involves no radiation exposure.

Electrocardiography (ECG)

During this test, small electrodes will be attached to your skin in several places and measurements will be taken of your heart rhythm and blood flow in and out of your heart.

Lung Function Tests

Spirometry: During the test, you will be asked to breathe in and out of a mouthpiece while a machine measures the amount of air you are breathing into and out of your lungs. These maneuvers may be somewhat difficult and you may become tired during the test but you will be allowed to rest periodically.

Plethysmography: This test is used to determine how much air you can hold in your lungs. You will sit in a small box, comparable to the size of a telephone booth, to undergo breathing tests similar to those described above. There is a chance that you may experience claustrophobia in addition to some fatigue.

Diffusing Capacity: This test is used to determine the overall ability of your lungs to transfer gas into and out of your blood.

Six Minute Walk Test

You will be asked to walk back and forth between a start and end point as many times as possible within 6 minutes. You may stop and rest if needed. Right before and right after the test you will be asked questions about how breathless you feel you are.

Blood Gas (PaO₂ and PaCO₂) and Blood Chemistry Analysis

A blood sample will be taken to measure the amount of oxygen and carbon dioxide in the sample. This blood sample will need to be taken from an artery (as opposed to a vein, which is done for the more routine blood tests), and therefore may be more painful than other blood tests that you may have had previously. Standard compounds and the number of blood cells will also be measured. You must have stopped smoking for at least 4 months to participate in this study. A blood test will be performed to confirm that you have stopped. It is important that you do not smoke during the study. In addition, the blood sample will be tested for alpha-1 antitrypsin deficiency and a marker for systemic inflammation (serum fibrinogen).

Pulmonary Rehabilitation Program

In order to participate in this study, you will have:

- Successfully completed a supervised pulmonary rehabilitation program within the past 6 months, or
- Be regularly performing maintenance respiratory rehabilitation if you completed the pulmonary rehabilitation program more than 6 months ago.

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Appendix 3. Example Informed Consent Form: Study Screening

The supervised pulmonary rehabilitation program must have required you to attend at least 2 visits to the pulmonary rehabilitation center each week. You will have to have documentation to show that you have attended at least 8 visits to the pulmonary rehabilitation center. If you do not meet the criteria above, you will be offered an opportunity to complete a supervised pulmonary rehabilitation program as part of your participation in the study. This supervised program will be paid for by the study sponsor and will be at no cost to you. Your doctor may also make changes to your emphysema medications at this time.

Financial Responsibility

The costs of any routine medical care administered during the study will be the responsibility of you and/or your health insurer. For such routine costs, you will be responsible for any co-payments or deductibles required under your insurance. You are not, however, expected to pay for any medical care that is specifically required by the screening tests for this study.

Questions

If you have any questions about the screening for this study you should ask your doctor or one of his or her staff members.

Informed Consent

I, _____, the undersigned hereby consent to be screened to find out if I may be a candidate for a research project titled: **Lung Function Improvement after Bronchoscopic Lung Volume Reduction with Pulmonx Endobronchial Valves used to Treat Emphysema.**

If I agree to be screened for the research study and if my questions are answered, I should sign this form. If I wish to refuse to be screened for the study, I may do so without any loss of medical care or benefits. Once I have consented, I still have the right to withdraw from being screened at any time. To withdraw, all I have to do is simply tell Dr. _____ or complete the Revocation of Consent at the bottom of this form.

I will be given a copy of this form to keep and to refer to as needed.

Printed Name of Participant (or legal representative): _____

Signature: _____

Date: _____

I declare that I have been present when the research study was explained to the above participant and I believe that the participant has an application and understanding of the explanation given.

Witness: _____

Date: _____

REVOCAION OF CONSENT

I hereby wish to **WITHDRAW** my consent to be screened for the research study described above. Withdrawal WILL NOT jeopardize any treatment or my relationship with _____ Hospital.

Printed Name of Participant (or legal representative): _____

Signature: _____

Date: _____

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Appendix 4. Screening Log

#	Screen ID	Met All Screening Eligibility Criteria		If no, list number for criterion not met
		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
1		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
2		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
3		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
4		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
5		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
6		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
7		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
8		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
9		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
10		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
11		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
12		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
13		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
14		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
15		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
16		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
17		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
18		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
19		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
20		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
21		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
22		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
23		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
24		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
25		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
26		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
27		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
28		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
29		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
30		<input type="checkbox"/> Yes	<input type="checkbox"/> No	

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Appendix 4. Screening Log

#	Screen ID	Met All Baseline Eligibility Criteria		If no, list number for criterion not met
		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
1		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
2		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
3		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
4		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
5		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
6		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
7		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
8		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
9		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
10		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
11		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
12		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
13		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
14		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
15		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
16		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
17		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
18		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
19		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
20		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
21		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
22		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
23		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
24		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
25		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
26		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
27		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
28		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
29		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
30		<input type="checkbox"/> Yes	<input type="checkbox"/> No	

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Appendix 4. Screening Log

#	Screen ID	Met All Study Procedure Eligibility Criteria		If no, list number for criterion not met
		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
1		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
2		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
3		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
4		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
5		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
6		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
7		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
8		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
9		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
10		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
11		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
12		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
13		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
14		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
15		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
16		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
17		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
18		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
19		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
20		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
21		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
22		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
23		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
24		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
25		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
26		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
27		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
28		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
29		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
30		<input type="checkbox"/> Yes	<input type="checkbox"/> No	

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Appendix 5. Screening Eligibility Criteria

Screening Inclusion Criteria	
1	Signed Screening or Study Procedure Informed Consent using a form that was reviewed and approved by the IRB
2	Age 40 to 75 years
3	BMI <u>less than</u> 35 kg/m ²
4	Stable with <u>less than</u> 20 mg prednisone (or equivalent) qd
5	Nonsmoking for 4 months prior to screening interview
Screening Exclusion Criteria	
6	Currently enrolled in another clinical trial studying an experimental treatment
7	Previously enrolled in this study for which protocol required follow up is not complete
8	Clinically significant (greater than 4 Tablespoons per day) sputum production
9	Two or more COPD exacerbation episodes requiring hospitalization in the last year at screening
10	Two or more instances of pneumonia episodes in the last year at screening
11	Unplanned weight loss >10% usual weight <90 days prior to enrollment
12	History of exercise-related syncope
13	Myocardial Infarction or congestive heart failure within 6 months of screening
14	Prior lung transplant, LVRS, bullectomy or lobectomy
15	Clinically significant bronchiectasis
16	Unable to safely discontinue anti-coagulants or platelet activity inhibitors for 7 days
17	Uncontrolled pulmonary hypertension (systolic pulmonary arterial pressure > 45 mm Hg) or evidence or history of CorPulmonale as determined by recent echocardiogram (completed within the last 3 months prior to screening visit)
18	Pulmonary nodule requiring surgery as noted by chest X-ray or CT scan
19	HRCT collected per CT scanning protocol within the last 3 months of screening date and evaluated by clinical site personnel using 510k cleared CT software shows:
a	Parenchymal destruction score of <u>greater than</u> 75% in all three right lobes or both left lobes
b	Emphysema heterogeneity score <u>less than</u> 15% (Not Applicable for Crossover subjects as of Revision H of protocol)
c	Large bullae encompassing <u>greater than</u> 30% of either lung
d	Insufficient landmarks to evaluate the CT study using the software as it is intended
20	Left ventricular ejection fraction (LVEF) less than 45% as determined by recent echocardiogram (completed within the last 3 months prior to screening visit)
21	Resting bradycardia (<50 beats/min), frequent multifocal PVCs, complex ventricular arrhythmia, sustained SVT
22	Dysrhythmia that might pose a risk during exercise or training
23	Post-bronchodilator FEV ₁ <u>less than</u> 15% or <u>greater than</u> 45% of predicted value at screening
24	TLC <u>less than</u> 100% predicted (determined by body plethysmography) at screening
25	RV <u>less than</u> 175% predicted (determined by body plethysmography) at screening
26	DLCO <u>less than</u> 20% predicted value at screening
27	6-minute walk distance <u>less than</u> 100 meters or <u>greater than</u> 450 meters at screening
28	PaCO ₂ <u>greater than</u> 50mm Hg (Denver greater than 55 mm Hg) on room air at screening
29	PaO ₂ <u>less than</u> 45 mm Hg (Denver less than 30 mm Hg) on room air at screening
30	Elevated white cell count (>10,000 cells/mcL) at screening
31	Presence of alpha-1 anti-trypsin deficiency as determined by local laboratory ranges
32	Plasma cotinine level <u>greater than</u> 13.7 ng/ml (or arterial carboxyhemoglobin > 2.5% if using nicotine products) at screening
33	Any disease or condition that interferes with completion of initial or follow-up assessments

Overview of HRCT Data Collection

HRCT acquired using Scan Acquisition Protocol

Site personnel reviews TLC scan using sponsor-provided 510k cleared CT software to determine screening eligibility of the study candidate. The study candidate is **INELIGIBLE** IF (s)he has:

- a) Parenchymal destruction score >75% in all three right lobes or both left lobes;
- b) Emphysema heterogeneity score <15% (see **Note** for cross over subjects)
- c) Large bullae encompassing >30% of either lung
- d) Insufficient landmarks to evaluate the CT study using the software as it is intended

For the first 5 candidates per site with conclusive (in)eligibility: export the CT analysis to CD and send to core reading laboratory for review

Upon determining that the study candidate meets all screening and baseline eligibility criteria, site personnel will:

- a) Complete the bronchoscopy plan
- b) Transmit screening HRCT scan data to the core reading laboratory

Site personnel will develop the bronchoscopy plan to:

- a) Pre-identify target treatment lobes for assessing collateral ventilation
- b) Plan the EBV placement strategy (only to be performed during the bronchoscopy if candidate meets study procedure eligibility and is randomly assigned to study treatment)

45-day and 1-year follow-ups* for Study Treatment Arm ONLY:

- a) Acquire HRCT and transmit scan data to core reading lab
- b) Determine lobar volume change from baseline
- c) Evaluate EBV placement
- d) Apprise clinical site and sponsor of findings within 5 working days after the site transmits the HRCT to the core reading lab

*Also 3-month follow-up for subjects with valve adjustment

NOTE: HRCT scans should be submitted to the core reading lab as soon as possible after their acquisition

CROSSOVER NOTE: Per Revision H of this protocol, the requirement of a heterogeneity score of 15% between lobes is not applicable for any remaining crossover subjects. The most diseased target can be treated regardless of heterogeneity, provided that the target lobe is collateral ventilation negative (CV-).

Protocol for Acquiring HRCT Scans

The scanning procedure described below will require approximately 15 minutes of the scanner time. Minimal respiratory motion and maximum accuracy and reproducibility are required for the duration of the scan. In unusual cases, this may require more time. However, in many cases the procedure will be completed in 10 minutes or less.

Preparation of the Patient (3 minutes)

Patients weighing more than 300 pounds (150 Kg) will not be scanned due to technical difficulties. The technologist will ask women if they might be pregnant and will not scan them if they answer affirmatively. The patient will lie in the **supine position going head first** into the CT gantry.

Breath-Holding Instruction (3 minutes).

The technologist will instruct the patient on the importance of breath-holding and immobility during scanning. An interpreter will assist in the instruction of patients not fluent in English. Technologists will be trained to coach patients to attain reproducible maximum inspiratory breath-hold. To ensure that the breath-hold maneuver is performed as close to pulmonary function laboratory standards. The CT programmed auto-voice is **never** used; instead patients are coached prior to scanning as follows:

For the TLC series:

“Take your biggest breath in until you feel your lungs are completely full, in the same way you do in the lung function laboratory, and hold the breath.”

For the RV series:

For the RV Scan (Sequence #2), the patient should be coached with emphasis on instruction to blow all their air out. The participant should be told *“to take another big breath in to fill up their lungs and then to blow all the air out as hard and fast as possible without moving their body and then to squeeze all their air out until they feel that their lungs are completely empty and then they should signal that they are empty and hold their breath”*. This can be done by asking the patient to keep their toes apart at the beginning of the maneuver and to bring their toes together when they feel they are completely empty. At this stage, the technologist should remind the subjects to hold their breath for the entire scan and start the scan.

Only after the technologist is satisfied that the patient understands the importance of breath-holding should s/he proceed.

Checking the Scout Image (1 minute).

The technologist will instruct the patient to take a deep breath in, and then to hold his/her breath (at end-inspiration) while acquiring anterior-posterior (A/P) and lateral scout image, beginning 10 mm above the sternal notch and ending 10 mm below the posterior costophrenic angle. This will provide an A/P and lateral view of the chest on the image monitor at the operator console. From this, the technologist will check patient centering and choose the position for the full chest scan. The table will be automatically moved to the start position. The technologist will check patient and phantom positioning in the scout image.

Imaging (6 minutes).

Total imaging time will be approximately 6-19 seconds (depending on scanner generation and configuration). The technologist will instruct the patient to relax on the table while s/he reconstructs the images and assesses the adequacy of positioning, and lack of respiratory motion.

Remember to keep consistent the selected FOV and table height for a patient at all study points.

The imaging procedure involves **the following mandatory sequence for all study patients:**

Supine, Full Chest at TLC

In this sequence, thoracic CT will be performed with the patient in the supine position with arms above the head if possible. Image data will be acquired during suspended end inspiration (TLC). **Images are non-gated and no intravenous contrast will be used.** Technical guidelines for thoracic CT image data acquisition will include:

- (a) TLC Scout: This series is to be acquired for planning the full chest CT and is to be acquired at TLC.
- (b) TLC Full Chest: Volumetric spiral studies will be performed through the entire chest at full inspiration.
 1. Breathing Instructions: Patient will be instructed to, *“take a deep breath in until you feel your lungs are completely full, in the same way you do in the lung function laboratory.”*
 2. Scanner Acquisition: See Table 1. Sample provided for each site; a protocol specific for chart will be provided.
 3. Anatomic Coverage: Entire thorax (full chest). Typically a ≤ 10 sec. acquisition on MDCT scanners.

4. Dose Consideration: For the above scan the estimated dose is 2-3msv compared with conventional CT Chest of 5-7 msv.

Supine, Full Chest at RV

In this sequence, thoracic CT will be performed with the patient in the supine position with arms above the head if possible. Image data will be acquired at residual volume (RV). **Images are non-gated and no intravenous contrast will be used.** Technical guidelines for thoracic CT image data acquisition will include:

- (a) RV scout – this series is to be acquired for planning the full chest CT and is to be acquired at RV.
- (b) RV Full Chest: Volumetric spiral studies will be performed through the entire chest using the same techniques as in Sequence 1 – except at residual volume: 10 mm collimation, pitch ≤ 1.5 reconstructed contiguously (i.e., every 10 mm) using a standard reconstruction algorithm.
 1. Breathing Instructions: The participant should be told “*to take another big breath in to fill up their lungs and then to blow all the air out as hard and fast as possible without moving their body and then to squeeze all their air out until they feel that their lungs are completely empty and then they should signal that they are empty and hold their breath*”. This can be done by asking the patient to keep their toes apart at the beginning of the maneuver and to bring their toes together when they feel they are completely empty. At this stage, the technologist should remind the subjects to hold their breath for the entire scan and start the scan.
 2. Sample Acquisition (This will be tailored for each site based on available CT technology): Siemens Sensation 16 scanner, 120 kVp, 80 “effective” mAs, 0.5 sec rotation time, 16 x 0.75 mm collimation, 18 mm/rotation table feed (pitch 1.5); **This will be specified for your site.**
 3. Anatomic coverage: Entire thorax (full chest). Typically a ≤ 10 sec. Acquisition on MDCT scanners.
 4. Sample reconstructions
 - i. Contiguous thick section – 10 mm thickness, 10 mm spacing, B30F reconstruction filter, Display Field of View of 35 cm (Typically 35 images)
 - ii. Overlapped thin section – 1.5mm thickness, 1 mm spacing, B50f reconstruction filter and DFOV = 35 cm (Typically 350 images).

Table 1.

Shaded fields are user input fields on the scanner console. Other values are either calculated or derived from user inputs.

<i>Techniques for Siemens Sensation 16</i> <i>16-slice/0.5 sec</i>	Helical – Full Chest at TLC REQUIRED
2.1.1.1 kV	120
2.1.1.2 Gantry Rotation Time	0.5 sec
2.1.1.3 mAs¹ (Regular patient- Large patient values)	80 – 100
2.1.1.4 Collimation (mm)	0.75 mm collimation
2.1.1.5 Table incrementation (mm/rotation) – I	18 mm
2.1.1.6 Detector Collimation (mm) – T	0.75 mm
2.1.1.7 Number of active channels – N	16
2.1.1.8 Detector Configuration – N x T	16 x 0.75 mm
2.1.1.9 Pitch ([mm/rotation] /beam collimation) – I/NT	1.5
2.1.1.10 Table Speed (mm/sec)	36 mm/sec
2.1.1.11 Scan Time (40 cm thorax)	12 sec
2.1.1.12 REQUIRED Reconstructed Thin Slice Width	1.5 mm
2.1.1.13 REQUIRED Thin Slice Reconstruction Interval	0.8 mm
2.1.1.14 REQUIRED Thick Slice Reconstruction Interval	5.0mm
2.1.1.15 REQUIRED Thin and Thick Slice Reconstruction Algorithm	B45f
2.1.1.16 REQUIRED # Images/Data set (40 cm) thin/thick	500/60

¹ – Siemens Scanners use the term “effective mAs” which is really [(mA*time)/Pitch]. Sites should enter the value in the mAs row at their scanner.

Definitions

T = Z axis collimation, or width of one data channel. In multi-detector CT scanners, several detector elements maybe grouped together to form one data channel.

N = # data channels, or the actual number of data channels used during an acquisition.

I = Increment, or the table increment *per rotation* of the x-ray tube in a helical scan.

Table 2.

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Appendix 6. HRCT Scan Acquisition Protocol

Shaded fields are user input fields on the scanner console. Other values are either calculated or derived from user inputs.

<i>Techniques for Siemens Sensation 16</i> <i>16-slice/0.5 sec</i>	Helical – Full Chest at RV REQUIRED
2.1.1.1 kV	120
2.1.1.2 Gantry Rotation Time	0.5 sec
2.1.1.3 mAs¹ (Regular patient- Large patient values)	80 – 100
2.1.1.4 Collimation (mm)	0.75 mm collimation
2.1.1.5 Table incrementation (mm/rotation) – I	18 mm
2.1.1.6 Detector Collimation (mm) – T	0.75 mm
2.1.1.7 Number of active channels – N	16
2.1.1.8 Detector Configuration – N x T	16 x 0.75 mm
2.1.1.9 Pitch ([mm/rotation] /beam collimation) – I/NT	1.5
2.1.1.10 Table Speed (mm/sec)	36 mm/sec
2.1.1.11 Scan Time (40 cm thorax)	12 sec
2.1.1.12 REQUIRED Reconstructed Thin Slice Width	1.5 mm
2.1.1.13 REQUIRED Thin Slice Reconstruction Interval	0.8 mm
2.1.1.14 REQUIRED Thick Slice Reconstruction Interval	5.0mm
2.1.1.15 REQUIRED Thin and Thick Slice Reconstruction Algorithm	B45f
2.1.1.16 REQUIRED # Images/Data set (40 cm) thin/thick	500/60

¹ – Siemens Scanners use the term “effective mAs” which is really [(mA*time)/Pitch]. Sites should enter the value in the mAs row at their scanner.

Definitions

T = Z axis collimation, or width of one data channel. In multi-detector CT scanners, several detector elements maybe grouped together to form one data channel.

N = # data channels, or the actual number of data channels used during an acquisition.

I = Increment, or the table increment *per rotation* of the x-ray tube in a helical scan.

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Appendix 7. Baseline Eligibility Criteria

Study Candidate Selection – Baseline Eligibility Criteria	
Baseline Inclusion Criteria	
1	Completed a supervised pulmonary rehabilitation program <u>less than equal to</u> 6 months prior to the baseline exam or is regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred <u>greater than</u> 6 months prior
2	Baseline evaluation occurred \leq 120 days after screening exam
3	Signed written informed consent to participate in study using a form that was reviewed and approved by the IRB
4	Continued nonsmoking between initial screening and baseline exams
5	Willing and able to complete protocol required study follow-up assessments and procedures
6	FEV ₁ between 15% and 45% of predicted value at baseline exam
7	Post-rehabilitation 6-minute walk distance between 100 meters and 500 meters at baseline exam
8	Current Pneumococcus vaccination
9	Current Influenza vaccination
Baseline Exclusion Criteria	
10	Myocardial infarction or diagnosis of congestive heart failure between screening and baseline exams
11	Fever or other clinical evidence of active infection at baseline exam
12	Two or more COPD exacerbation episodes between screening and baseline exams
13	Two or more pneumonia episodes between screening and baseline exams

Investigator Name: _____ Site ID# _____
Institution: _____ Participant ID: _____

Telephone: _____

Dear Patient:

You are being invited to participate in a clinical study involving research. This Informed Consent Letter describes the study and your role as a participant. If you choose to consider taking part in the study you must read this form carefully. You are urged to discuss any questions you have about the study with your physician and/or the hospital's research staff.

Persons who participate in a research study are entitled to certain rights. These rights include, but are not limited to, your right to:

- Be informed of the nature and purpose of the medical experiment (*ie.* study);
- Be given an explanation of the procedures to be followed in the study, and information about the drugs or devices to be used;
- Be given a description of any discomforts and risks that are reasonable to expect;
- Be given an explanation of any benefits that are reasonable to expect;
- Be given information about other appropriate treatments that might be given to you and information about their risks and benefits;
- Be informed of the medical treatments, if any, that are available to you if complications should arise after the investigational (*ie.* study) procedure;
- Be given an opportunity to ask questions concerning the study or the procedures involved in the study;
- Be informed that you may withdraw your consent to participate in the study at any time;
- Be given a copy of the consent form you signed;
- Be given the opportunity to decide for yourself whether or not you should consent to take part in the study.

Purpose of the Study

Since you are being asked to participate in this study, you have probably suffered an impaired lifestyle as a result of emphysema. Emphysema is a serious disease afflicting more than four million people worldwide. It is one form of Chronic Obstructive Pulmonary Disease, or COPD. Emphysema causes the lungs to lose the ability to move air in and out normally and to efficiently absorb oxygen. Eventually, breathing becomes more difficult as damaged parts of the lungs trap air. As the disease advances, the damaged, inelastic areas of the lung progressively expand within the chest cavity, leaving one constantly feeling out of breath.

Lung volume reduction surgery (LVRS) has been shown to offer relief to patients suffering from emphysema. With LVRS, some of the diseased portions of the lungs are removed. This allows the

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remaining lung tissue to function better. Other surgical procedures like plication (folding) and stapling of lung tissue, which are done without surgically removing parts of the lung, have been seen to have results similar to LVRS. These results suggest that removal of damaged lung tissue is not necessary and that a process that gets rid of the trapped air in the damaged regions of the lungs should work in the same way.

The purpose of this research is to study a medical device that is designed to produce lung volume reduction. This device is called the Pulmonx Endobronchial Valve (EBV). The EBV is a one-way valve that blocks off the diseased lung section to inhaled air but lets the trapped air already inside the area escape. With placement of the EBV, the diseased part of the lung collapses; this allows the healthier parts of the lung to expand. The EBV is considered experimental. This means that it has not yet been approved by the U.S. FDA (Food and Drug Administration) for commercial use in the United States.

The EBV can be placed by a doctor in a diseased section of the lungs using bronchoscopy. Bronchoscopy is a way to access your lungs using a small tube with a camera on the end. With bronchoscopy, your physician can reach the airways in your lung by passing the tube through either your mouth or nose. Use of bronchoscopy for performing lung volume reduction may have fewer risks than surgery and have reduced recovery time. This study is designed to investigate the safety and effectiveness of the Pulmonx EBV for treating your emphysema symptoms as compared to a standard medical therapy program alone.

Number of Patients in the Study

Approximately two hundred (200) patients will be enrolled into this study. In order to qualify for enrollment into this study, you must undergo a bronchoscopy procedure. During the bronchoscopy procedure, your doctor will measure some of the airways in your lungs using a device that measures airflow to find out if you meet the study criteria for having the EBV treatment. There is a chance that after measuring some of airways in your lungs you will not be eligible to take part in this study.

During the bronchoscopy procedure, one hundred and eighty-three (183) patients will be found to qualify for the study. The 183 patients who qualify for the study will be randomly assigned to the study treatment. Approximately two-thirds will be randomly assigned to the EBV treatment group and have EBV implanted in their lungs and approximately one-third will be randomly assigned to the control group and not have EBV implanted in their lungs. This means that during the bronchoscopy procedure if you are found to be eligible to participate in the study, you will have a 2 in 3 chance of receiving EBV and a 1 in 3 chance of not receiving EBV.

Tests and Evaluations

If you agree to participate in the study, the following tests and assessments will be performed. Most or all of these are routine medical assessments. If you should feel dizzy, or have chest pain, palpitations, nausea, severe difficulty breathing or wheezing, during any of the following testing, please tell your healthcare professional immediately.

Blood Gas (PaO₂ and PaCO₂) and Blood Chemistry Analysis

A blood sample will be taken to measure the amount of oxygen and carbon dioxide in the sample. This blood sample will need to be taken from an artery (as opposed to a vein). An arterial blood

sample may be more painful than a venous blood sample, which is usually done for more routine blood samples. Standard compounds and the number of blood cells will also be measured from the blood sample. You must have stopped smoking for at least 4 months to participate in this study. A blood test will be performed to confirm that you have stopped. It is important that you do not smoke during this study.

Chest X-ray

During this test, a simple X-ray will be made of your chest.

Echocardiogram

An echocardiogram will be done to assess your heart's function. An echocardiogram is a test that uses sound waves to create a moving picture of the heart. The picture is much more detailed than a plain x-ray image and involves no radiation exposure.

Fluoroscopy

Fluoroscopy is used to make a moving picture of your chest. In rare instances, fluoroscopy may be used by your study doctor if it is difficult for him/her to see your lung structures and anatomy using the bronchoscope alone.

Electrocardiography (ECG)

During this test, small electrodes will be attached to your skin in several places and measurements will be taken of your heart rhythm and blood flow in and out of your heart.

Lung Function Tests

Spirometry: During the test, you will be asked to breathe in and out of a mouthpiece while a machine measures the amount of air you are breathing into and out of your lungs. These breathing maneuvers may be somewhat difficult and you may become tired during the test but you will be allowed to rest periodically.

Plethysmography: This test is used to determine how much air you can hold in your lungs. You will sit in a small box, comparable to the size of a telephone booth, to undergo breathing tests similar to those described above. There is a chance that you may experience claustrophobia in addition to fatigue.

Diffusing Capacity: This test is used to measure the ability of your lungs to transfer carbon monoxide. You will be asked to breathe a mixture of helium, oxygen, nitrogen and carbon monoxide and hold your breath for 10 seconds. All together these lung function tests will take about 90 minutes.

HRCT (High Resolution Computed Tomography) of Chest

You will be asked to lie down on your back on an x-ray table that will slide into a large, tunnel-shaped machine. You must not move during the test and will be asked to relax and breathe normally. The technician will also ask you to do some breathing maneuvers such as take a deep breath in or out.

Pregnancy Test

If you are a woman of child-bearing potential, a urine or blood pregnancy test may be performed.

Six Minute Walk Test

You will be asked to walk back and forth between a start and end point as many times as possible within 6 minutes. You may stop and rest if needed. Right before and right after the test you will be asked questions about how breathless you feel you are.

Questionnaires

During the study, you will be asked to complete a few simple questionnaires. These questionnaires will ask you about your daily activities and your opinion about your general health status and quality of life. You will also be asked about frequency of visits to health care providers, such as your regular physician, emergent care facilities, and the hospital.

Pulmonary Rehabilitation Program—to be Eligible for the Study

In order to participate in this study, you will have:

- Successfully completed a supervised pulmonary rehabilitation program within the past 6 months, or
- Be regularly performing maintenance respiratory rehabilitation if you completed the pulmonary rehabilitation program more than 6 months ago.

The supervised pulmonary rehabilitation program must have required you to attend at least 2 visits to the pulmonary rehabilitation center each week. You will have to have documentation to show that you have attended at least 8 visits to the pulmonary rehabilitation center. If you do not meet the criteria above, you will be offered an opportunity to complete a supervised pulmonary rehabilitation program as part of your participation in the study. This supervised program will be paid for by the study sponsor and will be at no cost to you.

Daily Diary

At the baseline visit you will be given a paper based diary to answer some questions about your health and your pulmonary rehabilitation exercises. You will be asked to complete the diary immediately before going to bed every night and it is expected to take you approximately 15 minutes each time. The information that is recorded in the diary will be collected when you return for the bronchoscopy procedure.

- Pulmonary rehabilitation program
 - You will be asked about how long you spent doing pulmonary rehabilitation exercises that day and how many exercises you did.
- EXACT-PRO Questionnaire
 - You will be asked 14 questions about your COPD symptoms.
- Health status changes
 - You will be asked if you've had any change to your medications, any emphysema symptoms, and whether or not your activities or lifestyle has changed from normal due to your emphysema symptoms.

Description of the Study Treatment Groups

Control Group

All participants in this study will receive optimal medical therapy. Optimal medical therapy consists of smoking cessation support, selected medications, pulmonary rehabilitation therapy, and oxygen

supplementation as medically necessary. After their 1-year follow-up visit, control group participants may be eligible to receive the EBV treatment if they continue to meet study criteria. If they receive EBV treatment, these participants will be followed up according to the same visit schedule as the initial EBV treatment group.

EBV Treatment Group

In addition to optimal medical therapy, the EBV treatment group will undergo bronchoscopic lung volume reduction using the Pulmonx EBV.

Description of the Bronchoscopy Procedure

During the bronchoscopy procedure, your physician will measure some of the airways in your lungs using a device called the Chartis® Pulmonary Assessment System. This system is designed to measure air pressure and flow in lung airways. The air pressure and flow measurements that are collected using the Chartis System will help the physician decide if you are eligible to potentially have the EBV treatment. Your physician will plan the areas that will be measured before the day of the bronchoscopy procedure using the results of your CT scan.

If you are found to have air pressure and flow measurements that show you are **NOT eligible** to receive the EBV treatment, your physician and his or her team will stop the bronchoscopy procedure and you will not receive any further treatment during the bronchoscopy procedure.

If you are found to have air pressure and flow measurements that show you are **eligible** to receive the EBV treatment, you will be randomly assigned to either the EBV treatment group or the control group. If you are randomly assigned to the EBV treatment group, you will have the EBV treatment. If you are randomly assigned to the control group, you will not receive any further treatment during the bronchoscopy procedure.

Personnel from the study sponsor (Pulmonx) will attend your bronchoscopy procedure. The doctor's view of the procedure (the inside of your lung) may also be videotaped or photographed.

Description of the Study Procedure

The EBV Procedure

A bronchoscope (a tube with a camera at the tip, connected to a monitor) will be guided down an access tube all the way to the point where the EBV will be placed. Once your physician can clearly see the area where the EBV will be placed, he or she will guide a catheter (flexible tube), with the EBV attached, to the targeted treatment area. Once the catheter is in the proper position, he or she will implant the EBV in the lung. This may be done several times depending upon how many EBV are to be placed in your lungs.

If there is a problem with the EBV at any time during or after the procedure that makes it difficult or inappropriate to continue with the study, your physician may remove the EBV. In some cases, if the EBV is removed, it can be replaced. In rare cases, the EBV may not have been placed in the original procedure as it was intended to be (to completely stop the airflow from the damaged part of the lung). This may initiate a discussion between you and your physician about having another procedure to adjust the placement of the EBV.

After the Bronchoscopy Procedure

After the procedure, you will be taken to a recovery area of the hospital. If you are in the control group (did not receive the EBV) or were found to not be eligible for the study, you will be allowed to go home a few hours after the bronchoscopy procedure. If you had EBV placed (are in the study treatment group), you will be required to remain in the hospital for 5 nights. Before you are discharged your study physician will examine you first and review your chest x-ray to confirm you are not experiencing any complications. Your study physician may keep you in the hospital longer if he/she feels your health needs further monitoring.

If you received the EBV, a chest x-ray will be taken at 1 hour and once each day during your hospitalization including the day you are discharged. You may need to have additional x-rays at any time your study physician thinks it is medically necessary. The nurses in this area are trained to closely watch your recovery and assist you in awakening from the anesthesia. Your vital signs will be monitored, blood samples will be collected and any adverse events will be reviewed during your hospitalization. The medical team will often encourage you to cough in order to help expel the anesthesia and any accumulation of mucus. You may also experience the urge to cough. This coughing sensation is normal and typically goes away.

Before discharge from the hospital, you will be given a study bracelet to wear and a medical alert card to give to any physician that may need to treat you informing him/her of the pneumothorax risk. Additionally, you will be given post-discharge instructions by the study physician that you will be expected to follow.

After Discharge (For the EBV Treatment Group)

You will return to your study physician's office 7 days after discharge for an examination, chest X-ray, and to answer questions about your health status. At the 7 Day after Discharge visit, your study physician will examine you and ask you about potential symptoms of pneumothorax and about your use of medications. A chest x-ray will be taken of your lungs at this time. At this visit, the study doctor will assess you to determine if you may resume your regular activities and start the pulmonary rehabilitation program.

After you are discharged from the hospital, you will be contacted once daily for 10 days to answer questions about your health status.

After Discharge (For the EBV Treatment and Control Groups)

Pulmonary Rehabilitation after the Bronchoscopy Procedure

Within 30 days after the bronchoscopy procedure, you will be asked to begin a supervised pulmonary rehabilitation program. It will consist of 20 sessions, to be done 2-3 times a week for 7-10 weeks. Each pulmonary rehabilitation session will consist of endurance training and strength training for your upper and lower limbs.

After you have completed the supervised pulmonary rehabilitation program you will be expected to do a home-based maintenance program which will be described to you by your pulmonary rehabilitation

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specialist. As soon as you are done with the supervised program you will be encouraged to follow this home-based program at least three times a week. For the study, you should continue this program until at least your 1 year follow-up visit.

Daily Electronic Diary

From the first day after the bronchoscopy procedure until your 1 year follow-up visit, you will be expected to complete an electronic diary to answer some questions about your health and your pulmonary rehabilitation exercises. You will be asked to complete the diary immediately before going to bed every night and it is expected to take you approximately 15 minutes each time. The information that is recorded in the electronic diary will be collected at each of your study visits (up to your 1 year follow-up). The study staff will remind you to bring your electronic diary to your visits.

- Pulmonary rehabilitation program
 - You will be asked about how long you spent doing pulmonary rehabilitation exercises that day and how many exercises you did.
- EXACT-PRO Questionnaire
 - You will be asked 14 questions about your COPD symptoms.
- Health status changes
 - You will be asked if you've had any change to your medications, any emphysema symptoms, and whether or not your activities or lifestyle has changed from normal due to your emphysema symptoms.

Length of the Study and Patient Evaluations

The results of the study will be evaluated after all of the study participants have made the 1-year visit. For study participants who have EBV, they will be expected to continue coming to the research clinic once a year up through 5 years. In this study, you will be evaluated several different times. The following table outlines the tests and assessments, starting at the bronchoscopy procedure visit, that will be performed and when they will be performed. Depending on the hospital where you have the procedure, some of these tests are standard for emphysema treatment and some are not.

Table 1. Follow-up Tests and Assessments

Test or Assessment	7 days after discharge	Daily phone contact over 10 days*	30 days	45 days	3 months	6 months	9 months	1 year	Annual visits (2-5 years)	Early Termination Visit
Physical Exam	X^		X^	X	X	X		X		X
Medications & Events Review				X	X	X	X	X		
X-ray	X^		X^	X^						
Blood Work								X		
Lung function				X		X		X	X	X
6 minute walk distance test				X		X		X		
Quality of life surveys				X	X	X	X	X		
Health Care Utilization					X	X	X	X		
CT scan‡				X^	‡			X^		
Daily Diary	Complete the daily diary every day before going to bed at night starting on the first day after the bronchoscopy procedure until the 1 year follow-up visit. Bring the diary to every follow-up visit.									

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*You will be contacted at this interval by phone unless you are already being seen by your physician or you are still in the hospital.
 ‡Study participants who undergo the study treatment will have a CT scan at 45 days and 1 year. For study participants who have a study procedure (valve) adjustment, a CT scan will be collected at 3 months too.
 †It is expected that study participants will complete the daily diary at home every day before bedtime starting right after discharge from the hospital after the bronchoscopy procedure through the 1 year follow-up (approximately 365 days).
 ^EBV treated study participants only.

Random Assignment to the Control Group

If you are randomly assigned to the control group you potentially have the opportunity to receive the study treatment after you complete the 1-year follow up visit for the study.

Summary of Knowledge about Lung Volume Reduction using the EBV

The Pulmonx EBV device and procedure was tested extensively in laboratories and animals prior to clinical testing. The EBV device and procedure are currently used outside of the United States, in some countries in Europe and Asia, as a standard treatment for emphysema patients. The EBV was previously tested in the United States with a large study that included four hundred ninety-two (492) patients from both the United States and Europe. The results of this large (VENT) study are discussed below.

The Endobronchial Valve for Emphysema Palliation Trial (VENT study) was a multi-center, prospective, randomized, controlled study conducted in the United States and Europe to evaluate safety and effectiveness of endobronchial valve treatment (along with optimal medical management) compared to optimal medical management alone (control group). In the U.S. study, the endobronchial valve treatment was found to improve forced expiratory volume in one second (FEV₁) by an average value of 6.8% and the 6 minute walk distance test results by an average value of 5.8%. These results were significantly better than the results seen with medical management alone. The European patients had similar results.

After the VENT study was finished, the data was further analyzed. We found that patients who showed signs that the airflow in some parts of their lungs could be blocked off, had the best results with the EBV and procedure. For the study you are considering taking part in, we are planning to select patients who show these same signs BEFORE they have the study treatment. This will be done using the Chartis System during the bronchoscopy procedure. At the end of the study, we will then compare the results of the EBV treatment to the control treatment.

In the VENT study, some adverse events were seen. The type of major adverse events and the percentage of patients who had them are shown below:

Table 2. Adverse events that were seen through 90 days in the EBV Treatment Group in VENT Study

Event	% of Patients
COPD exacerbation (without hospitalization)	7.9%
COPD exacerbation (with hospitalization)	1.4%
Hemoptysis (coughing up any amount of blood)	5.6%
Massive Hemoptysis (coughing up a large amount of blood)	0.5%
Valve expectoration, aspiration, migration (valve moved from the place it was put by the physician)	4.7%

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Event	% of Patients
Pneumonia	2.3%
Pneumonia (distal, or behind, the valve)	0.9%
Formation of bronchial granulation (scab-like) tissue with valve	2.3%
Pulmonary infection (infection in the lung)	1.9%
Respiratory failure (poor lung function--too much carbon dioxide or too little oxygen in your blood--where you need to have assistance with breathing using a mechanical ventilator)	1.4%
Pneumothorax (air leak in the lung) that required treatment for more than 7 days	1.4%
Pneumothorax (air leak in the lung) that expanded, or got larger	1.4%
Pneumothorax (air leak in the lung) that was stable, or stayed the same size	1.4%
Hypoxemia (decreased oxygen in the blood)	1.4%
Hypercapnia (excess carbon dioxide in the blood)	0.9%
Death	0.9%
Noncardiac chest pain	0.5%
Bronchial (airway) trauma	0.5%

Removal of the EBV in the VENT Study

In some instances, patients enrolled in the valve treatment study group who experienced an adverse event required that the valves be removed. In the U.S. VENT study, 31 (14.5%) patients had valve(s) removed after the procedure. The reasons for removal included: valve migration, pneumonia, bleeding (hemoptysis), granulation, increased dyspnea (breathlessness), continuing COPD exacerbations, and patient request.

Alternative Treatments for Emphysema

Oxygen, drug therapy, nutrition and lifestyle changes are the standard therapies for patients with emphysema. An additional alternative treatment may be Lung Volume Reduction Surgery (LVRS).

Summary of Benefits and Risks of Participation in the LIBERATE Study

As the EBV is still an investigational device in the United States, the actual benefits and risks are unknown at this time. The investigators may learn from this study whether the EBV treatment and procedure is safe and effective. There may or may not be direct benefit from your participation in this study.

Potential Benefits

Potential benefits you may experience as a participant in the study include having improved lung function and other improvements that may be associated with improved lung function, such as improved quality of life. If it is determined that control group participants still meet study eligibility criteria and it seems clinically appropriate for them after their 1-year follow-up visit, the study sponsor will pay for these participants to undergo the EBV and bronchoscopy procedure.

Potential Risks

The primary risks associated with use of the Pulmonx EBV are similar to other bronchoscopic and surgical procedures used to treat emphysema. These are listed below. While this list is comprehensive, there may be other risks that are still unknown. The close monitoring that you will receive, as part of the study, should allow for detection of symptoms, should they be present. This, in turn, should allow for early intervention by your physician if that is necessary. Your physician will review all of the risks below with you so that you understand them.

Previous clinical trial experience and experience from other countries around the world, where the EBV device is commercially available, has shown that in some people EBV treatment is associated with having a pneumothorax as a potential complication. A pneumothorax is a condition in which air leaks from the lung into the space between the lung and chest wall. This prevents the healthy lung from working well and can cause chest pain and shortness of breath. As many as 1 in 5 patients may experience a pneumothorax after the study procedure. Most of these tend to occur in the early period following the valve placement and usually resolve after staying in hospital for a few days. Most frequently, a treatment using a small tube to drain out the air is required. In rare cases, a pneumothorax may require a surgical intervention. In addition, there is a chance that it can be a serious and life-threatening complication.

Potential Risks (Adverse Events)

Acute bronchitis (inflammation or infection of the airways)
Acute bronchospasm (spasm of the airway; may result in wheezing or increased shortness of breath)
Acute respiratory distress syndrome (sudden, severe injury to lungs)
Airway blockage due to implant migration
Airway perforation (hole in the airway wall)
Airway stenosis (narrowing)
Anxiety
Aphonia (difficulty talking)
Aspiration (inhalation of vomit)
Bowel function impairment
Bronchial (airway) trauma or ulceration
Chest pain
COPD exacerbation (acute worsening of COPD symptoms)
Death
Depression
Deep Vein Thromboembolism (DVT, blood clot)
Dysphonia (hoarse or rough sounding voice)
Empyema (presence of pus)
Fever
Formation of bronchial granulation (scab-like) tissue near the valve(s)
Fractured Rib
Headache
Heart arrhythmias (irregular heartbeats)
Heart Attack
Heart failure (heart function is impaired; could result in increased breathlessness or fluid retention)

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Hemoptysis (coughing up blood)
Hemothorax (accumulation of blood between the lungs and the chest wall)
Iatrogenic injuries (injury caused by medical procedure)
Impaired lung function
Increased cough
Increased dyspnea (shortness of breath)
Increased hypercapnea (excess carbon dioxide in the blood)
Increased hypoxemia (decreased oxygen in the blood)
Infection
Laryngospasm (throat spasm)
Lethargy and disorientation
Lung cancer or lung mass
Nausea
Pleural effusion (collection of fluid around the lungs)
Pleuritis (inflammation of chest lining)
Pneumonia
Pneumothorax (air leak in the lung)
Pulmonary shunting (uneven blood flow through the lung)
Pulmonary embolism (a blood clot in the lung which can lead to chest pain and shortness of breath)
Respiratory failure (poor lung function; could require you to have assistance with breathing using a mechanical ventilator)
Septicemia (severe infection)
Stroke or Transient Ischemic Attack (sudden temporary loss of neurological function)
Valve expectoration, aspiration, or migration (valve moves from the place it was put by your physician)
Vomiting
Wheeze or whistling of valve

Other Potential Risks of Procedures that are Required by this Study

Lung function and exercise tests. You will be exerting yourself to your limits in these tests. Lightheadedness, dizziness, fainting, chest pain, irregular heartbeats, and rarely death have been seen during exercise tests. You should inform the technicians or physicians if performing these tests makes you feel abnormal.

Vein or artery blood tests. The risks of drawing blood include temporary pain and discomfort and/or tenderness from the needle stick, redness, or bruising at the site, bleeding, fainting, and lightheadedness. While rare, there is a possibility of infection or a local blood clot with any procedure in which the skin is pierced by a needle.

Radiation. This study involves a radiation exposure from the CT scans and chest x-rays that is typical of other diagnostic tests using ionizing radiation. There is a small chance that the study doctor may choose to use fluoroscopy during the bronchoscopy procedure to be able to see the EBV better than he/she can using the bronchoscope and this may expose you to some additional minimal radiation. The amount of radiation exposure received in this study is below the levels that are thought to result in a significant risk of harmful effects. If you are especially concerned with radiation exposure, you should discuss this with your study doctor.

Antibiotics. Antibiotics will be provided to you around the time of the procedure and afterwards to minimize possible side effects. All pharmaceutical drugs have side effects. Antibiotics may also have side effects, including diarrhea, allergic reactions, and overgrowth of dangerous bacteria such as *C. difficile* which can result in a serious infection. However, antibiotics are used routinely to treat COPD exacerbations.

Anesthesia. The side effects of moderate procedural sedation or general anesthesia medications and other medications required to perform bronchoscopy include, but are not limited to, allergic reaction, drowsiness, slurred speech, tremor, fatigue, low blood pressure, slowing of the heart rate, anxiety, confusion, dizziness, temporary loss of consciousness, and respiratory depression. Trained medical professionals with extensive experience and expertise will administer the medications and will be responsible for your care during the course of the procedure.

Echocardiogram. If you have a transesophageal echocardiogram (TEE, as opposed to a transthoracic echocardiogram or TTE), some risks are associated with the medicine given to help you relax. For example, you may have a bad reaction to the medicine, problems breathing, and nausea (feeling sick to your stomach). Your throat also might be sore for a few hours after the test. Rarely, the tube used during TEE causes minor throat injuries.

Voluntary Participation and Study Withdrawal

Decisions regarding whether or not you should participate in this study are entirely voluntary. If you decide not to participate, you will not lose any benefits to which you are entitled, nor will you be denied access to other available treatments for emphysema. You will receive the standard treatment and care normally provided by your physician.

Information obtained in the operating room after anesthesia is given to you will affect whether or not you are eligible to receive treatment during the bronchoscopy procedure. This will happen, for instance, if it is determined that the air pressure and flow measured in the airways in your lungs make you

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ineligible to meet the study entry criteria or that the anatomy of your lung passageways does not allow the physician to place the EBV Implant. In such an event, and if you are randomly assigned to the control group, will be sent to the recovery room without the valve treatment.

Significant new findings discovered during the course of this study, which may affect your willingness to continue participating in the study, will be provided to you in writing. You may withdraw your consent to participate in this study at any time **without penalty or loss of benefits**. Also, your physician may terminate your participation if continuing participation does not appear to be in your best medical interest, or if Pulmonx, the study Sponsor, terminates the study.

Precautions

Within 30 days before and 30 days after participating in this study, you should not take part in any other research project. This is to protect you from possible injury arising from excessive blood drawing, excess x-rays, and interactions with other research devices or drugs, or similar hazards.

Pregnancy and Contraception (Birth Control)

Pregnant women may not participate in this research study as the risk of the procedure on an embryo or unborn fetus is unknown. Women of childbearing potential must actively utilize appropriate means of birth control to avoid becoming pregnant throughout the course of the study.

Confidentiality

Information derived from this study and from your medical record may be reviewed and photocopied by the Food and Drug Administration (FDA) and/or state and federal regulatory agencies and by the device manufacturer, Pulmonx Inc., with protection of confidentiality so far as permitted by applicable law. Information resulting from this study and from your medical record may be used for research purposes and may be published; however, you will not be identified by name in such publications.

Financial Responsibility

The costs of any routine medical care administered during the study will be the responsibility of you and/or your health insurer. For such routine costs, you will be responsible for any co-payments or deductibles required under your insurance. You are not, however, expected to absorb the cost of any medical care specifically required by participation in this study. The study Sponsor (Pulmonx) will pay for tests and procedures performed solely for the purpose of this study.

Research Related Injury

In the event that you believe participation in this research study has led to injury, contact your physician and he will review the matter with you. You should understand that neither _____ (hospital) nor the Federal Government has any programs to provide compensation for persons participating in research projects who may experience injury. However, necessary facilities, emergency treatment and professional services will be available to you. You should not expect anyone to pay you for pain, worry, lost income, or non-medical care costs that occur from taking part in this research study. No funds have been set aside by _____ (hospital) to pay you in case of injury, nor will the study Sponsor provide direct compensation to patients in the event of an injury.

Study Information at www.clinicaltrials.gov

A description of this clinical trial will be available on the <http://www.clinicaltrials.gov>, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Add Financial Compensation Section as Applicable

This section is site specific – include financial compensation information as needed.

Questions

If you have any questions about the study, its procedures, risks or benefits, your alternatives or your rights, or if you experience a potentially research related injury you should contact your doctor. If you cannot reach your doctor, contact the alternate individual listed below.

<u>Physician Contact Information (24 hour):</u>	<u>Alternate Contact Information (24 hour):</u>
Name: _____	Name: _____
Phone Number: _____	Phone Number: _____

Authorization to Use and Disclose Health Information

I agree to permit _____ (physician) and his/her staff (“Researchers”) to use and disclose health information that identifies me for the purposes described below. I also agree to permit _____ (hospital), my doctors, and my other health care providers to disclose health information in my medical records to the Researchers for the purposes described below.

1. The health information that may be used and disclosed includes all information collected during the research described in this document and health information in my medical records that is relevant to the research described.
2. The researchers and Pulmonx may use and share my health information to conduct research; disclose my health information to Pulmonx to confirm the research results; disclose my health information as required by law to representatives of government agencies and other persons who are required to watch over the safety, effectiveness and the conduct of the research; and remove from my health information my name and other information that could be used to identify me.
3. Once information that could be used to identify me has been removed, the information that remains is no longer subject to this authorization and may be used and disclosed by the researchers and Pulmonx as permitted by law including for other research purposes.
4. Once my health information has been disclosed to a third party, federal privacy laws may no longer protect it from further disclosure. However, the researchers and Pulmonx agree to protect my health information by using and disclosing it only as permitted by me in this Authorization. Also, no publication about the research will reveal my identity without my specific written permission. These limitations continue even if I revoke this Authorization.
5. Please note that you do not have to sign this authorization, but if you do not, you may not be allowed to participate in this research study. You may change your mind and revoke this authorization at any time. However, if you revoke this authorization, you may no longer be allowed to participate in this research study. Also, even if you revoke this authorization, the information already obtained may remain part of the research. To revoke this authorization, you must write to:

While the research is in progress, you will not be allowed to see your health information that is created or collected in the course of the research. After the research is finished, however, you may see this information as described in (hospital) Notice of Information practices.

6. This authorization does not have an expiration date.

Informed Consent

I, _____, the undersigned hereby consent to my involvement in the research project titled: **Lung Function Improvement after Bronchoscopic Lung Volume Reduction with Pulmonx Endobronchial Valves used in Emphysema.**

- 1) The nature, purpose, and contemplated effects of the project, so far as it affects me, have been fully explained to my satisfaction by the research worker. My consent is informed and given voluntarily.
- 2) The details of the procedure proposed have also been explained to me.
- 3) It has been explained to me that the purpose of this research project is to improve the quality of medical care, and that my involvement may not be of any benefit to me.
- 4) I have been given the opportunity to have a member of my family or a friend present while the project is explained to me.
- 5) I am informed that no information regarding my medical history will be divulged, other than that described in the consent form, and that my identity will be kept confidential in all published results of the study.
- 6) I have been informed that my involvement in the project will not affect my relationship with my medical advisors in their management of my health. I have also been told that I am free to withdraw from the project at any stage without prejudice for future treatment at this hospital, and if I so choose, I can ask for any information collected up to that point to be withheld from use in the research.
- 7) I declare that all of my questions have been answered to my satisfaction.

If I agree to participate in the research study and if my questions are answered, I should sign this form. If I wish to refuse to participate in the study, I may do so without any loss of medical care or benefits. Once I have consented, I still have the right to withdraw at any time. To withdraw, all I have to do is complete the Revocation of Consent portion of the form below and provide to or simply tell Dr.

_____.

I will be given a copy of this form to keep and to refer to as needed.

Printed Name of Participant (or legal representative): _____

Signature: _____

Date: _____

I declare that I have been present when the research study was explained to the above participant and I believe that the participant has an application and understanding of the explanation given.

Witness: _____

Date: _____

REVOCAION OF CONSENT

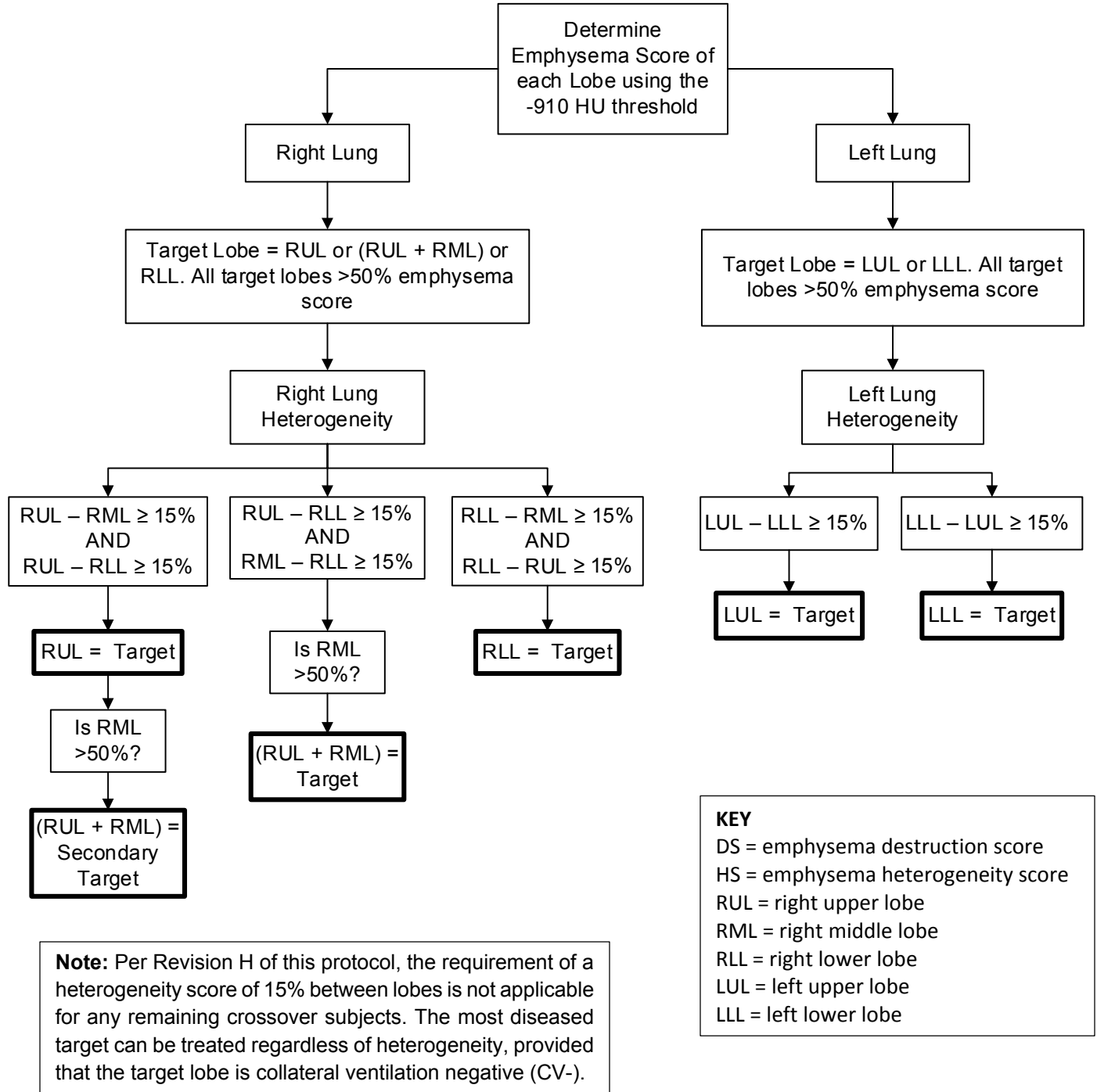
I hereby wish to **WITHDRAW** my consent to participate in the research proposal described above.
Withdrawal WILL NOT jeopardize any treatment or my relationship with _____
Hospital.

Printed Name of Participant (or legal representative): _____

Signature: _____

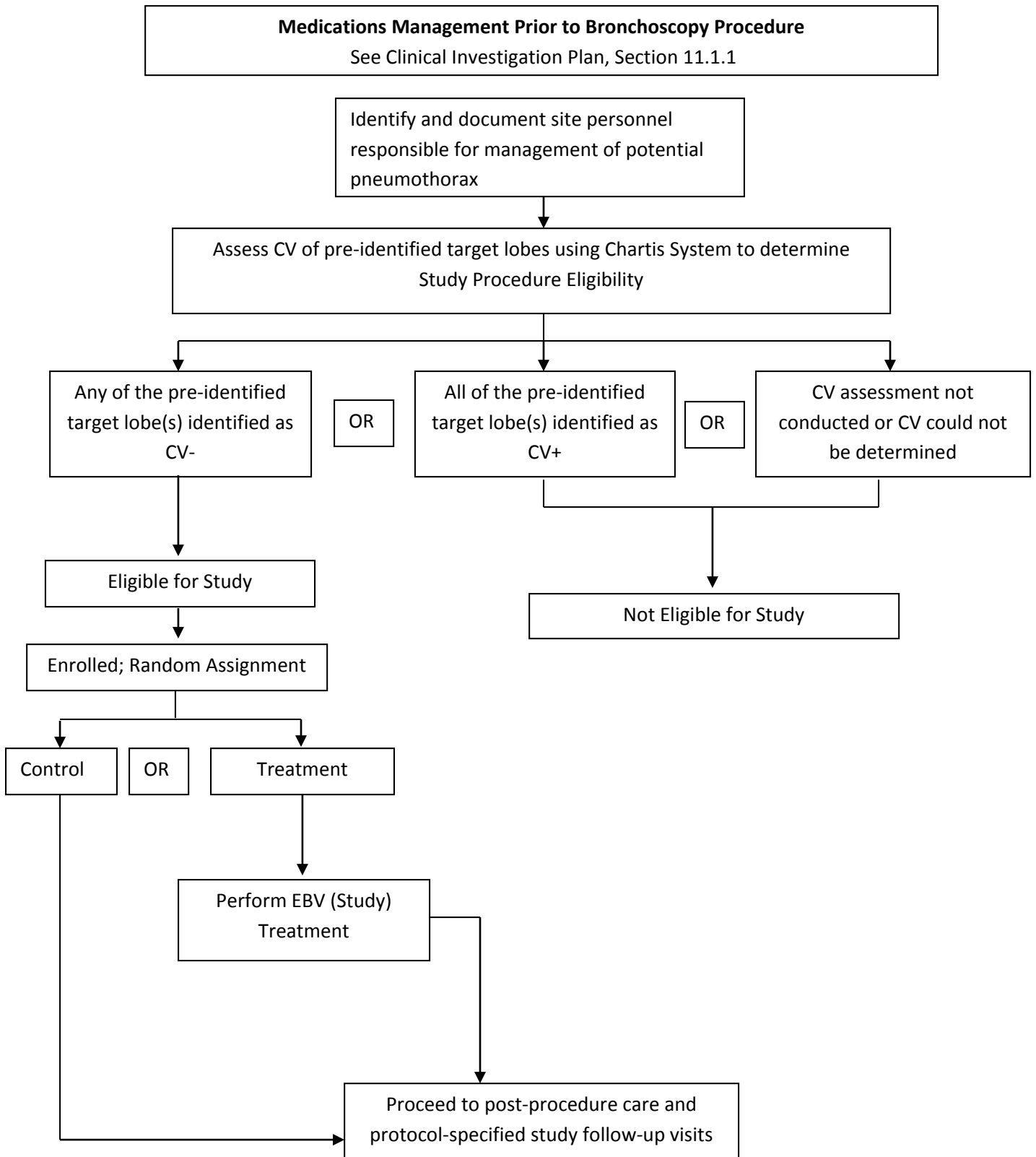
Date: _____

Instructions: Follow the procedure shown in the chart below to identify appropriate target lobes for study treatment. Targeted lobes will be assessed for collateral ventilation during the bronchoscopy procedure using the Chartis System to determine whether the study participant meets the study procedure eligibility criteria.



LIBERATE Study
Clinical Investigational Plan #630-0012-H
Appendix 10. Study Procedure Eligibility Criteria

Study Candidate Selection – Study Procedure Eligibility Criteria	
Study Procedure Inclusion Criteria	
1	Procedure occurs \leq 60 days following baseline exam
2	Continues to meet all screening and baseline eligibility criteria
3	Little or no collateral ventilation (CV-) as determined using the Chartis System
Study Procedure Exclusion Criteria	
3	Evidence of collateral ventilation (CV+) as determined using the Chartis System
4	Collateral ventilation could not be determined using the Chartis System
5	Collateral ventilation assessment was not conducted using the Chartis System



LIBERATE Study Clinical Investigation Plan #630-0012-H

Appendix 12. Required Schedule for Tests and Procedures at Screening and Baseline

TESTING	Screen Eligibility	Pre-Baseline	Baseline Eligibility & Assessment
IMAGING			
Chest X-ray			
High Resolution CT Scan	X		
LUNG FUNCTION TESTING			
Spirometry	X		X
Body Plethysmography	X		
Diffusing Capacity	X		
EXERCISE TOLERANCE			
Six-Minute Walk Test	X		X
BASIC MEDICAL			
Medical History	X		
Vital Signs / Physical Exam	X		X
ECG	X		
Echocardiogram	X		
Review of Medications	X		X
BLOOD WORK			
Arterial Blood Gases (ABGs)	X		
Complete Blood Counts (CBCs)	X		
Alpha-1 Antitrypsin	X		
Plasma Cotinine or Arterial Carboxyhemoglobin	X		
Serum Fibrinogen	X		
MEDICAL MANAGEMENT			
Pulmonary Rehabilitation		X	
Pneumococcal Vaccine			X
Influenza Vaccine			X
HEALTH SURVEYS			
SGRQ			X
MMRC			X
BDI/TDI			X
CAT			X
SF-36			X
EQ-5D			X
Health Care Utilization			X
DAILY DIARY*			
PR Program Compliance			X
Exact-PRO			X
Health Status Change			X

*paper diary

LIBERATE Study Clinical Investigation Plan #630-0012-H

Appendix 12. Required Schedule for Follow Up Tests and Procedures CONTROL Subjects

TESTING	Day 0 - Bronchoscopy	45 Days	3 Months	6 Months	9 Months	1 Year	ET/EWD
LUNG FUNCTION TESTING							
Spirometry		X		X		X	X
Body Plethysmography		X				X	
Diffusing Capacity		X				X	
EXERCISE TOLERANCE							
Six-Minute Walk Test		X		X		X	
BASIC MEDICAL							
Vital Signs / Physical Exam	X	X	X	X		X	X
Review of Medications		X	X	X	X	X	X
Electrocardiography						X	
Pulse Oximetry	X						
BLOOD WORK							
Arterial Blood Gases (ABGs)	X					X	
Complete Blood Counts (CBCs)						X	
Plasma Cotinine or Arterial Carboxyhemoglobin						X	
Serum Fibrinogen	X					X	
MEDICAL MANAGEMENT							
Pulmonary Rehabilitation*	X						
HEALTH SURVEYS							
SGRQ			X	X		X	
MMRC		X		X		X	
BDI/TDI			X	X	X	X	
CAT			X	X	X	X	
SF-36						X	
EQ-5D						X	
Health Care Utilization			X	X	X	X	
DAILY DIARY**							
PR Program Compliance		X	X	X	X	X	
Exact-PRO		X	X	X	X	X	
Health Status Change		X	X	X	X	X	
SAFETY							
Adverse Events	X	X	X	X	X	X	X

*starts within 30 days after bronchoscopy procedure; **daily diary recording to begin Day 1 after Bronchoscopy through 1 year follow up visit

LIBERATE Study Clinical Investigation Plan #630-0012-H

Appendix 12. Required Schedule for Follow Up Tests and Procedures TREATED Subjects

TESTING	Day 0 - Index Procedure	Day 1	Day 2	Day 3	Day 4	Day 5 (or day of discharge)	Daily Phone Call (for 10 days after discharge)*	Day 7 After Discharge	30 Days	45 Days	3 Months	6 Months	9 Months	1 Year	2 Years	3 Years	4 Years	5 Years	ET/EWD
IMAGING																			
Chest X-ray	X*	X	X	X	X	X		X	X	X									
Electrocardiography														X					
High Resolution CT Scan										X				X					
LUNG FUNCTION TESTING																			
Spirometry										X		X		X	X	X	X	X	X
Body Plethysmography										X				X					
Diffusing Capacity										X				X					
EXERCISE TOLERANCE																			
Six-Minute Walk Test										X		X		X					
BASIC MEDICAL																			
Pulse Oximetry (first 24 hours after procedure)		X																	
Vital Signs / Physical Exam	X					X		X	X	X	X	X		X					X
Symptom Checklist							X	X											
Review of Medications									X	X	X	X	X	X					X
BLOOD WORK																			
Arterial Blood Gases (ABGs)		X												X					
Complete Blood Counts (CBCs)														X					
Plasma Cotinine or Arterial Carboxyhemoglobin														X					
Serum Fibrinogen		X												X					
MEDICAL MANAGEMENT																			
Pulmonary Rehabilitation**								X											
HEALTH SURVEYS																			
SGRQ											X	X		X					
MMRC										X		X		X					
BDI/TDI											X	X	X	X					
CAT											X	X	X	X					
SF-36														X					
EQ-5D														X					
Health Care Utilization											X	X	X	X					
DAILY DIARY***																			
PR Compliance										X	X	X	X	X					
Exact-PRO		X	X	X	X	X	X	X	X	X	X	X	X	X					
Health Status Change		X	X	X	X	X	X	X	X	X	X	X	X	X					
SAFETY																			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*chest x-ray within one hour (± 30 minutes)

**must receive PI approval to resume normal activities and the post-bronchoscopy pulmonary rehabilitation program; Pulmonary rehabilitation must be initiated within the first 30 days following the bronchoscopy procedure

***daily diary recording to begin Day 1 after Index Procedure through 1 year follow up visit

TESTING	Adjustment Procedure Visit	Day 1	Day 2	Day 3	Day 4	Day 5 (or day of discharge)	Daily Phone Call (for 10 days after discharge)	Day 7 After Discharge	3 Months**
IMAGING									
Chest X-ray	X*	X	X	X	X	X		X	X
High Resolution CT Scan									X
LUNG FUNCTION TESTING									
Body Plethysmography									X
BASIC MEDICAL									
Pulse Oximetry (first 24 hours after procedure)		X							
Vital Signs/Physical Exam	X					X		X	
Symptom Checklist							X	X	
BLOOD WORK									
Arterial Blood Gases (ABGs)		X							
Serum Fibrinogen		X							
SAFETY									
Adverse Events		X	X	X	X	X	X	X	

*Chest X-ray within one hour (\pm 30 minutes)**Study participants who undergo a valve adjustment procedure will resume the study mandated follow-up schedule after the 7-Day Post-Discharge Visit following the the valve adjustment procedure, with the next planned clinic visit occurring at the 3 Month Visit after the initial study procedure. Study participants having a valve adjustment will undergo the testing required for all study treatment participants at the 3 Month Visit but will have additional testing consisting of CT scan, X-ray, and body plethysmography.

Post-Bronchoscopy Pulmonary Rehabilitation Manual of Operations

1.0 Background

It is not the intent of the LIBERATE study sponsor to constrain study participants from taking part in a multidisciplinary PR program consisting of elements other than those delineated herein but rather to allow a uniform set of recommendations relative to a PR exercise program. The LIBERATE study PR program itself includes both an in-clinic element and a home-based maintenance element.

2.0 Administrative Responsibilities

Investigative Study Center Representative

Each investigative study site will have a designated study representative(s) who is responsible for coordinating the care of study participants with the Pulmonary Rehabilitation (PR) centers. For most study centers, this responsibility will reside with the study coordinator; however, the responsibility may be delegated to other qualified personnel at the study site.

Pulmonary Rehabilitation Center Representative

Each Pulmonary Rehabilitation center will have a designated representative(s) responsible for communicating with the investigative study center representative. The designated PR representative will be responsible for ongoing coordination and communication with the designated Investigative Study Site Representative.

3.0 Pulmonary Rehabilitation Center Qualifications

The supervised PR program may be conducted at the investigative study site PR facility or at an off-site facility. The PR facilities utilized in the study should meet the qualifications outlined in this section.

Personnel

Each PR facility should have adequate staff. Staff members should include at a minimum:

- A Licensed Physician and/or Registered Nurse
- A Physical Therapist, Exercise Physiologist and/or Respiratory Therapist.

Equipment

The PR facility should have the following equipment in good working condition and readily available:

- Supplemental Oxygen Source
- Pulse Oximeter

- Heart Rate Monitor
- Treadmill
- Arm Ergometer
- Free Weights, Therabands or other suitable forms of variable resistance.

Training

Training of each PR facility should consist of providing the facility with a copy of the LIBERATE Study protocol, including this Manual of Operations.

Documentation

Pulmonary Rehabilitation Facility Information Form

This form is to be completed for each study participant and maintained in the study participant's binder. A copy of the form is attached to this manual as Appendix 13a.

4.0 Pulmonary Rehabilitation Agreement

It is anticipated that a Services Agreement will be executed between the investigative study site and the PR facility or the PR facility and the study sponsor.

5.0 Supervised In-Clinic Program

The study participant's initial visit to the PR facility should include the following elements:

- A review of the Pulmonary Rehabilitation Patient Information sheet and any other educational materials relevant to PR education.
- An assessment of the study participant's need to take part in a smoking cessation program. If determined necessary, the PR facility is expected to aid and encourage the study participant's attendance in such a program.
- An initial assessment of the study participant's physical condition including, at a minimum, the evaluation of:
 - Any physical limitations that may affect the selection of exercises to be performed.
 - Baseline characterization of strength and exercise tolerance.
 - Requirements for supplemental oxygen.
 - Establishment of specific PR exercise program and training for proper execution of each exercise maneuver.

Unless there are physical limitations, and in light of any limitations that exist, the PR exercise program is to consist of lower limb endurance training, upper limb endurance training, and lower and upper limb strength training.

Sample Program

Lower Limb Endurance Training

Lower limb endurance training is recommended to be done on a treadmill or freely ambulating indoors or outdoors. The goal of the training is to exercise for at least 20 minutes. Study participants may start at a lower duration and intensity and attempt to work up to this goal, with the starting level and progression guided by the therapist. If considered necessary by the therapist, oxygen saturation will be monitored during exercise.

Upper Limb Endurance Training

Upper limb endurance training consists of a group of exercises involving some form and level of resistance for each hand (e.g. dumbbells or Therabands). Appropriate exercises will be selected by the therapist. The exercises should remain constant during the course of the program and should include a minimum of eight (8) individual exercises. A list of some examples of these exercises is provided below.

Upper Limb Endurance Training Suggestions

1. Punching bag
2. Overhead scissors
3. Pump the tire
4. Windshield wipers
5. Crawl stroke
6. Backstroke
7. Breaststroke
8. Climb the mountain
9. Arm jog
10. Disco criss-cross

The group of exercises should be performed as a set, one right after the other, with each exercise performed for the same length of time. The goal of this training is to gradually and continually increase tolerance to both duration of the exercise and resistance level over the course of the program. The following general progression should apply:

- a. Select a resistance that can be tolerated while performing a complete set of exercises with a time of 20 seconds for each separate exercise.
- b. As the patient gets stronger, gradually increase the time for each exercise to a maximum of 90 seconds.

- c. When a time of 90 seconds for each exercise is achieved, increase the level of resistance and restart with a time of 20 seconds for each exercise.

Note: If the study participant is unable to perform unsupported arm exercises, an arm crank ergometer may be substituted at the therapist's discretion.

Lower and Upper Limb Strength Training

Lower and upper limb strength training consists of a group of exercises involving some form and level of resistance (e.g. dumbbells or Therabands). Appropriate exercises will be selected by the therapist. The exercises should remain constant during the course of the program and should include a minimum of eight (8) individual exercises. A list of suggested exercises is provided below.

Lower and Upper Limb Strength Training Suggestions

1. Chest butterfly (chest)
2. Sit to stand from chair (legs)
3. Side forward arm raise (shoulders)
4. Seated knee extension (quadriceps)
5. Sideward arm raise (shoulders)
6. Seated march (hip flexors & abdominals)
7. Shoulder shrugging (shoulders)
8. Standing hamstring curl (hamstrings)
9. T-tube pull-down (shoulders & back)
10. Standing toe raise (calves)

The group of exercises should be performed as a set with an appropriate amount of rest time between exercises. The goal of this training is to gradually and continually increase the patients' tolerance to both the number of repetitions and resistance level over the course of the program. The following general progression should apply for each exercise:

- a. Select a resistance that can be tolerated for 10 repetitions.
- b. As the study participant gets stronger, they should progress to 20 repetitions.
- c. When 20 repetitions are achieved on any given exercise increase the level of resistance and restart using 10 repetitions.

Documentation

Supervised In Clinic Pulmonary Rehabilitation Log

This log is to be filled out by the PR therapist after every session and is to be maintained at the PR facility. A copy of the log should be provided to the investigative study site representative on a weekly basis to enable monitoring of the study participant's progress and compliance with the PR program. A copy of the log is attached to this manual as Appendix 13b.

6.0 Home-Based Maintenance Pulmonary Rehabilitation Exercise Program

At the completion of the Supervised in clinic PR program the study participant will be provided with a written prescription for a home-based PR maintenance program. A copy of the written prescription should be provided to the Investigative Study Center Representative.

Study participants will be encouraged to follow this program at least three times a week beginning immediately and for the duration of their involvement in the study unless prevented from doing so by a medical condition.

The home-based maintenance PR program is recommended to consist of the following general components:

Lower Limb Endurance Training:

Walking for 20-30 minutes substituted for treadmill

Upper Limb Endurance Training:

As recommended by PR therapist, intended to be similar to in-clinic program.

Lower and Upper Limb Strength Training:

As recommended by PR therapist, intended to be similar to in-clinic program.

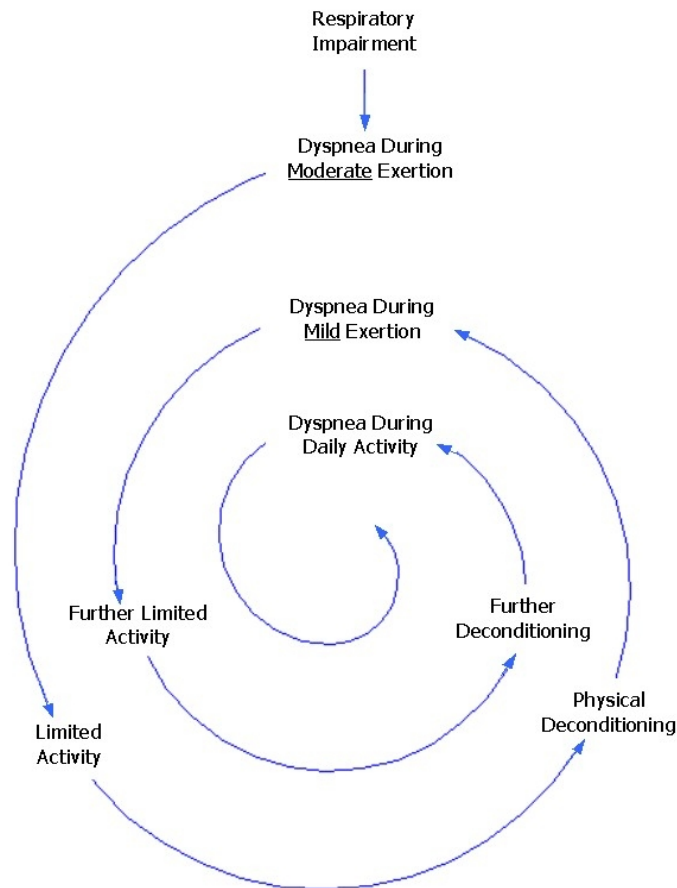
7.0 Patient Information

Scientific clinical studies have clearly demonstrated that those who comply with a regimen of pulmonary rehabilitation (PR) exercises and who remain physically active are in better overall health and function more effectively than their sedentary counterparts. The purpose of the Patient Information sheet is to provide study participants with the theory behind why this is the case, which may aid in their understanding of the importance of complying with the PR program for this study.

The Patient Information Sheet (see the following section) has been provided to use as an educational tool to be reviewed with each patient.

Patient Information Sheet

The nature of emphysema and its impact on your ability to function can contribute to a downward cycle of physical de-conditioning. This cycle has been described in several publications and is referred to as the “dyspnea cycle” or “downward spiral”. An illustration of this cycle is shown below¹.



The cycle starts as a result of respiratory impairment (reduced pulmonary function) brought on by emphysema. As this impairment progresses you may have begun to experience discomfort and breathing difficulty, or dyspnea, during physical activity or exertion. In order to avoid this discomfort you may understandably start to refrain from or limit this activity. As for everyone, even highly trained athletes, a withdrawal from exertion (exercise) can lead to general physical de-conditioning.

¹ Figure taken from “The Chronic Bronchitis and Emphysema Handbook”, Haas F, Hass SS, John Wiley & Sons, Inc., 2000.

Physical de-conditioning affects all of the systems in your body including the cardiovascular system and the musculoskeletal system. As you know, the health and strength of these systems are crucial to maintaining a lifestyle that is as active as possible.

Physical de-conditioning by itself (in the absence of a disease such as emphysema) is enough to contribute to discomfort during exercise for anyone. This problem of discomfort is likely to be increased in patients suffering from emphysema. The result of this discomfort during activity may cause you to further limit your physical exertion. This is the beginning of the “dyspnea cycle” or “downward spiral”.

It is possible that some amount of your dyspnea is due to physical de-conditioning which is compounded by your reduced pulmonary function. Although pulmonary rehabilitation has *not* been demonstrated to improve pulmonary function, it *has been* demonstrated to improve exercise tolerance². The reason for this is likely associated with some degree of “re-conditioning” of the bodies systems. It is reasonable to expect that improved exercise tolerance will result in your ability to perform daily tasks with less discomfort.

Conditioning as a result of exercise is a physiologically complex matter. It includes factors that are both easily comprehended and visually identifiable, such as improved muscle tone, as well as factors that are much more difficult to appreciate, such as improvements in blood flow due to a stronger heart muscle or improvements in the ability of the lungs to transfer oxygen to the blood and the ability of the recipient muscle cells to extract that oxygen. Although some of these things may happen on a cellular level and may not be evident to you as a patient, they are significant in their role in promoting the health and strength of your body.

The goal of your pulmonary rehabilitation program is to interrupt this “dyspnea cycle” in an effort to ensure that your physical limitations are as minimal as possible. For this reason it is important for all patients to be committed to their Pulmonary Rehabilitation program.

²Pulmonary Rehabilitation: Joint AACP/AACVPR Evidence-Based Guidelines. Chest 1997;112:1363-96□



Pulmonary Rehabilitation Facility Information Form

This form is to be completed by a representative from the Pulmonary Rehabilitation Facility to be involved in the LIBERATE Study.

Referring LIBERATE Study Site: _____
PR Facility Name: _____
Address: _____

Telephone: _____
Facsimile: _____
Email: _____
Director of PR Program: _____

Pulmonary Rehabilitation Personnel:

Designated Study Representative(s): _____

Address: _____
(If different than above) _____
Telephone: _____
Facsimile: _____
Email: _____
Licensed Physician(s): _____
Licensed Nurse(s): _____
Physical Therapist(s): _____
Exercise Physiologist(s): _____
Other (specify): _____
Other (specify): _____

Pulmonary Rehabilitation Facility Information Form

Facility Equipment:

- a. Number of treadmills? _____
- b. Number of cycle ergometers? _____
- c. Number of arm ergometers? _____
- d. Are there free weights, Therabands, or other suitable forms of variable resistance equipment? _____

Sources of supplemental oxygen for exercise training?

Pulse Oximeter available?..... Yes No

Heart Monitors available? Yes No

Designated and secure storage area for LIBERATE Study documentation? Yes No

Signature:

I hereby certify that the information above is true and correct to the best of my knowledge:

Signature: _____ Date: _____

Name (please print): _____

Name of Pulmonary Rehabilitation Facility (please print): _____



In-clinic Pulmonary Rehabilitation Log – POST-Bronchoscopy PR

Patient ID: _____ Facility Name: _____

Referring LIBERATE Study Site: _____

All LIBERATE study participants should participate in a supervised pulmonary rehabilitation program that is initiated within 30 days following the bronchoscopy procedure. The pulmonary rehabilitation program should include the elements recommended by the American Thoracic Society and European Respiratory Society Statement on Pulmonary Rehabilitation. In general, the post-bronchoscopy program should consist of an active ‘in clinic’ pulmonary rehabilitation component and a ‘home-based’ maintenance pulmonary rehabilitation component. The active ‘in clinic’ pulmonary rehabilitation program should be initiated for all study participants within the first 30 days following the bronchoscopy procedure. For the active ‘in clinic’ component of the program, the ATS/ERS practice guidelines recommend a minimum of 20 sessions be given at least three times per week although twice-weekly supervised plus one unsupervised home session may also be acceptable. For the maintenance component, study participants will be advised to adhere to a program consisting of at least 3 home-based sessions per week.

AT THE END OF EACH WEEK OF THE ACTIVE ‘IN CLINIC’ PROGRAM, A COPY OF THE COMPLETED LOG SHOULD BE SENT TO THE INVESTIGATIVE SITE, WHICH WILL BE MAINTAINED IN THE STUDY PARTICIPANT’S STUDY BINDER.

	Session 1	Session 2	Session 3
Date			
Duration of Entire Session (minutes)			
Therapist Initials			
	Session 4	Session 5	Session 6
Date			
Duration of Entire Session (minutes)			
Therapist Initials			
	Session 7	Session 8	Session 9
Date			
Duration of Entire Session (minutes)			
Therapist Initials			



In-clinic Pulmonary Rehabilitation Log – POST-Bronchoscopy PR

	Session 10	Session 11	Session 12
Date			
Duration of Entire Session (minutes)			
Therapist Initials			
	Session 13	Session 14	Session 15
Date			
Duration of Entire Session (minutes)			
Therapist Initials			
	Session 16	Session 17	Session 18
Date			
Duration of Entire Session (minutes)			
Therapist Initials			
	Session 19	Session 20	-----
Date			
Duration of Entire Session (minutes)			
Therapist Initials			

PLEASE ATTACH A COPY OF THE HOME-BASED PROGRAM SUGGESTED TO THE STUDY PARTICIPANT TO THIS FORM AT THE COMPLETION OF SESSION 20

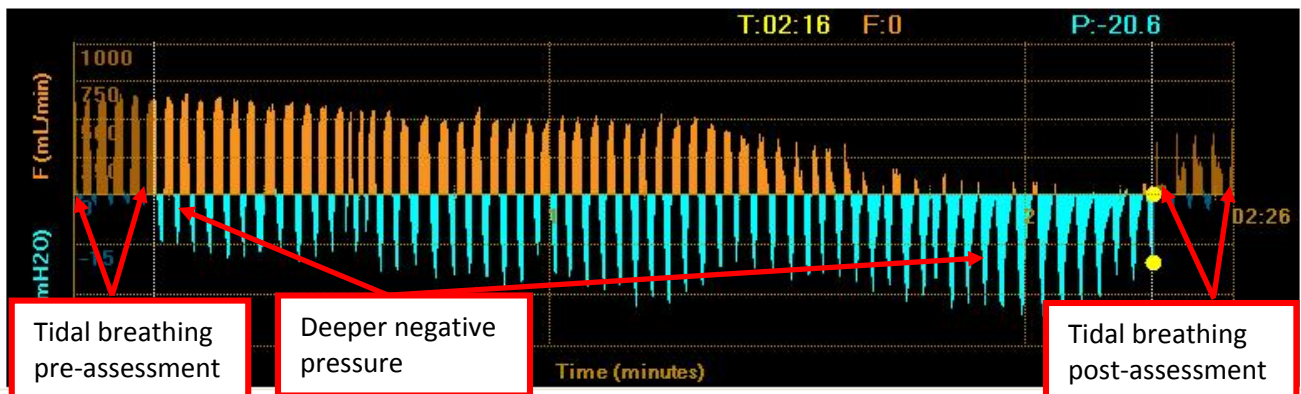
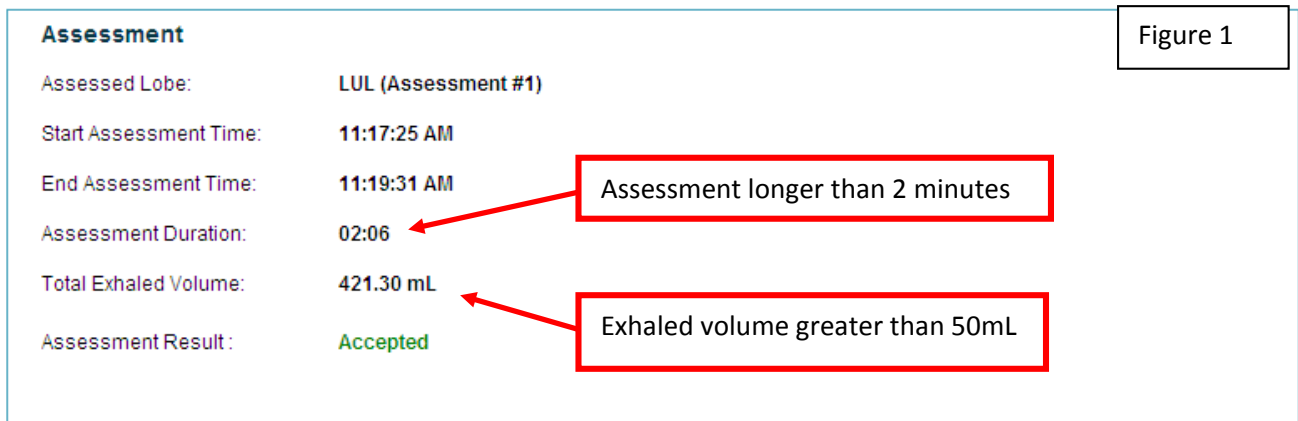
Collateral ventilation (CV) status of the targeted treatment lobe will be assessed by following the steps shown below:

1. Place the Chartis catheter balloon. The balloon should be placed to occlude all segments of the target treatment lobe.
2. The tip of the catheter should be placed in a manner that allows airflow from all segments of the target treatment lobe to reach the catheter tip.
3. Complete sealing of the target lobe by the balloon should be maintained throughout the entire duration of the assessment (including the 10-second pre-assessment and 10-second post-assessment periods).
4. NOTE:
 - a. If difficulties are encountered with occluding the target lobe, measurement of the adjacent lobe/lobes may be used as a proxy measure of the collateral ventilation status of the target lobe.
 1. Example: If the patient's anatomy does not allow placement of the balloon in the LLL, the collateral ventilation of the LUL can be assessed and used in the treatment decision since the lobes share a common interlobar fissure and hence their collateral ventilation status.
5. After completing the assessment of the target treatment lobe, remove the Chartis catheter.

An example output for an acceptable Chartis System assessment is shown in Figure 1 below.

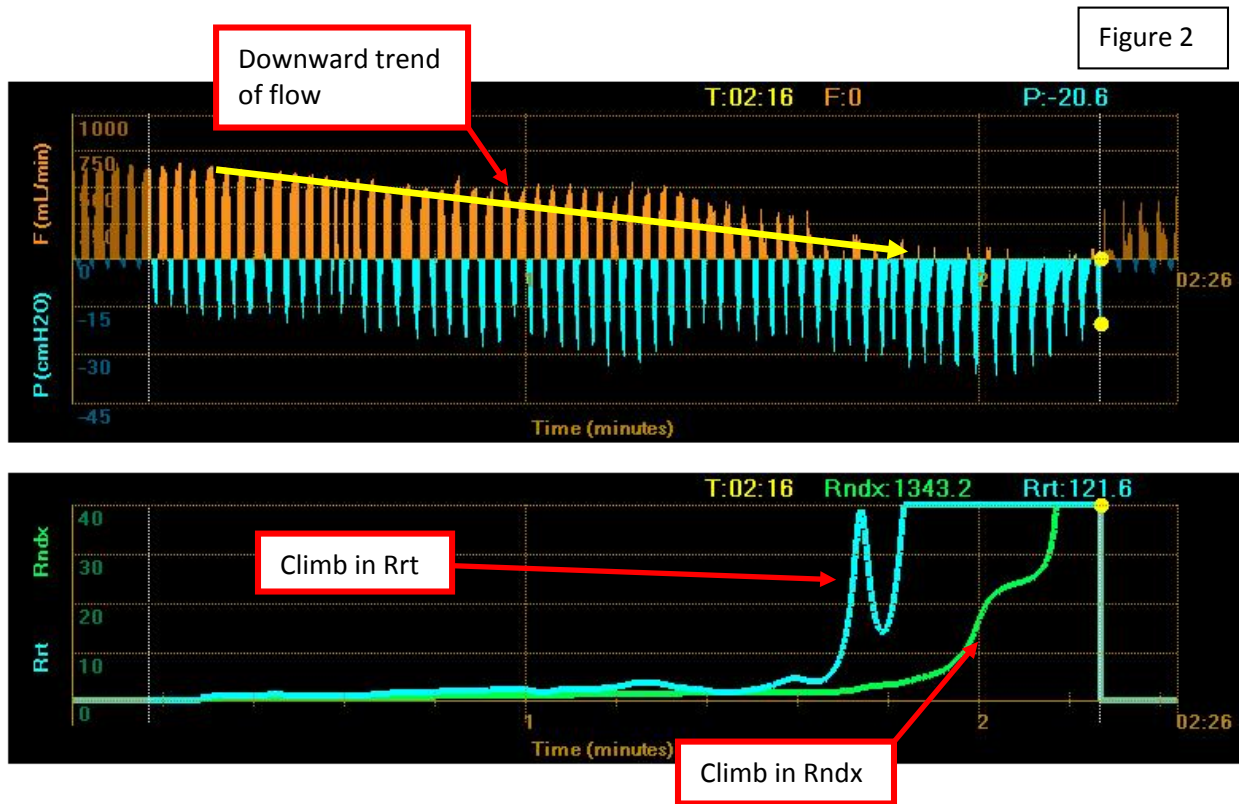
While assessing CV status of a targeted treatment lobe, there are several important items to note during the assessment, including:

- 1) The patient should demonstrate consistent tidal breathing prior to start of assessment. This indicates that the patient has been adequately sedated. Ensuring adequate sedation will aid in achieving complete sealing of the targeted segment with the Chartis catheter balloon.
- 2) Duration of the assessment should be 2 minutes or longer.
- 3) Throughout the assessment, consistent deeper negative pressure should be observed. This indicates that proper catheter balloon positioning and sealing has been achieved.
- 4) At the end of the assessment, the total volume of air exhaled by the patient during the assessment should have been greater than 50 ml.
- 5) During the post-assessment period, ensure that tidal breathing pattern has returned. The balloon seal should be maintained until the review screen appears.
- 6) During the assessment, if the patient coughs, the catheter tip clogs, or loss of the balloon seal is noted, the duration of the assessment should be extended. If any of these issues are significant, the assessment should be abandoned and a new one should be re-initiated.
- 7) During the assessment, if there is an instantaneous loss or drop in flow within the first 30 seconds and flow does not resume, the assessment should be abandoned and a new one should be re-initiated.



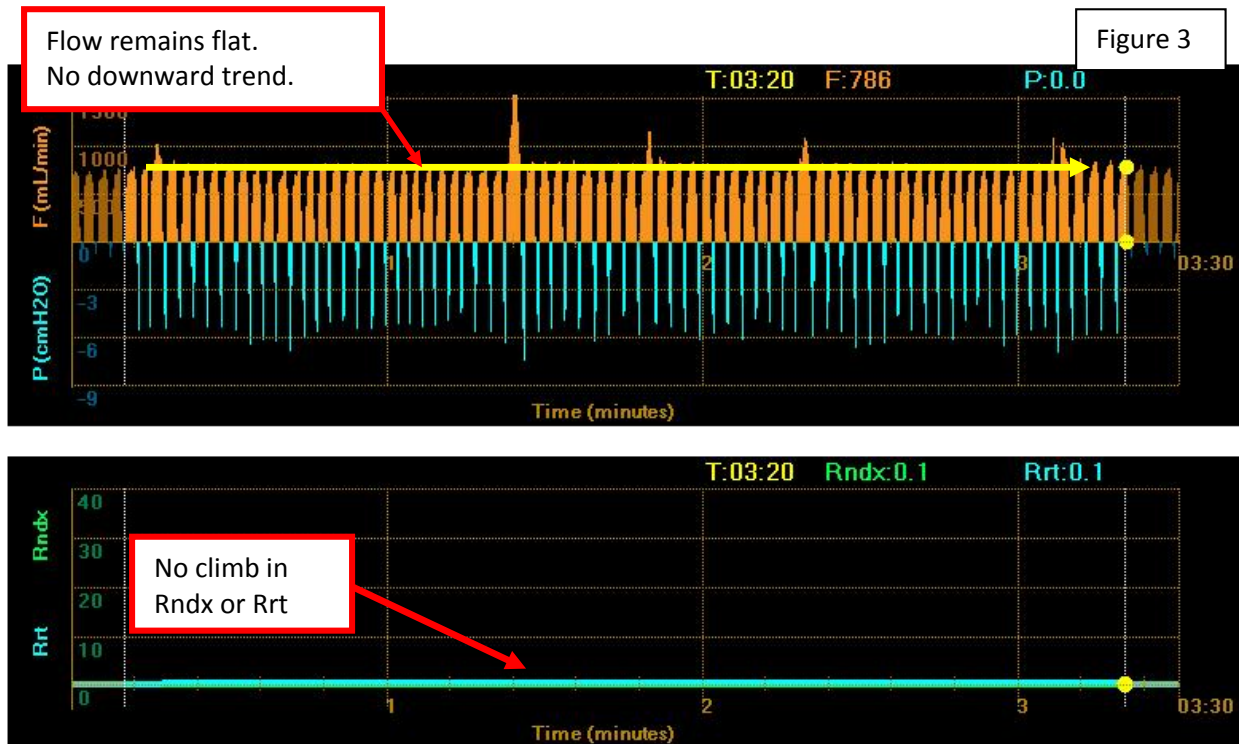
Assessment of a Lobe that has Little or No Collateral Ventilation (CV- Lobe)

1. When high resistance to collateral ventilation or high collateral resistance is noted, the Chartis assessment indicates that the target treatment lobe has little or no collateral ventilation (is CV negative or CV-).
2. An example of a CV- assessment is shown in Figure 2 below.
3. The key features of a CV- assessment include:
 - a. The peaks of the flow indicator waveforms (orange) show a steady downward trend.
 - b. The Collateral Resistance index (Rndx) and / or Collateral Resistance realtime (Rrt) profile lines climb in a stepwise and steady fashion.
 - c. Potential artifacts to avoid include:
 - i. Instantaneous climbing of the Rndx and Rrt lines should not be considered a CV- assessment. This observation could be an artifact of an underlying issue such as clogging of the catheter tip.
 - ii. An instantaneous drop in flow seen within the first 30 seconds of the assessment should not be considered a CV- assessment. This observation could be an artifact of distal airway collapse.



Assessment of a Lobe that has Collateral Ventilation (CV+ Lobe)

1. When low resistance to collateral ventilation or low collateral resistance is noted, the Chartis assessment indicates that the target treatment lobe has high collateral ventilation (CV positive or CV+).
2. An example of a CV+ assessment is shown in Figure 3 below.
3. The key features of a CV+ assessment include:
 - a. The peaks of the flow indicator waveforms (orange) remain flat and do not show a downward trend.
 - b. The Collateral Resistance index (Rndx) and / or Collateral Resistance realtime (Rrt) profile lines have little or no change and do not steadily increase.



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Appendix 14. Procedure for Assessing Target Treatment Lobe CV using the Chartis System

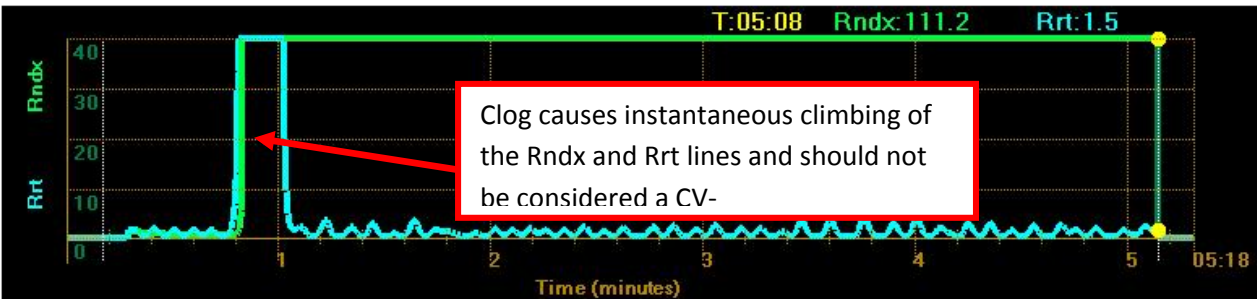
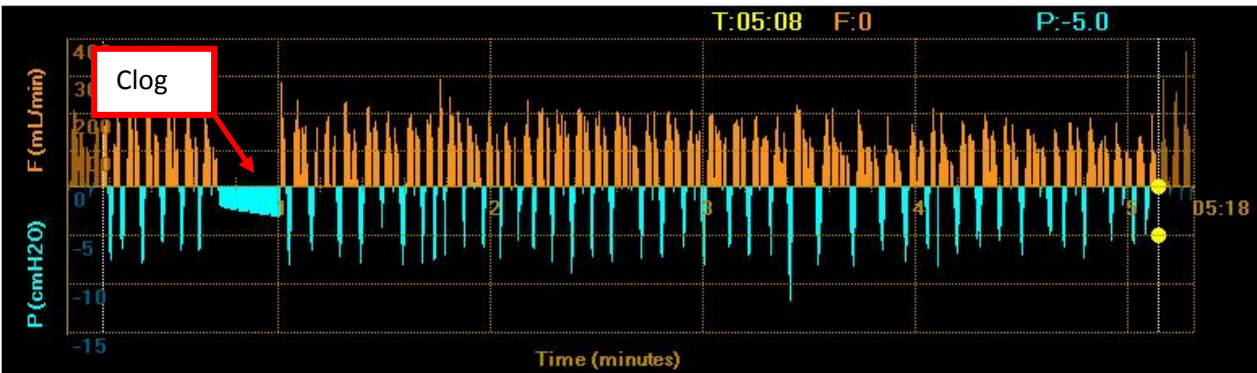
Other measurement anomalies which might affect the outcome of the collateral ventilation assessment include clogged catheter tip, instantaneous drop in flow, loss of balloon seal, and patient coughing. It should be noted that these anomalies can occur together or independently during the course of an assessment.

Assessment of a Lobe that has mucous clogging

An example of a case with clogging at the catheter tip is shown in Figure 4.

Assessment	
Assessed Lobe:	RLL (Assessment #3)
Start Assessment Time:	9:56:26 AM
End Assessment Time:	10:01:24 AM
Assessment Duration:	04:58
Total Exhaled Volume:	438.70 mL
Assessment Result:	Accepted

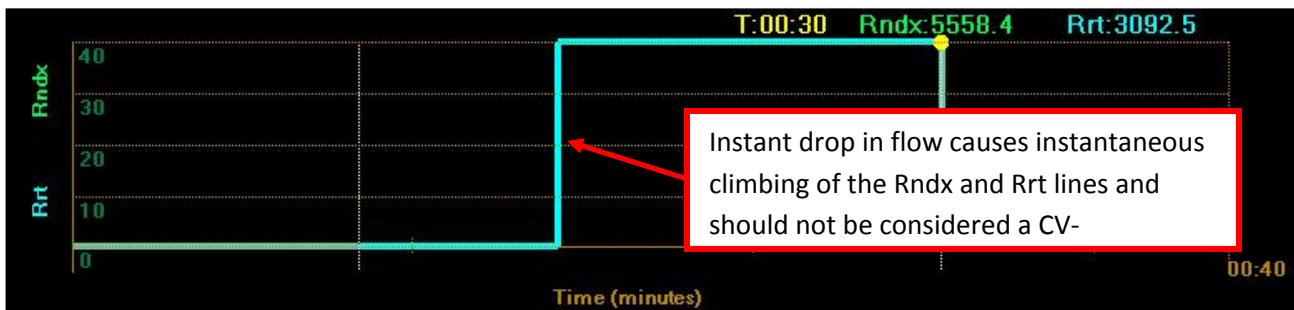
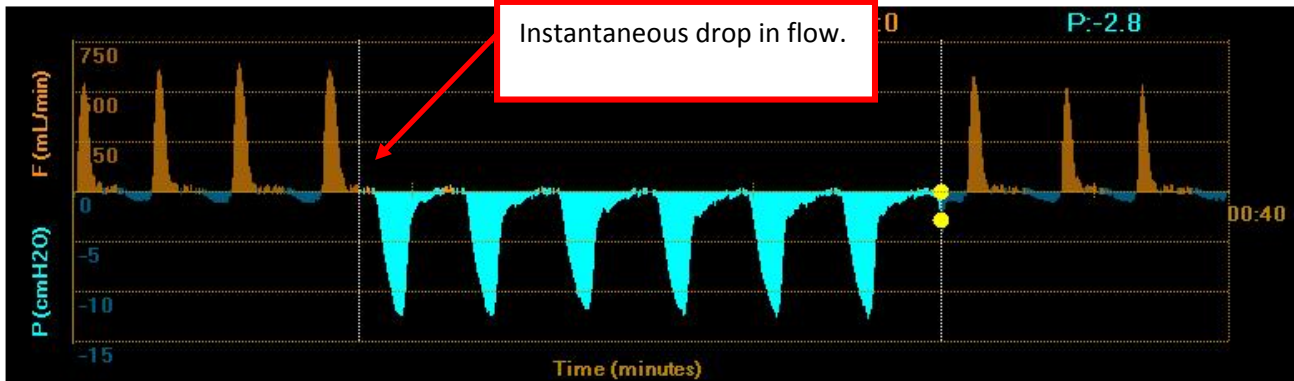
Figure 4



Assessment of a Patient with instantaneous drop in flow

An example of a case with an instantaneous drop in flow is shown in Figure 5.

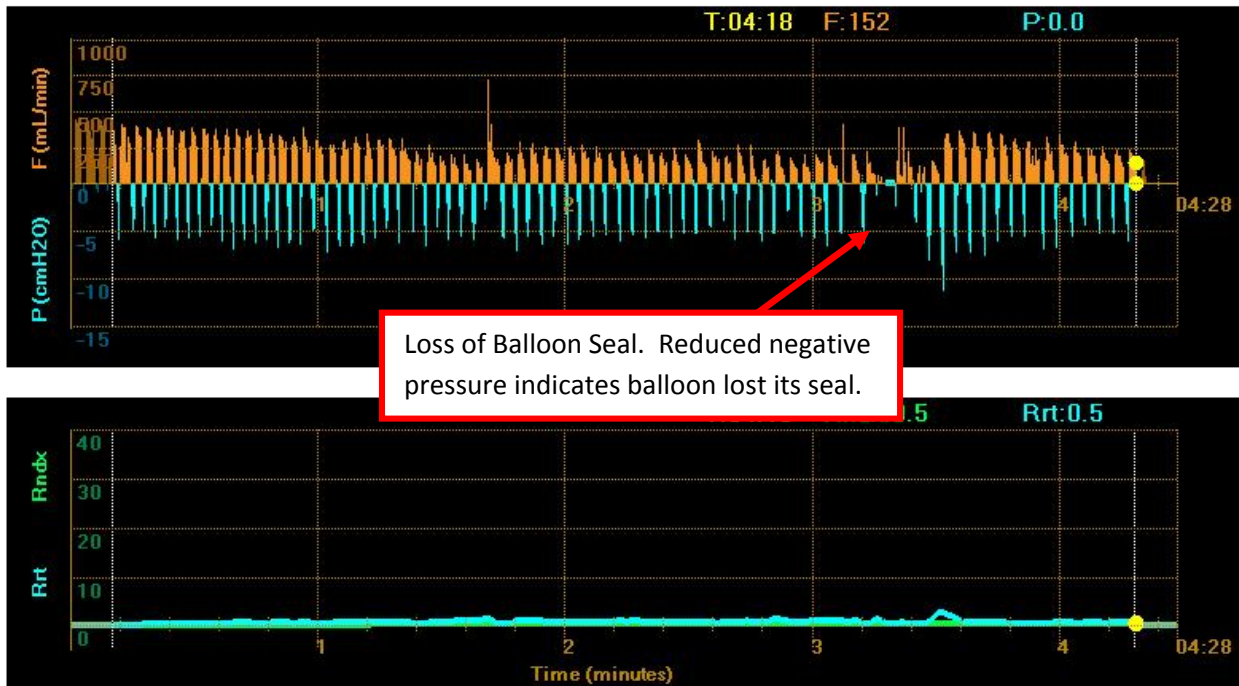
Assessment		Figure 5
Assessed Lobe:	LLL (Assessment #1)	
Start Assessment Time:	11:03:19 AM	
End Assessment Time:	11:03:40 AM	
Assessment Duration:	00:20	
Total Exhaled Volume:	28.62 mL	
Assessment Result:	Accepted	



Assessment of a Patient with Loss of Balloon Seal

An example of a case in which the balloon seal has been compromised is shown in Figure 6.

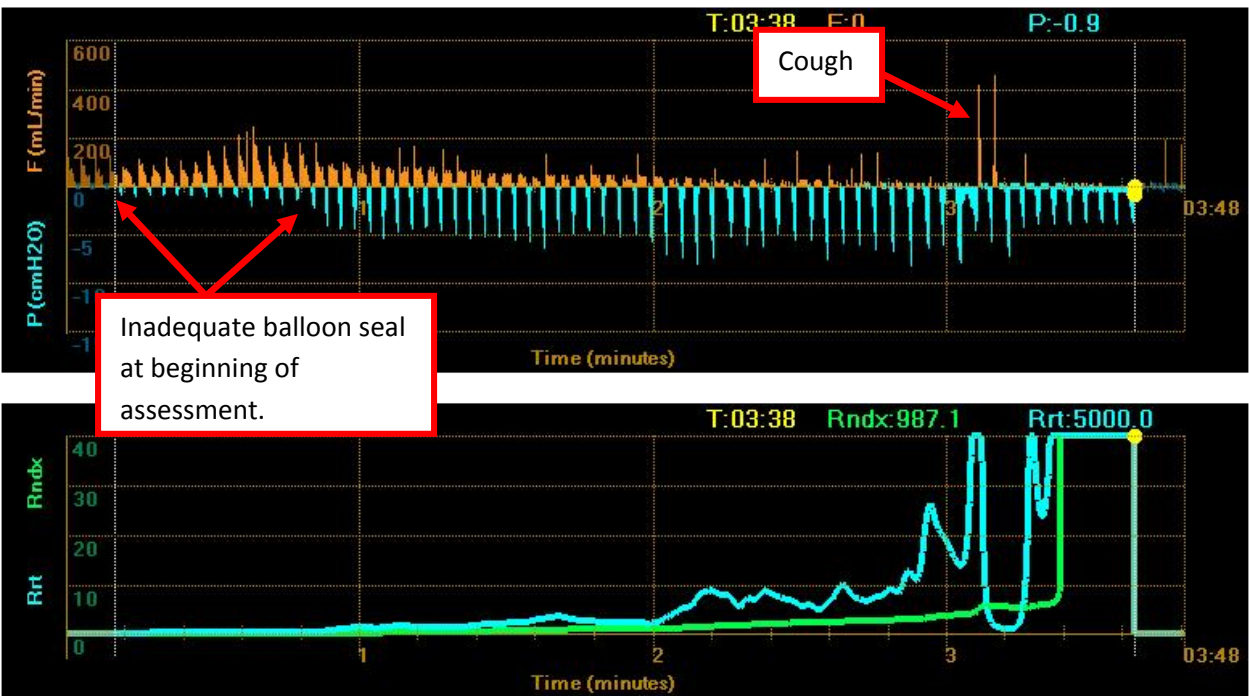
Assessment		Figure 6
Assessed Lobe:	RUL (Assessment #2)	
Start Assessment Time:	1:50:00 PM	
End Assessment Time:	1:54:08 PM	
Assessment Duration:	04:08	
Total Exhaled Volume:	600.83 mL	
Assessment Result:	Accepted	



Inadequate Balloon Seal and Coughing

An example of a case having inadequate balloon seal at the beginning of the assessment and a cough at the end of the assessment is shown in Figure 7.

Assessment		Figure 7
Assessed Lobe:	RUL (Assessment #7)	
Start Assessment Time:	9:43:42 PM	
End Assessment Time:	9:47:10 PM	
Assessment Duration:	03:28	
Total Exhaled Volume:	108.45 mL	
Assessment Result:	Accepted	



The information shown in the table below may be used as a guide for EBV placement in bronchial targets to achieve lobar occlusion.

	Bronchial Segment Number	Bronchi
Right Upper Lobe	B1	Apical
	B2	Posterior
	B3	Anterior
Right Middle Lobe	B4	Lateral
	B5	Medial
Right Lower Lobe	B6	Superior, lower lobe
	B7	Medial basal
	B8	Anterior basal
	B9	Lateral basal
	B10	Posterior basal
Left Upper Lobe	B1+2	Apicoposterior
	B3	Anterior
	B4	Superior lingular
	B5	Inferior lingular
Left Lower Lobe	B6	Superior, lower lobe
	B7+8	Anteromedial basal
	B9	Lateral basal
	B10	Posterior basal

Medical Alert Card - *Example*

Medical Alert

I, NAME OF PATIENT am enrolled in a clinical study for the treatment of emphysema being conducted at the NAME OF HOSPITAL, in NAME OF CITY AND STATE. As part of this study, one or more implants have been placed within my airways.

If I am involved in an accident or require other medical care, please first consult one of the contacts on the reverse side, unless the situation requires immediate emergent care. If symptoms of pneumothorax are evident (chest pain, nausea, shortness of breath), please treat me as appropriate for pneumothorax. If pneumothorax persists, please transfer me to the hospital specified above and on the back of this card.

(FRONT)

Medical Alert – Contact Information

Physician: NAME OF PHYSICIAN
24 hour contact number: (xxx) xxx - xxxx

Physician: NAME OF PHYSICIAN
Phone: (xxx) xxx - xxxx

Hospital Name: _____
Address: _____

Phone: (xxx) xxx - xxxx

Treated Lung: _____ (Lobe: LUL, LLL, RUL, RLL)

(BACK)

Post-EBV Procedure Discharge Instructions for the Study Treatment Arm

Key Points

- Please contact the study doctor if you should experience more shortness of breath than usual, severe chest pain and/or tightness, nausea and/or dizziness, or any other symptoms or changes in your health that you are worrisome to you
- Please wear your study bracelet and put your Medical Alert Card in your wallet in case of an emergency
- Do not drive yourself home from the hospital or drive for at least 7 days after your procedure
- Plan on having someone stay with you for the first few days and nights after you are discharged
- Only engage in light physical activities for at least 7 days after you are discharged and don't start pulmonary rehabilitation until the study doctor meets with you at your 7-day post-discharge visit

Discharge Day Schedule

Prior to your discharge, your study doctor will complete a physical examination and a chest x-ray to determine how you are doing and whether it is safe for you to leave the hospital. If the study doctor decides that it is safe for you to go home, he/she and his/her staff will ensure that you have appropriate transportation from the hospital to your home. You should not drive yourself home so you should plan on having a friend, relative, or colleague be available to drive you home. Also, you should plan on having someone stay with you for several days after you are discharged to help support your transition home and your recovery from this procedure. The study doctor and his/her team will provide you with a Medical Alert Card as well as the following set of discharge instructions.

Recovery & Symptoms

The time that it takes for you to recover from the Endobronchial Valve (EBV) procedure may vary depending on your age, physical well-being, and mental health. It is important that you allow yourself the time to recover at your own pace. Your regular doctor and the study doctor (as appropriate) can help manage any symptoms and problems that you may experience following the procedure. Such symptoms may include:

1) Fatigue/Lack of Energy

You have just undergone a fairly significant procedure so you may feel tired and have a lack of energy in the days and weeks following the procedure as your body heals, your general health status returns to normal, and you regain your strength. You should take it slow and easy and listen to your own body during this time so that you appropriately pace yourself and avoid overdoing it.

2) Decrease in Appetite

You may experience a temporary decrease in your appetite as the medicines from your procedure and post-procedure care wear off and your mouth and airways begin to recover from the bronchoscopy. Your appetite should return to normal within 1-2 weeks following the procedure. If your appetite is poor, attempt to eat smaller, nutrient-rich (high protein and high calorie), and frequent meals and ensure that you are drinking a lot of fluids throughout the day (6-8 cups/day unless instructed otherwise by your doctor). Sometimes, a decrease in appetite can be accompanied by feelings of nausea and/or dizziness. If you should experience either of these symptoms, please contact your study doctor immediately.

3) Pain/Discomfort

You may experience some pain and discomfort in your nose, throat, airways, and chest in the days and weeks following the procedure as your body recovers from the bronchoscopy. Normally, this pain and discomfort is only temporary and resolves within several days after the procedure. It is important that you take any pain medications that have been prescribed for these symptoms as you may need them. If you should experience any sudden feelings of chest pain and/or tightness that are sharper and more severe than normal, please contact your study doctor immediately.

4) Breathing Changes

As a result of this procedure, your breathing function may decrease, stay the same, or improve. It is important that you realize that you may not notice dramatic changes in your breathing function immediately following the procedure and it is possible that it may even decrease a little as your body heals and you regain your strength after the procedure. Hopefully, you will experience less shortness of breath in the weeks and months following the procedure but this cannot be guaranteed. If you should experience significantly more shortness of breath than usual, please contact your study doctor immediately.

5) Other Symptoms/Health Changes

You may also experience increased shortness of breath that is accompanied by increased cough and/or wheezing, increased sputum production, changes in sputum color, and fever, which may suggest that you are having a COPD exacerbation or an episode of pneumonia. Additionally, you may cough up a lot of blood or one of the valves or experience an increased or irregular heartbeat following the procedure, which may suggest some changes in your heart function. It is important that you call your family doctor and/or the study doctor (as appropriate) as soon as you begin experiencing any of the symptoms above. You should also call your family doctor and/or the study doctor (as appropriate) if you experience any other symptoms or changes in your health that seem out of the ordinary or worrisome to you.

General Instructions

It is important that you follow these general instructions as you continue your recovery from the EBV placement procedure at home in the days and weeks after this procedure. If you have any questions or concerns regarding these instructions, please discuss them with the study doctor and his/her study team.

Activity

In the days and week after discharge from the hospital, you should only engage in light physical activity as you are able and comfortable. This means that you can participate in such activities as self-care, light household chores like cooking and laundry, socializing with friends and family, and light exercise like walking on a straight and level track. For 7-10 days after discharge, you should avoid any activities that require heavy lifting, carrying, pushing, or pulling or put significant strain on your body, particularly your chest and arm muscles. This includes activities like vacuuming, carrying groceries, shoveling snow, lifting weights, jogging/running, swimming, playing tennis, or doing aerobics. Additionally, you will not be able to start your post-procedure pulmonary rehabilitation program until your study doctor has completed a physical examination, performed a chest x-ray, and authorized you to resume your normal daily activities during your visit with him or her 1 week following your discharge from the hospital.

Driving/Traveling

You should not drive for the first few days after discharge. This is the amount of time that is usually required for you to regain the necessary mobility and strength to safely navigate and steer a car. Additionally, you should avoid travelling out of state and particularly by air for at least 1 week after discharge. If you have any problems or complications, this will help ensure that you are within close proximity and will have easy access to the treating hospital for evaluation and treatment.

Returning to Work

You should not return to work full-time until you feel physically and mentally strong enough to resume your normal work activities. Depending on your job and required activity level, you may not be able to return to your full set of work responsibilities for 1-2 weeks after the procedure. If you have any questions or concerns or need special assistance regarding this instruction, please check with your study doctor.

Medications

After your procedure and prior to your discharge, your medications may change. It is important that you take any new prescriptions and follow any new medication instructions provided to you by your study doctor and his/her team. It is possible that you may need additional medications after you are discharged. You should contact your family doctor and the study doctor (as appropriate) if you have any questions or concerns or have additional medication requirements.

Problems after the Study Procedure

You should ensure that your family doctor has been informed of your EBV placement procedure as he/she will continue to provide your ongoing regular medical care and management once you are discharged. If you have any questions, concerns, or needs regarding your regular medical care after you are discharged, you should contact your family doctor. If you have questions, concerns, or needs as they relate to this procedure or study, please contact your study doctor and his/her study team.

Please keep your study doctor and his/her study team informed of any changes in your health or medications regardless of their relationship to this procedure or study. Additionally, please ensure that you wear your study bracelet and place your Medical Alert Card for this study in your wallet so that it is readily accessible to a health care professional(s) in the event that you experience a medical emergency.

Calling the Study Doctor

Please contact the study doctor for any of the following reasons:

- increased shortness of breath
- nausea and/or dizziness
- sudden onset of sharp and severe chest pain/tightness
- fever
- increased cough and/or wheeze with or without increased sputum production and changes in color/thickness of sputum
- coughing up significant amounts of blood

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Appendix 17. Post-EBV Procedure Discharge Instructions for the Study Treatment Arm

- coughing up valve(s)
- irregular or increased heartbeat
- any other worrisome problem or symptom

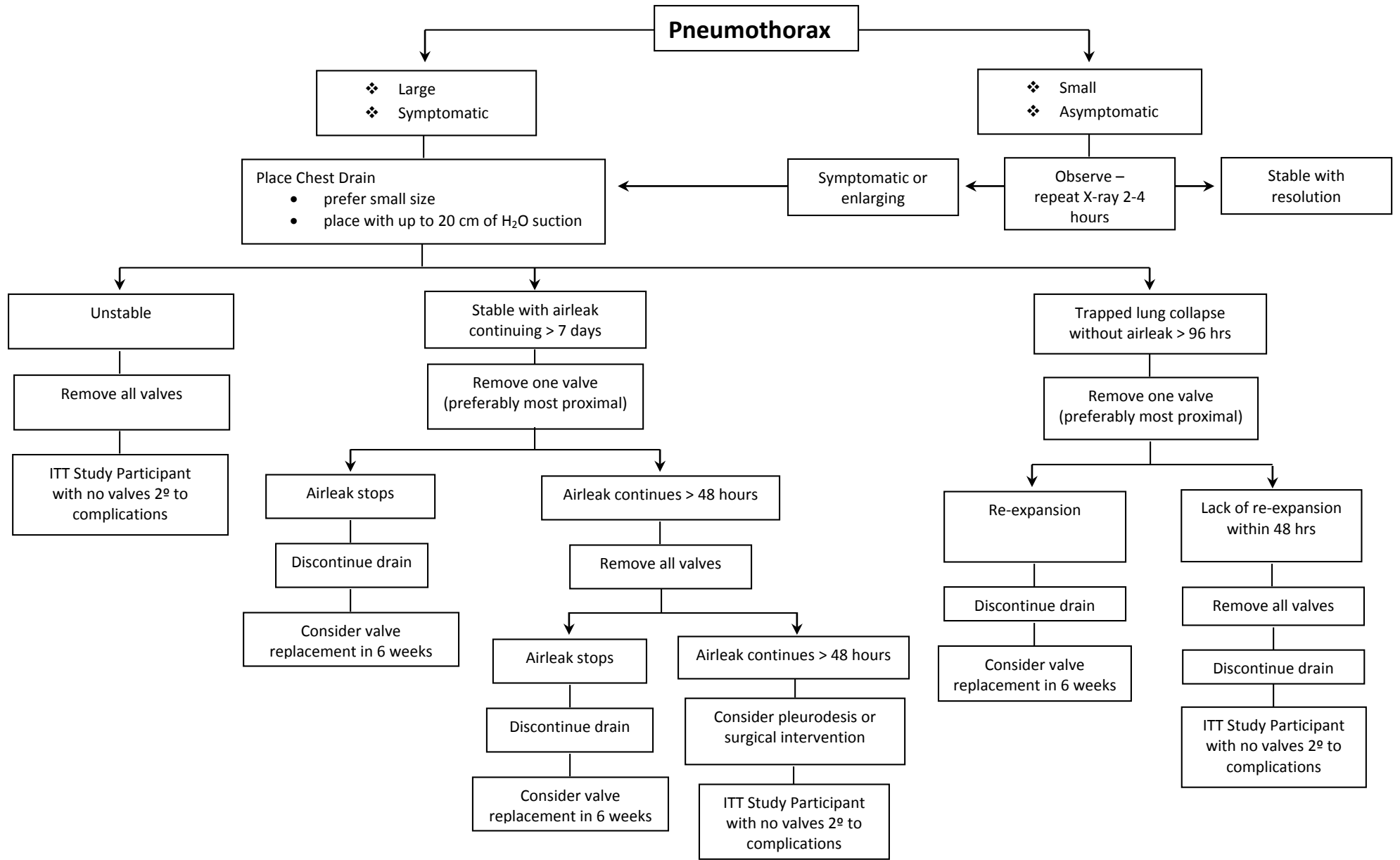
If you have any questions or concerns after you leave the hospital, please contact your study doctor's office or 24-hour number as follows:

Dr. [PI Name] Office: [PI Office #] 24-hour: [PI Office #]

Dr. [Co-PI Name] Office: [Co-PI Office #] 24-hour: [Co-PI Office #]

Dr. [Sub-I Name] Office: [Sub-I Office #] 24-hour: [Sub-I Office #]

 [SC Name] Office: [SC Office #]



Management Considerations for EBV Patients at Potentially Increased Risk for Pneumothorax in the Immediate Post-EBV Procedure Period

Case-related experience suggests that the development of substantial atelectasis in the immediate post-EBV procedure period may be associated with a higher risk of pneumothorax-related complications. A higher risk patient is defined as any patient that experiences acute, significant volume reduction immediately post-EBV treatment, usually determined by volume reduction visible on the 1-hour post-treatment chest x-ray. Out of an abundance of caution in this situation, the clinician should consider the following:

- Performing a CT scan of the chest without contrast to evaluate for pneumothorax that may not be visible on plain x-ray imaging
- Keep chest drainage set easily accessible and consider placement of a small bore catheter if any size pneumothorax is identified
- Application of oxygen (FiO₂ of 100%)
- Consider reducing patient's exertion for 48 hours

Consider the methods suggested in a recent publication (Herzog 2015) where patients following a modified post-EBV care that included 48 hours of strict bed rest and, if needed, 16 mg codeine up for cough to three times a day (TID), experienced statistically significant fewer pneumothoraces.

Also, in the event of acute clinical deterioration, usual management protocols need to be followed. Placement of a chest tube should be considered if even a small pneumothorax is found on chest CT scanning following substantial atelectasis in the immediate post EBV procedure period. Additionally if clinical deterioration occurs that requires endotracheal intubation and positive pressure ventilation, bilateral chest drains should be placed if there is any suspicion of bilateral pneumothoraces.

References

1. Cormier Y, Laviolette M, Tardif A [Prevention of pneumothorax in needle lung biopsy by breathing 100% oxygen.](#) *Thorax.* 1980 Jan;35(1):37-41.
2. Herzog D, Poellinger A, Doellinger F, Schuermann D, Temmesfeld-Wollbrueck B, Froeling V, Schreiter NF, Neumann K, Hippenstiel S, Suttorp N, Hubner RH. [Modifying Post-Operative Medical Care after EBV Implant May Reduce Pneumothorax Incidence.](#) *PLoS One.* 2015 May 26;10(5):e0128097.

Analysis Summary

Study Title: Lung Function Improvement after Bronchoscopic Lung Volume Reduction with Pulmonx Endobronchial Valves used in Treatment of Emphysema (Clinical Protocol 630-0012).

Patient Population: Male and female patients with severe heterogeneous emphysema meeting the study eligibility criteria.

Study Design: This will be a multi-center, prospective, randomized, controlled study with EBV treatment statistically evaluated using Intent-to-Treat (ITT) analyses. A maximum of 183 ITT study participants, who meet study entry criteria, consisting of screening eligibility criteria, baseline eligibility criteria, and procedure eligibility criteria, will be enrolled. Safety and effectiveness of bronchoscopic lung volume reduction (BLVR) using the Pulmonx EBV will be evaluated at 1 year. An interim analysis designed to evaluate effectiveness for continuing crossover of control participants at 1 year to EBV treatment will be performed when 74 study participants have completed the 1-year follow-up. For study participants who have been treated with EBV, a secondary valve intervention such as valve removal, replacement, or adjustment may be considered during the study follow-up. Long-term data will be collected annually for EBV-treated study participants through 5 years. Per the regulatory plan agreed to with FDA, 1 year of follow-up is required pre-approval and the remaining 4 years of follow-up will be conducted post-approval.

Primary Effectiveness Endpoint

The percentage of study participants in the Endobronchial Valve (EBV) treatment arm who meet the threshold of $\geq 15\%$ improved forced expiratory volume in one second (FEV₁) as compared to the control arm at 1 year. Improved FEV₁ will be calculated by determining the percentage change for FEV₁ from baseline to 1 year post-procedure for individual study participants.

Secondary Effectiveness Endpoints

- 1) Treatment Lobe Volume Reduction (TLVR) for the Treatment Arm
 - a. TLVR, measured as the 'absolute change from baseline' for treated lobe volume as seen via HRCT (high resolution computed tomography), will be evaluated at 45 days and 1 year.
 - b. TLVR, measured as the 'percentage change from baseline' for treated lobe volume as seen via HRCT, will be evaluated at 45 days and 1 year.
- 2) St. George's Respiratory Questionnaire
 - a. Difference between study arms in 'absolute change from baseline' for SGRQ score at 1 year.

- 3) FEV₁
 - a. Persistence of treatment effect will be evaluated by determining the difference between study arms for 'absolute change from baseline' for FEV₁ at 45 days, 6 months, and 1 year.
 - b. Persistence of treatment effect will be evaluated by determining the difference between study arms for 'percentage change from baseline' for FEV₁ at 45 days, 6 months, and 1 year.
- 4) 6-Minute Walk Distance (6MWD)
 - a. Difference between study arms in 'absolute change from baseline' for 6MWD at 1 year.
 - b. Difference between study arms in 'percentage change from baseline' for 6MWD at 1 year.

Safety Endpoint

Evaluation of the short- and long-term adverse events profile of the EBV treatment arm during the treatment period, defined as the day of the study procedure until 45 days after the study procedure (short), and in the post-treatment period, defined as 46 days after the study procedure until the 1-year follow-up visit (long).

Additional Measures

- Spirometry, including FEV₁, forced vital capacity (FVC) and the ratio of FEV₁/FVC
- Body plethysmography, including residual volume (RV), inspiratory capacity (IC), functional residual capacity (FRC), TLC, and the ratios of RV/TLC and IC/TLC
- SGRQ global and domain (ie. 'symptoms', 'activity' and 'impacts on daily life') scores
- Modified Medical Research Council (mMRC) Dyspnea Scale Score
- BODE Index
- Transitional Dyspnea Index (TDI) from Baseline Dyspnea Index (BDI)
- COPD Assessment Test (CAT)
- SF-36 Health Survey score
- EQ-5D Health Survey score
- Health Care Utilization Questionnaire
- 6MWD test
- Borg scale dyspnea scores before and after 6MWD test
- Change in use of 'maintenance' medications, including bronchodilators, corticosteroids, antibiotics, and anti-inflammatories
- Pulmonary rehabilitation compliance diary responses
- EXACT-PRO diary responses
- Health status change responses
- Carbon Monoxide Diffusing Capacity (DL_{CO})
- Lung radiographic features

Interim Analysis

An interim data analysis designed to evaluate effectiveness for continuing crossover of control arm study participants at 1 year to EBV treatment will be performed when 74 (50% of the total 147) study participants have completed the 1 year follow-up. The interim analysis will be

reviewed by the DSMB and FDA. If crossover of control arm study participants is found to be justified by the interim analysis, then crossover of control arm study participants may be continued. If the DSMB recommends not continuing crossing control arm participants to EBV treatment, then those control arm patients who have not yet crossed over will exit from the study per protocol after the 1-year visit.

Long-Term Follow-up

Data will be collected annually through 5 years. Per the regulatory plan agreed to with FDA, 1 year of follow-up is required pre-approval and the remaining 4 years will be conducted post-approval. The 2-, 3-, 4-, and 5-year data will consist of FEV₁ and adverse events.

Definition of Study Success: The study will be a success if the difference between the EBV Treatment arm and Control arm for the percentage of study participants meeting the threshold of $\geq 15\%$ improved in FEV₁ differs significantly (two-sided test at $p \leq 0.05$) in favor of the treatment group at 1 year. This evaluation will be conducted at 1-year post-randomization.

Number of Study Participants: 183

Statistical Methods

I. Descriptive Statistics

Means, standard deviations, medians, and confidence intervals will be reported for all continuous variables. Dichotomous variables will be reported as percentages and the numerator and denominator will be reported and defined. The frequency of adverse events will be reported as percentage rates with computed 95% two-sided exact confidence intervals (upper and lower).

II. Analyses of the Patient Populations

These analyses are intended to determine the similarity of two treatment groups and similarity of patients from different study sites with respect to important demographic or other variables, either known or suspected to have an influence on the outcome variables. The absence of similarity for any variable will identify that variable as a potential covariate in subsequent analyses.

- A. **Comparability of Treatment Groups** – To assess the success of the randomization process, the demographic and prognostic variables measured at study entry will be compared between the Treatment and Control arms. Continuous variables will be compared with the two-sample t-test or the Wilcoxon two-sample rank test, and categorical variables will be compared with the Fisher's exact test or a Chi-square test. Comparability analyses will be done with two-sided tests with significance level of 0.05.
- B. **Study Site Comparability** –The appropriateness of pooling the data across study sites will be determined on a clinical basis, i.e., to ascertain if the sites used a common protocol, the sponsor adequately monitored the study to assure protocol compliance, and the data gathering and validation mechanisms were the same across all study sites (Meinert, 1986).

An analysis will be done to determine if the magnitude of the clinical effect of the primary outcome is maintained if sites and/or site by treatment interactions are included in an analysis of covariance model. We expect the majority of sites will show the treatment to be beneficial but statistically one would not expect all sites to show the treatment to be beneficial. For those sites with contrary results, an analysis will be attempted to determine what factors at those sites led to the result (See expert statistical testimony from Dispute Resolution Panel transcript September 6, 2001).

- C. In study sites with small numbers of patients, it will not be possible to evaluate site or site by treatment interaction. The reason is that what may appear to be a site by treatment interaction may be a small numbers phenomenon. For example, if there were only three patients from a given study site with one in the control group and two in the treated group, one success in each arm will appear to be a site by treatment interaction (100% success in the controls but 50% success in the treated arm). Hence, study sites with fewer than three patients in either treatment arm will be combined into one or more pseudo-sites to allow the comparison to be done. The size of any pseudo-site created in this way will not exceed the size of the study site with the largest enrollment.

III. Analyses Populations

- A. Geographic Cohort: This study will be conducted at clinical sites inside and outside the U.S.
- B. Endpoint Analyses: Primary and secondary study endpoints will be analyzed utilizing an intent-to-treat (ITT) population defined as all randomized patients analyzed by the groups to which they were randomly assigned (EBV treatment or control). Consenting patients who qualify for the study and are randomized into the study will be included in the ITT population, regardless of the actual treatment received. Consented patients who are found not to meet the study eligibility criteria prior to randomization will not be included in the intent-to-treat group.
- C. Secondary Analyses: Secondary analyses will also be performed on the study primary and secondary endpoints on a Completed Cases (CC) basis and Per-Protocol (PP) basis. The CC population is defined as all randomized and eligible patients who received study-directed treatment and had 1 year of follow-up. The PP population is defined as all randomized patients who meet study eligibility criteria, who were treated as randomly assigned, and had follow-up for the endpoints. Any visits where protocol violations occurred will be reviewed for possible exclusion from impacted analyses.
- D. Safety Analysis Population: Both the ITT analysis population and ‘As Treated’ (AT) analysis population will be used to assess the safety data. For the AT analysis, study participants will be analyzed based on the treatment they actually received.
- E. Secondary Valve Procedures: If applicable, statistical analyses will also be conducted after sorting patients by the actual treatment received, specifically valve removal, valve replacement, and valve adjustment.

IV. Effectiveness Analyses

There is one primary effectiveness variable, four secondary effectiveness variables, and several additional effectiveness variables.

A. Analysis of the Primary Effectiveness Endpoint

Both an interim and an end of study analysis for the primary effectiveness endpoint are planned. The primary effectiveness endpoint is the difference between the EBV treatment arm and control arm in percentage of study participants who reach a threshold of $\geq 15\%$ improved FEV₁, collected post-bronchodilator, at 1 year (see Table 1). The FEV₁ value will be calculated by determining the percentage change for FEV₁ from baseline to 1-year post-procedure using: $((\text{FEV}_1 \text{ at 1 year follow-up} - \text{FEV}_1 \text{ at baseline}) / \text{FEV}_1 \text{ at baseline})$ for individual study participants. The two arms will be compared using the standard normal Z-statistic.

Table 1. Primary Effectiveness Endpoint

Variable	Unit	Values Statistically Evaluated
Forced Expiratory Volume (FEV ₁)	$\geq 15\%$ improved	percentage of participants

An interim data analysis designed to evaluate effectiveness for continuing crossover of control arm study participants at the 1 year follow-up to EBV treatment will be performed

when 74 (50% of the total 147) study participants have completed the 1 year follow-up. The interim analysis will be reviewed by the DSMB.

To account for the interim analysis, the power spending function, defined as:

$$\alpha(t) = \alpha t^\phi$$

will be used to preserve an overall type I error rate of 0.05 for the study. Using the nTerim program (Statistical Solutions) to calculate the power spending function with:

$$\alpha = .05, \phi = 2.3 \text{ and } t = .5, \alpha(t) = .01,$$

the value of the Z-statistic must exceed 2.571 (nominal alpha <0.01) for the null hypothesis to be rejected at this interim look (see Table 2).

Table 2. Power Spending Function for Interim Analysis

Looks	1	2
Time	0.5	1
Lower Bound	-2.57057	-2.00360
Upper Bound	2.57057	2.00360
Nominal Alpha	0.01015	0.04511
Incremental Alpha	0.01015	0.03985
Cumulative Alpha	0.01015	0.0500
Exit Probability	38.75	50.52
Cumulative Exit Probability	38.75	89.28

If $Z \geq 2.571$ then continuing crossover of control arm study participants will be strongly justified since the p-value will be ≤ 0.01 . This observation may provide evidence to stop the trial early.

The study hypothesis will be tested again at the end of the study. The Z-statistic will be calculated again, and by taking into account the interim analysis, will have a final critical boundary value of 2.004, per the nTerim program. If the trial is not stopped as a result of the interim analysis, then the final Z-statistic must be greater than or equal to 2.004 in order to reject the null hypothesis at the final analysis (at the overall 2-sided 5% significance level). Test statistic is “Z” as defined as:

$$Z = \frac{p_T - p_C}{\sqrt{p(1-p)\left(\frac{1}{n_T} + \frac{1}{n_C}\right)}}$$

Where,

p_T and p_C are the proportions of success for the primary endpoint in the treatment and control groups, respectively, p is the pooled estimate of the success rate, and

n_T and n_C are the sample sizes obtained in the treatment and control groups, respectively. Two sets of (p, p_T, p_C, n_T, n_C) will be obtained: one at the interim analysis and one at end of the study.

B. Analysis of the Secondary Effectiveness Endpoints

a. Treatment Lobe Volume Reduction for the Study Treatment Arm

- i. TLVR measured as the 'absolute change from baseline' in treated lobe volume as seen via HRCT (high resolution computed tomography), will be evaluated at 45 days. TLVR will be calculated for each study participant using: (treatment lobe volume at 45 days follow-up subtracted from the treatment lobe volume at baseline). Descriptive statistics will be calculated for the study treatment arm and will include the mean, standard deviation and 95% confidence interval. A one-sample t-statistic will be used to quantify the magnitude of the difference.
- ii. TLVR measured as the 'percentage change from baseline' in treated lobe volume as seen via HRCT, will be evaluated at 45 days. TLVR will be calculated for each study participant using: (treatment lobe volume at 45 days follow-up subtracted from the treatment lobe volume at baseline divided by treatment lobe volume at baseline). Descriptive statistics will be calculated for the study treatment arm and will include the mean, standard deviation and 95% confidence interval. A one-sample t-statistic will be used to quantify the magnitude of the difference.
- iii. TLVR measured as the 'absolute change from baseline' in treated lobe volume as seen via HRCT (high resolution computed tomography), will be evaluated at 1 year. TLVR will be calculated for each study participant using: (treatment lobe volume at 1 year follow-up subtracted from the treatment lobe volume at baseline). Descriptive statistics will be calculated for the study treatment arm and will include the mean, standard deviation and 95% confidence interval. A one-sample t-statistic will be used to quantify the magnitude of the difference.
- iv. TLVR measured as the 'percentage change from baseline' in treated lobe volume as seen via HRCT, will be evaluated at 1 year. TLVR will be calculated for each study participant using: (treatment lobe volume at 1 year follow-up subtracted from the treatment lobe volume at baseline divided by treatment lobe volume at baseline). Descriptive statistics will be calculated for the study treatment arm and will include the mean, standard deviation and 95% confidence interval. A one-sample t-statistic will be used to quantify the magnitude of the difference.

b. St. George's Respiratory Questionnaire (SGRQ)

- i. Difference between study arms in 'absolute change from baseline' for SGRQ score at 1 year. Descriptive statistics will include means, standard deviations and 95% confidence intervals. A two sample t-statistic will be used to quantify the magnitude of the difference between study groups.
- ii. Difference between study arms in 'percentage change from baseline' for SGRQ score at 1 year. Descriptive statistics will include means, standard deviations and 95% confidence intervals. A two sample t-statistic will be used to quantify the magnitude of the difference between study groups.

- c. FEV₁
 - i. Persistence of the treatment effect will be evaluated by determining the difference between study arms for ‘absolute change from baseline’ for FEV₁ at 45 days, 6 months, and 1 year. The FEV₁ value will be calculated using: ((FEV₁ at each of the follow-up time points) subtracted from (FEV₁ at baseline)) for individual study participants to determine the mean absolute change for each study arm. At each of the three time points, descriptive statistics will include means, standard deviations and 95% confidence intervals. A two-sample t-statistic will be used to quantify the magnitude of the difference between study groups. A repeated-measures model (GEE with an identity link function and exchangeable correlation structure) will be used to model the entire time course of outcomes as a function of baseline value and a main effect indicating treatment group membership.
 - ii. Persistence of the treatment effect will be evaluated by determining the difference between study arms for ‘percentage change from baseline’ for FEV₁ at 45 days, 6 months, and 1 year. The FEV₁ values will be calculated using: ((FEV₁ at each of the follow-up times) subtracted from (FEV₁ at baseline divided by FEV₁ at baseline)) for individual study participants to determine the mean absolute change for each study arm. At each of the three time points, descriptive statistics will include means, standard deviations and 95% confidence intervals. A two-sample t-statistic will be used to quantify the magnitude of the difference between study groups. A repeated-measures model (GEE with an identity link function and exchangeable correlation structure) will be used to model the entire time course of outcomes as a function of baseline value and a main effect indicating treatment group membership.
- d. 6-Minute Walk Distance (6MWD)
 - i. Difference between study arms in ‘absolute change from baseline’ for 6MWD at 1 year. Descriptive statistics will include means, standard deviations and 95% confidence intervals. A two sample t-statistic will be used to quantify the magnitude of the difference between study groups.
 - ii. Difference between study arms in ‘percentage change from baseline’ for 6MWD at 1 year. Descriptive statistics will include means, standard deviations and 95% confidence intervals. A two sample t-statistic will be used to quantify the magnitude of the difference between study groups.
- e. The secondary effectiveness endpoints are summarized in Table 3.

Table 3. Secondary Effectiveness Endpoints

Variable	Unit	Values Statistically Assessed
Target Lobe Volume Reduction (TLVR)	milliliters	mean absolute change
TLVR	percent	mean percent change
SGRQ Global Score	Points	mean absolute change
SGRQ	percent	mean percent change
FEV ₁	Liters	mean absolute change
FEV ₁	percent	mean percent change
6-Minute Walk Distance	Meters	mean absolute change

6MWD	percent	mean percent change
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C. Analysis of Additional Effectiveness Endpoints

a. Supporting Evidence for Effectiveness

The following additional effectiveness endpoints will be measured for both study arms. These are expected to provide supporting evidence of the effectiveness of EBV treatment. Results will be described with summary statistics. These endpoints will be described for each study arm separately and comparatively between arms by calculating mean change or difference in proportions, whichever is appropriate for the variable being analyzed. The definitions for these additional effectiveness endpoints are shown in Table 4.

Table 4. Additional Effectiveness Endpoints

Spirometry Measures		
FEV ₁	≥12% improved	Percentage of participants
Forced Vital Capacity (FVC)	liters	mean absolute and percent change
FEV ₁ /FVC	ratio	mean absolute change
DL _{co}	percentage	mean absolute and percent change
Body Plethysmography Measures		
Residual Volume (RV)	liters	mean absolute and percent change
Inspiratory Capacity (IC)	liters	mean absolute and percent change
Functional Residual Capacity (FRC)		mean absolute and percent change
Total Lung Capacity (TLC)	liters	mean absolute and percent change
RV/TLC	ratio	mean absolute change
IC/TLC	ratio	mean absolute change
Patient-Reported Health Status Measures		
SGRQ Global Score	≥4 points improved	percentage of participants
	≥8 points improved	percentage of participants
SGRQ Domain Scores		
‘Symptoms’	points	mean absolute change
‘Activity’	points	mean absolute change
‘Impacts Daily Life’	points	mean absolute change
mMRC Score	semi-quantitative scale score	mean absolute change
COPD Assessment Test (CAT)	points	mean absolute change
Transitional Dyspnea Index (TDI)	points	mean absolute change
	≤1 point improved	percent of participants
Short Form (SF)-36 Health Survey	points	mean absolute change
EQ-5D Health Survey	points	mean absolute change
Other Measures		
BODE Index	semi-quantitative scale score	mean absolute change

	≤1, 0, ≥1 change	percentage of participants
6MWD – subjects stratified by distance walked at baseline	meters	mean absolute change
	≥25 meters improved	percentage of participants
	≥54 meters improved	percentage of participants
Borg Scale Dyspnea Score: Before 6MWD test	semi-quantitative scale score	mean absolute change
Borg Scale Dyspnea Score: After 6MWD test	semi-quantitative scale score	mean absolute change

b. Informational Purposes:

The following additional effectiveness endpoints will be measured in both treatment groups for informational purposes. Results will be described with summary statistics (see Table 5). These endpoints will be described for each treatment group separately and comparatively between groups by calculating mean change or difference in proportions, whichever is appropriate for the variable being analyzed.

Table 5. Informational Variables

Variable	Unit	Values Statistically Assessed
Maintenance Medications		
Bronchodilators	change in medication regimen	percentage of participants
Corticosteroids	change in medication regimen	percentage of participants
Antibiotics	change in medication regimen	percentage of participants
Anti-Inflammatories	change in medication regimen	percentage of participants
Pulmonary Rehabilitation Compliance Diary	reported adherence to program	percentage of participants
Adherence to program	number of sessions / week	mean absolute number
Intensity of program	length of reported sessions	mean absolute number
EXACT-PRO Diary Entries	points	mean absolute number
Health Utilization Measures	frequency of use	percentage of participants
Lung Radiographic Features		
TLVR	volumetric change	mean percentage change
valve occlusion	qualitative assessment	percentage of participants
inter-lobar fissures	percent complete	percentage of participants

V. Adjustment for Potential Confounders

The covariates shown in Table 6 may be potentially influential with respect to the effectiveness endpoints. If any of these covariates are found to be out of balance between the groups (at the two-sided 0.10 level), they will be included in a multivariate analysis, along with an indicator of treatment group, to evaluate their potential effect on the study conclusions. A multivariate logistic regression model will be used.

Table 6. Covariates

	Baseline	Procedure	Follow-Up
Gender	X		
Age	X		
Clinical Site	X		
6MWD	X		
Patient-reported health status measures (e.g. SGRQ)	X		
Body Mass Index	X		
BODE Index	X		
Medication Use	X		
Residual Volume (RV)	X		
RV % Predicted	X		
Total Lung Capacity (TLC)	X		
TLC % Predicted	X		
RV/TLC	X		
IC/TLC	X		
Vital Capacity	X		
Forced Vital Capacity (FVC)	X		
FVC % Predicted	X		
FEV ₁	X		
FEV ₁ % Predicted	X		
FEV ₁ / FVC	X		
Lobar Volume	X		
Lobar Destruction Scores	X		
Ipsilateral DS Heterogeneity	X		
Severity of emphysema (GOLD classification)	X		
Co-Morbidities	X		
Target Treatment Lobe		X	
Treatment Group		X	
Target Lobe Volume Reduction			X
Lobar Occlusion			X

VI. Secondary Valve Procedures

Secondary valve procedures will be evaluated by examining the proportion of patients who undergo valve removal, valve replacement, or valve adjustment, and describing the reasons they occurred. Data for these study participants will be contrasted to data for study participants who did not receive a secondary valve procedure.

VII. Safety Analyses

Evaluation of the short- and long-term adverse events profile of the EBV treatment arm during the treatment period, defined as the day of the study procedure until 45 days after the study procedure (short), and in the post-treatment period, defined as 46 days after the study procedure until the 1-year follow-up visit (long). Safety analyses will be performed by examining the proportion of patients in the EBV study arm that experiences adverse events. The rates and 95% exact confidence intervals will be presented on an event and on a per-patient basis.

Adverse events will be categorized into clinically relevant groups (e.g.: stable pneumothorax with no intervention, pneumothorax resolved with chest tube insertion in less than 7 days, prolonged air leak, etc.). Adverse events occurring in the treatment arm will be further categorized by severity and as device-related, procedure-related, or neither, and by those occurring during procedure hospitalization and those occurring post-discharge. Rehospitalization rates will be reported by study arm on a Per-Patient (PPt) basis and on a Per-Event (PE) basis. In study participants who receive EBV treatment, adverse events will be evaluated by stratifying participants by use of conscious sedation and general anesthesia during the bronchoscopy procedure as well as evaluating number of valves received and sites EBV were placed.

VIII. Mortality

A Kaplan-Meier survival curve for each study arm will graphically display the time to death from the time of randomization and a log rank test will be used to compare Kaplan-Meier curves between study arms. A Cox proportional hazards model will be used to control for study site along with other significant co-variates as applicable.

IX. Patient Accountability and Missing Data

Every effort will be made to collect all data points in the study. The sponsor plans to minimize the amount of missing data by appropriate management of the prospective clinical trial, proper screening of study subjects, and training of participating investigators, monitors and study coordinators.

The analysis for the primary endpoint will be performed by imputing missing data. For study participant FEV₁ data that is 'intermittent', missing outcomes will be imputed by linear interpolation using the FEV₁ value from the latest non-missing data point before the missed data point and the earliest non-missed data point after the missed data point. For study participants with truncated data (e.g. participants who drop out or are lost to follow-up), a multiple imputation strategy will be performed using the propensity score method. In brief, for a particular outcome, the propensities for study participants to have missing data (for each treatment group separately), modeled by logistic regression, are grouped into strata based on percentiles of the logistic propensity score model. Within a stratum, a study participant with a missing observation has an imputed value assigned by randomly choosing a value from among the study participants in the same stratum with non-missing observations. This procedure will be repeated 20 times on the entire dataset, resulting in 20 different 'complete' datasets allowing for estimation of the effect on the outcome of interest, accounting for missing data.

An additional analysis for the primary endpoint will be performed based on not imputing data. All partial data that is available on subjects who drop out during the course of the study will be included. In addition, sensitivity analyses such as worse-case or best-case imputation will be performed although it is recognized that they are biased.

X. Comparison of Crossed-Over Control versus Study Treatment Outcomes

a. Effectiveness Outcomes

Table 7. Effectiveness Endpoints for Control Arm Crossovers (comparison based on paired Control versus EBV Treatment differences)

Variable	Unit	Values Statistically Evaluated
Forced Expiratory Volume (FEV ₁)	≥15% improved	percentage of participants
FEV ₁	Liters	mean absolute change
FEV ₁	percent	mean percent change
SGRQ Global Score	Points	mean absolute change
mMRC Score	semi-quantitative scale score	mean absolute change
6-Minute Walk Distance	Meters	mean absolute change
6MWD – subjects stratified by distance walked at baseline	meters	mean absolute change
6MWD	≥25 meters improved	percentage of participants
DL _{CO}	percentage	mean absolute and percent change
Residual Volume (RV)	liters	mean absolute and percent change
Inspiratory Capacity (IC)	liters	mean absolute and percent change
Total Lung Capacity (TLC)	liters	mean absolute and percent change
RV/TLC	ratio	mean absolute change
IC/TLC	ratio	mean absolute change

The time-course of outcomes will be described. A paired t-test statistic will be used to quantify the magnitude of the difference between treatment modalities for the quantitative outcomes. For binary outcomes, a McNemar test-statistic will be used to quantify the magnitude of the difference between the two treatment modalities.

b. Safety Outcomes

Evaluation of the short- and long-term adverse events profile of crossed-over participants during the second year of follow-up, when they have the EBV treatment, will be assessed as in Section VII above. Additionally, the time-course of occurrence of Serious Adverse Events (SAEs) will be contrasted and compared for the first year (Control Treatment) versus second year (EBV Treatment) periods. For those SAEs that could occur with either Control or EBV Treatment, a McNemar test-statistic will be used to quantify the magnitude of the difference between the two treatment modalities.

XI. Randomization Assignment Method

Study participants who are determined to meet screening, baseline, and procedure eligibility criteria will be randomly assigned to Study Treatment (EBV or Control). Random assignment will be performed using a stratified permuted block design, generated separately for each clinical site, with assignment stratified by anatomical site of the planned treatment (e.g. right lung or left lung). Mixed block sizes will be used.

XII. Device Malfunction Analyses

Results of any device malfunctions and their sequelae are to be presented descriptively. The rate and exact 95% confidence intervals will be computed.

XIII. Statistical Software

The parametric and non-parametric analysis of variance and other primary analyses will be done using SAS, Version 9.2 or later or StatXact.

References

1. Meinert, C. (1986). *Clinical Trials: Design, Conduct, and Analysis*. Oxford University Press, New York.
2. Medical Devices Dispute Resolution Panel Meeting of September 6, 2001 (Panel Transcript)

Investigator Name: _____

Site ID# _____

Institution: _____

Participant ID: _____

Telephone: _____

Dear Patient:

You are being asked to participate in the treatment portion of the LIBERATE study because you have an impaired lifestyle as a result of emphysema, have successfully completed one year of participation in the control arm of the study and still meet the eligibility requirements. Emphysema is a serious disease that afflicts more than four million people worldwide. It is one form of Chronic Obstructive Pulmonary Disease, or COPD. Emphysema causes the lungs to lose the ability to move air in and out normally and to efficiently absorb oxygen, making breathing more difficult. What you should know about a research study:

- Someone will explain this research study to you.
- You volunteer to be in a research study.
- Whether you take part is up to you.
- You can choose not to take part in the research study.
- You can agree to take part now and later change your mind.
- Whatever you decide, it will not affect your care.
- Feel free to ask all the questions you want before and after you decide.

Purpose of the Study

The purpose of this research is to study a medical device that is designed to be placed by a doctor in a diseased section of the lungs. This device is called the Pulmonx Endobronchial Valve (EBV). The EBV is a one-way valve that blocks off the diseased lung section to inhaled air but lets the trapped air already inside the area escape. With placement of the EBV, the diseased part of the lung collapses; this allows the healthier parts of the lung to expand. The aim of the EBV treatment is to help someone with emphysema breathe more easily by allowing the healthier parts of the lung to work better. This research study is designed to investigate the safety and effectiveness of the Pulmonx EBV for treating emphysema symptoms.

The EBV is considered experimental. This means that it has not yet been approved by the U.S. FDA (Food and Drug Administration) for commercial use in the United States.

Since you have successfully completed the 1-year visit, you may consider crossover to the study treatment. In order to qualify for crossover, you must have been followed up successfully through 1 year and demonstrate lack of a clinically important response.

The crossover procedure must be scheduled to occur within the 60 days after the 1 year visit. After treatment, the follow-up visits and testing at each visit will be identical to the study schedule for treatment arm participants.

Number of Patients in the Cross-over Portion of the Study

About 60 patients are expected to be enrolled in the cross-over portion of the study at all research sites across the country. In order to qualify for enrollment into the cross-over portion of the study, you must undergo a bronchoscopy procedure. During the bronchoscopy procedure, your doctor will use a device that measures airflow in your lungs to find out if you meet the study criteria for having the EBV treatment. There is a chance that after measuring some of airways in your lungs you will not be eligible to take part in this study. During the bronchoscopy procedure, you may be found NOT to qualify for the cross-over portion of the study.

Tests and Evaluations

A number of tests and assessments will be performed. All of these tests will be the same as you had when you initially started participating in the study. The results of the tests and assessments you completed at your 1-year follow-up visit will be used to decide if you qualify for the cross-over portion of the study. In addition, you will have a high resolution CT scan, similar to the one you had when you first decided to join the study. All of the tests are described in detail below. If you qualify, you will have EBV implanted in your lungs. The study doctor will make the final determination of your eligibility during the bronchoscopy procedure. If you are found to be eligible to participate in the cross-over portion of the study, you will receive EBV.

Blood Gas (PaO₂ and PaCO₂) and Blood Chemistry Analysis

A blood sample will be taken to measure the amount of oxygen and carbon dioxide in the sample. This blood sample will need to be taken from an artery (as opposed to a vein). An arterial blood sample may be more painful than a venous blood sample, which is usually done for more routine blood samples. Standard compounds and the number of blood cells will also be measured from the blood sample. You must have stopped smoking for at least 4 months to participate in this study. A blood test will be performed to confirm that you have stopped. It is important that you do not smoke during this study.

Chest X-ray

During this test, a simple X-ray will be made of your chest.

Lung Function Tests

Spirometry: During the test, you will be asked to breathe in and out of a mouthpiece while a machine measures the amount of air you are breathing into and out of your lungs. These breathing maneuvers may be somewhat difficult and you may become tired during the test but you will be allowed to rest periodically.

Plethysmography: This test is used to determine how much air you can hold in your lungs. You will sit in a small box, comparable to the size of a telephone booth, to undergo breathing tests similar to those described above. There is a chance that you may experience claustrophobia in addition to fatigue.

Diffusing Capacity: This test is used to measure the ability of your lungs to transfer carbon monoxide. You will be asked to breathe a mixture of helium, oxygen, nitrogen and carbon monoxide and hold your breath for 10 seconds.

All together these lung function tests will take about 90 minutes.

HRCT (High Resolution Computed Tomography) of Chest

You will be asked to lie down on your back on an x-ray table that will slide into a large, tunnel-shaped machine. You must not move during the test and will be asked to relax and breathe normally. The technician will also ask you to do some breathing maneuvers such as take a deep breath in or out.

Pregnancy Test

If you are a woman of child-bearing potential, a urine or blood pregnancy test may be performed.

Six Minute Walk Test

You will be asked to walk back and forth between a start and end point as many times as possible within 6 minutes. You may stop and rest if needed. Right before and right after the test you will be asked questions about how breathless you feel you are.

Questionnaires

During the study, you will be asked to complete a few simple questionnaires. These questionnaires will ask you about your daily activities and your opinion about your general health status and quality of life. You will also be asked about frequency of visits to health care providers, such as your regular physician, emergent care facilities, and the hospital.

Pulmonary Rehabilitation Program—to be Eligible for the Study

In order to participate in the cross-over portion of the study, you will have to:

- Be regularly performing maintenance respiratory rehabilitation.

Description of the Bronchoscopy Procedure

During the bronchoscopy procedure, your physician will measure some of the airways in your lungs using a device called the Chartis® Pulmonary Assessment System. This system is designed to measure air pressure and flow in lung airways. The air pressure and flow measurements that are collected using the Chartis System will help the physician decide if you are eligible to potentially have the EBV treatment. Your physician will plan the areas that will be measured before the day of the bronchoscopy procedure using the results of your CT scan.

If you are found to have air pressure and flow measurements that show you are **NOT eligible** to receive the EBV treatment, your physician and his or her team will stop the bronchoscopy procedure and you will not receive any further treatment during the bronchoscopy procedure.

If you are found to have air pressure and flow measurements that show you are **eligible** to receive the EBV treatment, you will have the EBV treatment.

In rare instances, fluoroscopy may be used by your study doctor if it is difficult for him/her to see your lung structures and anatomy using the bronchoscope alone. Fluoroscopy is making a moving picture of your lungs with x-rays.

Personnel from the study sponsor (Pulmonx) will attend your bronchoscopy procedure. The doctor's view of the procedure (the inside of your lung) may also be videotaped or photographed.

Description of the Study Procedure

The EBV Procedure

A bronchoscope (a tube with a camera at the tip, connected to a monitor) will be guided down an access tube all the way to the point where the EBV will be placed. Once your physician can clearly see the area where the EBV will be placed, he or she will guide a catheter (flexible tube), with the EBV attached, to the targeted treatment area. Once the catheter is in the proper position, he or she will implant the EBV in the lung. This may be done several times depending upon how many EBV are to be placed in your lungs.

If there is a problem with the EBV at any time during or after the procedure that makes it difficult or inappropriate to continue with the study, your physician may remove the EBV. In some cases, if the EBV is removed, it can be replaced. In rare cases, the EBV may not have been placed in the original procedure as it was intended to be (to completely stop the airflow from the damaged part of the lung). This may initiate a discussion between you and your physician about having another procedure to adjust the placement of the EBV.

After the Bronchoscopy Procedure

After the procedure, you will be taken to a recovery area of the hospital. If you are found to not be eligible for the study, you will be allowed to go home a few hours after the bronchoscopy procedure. If you had EBV placed, it is anticipated that you will remain in the hospital for 5 nights. Before you are discharged your study physician will examine you first and review your chest x-ray to confirm you are not experiencing any complications. Your study physician may keep you in the hospital longer if he/she feels your health needs further monitoring.

If you received the EBV, a chest x-ray will be taken at 1 hour and once each day during your hospitalization including the day you are discharged. You may need to have additional x-rays at any time your study physician thinks it is medically necessary if you are in the hospital longer than 5 days after the study procedure. The nurses in this area are trained to closely watch your recovery and assist you in awakening from the anesthesia. Your vital signs will be monitored, blood samples will be collected and any adverse events will be reviewed during your hospitalization. The medical team will often encourage you to cough in order to help expel the anesthesia and any accumulation of mucus. You may also experience the urge to cough. This coughing sensation is normal and typically goes away.

Before discharge from the hospital, you will be given a study bracelet to wear and a medical alert card to give to any physician that may need to treat you informing him/her of the pneumothorax risk. Additionally, you will be given post-discharge instructions by the study physician that you will be expected to follow.

After Discharge

You will return to your study physician's office 7 days after discharge for an examination, chest X-ray, and to answer questions about your health status. At the 7 Day after Discharge visit, your study physician will examine you and ask you about potential symptoms of pneumothorax and about your use of medications. A chest x-ray will be taken of your lungs at this time. At this visit, the study doctor will

assess you to determine if you may resume your regular activities and start the pulmonary rehabilitation program.

After you are discharged from the hospital, you will be contacted once daily for 10 days to answer questions about your health status.

After Discharge

Pulmonary Rehabilitation after the Bronchoscopy Procedure

Within 30 days after the bronchoscopy procedure, you will be asked to begin a supervised pulmonary rehabilitation program. It will consist of 20 sessions, to be done 2-3 times a week for 7-10 weeks. Each pulmonary rehabilitation session will consist of endurance training and strength training for your upper and lower limbs.

After you have completed the supervised pulmonary rehabilitation program you will be expected to do a home-based maintenance program which will be described to you by your pulmonary rehabilitation specialist. As soon as you are done with the supervised program you will be encouraged to follow this home-based program at least three times a week. For the study, you should continue this program until at least your 1 year post-EBV placement follow-up visit.

Length of the Study and Patient Evaluations

The results of the study will be evaluated after all of the study participants have made the 1-year post-bronchoscopy follow-up visit. You will be expected to continue coming to the research clinic once a year up through 5 years. In this study, you will be evaluated several different times. The following table outlines the tests and assessments, starting at the baseline visit, that will be performed and when they will be performed. Depending on the hospital where you have the procedure, some of these tests are standard for emphysema treatment and some are not.

LIBERATE Study
Clinical Investigational Plan #630-0012-H
Appendix 20. Example Crossover Informed Consent

Table 1: List of Tests/Assessments

Test or Assessment	Baseline Eligibility & Assessment*	Day 0 Index-procedure	Days 1-4 Hospital Stay	Day 5 (or day of Discharge)	Daily phone contact over 10 days*	7 Days after Discharge	30 Days	45 days	3 months	6 months	9 months	1 year	Annual visits (2-5 years)	Early Termination Visit
Vital Signs / Physical Exam	X	X		X		X	X	X	X	X		X		X
Medications & Events Review	X						X	X	X	X	X	X		X
Blood Work	X		X•									X		
Arterial blood gases	X		X•									X		
Pulse oximetry 24 hours after procedure			X											
Spirometry	X							X		X		X	X	X
Body Plethysmography	X							X	X‡			X		
Diffusing Capacity	X							X				X		
Symptom checklist					X	X								
6 minute walk distance test	X							X		X		X		
Quality of life surveys and questionnaires	X							X	X	X	X	X		
Health Care Utilization	X								X	X	X	X		
CT scan	X							X	X‡			X		
Chest x-ray		X	X	X		X	X	X	X‡					
Electrocardiography	X											X		
Pulmonary rehab compliance	X							X	X	X	X	X		
Pulmonary rehabilitation						X+								
Health status change	X		X	X	X			X	X	X	X	X		
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X

+ Pulmonary rehabilitation starts within 30 days after bronchoscopy procedure - must receive PI approval to resume normal activities and the post-bronchoscopy pulmonary rehabilitation program; *all of this testing but the CT scan were obtained at your 1-year follow-up visit as a control; • X• serum fibrinogen and ABG only at day 1 hospital stay, ‡ for study participants who have a study procedure (valve) adjustment, a CT scan, chest x-ray, and body plethysmography will be collected at 3 months post-new procedure.

Summary of Knowledge about Lung Volume Reduction using the EBV

The Pulmonx EBV device and procedure was tested extensively in laboratories and animals prior to clinical testing. The EBV device and procedure are currently used outside of the United States, in some countries in Europe and Asia, as a standard treatment for emphysema patients. The EBV was previously tested in the United States with a large study that included four hundred ninety-two (492) patients from both the United States and Europe. The results of this large (VENT) study are discussed below.

The Endobronchial Valve for Emphysema Palliation Trial (VENT study) was a multi-center, prospective, randomized, controlled study conducted in the United States and Europe to evaluate safety and effectiveness of endobronchial valve treatment (along with optimal medical management) compared to optimal medical management alone (control group). In the U.S. study, the endobronchial valve treatment was found to improve forced expiratory volume in one second (FEV₁) by an average value of 6.8% and the 6 minute walk distance test results by an average value of 5.8%. These results were significantly better than the results seen with medical management alone. The European patients had similar results.

After the VENT study was finished, the data was further analyzed. We found that patients who showed signs that the airflow in some parts of their lungs could be blocked off, had the best results with the EBV and procedure. For the study you are considering taking part in, we are planning to select patients who show these same signs BEFORE they have the study treatment. This will be done using the Chartis System during the bronchoscopy procedure. At the end of the study, we will then compare the results of the EBV treatment to the control treatment.

In the VENT study, some adverse events were seen. The type of major adverse events and the percentage of patients who had them are shown below:

Table 2. Adverse events that were seen through 90 days in the EBV Treatment Group in VENT Study

Event	% of Patients
COPD exacerbation (without hospitalization)	7.9%
COPD exacerbation (with hospitalization)	1.4%
Hemoptysis (coughing up any amount of blood)	5.6%
Massive Hemoptysis (coughing up a large amount of blood)	0.5%
Valve expectoration, aspiration, migration (valve moved from the place it was put by the physician)	4.7%
Pneumonia	2.3%
Pneumonia (distal, or behind, the valve)	0.9%
Formation of bronchial granulation (scab-like) tissue with valve	2.3%
Pulmonary infection (infection in the lung)	1.9%
Respiratory failure (poor lung function--too much carbon dioxide or too little oxygen in your blood--where you need to have assistance with breathing using a mechanical ventilator)	1.4%
Pneumothorax (air leak in the lung) that required treatment for more than 7 days	1.4%

Pneumothorax (air leak in the lung) that expanded, or got larger	1.4%
Pneumothorax (air leak in the lung) that was stable, or stayed the same size	1.4%
Hypoxemia (decreased oxygen in the blood)	1.4%
Hypercapnia (excess carbon dioxide in the blood)	0.9%
Death	0.9%
Noncardiac chest pain	0.5%
Bronchial (airway) trauma	0.5%

Removal of the EBV in the VENT Study

In some instances, patients enrolled in the valve treatment study group who experienced an adverse event required that the valves be removed. In the U.S. VENT study, 31 (14.5%) patients had valve(s) removed after the procedure. The reasons for removal included: valve migration, pneumonia, bleeding (hemoptysis), granulation, increased dyspnea (breathlessness), continuing COPD exacerbations, and patient request.

Alternative Treatments for Emphysema

Oxygen, drug therapy, nutrition and lifestyle changes are the standard therapies for patients with emphysema. An additional alternative treatment may be Lung Volume Reduction Surgery (LVRS).

Summary of Benefits and Risks of Participation in the LIBERATE Study

As the EBV is still an investigational device in the United States, the actual benefits and risks are unknown at this time. The investigators may learn from this study whether the EBV treatment and procedure is safe and effective. There may or may not be direct benefit from your participation in this study.

Potential Benefits

Potential benefits you may experience as a participant in the cross-over portion of the study include having improved lung function and other improvements that may be associated with improved lung function, such as improved quality of life.

Potential Risks

The primary risks associated with use of the Pulmonx EBV are similar to other bronchoscopic and surgical procedures used to treat emphysema. These are listed below. While this list is comprehensive, there may be other risks that are still unknown. The close monitoring that you will receive, as part of the study, should allow for detection of symptoms, should they be present. This, in turn, should allow for early intervention by your physician if that is necessary. Your physician will review all of the risks below with you so that you understand them.

Previous clinical trial experience and experience from other countries around the world, where the EBV device is commercially available, has shown that in some people EBV treatment is associated with having a pneumothorax as a potential complication. A pneumothorax is a condition in which air leaks from the lung into the space between the lung and chest wall. This prevents the healthy lung from working well and can cause chest pain and shortness of breath. As many as 1 in 3 patients may

experience a pneumothorax after the study procedure. Most of these tend to occur in the early period following the valve placement and usually resolve after staying in hospital for a few days. Most frequently, a treatment using a small tube to drain out the air is required. In rare cases, a pneumothorax may require a surgical intervention. In addition, there is a chance that it can be a serious and life-threatening complication.

Specifically in this study, the observed rate of pneumothorax events for patients treated with valves to date (16 June 2017) is 58 events out of 159 patients (36%). Forty-six (46) of the 58 pneumothorax events (79%) occurred during the first 5 days following the procedure while the patient was still under supervision within the hospital.

In addition, the observed rate of death in the first year for patients treated with valves in the LIBERATE Study is 5 events out of 128 patients (3.9%). In 2 cases, the patient had a “Do Not Resuscitate” (DNR) directive in place that prevented potential life-saving interventions by the physicians.

Based on new information gained from this study so far, if the valve is not placed in the most diseased area of your lung, there is a higher risk that you could experience a pneumothorax that may require surgical intervention or that could be serious and life threatening. Your physician will discuss with you the area of the lung that will be treated so that you can understand whether you are at a higher risk of experiencing such an event.

Potential Risks (Adverse Events)

Acute bronchitis (inflammation or infection of the airways)
Acute bronchospasm (spasm of the airway; may result in wheezing or increased shortness of breath)
Acute respiratory distress syndrome (sudden, severe injury to lungs)
Airway blockage due to implant migration
Airway perforation (hole in the airway wall)
Airway stenosis (narrowing)
Anxiety
Aphonia (difficulty talking)
Aspiration (inhalation of vomit)
Bowel function impairment
Bronchial (airway) trauma or ulceration
Chest pain
COPD exacerbation (acute worsening of COPD symptoms)
Death
Depression
Deep Vein Thromboembolism (DVT, blood clot)
Dysphonia (hoarse or rough sounding voice)
Empyema (presence of pus)
Fever
Formation of bronchial granulation (scab-like) tissue near the valve(s)
Fractured Rib
Headache
Heart arrhythmias (irregular heartbeats)

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Appendix 20. Example Crossover Informed Consent

Heart Attack
Heart failure (heart function is impaired; could result in increased breathlessness or fluid retention)
Hemoptysis (coughing up blood)
Hemothorax (accumulation of blood between the lungs and the chest wall)
Iatrogenic injuries (injury caused by medical procedure)
Impaired lung function
Increased cough
Increased dyspnea (shortness of breath)
Increased hypercapnea (excess carbon dioxide in the blood)
Increased hypoxemia (decreased oxygen in the blood)
Infection
Laryngospasm (throat spasm)
Lethargy and disorientation
Lung cancer or lung mass
Nausea
Pleural effusion (collection of fluid around the lungs)
Pleuritis (inflammation of chest lining)
Pneumonia
Pneumothorax (air leak in the lung)
Pulmonary shunting (uneven blood flow through the lung)
Pulmonary embolism (a blood clot in the lung which can lead to chest pain and shortness of breath)
Respiratory failure (poor lung function; could require you to have assistance with breathing using a mechanical ventilator)
Septicemia (severe infection)
Stroke or Transient Ischemic Attack (sudden temporary loss of neurological function)
Valve expectoration, aspiration, or migration (valve moves from the place it was put by your physician)
Vomiting
Wheeze or whistling of valve

Other Potential Risks of Procedures that are Required by this Study

Lung function and exercise tests: You will be exerting yourself to your limits in these tests. Lightheadedness, dizziness, fainting, chest pain, irregular heartbeats, and rarely death have been seen during exercise tests. You should inform the technicians or physicians if performing these tests makes you feel abnormal.

Vein or artery blood tests: The risks of drawing blood include temporary pain and discomfort and/or tenderness from the needle stick, redness, or bruising at the site, bleeding, fainting, and lightheadedness. While rare, there is a possibility of infection or a local blood clot with any procedure in which the skin is pierced by a needle.

Radiation: This study involves a radiation exposure from the CT scans and chest x-rays that is typical of other diagnostic tests using ionizing radiation. The amount of radiation exposure received in this study is below the levels that are thought to result in a significant risk of harmful effects. If you are especially concerned with radiation exposure, you should discuss this with your study doctor.

Antibiotics: Antibiotics will be provided to you around the time of the procedure and afterwards to minimize possible side effects. All pharmaceutical drugs have side effects. Antibiotics may also have side effects, including diarrhea, allergic reactions, and overgrowth of dangerous bacteria such as *C. difficile* which can result in a serious infection. However, antibiotics are used routinely to treat COPD exacerbations.

Anesthesia: The side effects of moderate procedural sedation or general anesthesia medications and other medications required to perform bronchoscopy include, but are not limited to, allergic reaction, drowsiness, slurred speech, tremor, fatigue, low blood pressure, slowing of the heart rate, anxiety, confusion, dizziness, temporary loss of consciousness, and respiratory depression. Trained medical professionals with extensive experience and expertise will administer the medications and will be responsible for your care during the course of the procedure.

Voluntary Participation and Study Withdrawal

Decisions regarding whether or not you should participate in this study are entirely voluntary. If you decide not to participate, you will not lose any benefits to which you are entitled, nor will you be denied access to other available treatments for emphysema. You will receive the standard treatment and care normally provided by your physician.

Information obtained in the operating room after anesthesia is given to you will affect whether or not you are eligible to receive treatment during the bronchoscopy procedure. This will happen, for instance, if it is determined that the air pressure and flow measured in the airways in your lungs make you ineligible to meet the study entry criteria or that the anatomy of your lung passageways does not allow the physician to place the EBV Implant. In such an event, you will be sent to the recovery room without the valve treatment.

Significant new findings discovered during the course of this study, which may affect your willingness to continue participating in the study, will be provided to you in writing. You may withdraw your consent to participate in this study at any time **without penalty or loss of benefits**. Also, your

physician may terminate your participation if continuing participation does not appear to be in your best medical interest, or if Pulmonx, the study Sponsor, terminates the study.

Precautions

Within 30 days before and 30 days after participating in this study, you should not take part in any other research project. This is to protect you from possible injury arising from excessive blood drawing, excess x-rays, and interactions with other research devices or drugs, or similar hazards.

Pregnancy and Contraception (Birth Control)

Pregnant women may not participate in this research study as the risk of the procedure on an embryo or unborn fetus is unknown. Women of childbearing potential must actively utilize appropriate means of birth control to avoid becoming pregnant throughout the course of the study.

Confidentiality

Information derived from this study and from your medical record may be reviewed and photocopied by the Food and Drug Administration (FDA) and/or state and federal regulatory agencies and by the device manufacturer, Pulmonx Inc., with protection of confidentiality so far as permitted by applicable law. Information resulting from this study and from your medical record may be used for research purposes and may be published; however, you will not be identified by name in such publications.

Financial Responsibility

The costs of any routine medical care administered during the study will be the responsibility of you and/or your health insurer. For such routine costs, you will be responsible for any co-payments or deductibles required under your insurance. You are not, however, expected to absorb the cost of any medical care specifically required by participation in this study. The study Sponsor (Pulmonx) will pay for tests and procedures performed solely for the purpose of this study.

Research Related Injury

In the event that you believe participation in this research study has led to injury, contact your physician and he will review the matter with you. You should understand that neither _____ (hospital) nor the Federal Government has any programs to provide compensation for persons participating in research projects who may experience injury. However, necessary facilities, emergency treatment and professional services will be available to you. You should not expect any one to pay you for pain, worry, lost income, or non-medical care costs that occur from taking part in this research study. No funds have been set aside by _____ (hospital) to pay you in case of injury, nor will the study Sponsor provide direct compensation to patients in the event of an injury.

Study Information at www.clinicaltrials.gov

A description of this clinical trial will be available on the <http://www.clinicaltrials.gov>, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Add Financial Compensation Section as Applicable

This section is site specific – include financial compensation information as needed.

Questions

If you have any questions about the study, its procedures, risks or benefits, your alternatives or your rights, or if you experience a potentially research related injury you should contact your doctor. If you cannot reach your doctor, contact the alternate individual listed below.

<u>Physician Contact Information (24 hour):</u>	<u>Alternate Contact Information (24 hour):</u>
Name: _____	Name: _____
Phone Number: _____	Phone Number: _____

Authorization to Use and Disclose Health Information

I agree to permit _____ (physician) and his/her staff (“Researchers”) to use and disclose health information that identifies me for the purposes described below. I also agree to permit _____ (hospital), my doctors, and my other health care providers to disclose health information in my medical records to the Researchers for the purposes described below.

1. The health information that may be used and disclosed includes all information collected during the research described in this document and health information in my medical records that is relevant to the research described.
2. The researchers and Pulmonx may use and share my health information to conduct research; disclose my health information to Pulmonx to confirm the research results; disclose my health information as required by law to representatives of government agencies and other persons who are required to watch over the safety, effectiveness and the conduct of the research; and remove from my health information my name and other information that could be used to identify me.
3. Once information that could be used to identify me has been removed, the information that remains is no longer subject to this authorization and may be used and disclosed by the researchers and Pulmonx as permitted by law including for other research purposes.
4. Once my health information has been disclosed to a third party, federal privacy laws may no longer protect it from further disclosure. However, the researchers and Pulmonx agree to protect my health information by using and disclosing it only as permitted by me in this Authorization. Also, no publication about the research will reveal my identity without my specific written permission. These limitations continue even if I revoke this Authorization.
5. Please note that you do not have to sign this authorization, but if you do not, you may not be allowed to participate in this research study. You may change your mind and revoke this authorization at any time. However, if you revoke this authorization, you may no longer be allowed to participate in this research study. Also, even if you revoke this authorization, the information already obtained may remain part of the research. To revoke this authorization, you must write to:

While the research is in progress, you will not be allowed to see your health information that is created or collected in the course of the research. After the research is finished, however, you may see this information as described in (hospital) Notice of Information practices.

6. This authorization does not have an expiration date.

Informed Consent

I, _____, the undersigned hereby consent to my involvement in the research project titled: **Lung Function Improvement after Bronchoscopic Lung Volume Reduction with Pulmonx Endobronchial Valves used in Emphysema.**

- 1) The nature, purpose, and contemplated effects of the project, so far as it affects me, have been fully explained to my satisfaction by the research worker. My consent is informed and given voluntarily.
- 2) The details of the procedure proposed have also been explained to me.
- 3) It has been explained to me that the purpose of this research project is to improve the quality of medical care, and that my involvement may not be of any benefit to me.
- 4) I have been given the opportunity to have a member of my family or a friend present while the project is explained to me.
- 5) I am informed that no information regarding my medical history will be divulged, other than that described in the consent form, and that my identity will be kept confidential in all published results of the study.
- 6) I have been informed that my involvement in the project will not affect my relationship with my medical advisors in their management of my health. I have also been told that I am free to withdraw from the project at any stage without prejudice for future treatment at this hospital, and if I so choose, I can ask for any information collected up to that point to be withheld from use in the research.
- 7) I declare that all of my questions have been answered to my satisfaction.

If I agree to participate in the research study and if my questions are answered, I should sign this form. If I wish to refuse to participate in the study, I may do so without any loss of medical care or benefits. Once I have consented, I still have the right to withdraw at any time. To withdraw, all I have to do is complete the Revocation of Consent portion of the form below and provide to or simply tell Dr.

_____.

I will be given a copy of this form to keep and to refer to as needed.

Printed Name of Participant (or legal representative): _____

Signature: _____

Date: _____

I declare that I have been present when the research study was explained to the above participant and I believe that the participant has an application and understanding of the explanation given.

Witness: _____

Date: _____

REVOCAION OF CONSENT

I hereby wish to **WITHDRAW** my consent to participate in the research proposal described above.
Withdrawal WILL NOT jeopardize any treatment or my relationship with _____
Hospital.

Printed Name of Participant (or legal representative): _____

Signature: _____

Date: _____