Endobronchial Valve for Emphysema Palliation Trial (VENT) Investigational Plan / Study Protocol

PROTOCOL NUMBER: 630-0001 - J

Study Sponsor:

Emphasys Medical, Inc.
700 Chesapeake Dr.
Redwood City, California, 94063
U.S.A

Study Sponsor Contacts:

Jennifer Hebert
Director, Clinical Affairs
Phone: 650.364.0400 x 125
Fax: 650.364.0403
jhebert@emphasysmedical.com

Todd Cornell
Area Director
650.364.0400 Ext. 151 VM
770.363.7053 Cell
678.366.0113 Fax
tcornell@emphasysmedical.com

CONFIDENTIAL – The contents of this document are proprietary and confidential. This protocol contains valuable engineering, clinical and commercial information which must not be disclosed to potential competitors. Duplication and distribution of this document requires prior approval from Emphasys Medical.

VENT Protocol Summary

Title:	Emphasys Medical, Inc. Endobronchial Valve for Emphysema Palliation Trial (VENT)
VENT Study Primary Investigator:	Frank Sciurba, M.D. University of Pittsburgh Medical Center, Pittsburgh, PA
Study Design:	A multi-center, randomized, prospective, clinical trial designed to study the safety and efficacy of the Emphasys Endobronchial Valve (EBV) and procedure.
Purpose:	The purpose of this study is to assess the safety and efficacy of the Emphasys Endobronchial Valve (EBV) and procedure (with pulmonary rehabilitation) compared to optimal medical management (with pulmonary rehabilitation) in patients with heterogeneous emphysema.
Sample Size:	Up to 270 patients (maximum of 50 patients per center)
Allocation Ratio:	2:1 Treatment: Control Allocation Ratio
Analysis Plan:	Intention-to-treat
Target Enrollment Period	September 2003 – June 2005
Number of Sites:	Not to exceed 40 Centers
Patient Population:	Patients with heterogeneous emphysema as defined in the inclusion/exclusion criteria and radiological inclusion criteria.
Primary Efficacy Endpoint:	Change in FEV_1 AND 6MWT in the treatment group as compared to control group at 180 days post procedure.
Primary Safety Endpoint:	Major Complications Composite at 180 days post procedure.
Secondary Endpoints:	Mean change in RV, $DL_{CO,}$ QOL (as measured by St. George's Respiratory Questionnaire and Quality of Well Being Scale), BODE index[1], maximal work load as measured by cycle ergometry and an assessment of room oxygen requirement. Per-patient success rate of clinically significant improvement/maintenance in FEV_1 and in 6MWT. Per-patient failure rate of clinically significant decline in FEV_1 and in 6MWT. Procedure and technical success rate (EBV only). Complications, device-related Adverse Events during procedure, re-hospitalization, and device-related Adverse Events post discharge.

Table of Contents

1.0 Introduction 6
1.1 Background 6
1.2 Summary Device Description 6
1.3 Anatomical Response and Clinical Hypothesis 6

2.0 Study Objectives 7
2.1 Primary Objective 7
2.2 Secondary Objectives 8

3.0 Intended Use 8

4.0 Study Device / Technology Description 8
4.1 Endobronchial Valve 8
4.2 Delivery Catheter 8

5.0 Basis and Justification for the Clinical Investigation 9
5.1 Potential Benefits 9
5.2 Potential Risks 9
5.3 Clinical Observations 11
5.4 Risk Minimization 11

6.0 Study Design 12
6.1 Primary Analysis Population 12
6.2 Secondary Analysis Population 12
6.3 Crossover 13
6.4 Training 13
6.5 Patient Recruitment 14
6.6 Patient Selection 15
6.7 Screening Procedures 17

7.0 Description of Treatments 21
7.1 Optimal Medical Therapy 21
7.2 Education 22
7.3 Pharmacological Treatment 22
7.4 Non-Pharmacological Treatment 22
7.5 Randomization 24
7.6 Standard Tests and Procedures 25
7.7 Enrollment to the Control Arm 27
7.8 Enrollment to the Treatment Arm (Emphasys Endobronchial Valve) 28
7.9 Post-procedure 31
7.10 Valve Removal 32
7.11 Follow-up Procedures 33
7.12 Spirometry, Body Plethysmography, Diffusing Capacity Testing 33
7.13 Six-Minute Walk Testing 34
7.14 Quality of Life Measurement 34
7.15 Cycle Ergometry 35
7.16 Room Oxygen Assessment 35

8.0 Data Analysis overview 36
8.1 Primary Effectiveness Endpoints 36
8.2 Secondary Effectiveness Endpoints 36
8.3 Primary Safety Endpoint 37
8.4 Secondary Safety Endpoints 37

8.5 Overall Definition of Success 38
8.6 Statistical Analysis Plan 38
8.7 Statistical Significance 38
8.8 Subset Analysis 38
8.9 Interim Analysis 38

9.0 Statistical Justification 38
9.1 Historical Data 38
9.2 Sample Size Rationale 39

10.0 Study Data Reporting and Processing 39
10.1 Study Data Collection 39
10.2 Site Data Monitoring and Quality Control 40
10.3 Data Processing and Quality Control 41
10.4 Confidentiality and Protection of Study Files 42

11.0 Study Management 42
11.1 Operations Committee 42
11.2 Data and Safety Monitoring Board 43
11.3 Clinical Events Committee 43
11.4 Core Radiology Lab 43
11.5 Investigator Access to the Data and Publication Policies 43

12.0 Adverse Event Reporting 44
12.1 Duration of Follow-up after Adverse Events 44
12.2 Device Failures and Malfunctions 44

13.0 Regulatory Responsibilities 45
13.1 Investigator Responsibilities 45
13.2 Sponsor Responsibilities 47
13.3 Training 47
13.4 Sponsor Monitoring on Site 47
13.5 Other Institutions 48

14.0 Glossary of Terms 49

References 51

Tables

Table 1: Major Complications 9
Table 2: Complications 10
Table 3: Clinical Observations....11
Table 4: VENT Inclusion Criteria 15
Table 5: VENT Exclusion Criteria 16
Table 6: Emphysema Scores....19
Table 7: Example Emphysema Score 19
Table 8: Heterogeneity Score and Destruction Score 20
Table 9: Eligible Emphysema Score Combinations for Upper and Lower Lobes....21
Table 10: Follow-up Visits, Tests and Procedures....26
Table 11: Ranges for Scheduling Follow-up Visits 27
Table 12: Summary of Procedure Medications (or equivalent) 28
Table 13: Segmental Bronchial Targets for Lobar Exclusion....30
Table 14: Schedule for Case Report Form and Test Report Submission 40
Table 15: Reports Required from Clinical Investigators 46

Figures

Figure 1: Patient Selection Process 17
Figure 2: Follow-up and Balanced Patient/Physician Contacts between Arms 27
Figure 3: Targeting Algorithm for Lobar Exclusion....30
Figure 4: Patient Flow for Atelectasis 32
Figure 5: Technical, Procedural, and Clinical Success Criteria 37

Appendix A ***Draft* Instructions for Use**
Appendix B **Event Reporting Key**
Appendix C ***Example* Informed Consent**
Appendix D **Patient Diary**
Appendix E ***Example* Medical Alert Card**
Appendix F ***Draft* Case Report Form**
Appendix G **Cost Effectiveness Sub-study Protocol Summary**
Appendix H **Statistical Analysis Plan**

1.0 INTRODUCTION

1.1 Background

Emphysema, caused primarily by smoking, is characterized by the gradual, irreversible breakdown of tissue and loss of elastic recoil within the lungs, causing them to lose the ability to expel air and efficiently absorb oxygen. As this chronic condition inexorably progresses, the diseased, hyperinflated areas of the lung eventually fill the chest cavity, leaving less and less volume available for the viable lung tissue.

Lung volume reduction surgery (LVRS) has been shown to offer relief to patients suffering from emphysema when other treatment options fail.[2,3,4,5,6] Researchers have continued to refine both technique and patient selection in order to improve outcomes.[7,8,9] The objective of lung volume reduction is to eliminate dysfunctional, over-inflated regions of lung[10]. Results similar to surgical removal have been obtained by plication (folding) and stapling without tissue removal.[11,12,13,14] These results suggest that isolation of the dysfunctional lung region can achieve similar results to tissue removal.

The National Emphysema Treatment Trial (NETT) results comparing LVRS to optimal medical management were recently published in the New England Journal of Medicine.[15] This study, jointly sponsored by the NIH and NHLBI, randomized 1,218 patients with advanced emphysema comparing LVRS with medical therapy. In NETT, patients with bilateral, predominantly upper-lobe disease and low exercise capacity showed improved 2-year survival with LVRS vs. medical therapy. This important finding validates earlier reports that patients with advanced heterogeneous emphysema may benefit from LVRS.

The paradoxical effect of improving lung function by removing (or isolating) lung tissue demonstrates that breathlessness due to emphysema is a function of mechanical inefficiencies in addition to loss of gas-transfer surface area and other physiological mechanisms. At least in some patients, the mechanical compromise is the primary cause of their pulmonary incapacitation and these patients can benefit by addressing their inability to effectively inhale and exhale. Because LVRS reduces trapped gas, others have speculated that results similar to LVRS could be achieved bronchoscopically by reducing the volume of the hyperinflated regions with, or without, atelectasis.

1.2 Summary Device Description

Emphasys has developed a bronchoscopic approach to block the inspiratory airflow into targeted, hyperinflated regions of the lung, while permitting exhaled gas to escape. Emphasys Medical theorized that if a one-way valve was utilized to block inspiratory airflow, there would be a vent for collateral airflow and mucus. This approach may provide some of the clinical benefits of LVRS without the high risks and costs associated with such an invasive surgical procedure.

1.3 Anatomical Response and Clinical Hypothesis

When an endobronchial valve is placed in a bronchial lumen and is performing as intended (air restricted from going through or around valve during inspiration, gas allowed to vent during expiration) there are two potential anatomical responses depending on the existing pathology and anatomy.[16]

1.3.1 Atelectasis

In the first scenario, if the valved lobe is effectively a closed system (*i.e.:* little or no collateral ventilation from adjacent areas), the isolated lung region is expected to collapse over multiple respiratory cycles. In addition to the gas venting through the valve, there will be some rate of gas absorption[17]. As this targeted area collapses, a localized pneumothorax[18] may be observed radiologically surrounding the atelectatic region. Compressed areas of non-emphysematous lung may be observed expanding as the blocked, previously hyperinflated areas collapse. This is evidence that obstructive atelectasis is occurring.

When hyperinflated, emphysematous lung is isolated via endobronchial valves, collapse of these areas should result in improved lung mechanics via the same mechanisms that drive improvement via LVRS.[19,20,21,22] This should lead to better overall lung function (FEV_1, DL_{CO}, FVC), improved quality of life and increased exercise capacity.

1.3.2 Reduced Dead-Space Ventilation and Reduced Dynamic Hyperinflation

The second scenario in which endobronchial valves improve lung function is in the case where atelectasis does not occur. The one-way endobronchial valve blocks inspiratory ventilation to poorly perfused emphysematous lung, thereby enhancing ventilation to better perfused areas of non-emphysematous lung and improving ventilation/perfusion (V/Q) matching.[23]

The patients may also benefit from the mitigation of dynamic hyperinflation.[24] During exercise when the metabolic demands of the patient increase, some patients may be subjected to increased dyspnea due to the higher compliance of the emphysematous region relative to the rest of the lung. As the patient's tidal volume increases, the poorly ventilated, poorly perfused, diseased area preferentially hyperinflates, resulting in diminished expansion capability of the healthier, less compliant lung. Again, by blocking inspiratory ventilation to diseased areas, the valve would limit dynamic hyperinflation.

In these cases, the patient may benefit from functional improvement including increased IC, FEV_1 and FVC, decreased RV and TLC, and increased diffusing capacity, QOL, and exercise capacity without obtaining atelectasis.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the safety and efficacy of the Emphasys Endobronchial Valve (EBV) and procedure (with pulmonary rehabilitation) compared to optimal medical management (with pulmonary rehabilitation) in patients with heterogeneous emphysema.

2.2 Secondary Objectives

Other objectives are to identify patient characteristics that may affect the outcome of the EBV procedure and to shed further light on the mechanisms of improvement with the EBV procedure. In light of the NETT results showing that exercise tolerance and disease distribution are covariate predictors of outcomes with LVRS, VENT will stratify in a similar fashion to evaluate this relationship in the context of EBV.

3.0 INTENDED USE

The Emphasys Endobronchial Valve (EBV) is an implantable bronchial valve intended to improve FEV_1 and 6MWT in patients with heterogeneous emphysema who meet the eligibility criteria.

4.0 STUDY DEVICE / TECHNOLOGY DESCRIPTION

The Emphasys Endobronchial Valve (EBV) is a device that incorporates a one-way valve that is implanted in a bronchial lumen. The one-way valve is supported by a stent-like self-expanding retainer that secures the implanted EBV in place during all physiological conditions, including coughing. The implanted EBV allows air to be vented from the isolated lung segment while preventing air from refilling the isolated lung area during inhalation.

4.1 Endobronchial Valve

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

4.1.1 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).

4.1.2 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.

4.2 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.

5.0 BASIS AND JUSTIFICATION FOR THE CLINICAL INVESTIGATION

5.1 Potential Benefits

In prior human clinical studies, the placement of Emphasys Endobronchial Valves appears to provide clinical benefits in patients with late-stage emphysema at an acceptably low risk. A definitive, pivotal study is necessary in order to statistically assess whether these clinical benefits are reproducible, significant, and durable.

5.2 Potential Risks

The primary risks associated with use of the Emphasys Endobronchial Valve, as proposed in this study protocol, are similar to other bronchoscopic and surgical procedures. Based on clinical experience to date, these risks are expected to be at an acceptable rate given the potential benefits of improved lung function resulting in improvements in exercise capacity and quality of life.

Adverse Events that are considered anticipated and may occur as a direct result of the treatment or the anesthetic used during the procedure are identified and classified in the following tables.

Major Complication and complication subsets will be reported including device-related (e.g., post-obstructive pneumonia), procedure-related (e.g., failure to wean from ventilator post-procedure), and non-device or procedure related.

5.2.1 Major Complications

Events considered Major Complications are reflected in Table 1.

Table 1: Major Complications

Death, all-cause
Empyema confirmed by at least one of the following: gross puss on inspection of pleural fluid; gram stain; positive culture for bacteria; or pleural fluid ph < 7.1
Massive hemoptysis resulting in respiratory failure or blood loss >300cc in ≤24hr
Pneumonia distal to the implanted valves confirmed by infiltrate on X-ray and clinical syndrome of active infection
Pneumothorax or prolonged air leak > 7 days (measured from time of chest tube insertion to the time that no inducible air leak is present)
Respiratory failure (dependency on mechanical ventilation for >24 hours)

5.2.2 Complications

Adverse Events classified as Complications are presented in Table 2.

Table 2: Complications

Acute respiratory distress syndrome
COPD exacerbation (including increased dyspnea, acute bronchitis, and new persistent cough) requiring hospitalization
Fever of > 101° F (oral) or > 102° F (rectal)
Heart Arrhythmia – newly onset
Heart failure – new diagnosis of heart failure or an increase in NYHA functional classification score status of 1 or more.
New onset or worsening hypercapnea - PaCO2 >45 mmHg and an increase of >10mmHg above baseline
Hypoxemia - increased oxygen requirement (> 24 hour hours post-procedure) to maintain oxygen saturation >90% where increased oxygen requirement is defined as either: a) ≥ 1.5 liter/min increase over baseline if by nasal cannula b) ≥10% increase in FiO2 over baseline if by mask
Iatrogenic injuries
Pleural effusion confirmed by lateral decubitus x-ray
Post-procedure valve removal
Pulmonary embolism - high probability V/Q evidence of segmental or larger perfusion defects or direct anatomic evidence of pulmonary embolism by other means (e.g. CT, echo or other).
Residual volume (RV) increase from baseline ≥ 15%
Sepsis – systemic inflammatory response syndrome (SIRS) with proven microbial etiology established by positive blood culture, where SIRS is defined as patient having two or more of the following conditions: (1) fever (oral temperature >38°C) or hypothermia (<36°C); (2) tachypnea (>24 breaths/min); (3) tachycardia (heart rate >90 beats/min); (4) leukocytosis (>12,000/µL), leukopenia (<4,000/µL), or >10% bands
Expanding Pneumothorax (>30% of hemithorax confirmed by X-ray due to an active air leak.
Transient Ischemic Attack / Cerebral Vascular Accident (Stroke)
Valve expectoration or aspiration
Ventilatory support required < 24 hours (excluding operative use)

5.2.3 Unanticipated Adverse Device Effect

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol and/or IFU or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the patient.

Under the requirements of the FDA's IDE Regulations, an investigator must submit to the sponsor (or its designee) and to the reviewing Institutional Review Board any unanticipated adverse device event occurring during the study as soon as possible,

but in no event later than ten (10) working days after the investigator first learns of the effect.

Investigators will be notified by the sponsor (or its designee) of the occurrence of unanticipated adverse device effects.

5.3 Clinical Observations

In addition to reporting Adverse Events, the physician will be asked to report any observations of note on the appropriate CRF. Events that are self-limiting and require no intervention are reported as observations. Patients may experience secondary effects of bronchoscopy and / or anesthesia (*e.g.,* vomiting, nausea). Secondary effects of bronchoscopy and / or anesthesia are not device-related complications and are commonly recognized as part of the recovery post bronchoscopy. These events will be reported on the appropriate CRF and will be categorized as observations unless they require medical intervention.

Specific examples of observations are reflected in Table 3.

Table 3: Clinical Observations

Acute bronchospasm
Airway stenosis
Anxiety
Aphonia
Bowel function impairment
Bronchial granuloma formation
Bronchial ulceration
Chest pain
Depression
Fever of < 101° F (oral) or < 102° F (rectal)
Headache
Hemoptysis, self-limiting – blood visible in sputum
Lethargy and disorientation
Nausea or vomiting
Pain
Stable Pneumothorax
Wheeze or whistling of valve

Any of these observations that reach an unexpected level of severity, frequency, duration or patient impairment will be classified as complications.

5.4 Risk Minimization

Risks to the patient are minimized due to:

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 experience, baseline safety and efficacy have been established via prior clinical studies,

d) The well established, standard nature of the bronchoscopic procedure and technique (i.e., used in placement of bronchial stents),

e) The ability to safely abort the procedure at any time, the physician may elect to discontinue the use of the Emphasys Endobronchial Valve at any time in favor of alternative medical or surgical procedures, and

f) Reversibility, as the Emphasys Endobronchial Valves may be removed.

6.0 STUDY DESIGN

The Emphasys Endobronchial Valve IDE Trial is a two-arm, randomized, controlled, multi-center trial enrolling a maximum of 270 patients with heterogeneous emphysema, meeting all entry criteria. Randomization will be at a ratio of 2 to 1, (*i.e.,* two patients will be randomized to the study device treatment arm for every one randomized to the control group). In this way a maximum of 180 patients will be treated with the study device and a maximum of 90 will be assigned as controls. The study endpoints will consist of clinical outcomes at 180 days post procedure as evaluated by specific spirometry, body plethysmography, diffusing capacity, QOL and exercise tests. To enable further investigation of the covariate predictors identified in the NETT, patients will be stratified according to lobar exclusion region (upper versus lower) and exercise capacity (low versus non-low).

A critical assessment of valve related safety will be performed at 1-year post procedure.

6.1 Primary Analysis Population

The primary endpoints, and all secondary endpoints, will be analyzed as an intent-to-treat (ITT) population defined as all randomized patients. Consenting patients who qualify for the study and are randomized into the study will be included in the primary analysis population, regardless of the actual treatment received. Patients who withdraw consent prior to enrollment, or who are found not to meet the inclusion/exclusion criteria prior to enrollment, will be recorded on a screening log at each clinical site and will not be included in the intent-to-treat group.

The modified Intent-to-Treat (mITT) population is defined as all randomized patients who received study-directed treatment and had any follow-up. The mITT population will be used for the safety analyses.

6.2 Secondary Analysis Population

Secondary analyses will be performed on a Per-Protocol (PP) basis and Completed Cases (CC) basis.

The PP population is defined as all randomized and eligible patients who received study-directed treatment and had at least three months of follow-up. Any visits where protocol violations occurred will be excluded from all analyses.

The CC population is defined as all randomized and eligible patients who received study-directed treatment and had 6 months of follow-up. Any visits where protocol violations occurred will be excluded from all analyses.

These analyses will evaluate study endpoints sorting patients by the actual treatment received regardless of their randomization assignment (Treatment Received) and by Treatment Received including only patients who were enrolled and treated in compliance with the protocol (Per Protocol).

6.3 Crossover

Crossover between study arms will **NOT** be permitted in this study. Patients in both arms will be allowed to receive other treatments such as LVRS after the 180-day assessment has been completed. Patients will be analyzed as randomized without respect to the nature of subsequent treatment (inclusive of LVRS) in the primary analysis population.

6.4 Training

Prior to enrolling the first patient, the Site Principal Investigator(s) (Site PI) and the Study Coordinator(s) will go through the Emphasys Medical Training Program. This includes instruction on the system, procedure, and protocol.

The PI at each site will be responsible for the supervision of the trial and will provide direction and training to all other research staff (as necessary).

6.4.1 Procedure and Training Videos

All Site PIs participating in the study will watch a procedural "How To" video for technical and procedural aspects of the procedure.

6.4.2 Physician Hands-on Training

All Site PIs will be trained on an anatomical bronchial model which simulates the clinical experience. After instruction from a qualified Emphasys trainer, the physician will demonstrate successful placements as well as successful removals of valves into and from the bronchial model.

6.4.2.1 Valve Placement

A minimum of 4 consecutive successful placements must be demonstrated in different anatomical locations (an example is provided below). A successful placement has been achieved when the trainer verifies appropriate placement.

- At least 2 large valves shall be successfully placed. One (1) in the right upper and one (1) in the left upper bronchus.
- At least 2 small valves shall be successfully placed. One (1) in the right apical bronchus and one (1) in the left apicoposterior bronchus.

6.4.2.2 Valve Removal

A minimum of 2 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.

6.4.3 Protocol Training

Prior to patient enrollment, the Site PI(s) and the Study Coordinator will meet with Emphasys personnel to discuss the protocol and to ensure that all inclusion, exclusion criteria are well understood as well as all other aspects of the protocol. A training record shall be maintained for each Site PI and Study Coordinator and shall be used to document successful training completion.

6.4.4 Assistant Physicians, Scrub Nurses, and Techs

The Site PI (or designee) will be responsible for providing all allied health personnel who will be assisting during the procedures an overview of the study device, procedure and protocol.

6.4.5 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 procedures. These designees will undergo extensive training in loading techniques by qualified Emphasys personnel. They will then be certified on loading by demonstrating five successful valve loadings.

6.4.6 Nursing Staff In-service

The nursing staff responsible for post-procedure care will receive an overview of the device and post-procedure patient management by the Site PI (or designee).

6.4.7 Study Coordinator Training

The Study Coordinator with primary responsibility for managing the VENT study at each site will be provided with comprehensive training on the device, procedure, post-procedure patient management, 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, CRF's, an example informed consent and study contact information.

6.5 Patient Recruitment

Sites will be encouraged to advertise for local recruitment and web-links to study information will be provided to relevant organizations (*e.g.:* ALA, NEF). Additionally, the enrolling physicians will be given study information and slides to present to referring physicians in their regions.

As enrollment proceeds, compliance with the protocol will be closely monitored. In addition, ongoing monitoring of each site will be conducted relative to meeting enrollment guidelines and accurate and timely submission of data forms and test results.

6.6 Patient Selection

6.6.1 Patient Selection-Criteria for Eligibility

Candidates for this study must meet **ALL** of the following criteria:

Table 4: VENT Inclusion Criteria

a	Patient diagnosed by HRCT Core Lab with eligible heterogeneous disease distribution as described in Section 6.7.5 of the protocol.
b	Age from 40 to 75 years.
c	BMI $\leq$ 31.1 kg/m^2 (men) or $\leq$ 32.3 kg/m^2 (women).
d	FEV_1 < 45% of predicted value.
e	Patient has provided written informed consent using a form that has been reviewed and approved by the IRB / EC.
f	Stable with < 20 mg prednisone (or equivalent) qd.
g	TLC > 100% predicted.
h	RV > 150% predicted.
i	$PaCO_2$ < 50mm Hg (Denver < 55 mm Hg).
j	PaO_2 > 45 mm Hg (Denver > 30 mm Hg) on room air.
k	Post rehabilitation 6-min walk of $\geq$ 140m.
l	Plasma continine level < 13.7 ng/ml (or arterial carboxyhemoglobin < 2.5% if using nicotine products).
m	Nonsmoking for 4 months prior to initial interview and throughout screening.
n	The patient agrees to all protocol required follow-up intervals.
o	The patient has no child bearing potential OR a negative pregnancy test in a woman of childbearing potential.
p	The patient is willing and able to complete protocol required baseline assessments and procedures.

6.6.2 Patient Selection-Criteria for Exclusion

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

Table 5: VENT Exclusion Criteria

a	FEV_1 < 15% predicted value.
b	DLCO < 20% predicted value.
c	Evidence of large bullae (Encompassing >30% of either lung) in a non-target lobe.
d	An HRCT Emphysema Score of 4-4-4 in the right lung or 4-4 in the left lung.
e	Unplanned weight loss of >10% usual weight in 90 days prior to enrollment or total body weight < 70% of ideal body weight.
f	Prior lung transplant, LVRS, Median sternotomy, bullectomy or lobectomy.
g	Alpha-1 antitrypsin deficiency.
h	Pleural or interstitial disease that precludes surgery.
i	Clinically significant bronchiectasis.
j	Pulmonary nodule requiring surgery.
k	History of recurrent respiratory infections (> 1 hospitalization in the last year).
l	Clinically significant (> 4 Tablespoons per day) sputum production.
m	Fever, elevated white cell count, or other evidence of active infection.
n	Dysrhythmia that might pose a risk during exercise or training.
o	Congestive heart failure within 6 mo and LVEF < 45%.
p	Clinical suspicion or proven history of pulmonary hypertension
q	Evidence or history of Cor Pulmonale.
r	Resting bradycardia (< 50 beats/min), frequent multifocal PVCs, complex ventricular arrhythmia, sustained SVT.
s	History of exercise-related syncope.
t	MI within 6 mo and LVEF < 45%.
u	Evidence of systemic disease or neoplasia expected to compromise survival during 5-yr period.
v	Any disease or condition that interferes with completion of initial or follow-up assessments.
w	Patient is currently enrolled in another clinical trial or has been previously enrolled in the VENT Trial for which protocol required follow up is not complete.
x	Patient is unable to complete 3 minutes of unloaded peddling on cycle ergometer.

6.7 Screening Procedures

Patients who are screened for enrollment will be entered on a screening log maintained at each of the clinical sites. Patients referred for screening will be given an explanation of the study by the study coordinator or other qualified medical professional versed in the study design. Subjects interested in study participation will begin the patient selection process as detailed in Figure 1.

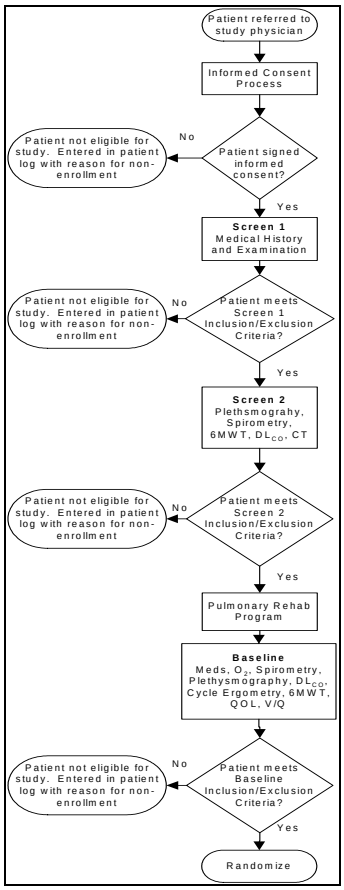

Figure 1: Patient Selection Process

6.7.1 Informed Consent

The Investigator or a member of his/her staff should approach the referred patient to obtain written informed consent. If the family of the patient is available, they should also be consulted. The background of the proposed study and the benefits and risks of the procedures and study should be explained to the patient. The patient will be given the plain language Patient Information Letter (example provided as **Appendix C**) summarizing the study. The patient will be provided with time to read the summary and discuss it with their family and physician. The patient must sign the consent form prior to enrollment. This form or a modification of it must have prior approval of the study site's Institutional Review Board (IRB). Failure to provide informed consent renders the patient ineligible for the study. Patients may not be consented after receiving any medication that might alter their ability to comprehend the consent form (*e.g.*, sedatives, narcotics, etc.).

6.7.2 Screening Assessment 1

Consented Patients will then undergo an initial medical screening to assess preliminary eligibility. This screening is detailed in the Case Report Form (CRF), and includes taking demographic data, a medical history, a physical exam, and inclusion/exclusion criteria screening.

A draft of the Case Report Form to be used in this study is provided as **Appendix F**.

6.7.3 Screening Assessment 2

To further ensure patient eligibility, patients that meet all Screening Assessment 1 criteria will be scheduled for Screening Assessment 2. This screening is detailed in the CRF, and includes spirometry, plethysmography, diffusing capacity, exercise tolerance, and a high resolution computed tomography (HRCT) scan of the chest.

HRCT scans must be obtained according to the HRCT core lab protocol located in the site study binder. If the patient has undergone a HRCT within the last 60 days and the images were obtained in accordance with the HRCT core lab protocol, a repeat scan is not necessary.

Upon enrollment into the study (typically prior to commencement of the patient's rehabilitation program), the baseline HRCT scan will be provided to a HRCT core lab. A HRCT core lab will be used for scoring to obtain standardized measure of disease distribution and severity. The core lab will review the baseline scan for each patient and provide the scoring results to the physician prior to the procedure on a form titled "HRCT Scoring Form". This form has been formatted to include reference to all relevant inclusion and exclusion criteria.

6.7.4 HRCT Scoring at Core Lab

Disease categorization will be performed using a modification to the convention as utilized in the NETT study, a system adapted from prior work by Goddard et al,[25] Bergin et al,[26] and Bankier at al.[27] In this system the extent of emphysema is graded on a lobar level on a scale from 0 to 4, with a grade of 0 indicating no emphysema and a grade of 4 indicating the presence of emphysema in more than 75 percent of the lobe (see Table 6). Because the intent of EBV treatment in the VENT trial is to completely isolate a targeted lobe, HRCT scoring will be done by lobe with each lobe being graded separately according to the percentage area that demonstrates emphysemic changes (low attenuation, lung destruction, and vascular disruption) suggestive of emphysema. The core lab radiologists will be blinded to any clinical or physiological information.

In addition to the 0-4 convention utilized in NETT, the core lab will provide Emphasys with actual percent-emphysema scores derived via quantitative CT analysis for each lobe. This will enable subset analysis (see Section 8.9) to compare the predictive power of each scale. For example, endpoints will be analyzed based on heterogeneity greater than or less than a 20 percentage point difference in % emphysema scores between lobes.

Selection criteria for the core lab will include verification of experience and familiarity with this method of disease categorization. Emphasys personnel will briefly review the scoring methodology and will explicitly review VENT trial radiological inclusion and exclusion criteria with the principal participating radiologists at the core lab. The principal participating radiologist at the core lab will be responsible for the supervision and training all other core lab personnel.

Table 6: Emphysema Scores

% of Parenchyma with Abnormalities Suggestive of Emphysema	Emphysema Score
0	0
1-25%	1
26-50%	2
51-75%	3
>75%	4

Table 7 shows an example of a patient emphysema scores.

Table 7: Example Emphysema Score

	Right	Left
Upper Lobe	4	4
Middle Lobe	2	n/a
Lower Lobe	1	1

6.7.5 HRCT Results Analysis

The HRCT core lab will complete a ”HRCT Scoring Form” for each patient and will, by answering all the questions on the form, determine whether the patient is radiologically eligible to enroll in the study.

Patients will be excluded from the study if all lobes of either lung have Emphysema Scores of 4. Patients will also be excluded if there is a large bulla (comprising greater than 30% of the lung volume) located in a non-targeted lobe of the lung.

In order to be radiologically eligible for the study, patients must have at least one lung that satisfies the minimum criteria for heterogeneity and degree of parenchymal destruction. To characterize these criteria, Emphasys has defined a Heterogeneity Score (HS) and Destruction Score (DS) both based on assigned Emphysema Scores (ES) (see Table 8).

Table 8: Heterogeneity Score and Destruction Score

Heterogeneity Score (HS)	|Upper Lobe ES - Lower Lobe ES| *(i.e.: the absolute value of the difference between the upper and lower emphysema scores)*
Destruction Score (DS)	|Upper Lobe ES + Lower Lobe ES| *(i.e.: the absolute value of the sum of the upper and lower emphysema scores)*

If there is a difference in ES between the Upper and Lower Lobes within a lung (*i.e.:* HS $\geq$ 1) the disease is considered heterogeneous. Heterogeneous disease is the intended disease distribution in this study. A patient with hybrid disease (*i.e.:* one lung has heterogeneous disease and the other lung has homogeneous disease) may be included in the study as long as the lung with heterogeneous disease qualifies for treatment and the lung with homogeneous disease is not rated with maximal destruction as measured by Emphysema Score (i.e.: Right Lung Scores of U=4, M=4, L=4 or Left Lung Scores of U=4, L=4).

In addition to determining radiological eligibility, these scores will also be used by the HRCT core lab to determine the valve targeting (see Section 7.8.2)

Table 9 presents a pair of charts wherein all possible ES eligible Emphysema Score combinations for the upper and lower lobes for a given patient are shown as unshaded boxes. The radiologist does not need to calculate either the Heterogeneity or Destruction score because the minimum requirement for heterogeneity and parenchymal destruction are implicit in the configuration of these charts.

In order to be radiologically eligible for the trial the patient must have

EITHER

left lung scores such that an un-shaded box of Table 9 applies

AND / OR

right lung scores such that an un-shaded box of Table 9 applies

The "HRCT Scoring Form" requires the radiologist to answer questions that will verify the patient's radiological eligibility.

Table 9: Eligible Emphysema Score Combinations for Upper and Lower Lobes

RIGHT LUNG	LEFT LUNG

		Lower Lobe ES				
		0	1	2	3	4
Upper Lobe ES	0					
	1					
	2					
	3					
	4					

		Lower Lobe ES				
		0	1	2	3	4
Upper Lobe ES	0					
	1					
	2					
	3					
	4					

The completed "HRCT Scoring Form" is then returned to the treating physician. Section 7.8.2 describes the algorithm for determination of appropriate targeting strategy.

6.7.6 Optimal Medical Management Program

Patients that have met the Screening Assessment 1, Screening Assessment 2 and HRCT screening requirement will be enrolled in the Optimal Medical Management program that is detailed in Section 7.1.

6.7.7 Baseline Testing and Final Eligibility Determination

Following successful completion of the optimal medical management program, baseline testing is performed along with a final determination of eligibility. This testing is detailed in the case report form (CRF) and includes the following:

- Physical Exam
- Quality of Life Surveys
- Cardiac Assessment
- Blood Work
- Pregnancy Test *(if applicable)*
- Imaging
- Lung Function Testing
- Exercise Tolerance Testing
- Current Medications

7.0 DESCRIPTION OF TREATMENTS

7.1 Optimal Medical Therapy

Optimal medical therapy is defined, for the purposes of this protocol, as maximal medical treatment for stable COPD as presented in the 2001 NIH/WHO GOLD guidelines[28]. As recommended in the GOLD standards, each patient enrolled in the study will receive therapy that will consist of the following components:

- Education
  - Smoking Cessation Support
- Pharmacological Treatment
  - Bronchodilators
  - Influenza and Pneumococcus Vaccination
- Non-Pharmacological Treatment
  - Pulmonary Rehabilitation
  - Oxygen Therapy

7.2 Education

7.2.1 Smoking Cessation Support

All patients will have access to a smoking cessation program support system during the course of the study.

7.3 Pharmacological Treatment

7.3.1 Bronchodilators

As recommended in the GOLD standards, maintenance bronchodilator therapy will be given to all patients in the study and will include an inhaled long acting beta-agonist, an inhaled anticholinergic, or both, and will 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. The treatment will begin at randomization, and for those patients in the treatment arm of the study, the treatment regime will be stable for one month prior to the implant procedure. The investigators will only modulate the regimen of the subject's primary physician if it is not consistent with these standards. Similar standards will be applied to long-term post-surgery management. As patients may have variable responses to bronchodilators and may need varying intensity of treatment associated with perioperative exacerbation, there will not be a standardized regimen for all subjects.

7.3.2 Influenza and Pneumococcus Vaccination

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

7.4 Non-Pharmacological Treatment

7.4.1 Pulmonary Rehabilitation

All patients in both arms of the study will be given a course of in-clinic pulmonary rehabilitation (PR) before randomization and will be expected to comply with a subsequent home rehabilitation program. The pulmonary rehabilitation program will focus on exercise training as this has been shown to be the major benefit of pulmonary rehabilitation. Assessment of the outcome of pulmonary rehabilitation typically involves testing of exercise tolerance, level of dyspnea, and quality of life. Measurement of all of these will be performed at baseline and at all study endpoints.

A Pulmonary Rehabilitation Manual for the study will be provided to each study site. This manual will contain details regarding administration of the PR program including definitions of responsibilities and requirements for:

- PR facility identification & qualification.
- Monitoring, documenting and reporting of PR related activities.

7.4.1.1 In-Clinic Pulmonary Rehabilitation Program

A patient who has recently (within the last 60 days) completed pulmonary rehabilitation may proceed to baseline testing provided that the rehab program is documented and meets the criteria specified by the VENT Study. In addition, the patient must meet all criteria specified in Screening Assessment 1 and Screening Assessment 2.

The pulmonary rehabilitation program for the study will last 6-8 weeks with 2 visits to the rehabilitation center per week. Minimum attendance of 75% (12 of 16 visits) is required to fulfill the pre-randomization pulmonary rehabilitation requirement. Any patient who does not complete 12 visits is not eligible to enter the study. There is a maximum of 18 sessions over the course of 8 weeks for patients who choose to attend sessions more than twice in a week.

The program will consist of the following components[29]:

- Lower limb endurance training
- Upper limb endurance training
- Lower and upper limb strength training

If deemed necessary by the therapist, oxygen saturation will be monitored during exercise to ensure that the patient does not desaturate.

The goal of this training is to gradually and continually increase the patients' tolerance to both duration of exercise and resistance level over the course of the program.

Lower Limb Endurance Training

Lower limb endurance training may be done on a treadmill, on an exercise bicycle, or both, based on the treating therapist's assessment of individual circumstances. A list of suggested exercises is provided in the Pulmonary Rehabilitation Manual.

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. A list of suggested exercises is provided in the Pulmonary Rehabilitation Manual.

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. A list of suggested exercises is provided in the Pulmonary Rehabilitation Manual.

7.4.1.2 Home Pulmonary Rehabilitation Program

Following the completion of the 6 - 8 week in-clinic pulmonary rehabilitation program, the patient will be encouraged to follow a home maintenance program at least twice a week. The program will be as follows:

Lower Limb Endurance Training

Walking for 20-30 minutes substituted for treadmill or exercise bicycle.

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.

7.4.2 Oxygen Therapy

Patients meeting requirements for supplemental oxygen therapy ($SaO_2 \leq 88\%$, or $\leq 90\%$ in the presence of polycythemia or cor pulmonale) will be on the appropriate liter flow rate necessary to achieve resting and 6 minute walk test exercise oxygen saturation to >90%.

7.5 Randomization

If a patient successfully completes their pulmonary rehabilitation program and continues to meet all protocol entry criteria, the patient will be randomized to either the Treatment or Control

group. Randomization will be at a ratio of 2 to 1, (*i.e.,* two patients will be randomized to the study device treatment arm for every one randomized to the control group).

Randomization will be further stratified into the following four groups based on core lab analysis of the patient's HRCT and based on the patient's cycle ergometry testing:

- Upper lobe, low exercise tolerance
- Upper lobe, non-low exercise tolerance
- Lower lobe, low exercise tolerance
- Lower lobe, non-low exercise tolerance

Upper vs. lower lobe stratification will be based on the location of the target treatment lobe.

Exercise tolerance stratification will be based on gender and maximal workload. For women, the low exercise tolerance cutoff is maximal workload $\leq$ 25 W by cycle ergometry and the non-low exercise tolerance is > 25 W. For men, the low exercise tolerance cutoff is maximal workload $\leq$ 40 W by cycle ergometry and the non-low exercise tolerance is > 40 W.

The goal of stratification will be to ensure a 2:1 randomization mix within each stratum rather than to ensure a specific number of patients in each group.

7.6 Standard Tests and Procedures

Table 10 displays the required schedule for treatment and evaluation for all patients enrolled in the study from initial screening through the 365 day follow up visit.

Table 10: Follow-up Visits, Tests and Procedures

	Screen 1 (Medical)	Screen 2 (Lung function)	6-8 wk. Pulm. Rehab	Baseline Pre-randomize	Immed Post proced	24 Hr	2-3-day*	7 -10 day*	30-day	90-day	180-day	365-day
BASIC MEDICAL												
Medical History	X											
Review Medications Being Taken				X			X	X	X	X	X	X
Record Supplemental Oxygen Use	X			X					X	X	X	X
Vital Signs/Physical Exam	X			X		X			X	X	X	X
ECG		X		X							X	
Review of Adverse Events					X	X	X	X	X	X	X	X
LUNG FUNCTION TESTING												
Spirometry		X		X					X	X	X	X
Body Plethysmography		X		X					X	X	X	X
Diffusing Capacity		X		X					X	X	X	X
EXERCISE TOLERANCE												
Six-Minute Walk Test		X		X					X	X	X	X
Cycle Ergometry				X					X	X	X	X
QUALITY OF LIFE												
SGRQ Survey				X						X	X	X
QWB Survey				X					X	X	X	X
MMRC Survey				X					X	X	X	X
IMAGING												
High Resolution CT Scan		X									X	
Chest X-ray				X	w/in 1 hr	X			if indicated		X	
V/Q Scan				X							X	
BLOOD WORK												
PaO2 and PaCO2		X		X		X			X	X	X	X
Arterial SAT		X		X		X			X	X	X	X
Pulse Oximetry					24hrs **							
Blood Chemistry & Electrolytes				X							X	
Liver Profile				X							X	
Renal Profile				X							X	
Complete Blood Count				X							X	
Pregnancy Test				X								
Continine Level		X		X							X	
Alpha-1 Levels		X										

** Telephone contact if patient discharged from hospital or enrolled into the control arm.*
*** Monitored during the first 24 hours post-procedure.*

Follow-up visits and testing will be scheduled within the ranges specified in Table 11.

Table 11: Ranges for Scheduling Follow-up Visits

Visit	Range
24-Hour *(Treatment arm only)*	+/- 8 hours
2 to 3-Day or Prior to Discharge	+ / - 8 hours
7 to 10-Day	+ / - 2 days
30-Day	+ / - 7 days
90-Day	+ / - 7 days
180-Day	+ / - 14 days
365-Day	+ / - 21 days

7.7 Enrollment to the Control Arm

The control group will receive optimal medical management at the participating center. Additionally, they will undergo the same follow-up as the Treatment Arm, including an Office Visit in lieu of the Treatment (see Figure 2).

At the time of the Control Arm Office Visit, all patients will be provided with a study diary to be used as a memory aid throughout the duration of the study.

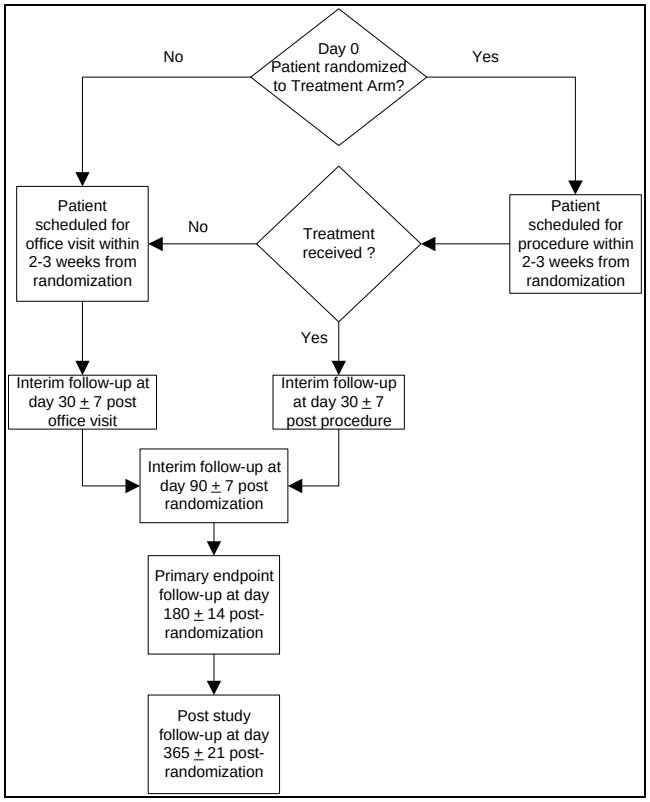

Figure 2: Follow-up and Balanced Patient/Physician Contacts between Arms

7.8 Enrollment to the Treatment Arm (Emphasys Endobronchial Valve)

The procedure may be performed with the patient under general anesthesia and on a ventilator or under conscious sedation with unassisted breathing. All patients will be given antibiotics just prior to and for 7 days following the procedure. The anesthetic will be according to standard local protocols for bronchoscopy. For general anesthetic 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. Patients who are not on a ventilator may have a bite block to provide access.

The bronchoscopic procedure must be recorded on video or CD ROM and a copy included in the patient file to be provided to Emphasys.

7.8.1 Implant Procedure Medication

In addition to the medications described in Section 7.3, Pharmacological Treatment, the following medications (or equivalent) will be required for all patients enrolled in the treatment arm of the study:

7.8.1.1 Medications Prior to Trial Procedure

Patients will be asked to withhold aspirin for 3 days prior to the procedure.

7.8.1.2 Medications During Trial Procedure

Just prior to and for the 24 hours after the procedure, all patients will be given intravenous second or third generation cephalosporin or quinolone (*e.g.:* Ancef, Kefzol, Cefaclor). The anesthetic will be according to standard local protocols for bronchoscopy.

7.8.1.3 Medications Following Trial Procedure

Beginning 24 hours after the procedure, all patients will receive a 7 day prophylactic course of oral second or third generation cephalosporin or quinolone antibiotics. A summary of the study medications is provided in Table 12.

Table 12: Summary of Procedure Medications (or equivalent)

Medication	During Procedure	Post-Procedure
Cephalosporin or Quinolone, IV	X	
Anesthetic	X	
Cephalosporin or Quinolone, oral		X

7.8.2 Treatment Targeting

The ”HRCT Scoring Form” will be used by the HRCT Core Lab to determine the appropriate treatment strategy for each patient. Treatment targeting is based on the HRCT Emphysema Scores, the calculated Heterogeneity Scores (HS) and Destruction Scores (DS) for both lungs (please see Section 6.7.5 and for a description of this

calculation). A flowchart of the targeting algorithm is presented in Figure 3. Only one lobe of one lung is treated. This flowchart describes the process of determining which lung and which lobe to treat. The targeting algorithm is as follows:

A. Determine Which Lung to Treat

1. Target the lung with either an Upper or Lower Lobe ES $\geq$ 3 AND an Upper or Lower Lobe at least 1 Emphysema Score lower.
2. If #1 is true for both lungs, target the lung with the highest HS.
3. If #1 is true for both lungs and both lungs have the same HS, target the lung with the highest DS.
4. If both lungs are equally eligible based on points 1-3 above, target the lung with the greater heterogeneity (as calculated using the actual quantitative % emphysema scores determined by the core lab). Within that lung, target the lobe with the greatest emphysema score.

B. Determine Which Lobe to Treat

In all cases, once the appropriate side of the lung has been determined, target the upper or lower lobe of that lung that has the highest ES. In this study the lingula is considered part of the upper left lung and the Middle Lobe of the right is never targeted.

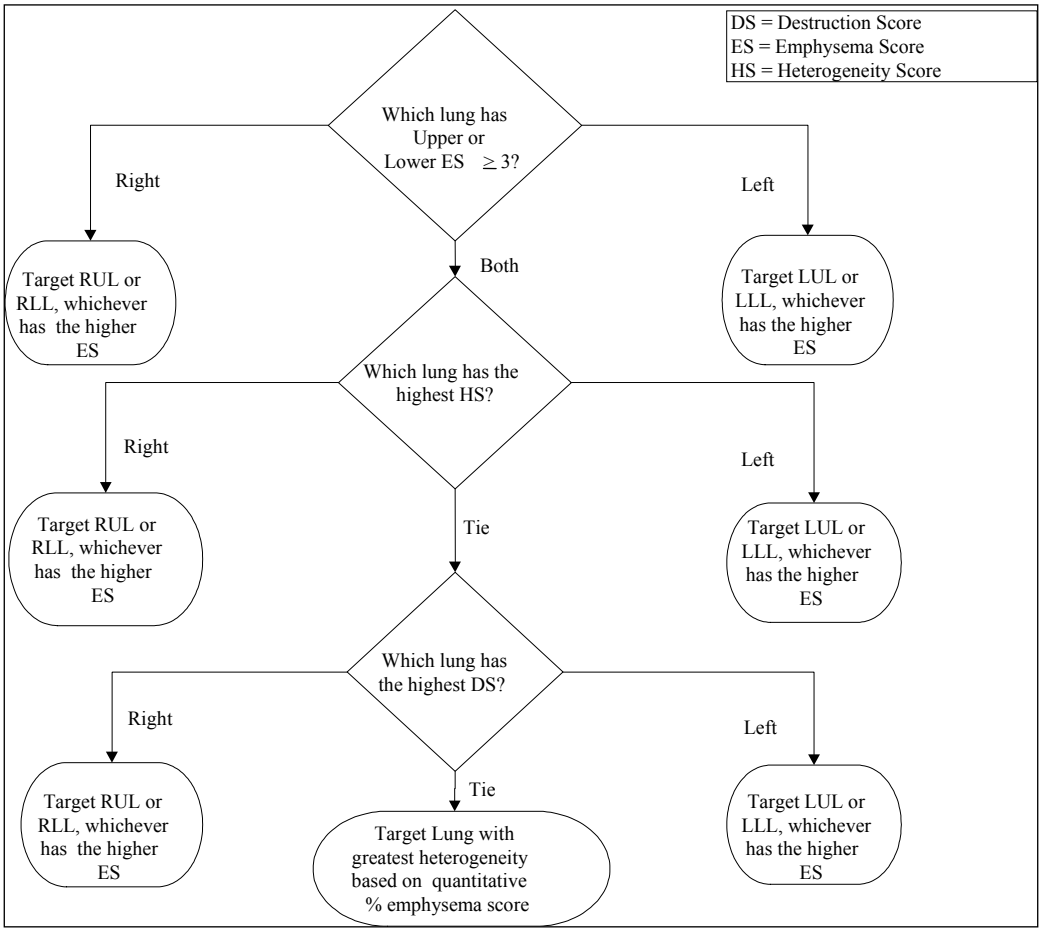

Figure 3: Targeting Algorithm for Lobar Exclusion

C. Achieving Lobar Exclusion:

The target lobe is intended to be completely excluded (meaning that all airways feeding that lobe are to be blocked with a valve). Lobar exclusion is required as the segmental boundaries are often largely destroyed in cases of advanced emphysema. If an entire lobe is not excluded by valves, 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 patient. 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). Targets at the segmental bronchi level for lobar exclusion are shown in Table 13. Valves must be placed according to the manufacturer's Instructions for Use. A draft copy is provided as **Appendix A**.

Table 13: Segmental Bronchial Targets for Lobar Exclusion

	Bronchial Segment Number	**Bronchi**
Right Upper Lobe	B1	apical
	B2	posterior
	B3	anterior
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

7.8.3 Bilateral Placement

Bilateral valve placement will not be permitted in this study.

7.8.4 Staged Procedures

Staged procedures will not be permitted in this study. Lobar exclusion is intended to

be achieved during one procedure.

7.9 Post-procedure

Successful lobar exclusion must be determined, via bronchoscopy, immediately following valve placement and recorded on the appropriate CRF.

Patients will recover from the anesthesia per the hospital's protocol. The patient's vital signs will be monitored with strict attention to the patient's respiratory condition. A chest X-ray will be performed within one hour postoperatively.

Pulse oximetry will be used during the first 24 hours post-procedure to monitor patient status. Arterial blood gases will be analyzed prior to hospital discharge. Blood gases should be collected with patient breathing room air. If the patient 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, the patient's oxygen saturation falls below 80%, supplemental oxygen should be provided and increased in 1liter/min increments every 3 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.

As patients recover, they will be encouraged to cough (assisted by physiotherapy) in order to clear any mucus or air remaining behind the valve, unless there is evidence of atelectasis in which case they will be discouraged from coughing. All patients will be given a prophylactic full course of oral antibiotics. All patients will receive post-operative inhaled bronchodilators.

Any patient with radiographic evidence of atelectasis will be kept in-hospital, under observation for at least 2 days post procedure (see flowchart in Figure 4). A stable pneumothorax is an expected response to atelectasis and should not be treated via aspiration or chest tube[30,31,32,33] unless it persists. If a stable pneumothorax is still present after the 2-day observation period the clinician should consider further observation, needle aspiration, or chest tube insertion. If a tension pneumothorax or expanding pneumothorax is diagnosed, a chest tube will be positioned in the pleural cavity and attached to a water seal or suction at the discretion of the treating physician or surgeon. When signs of air leak have ceased, the chest tube will be removed.

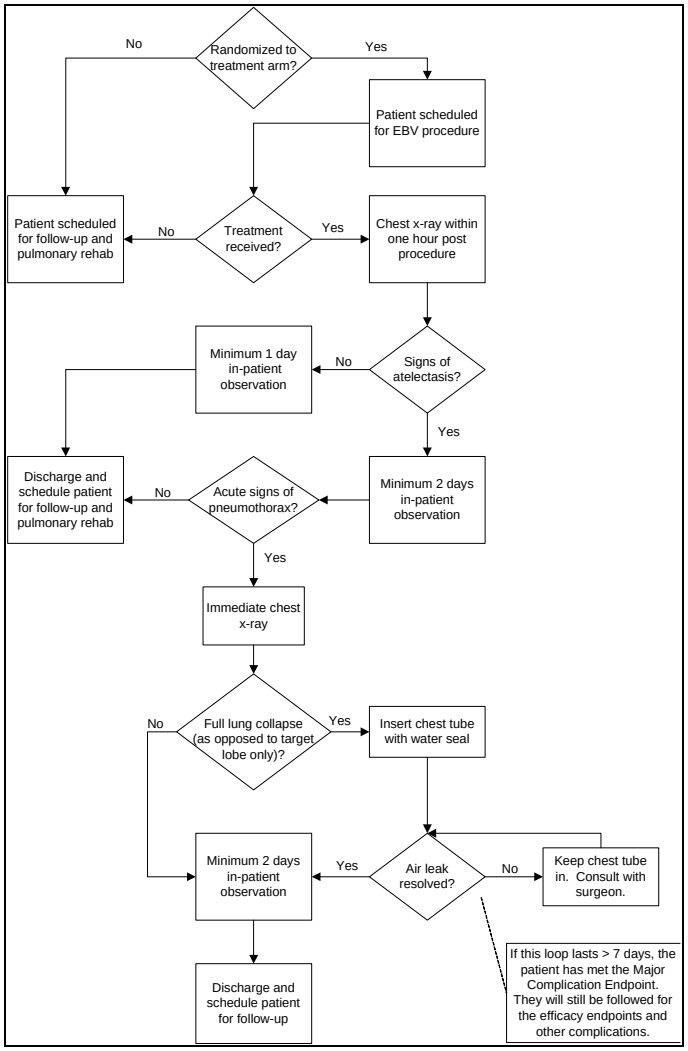

Figure 4: Patient Flow for Atelectasis

7.10 Valve Removal

All valves must be removed according to the Manufacturer's Instructions for Use.

If the patient undergoes symptom driven testing between day 1 and day 30 post procedure and the results demonstrate that the patient is experiencing either one or both of the following, the patient may be scheduled to undergo a valve removal procedure.

- Increase in RV > 15%
- FEV1 decrease of > 15% and an RV decrease of $\leq$ 5%

All patients treated with the EBV device, regardless of valve removal, will be monitored for safety and efficacy for the entire study follow-up period as outlined in Section 7.6.

7.11 Follow-up Procedures

During the procedure hospitalization, the patient will be provided with a study diary to be used as a memory aid throughout the course of the study. A copy of the patient diary is provided as **Appendix D**. In addition to the diary, a Medical Alert Card completed by the research staff to contain emergency contact information will be provided. An example of the Medical Alert Card is provided as **Appendix E**.

Prior to hospital discharge for the Treatment Arm and during the Control Arm Office Visit post-randomization for the Control Arm, the study coordinator should schedule the appropriate follow-up visits (see section 7.6 Table 10). This will include two safety assessment phone follow-up contacts, one between 2-3 days, and one between 7-10 days, post procedure / Control Arm Office Visit (depending on randomization). For any patients in the treatment arm that have not been discharged from the hospital by the time of these two safety assessments, these contacts will be carried out during hospitalization.

Additional follow-up for this study is scheduled for 30 days post treatment for the EBV treatment arm and 30 days post Office Visit for the Control arm. In addition, both groups will be asked to return for follow-up at 90, 180 and 365 days post-randomization.

If at any time during the follow-up period a bronchoscopy is clinically indicated, all images must be recorded on video or CD-ROM and kept with patient files throughout the course of the study.

7.12 Spirometry, Body Plethysmography, Diffusing Capacity Testing

Spirometry will be performed based on the "Standardization of Spirometry – 1994 Update"[34] by the American Thoracic Society. For example, measuring FEV_1 requires a spirometer capable of measuring at least 8 liters. The spirometer must measure FEV_1 within an accuracy of at least +/- 3% of reading or +/- 0.050 liters, whichever is greater, with flows between zero and 14 L/s. The start of the test for purposes of timing must be determined by the back extrapolation method or a method shown to be equivalent. Acceptability and reproducibility criteria are summarized in Table 8 of the ATS document. **Spirometry values recorded on the CRF will be both pre- and post-bronchodilator**.

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".[35] 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 FRC or at some other level; should be compared with other lung volume determinations (He dilution, N_2 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 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. 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 patient should be kept constant to aid in interpretation. Consensus of the group suggests a range of 90-150 cycles per minute (1.5-2.5 Hz). **Body plethysmography values recorded on the CRF will be post-bronchodilator.**

Diffusing capacity (DL_{CO}) will be measured using the single-breath carbon monoxide method. The test will be conducted per the ATS document "Single-breath Carbon Monoxide Diffusing Capacity (Transfer Factor): Recommendations for a Standard Technique – 1995 Update".[36] Acceptable test criteria include the use of proper quality controlled equipment, inspired volume of >90% of vital capacity in less than 4 seconds, a stable breath-hold for 9 to 11 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. 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.

The Hankinson[37] standard will be used to calculate the % predicted values for this study.

7.13 Six-Minute Walk Testing

Six-Minute Walk testing will be performed according to the "ATS Statement: Guidelines for the Six-Minute Walk Test – March 2002".[40] 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 patient 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 document.

7.13.1 Dyspnea Measurement

Dyspnea and overall fatigue will be measured in all patients using the Borg Scale[38,39] prior to and immediately following performance of the 6-minute walk test (6MWT). The American Thoracic Society standards for the 6MWT will be followed,[40] and will be performed at baseline and at all following study endpoints.

7.14 Quality of Life Measurement

Health Related Quality of Life (QOL) measurement is an important tool for measuring health status changes in patients receiving an intervention. Two measures, the St. George's Respiratory Questionnaire (SGRQ) and the Quality of Well Being Scale (QWB), will be used to measure quality of life changes in patients in both arms of the study. Patients will also be asked to

complete a Modified Medical Research Council (MMRC) survey. All surveys will be administered at baseline, at the 180-day follow-up, and at the 365-days post procedure. The QWB and the MMRC will be administered at the 30-day follow-up. Administration of the SGRQ will not be done at the 30–day evaluation as it is written to assess changes in patient health status during the previous 3 months, and this time will not have passed since baseline evaluation. If the patient does not have sufficient command of English, the surveys will be administered in the patient's native language. If validated translations are not available, the test will not be administered for the patient.

The VENT Study will include a health-economics sub-study to evaluate the cost effectiveness of the EBV device and procedure. A summary of the Cost Effectiveness Sub-study protocol is provided as **Appendix G**. The final protocol will be reviewed and approved by each site's IRB prior to commencement.

7.15 Cycle Ergometry

Based on findings from the NETT Study, maximum exercise capacity as determined by cycle ergometry has been identified as a valuable outcome measure for evaluating new therapies in patients with advanced emphysema. As such, this metric will be measured in the VENT Study. The testing protocol that will be used is closely modeled after the cycle ergometry testing protocol utilized in NETT. All patients will be given supplemental oxygen ($FiO_2 = 0.3$) and will be allowed to rest 10 minutes in a chair prior to testing. Following this rest period, patients will be positioned on the cycle ergometer and allowed to rest for an additional 5 minutes. After this rest, patients will initiate a 3 minute period of unloaded pedaling at a target rate of 40-70 RPM. Patients will then undergo a ramped workload test in which resistance will be increased every minute until the patient can no longer sustain a pedaling rate of 40 RPM; or until the patient requests termination; or until the technician halts the study for safety reasons. Maximum workload (in watts) achieved will be recorded. Borg testing will be undertaken throughout the test to assess perceived dyspnea and leg muscle fatigue. A copy of the detailed cycle ergometry testing protocol is provided in the site binder.

7.16 Room Oxygen Assessment

Subjects will have room oxygen requirement recorded at Screen 1, Baseline and at the 30-day, 90-day, 180-day and 365-day follow up intervals. The patient reported conditions of usage (continuous, rest, sleep, and exertional); duration of use (hours/day) and flow rate (liters/min) will be gathered from the patient record and documented on the appropriate case report form. It is recommended that oxygen be prescribed as follows:

- Long-term oxygen therapy is indicated when $PaO_2 \leq 55$ mmHg or $SaO_2 \leq 88\%$.
- Long-term oxygen therapy is indicated when PaO_2 is between 55 mmHg and 59 mmHg or SaO_2 is at or below 89% if there is evidence of pulmonary hypertension, tissue hypoxia such as cor pulmonale, peripheral edema suggesting congestive heart failure, polycythemia (hematocrit > 55%), or impaired mental status.
- Long-term oxygen therapy is indicated only in specific situations when $PaO_2 > 60$ mmHg or $SaO_2 > 89\%$.

- If the patient meets criteria at rest, O_2 should also be prescribed during sleep and exercise, appropriately titrated.
- If the patient is normoxemic at rest but desaturates during exercise or sleep ($PaO_2 \leq 55$ mmHg), O_2 should be prescribed for these indications. Also consider nasal CPAP or BiPAP.
- The goal of long-term oxygen therapy is to increase baseline PaO_2 to at least 60 mmHg or to produce SaO_2 at least 90%.

8.0 DATA ANALYSIS OVERVIEW

8.1 Primary Effectiveness Endpoints

The co-primary effectiveness endpoints are the mean changes in both FEV_1 and 6MWT in the treatment group as compared to the control group for the 180 days post randomization.

8.2 Secondary Effectiveness Endpoints

Continuous secondary effectiveness endpoints include mean change of the following:

- RV
- DL_{CO}
- St. George's Respiratory Questionnaire
- QWB
- Assessment of room oxygen requirement
- Maximum workload as measured by cycle ergometry
- Dichotomous secondary effectiveness endpoints include:
- Per-patient clinical success / failure rates for FEV_1
- Per-patient clinical success / failure rates for 6MWT
- Procedure and technical success rate (EBV only)

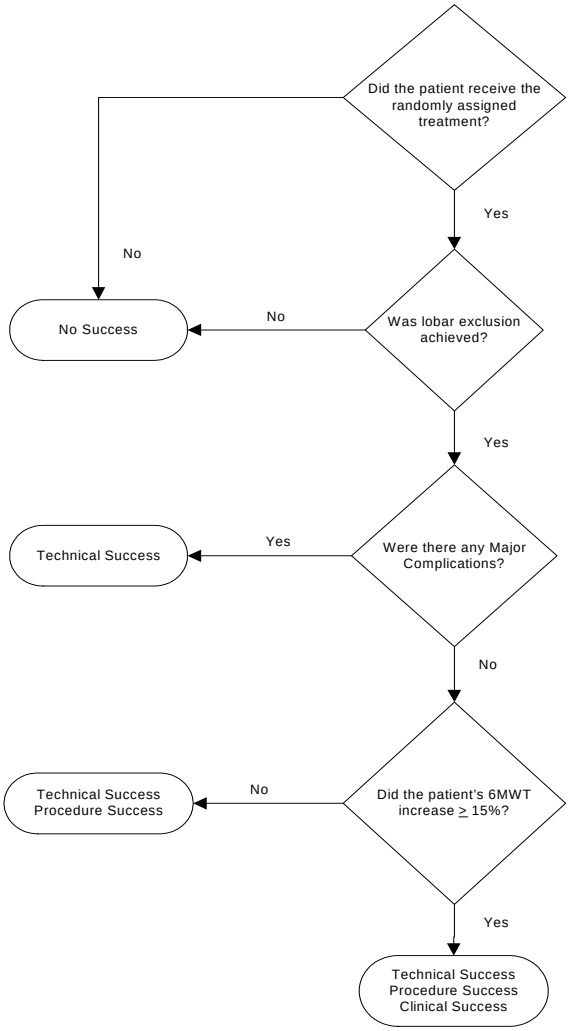

Figure 5: Technical, Procedural, and Clinical Success Criteria

8.3 Primary Safety Endpoint

The primary safety endpoint is Major Complication Composite (MCC) at Day 180.

The Complication Composite endpoint is met when one of the composite complications occurs. There can only be one Complication Composite endpoint per patient; however, each event will be recorded and reported along with other complications.

8.4 Secondary Safety Endpoints

The secondary safety endpoints are:

- Complications (type, timing, and severity).
- Device-related Adverse Events during procedure hospitalization.
- Device-related Adverse Events post discharge.

8.5 Overall Definition of Success

The Company believes a successful trial result is achieved if:

The co-primary effectiveness endpoints (FEV_1 and 6MWT) for the EBV arm both reach statistical significance ($p<0.05$) when compared to the control arm and the 95% upper confidence interval for the MCC rate delta between the EBV arm and the control arm is $\leq$ 30%.

8.6 Statistical Analysis Plan

A statistical analysis plan is provided in **Appendix H**.

8.7 Statistical Significance

A p-value of 0.05 or less will be considered statistically significant.

8.8 Subset Analysis

Subset analysis will be used to examine EBV mechanism of action as well as to demonstrate which subpopulations fared better. A detailed subset analysis plan is included in Appendix H

8.9 Interim Analysis

No interim analyses are planned; therefore an interim unmasking strategy is not required.

9.0 STATISTICAL JUSTIFICATION

9.1 Historical Data

Based on the most recent clinical data from the 38 patients in the lobar-exclusion subset with matched baseline and 90-day follow-up data, a 14.9% +/- 33.7% average improvement from baseline has been observed for FEV_1 and a 20.4% +/- 41.5% for 6MWT.

Based on the most recent clinical data from the 38 patients in the lobar-exclusion subset, a 19.1% major complication composite (MCC) rate has been observed. The literature suggests an 8.8% major complication composite (MCC) rate for optimal medical management (OMM). An acceptable EBV rate would need to be justified on the basis of FEV_1 and 6MWT advantage. If major complications were medically manageable, a higher MCC rate could also be accepted for EBV.

9.2 Sample Size Rationale

The null hypothesis and alternative hypothesis are presented below where ΔFEV_1 equals the mean percent improvement response in FEV_1 from baseline for each group at 180 days.

$$H_o: \Delta FEV_1(EBV) - \Delta FEV_1 (Control) = 0\%$$

$$H_A: \Delta FEV_1(EBV) - \Delta FEV_1 (Control) \neq 0\% (=15\%)$$

The sample size has been estimated to detect a 15% difference between the study arms for the mean change of FEV_1 and a 17% change of 6MWT from baseline to 180 days. The 15% improvement in FEV_1 is a clinically significant difference based on the ATS upper threshold bronchodilator response for FEV_1 of 12% - 15%.[41] For the 6MWT, Redelmeier et al considers a 15% improvement (54 meters in an average 371 meters baseline cohort) from baseline to be clinically meaningful.[42] A 17% change in 6MWT was selected for detection because it is between the clinically meaningful threshold (15%) and the 6MWT historical results (20.4%).

A 2:1 treatment allocation favoring EBV versus OMM (Control) will be utilized to gather more safety and effectiveness data for the study device. Based on a 0.41 correlation between the 6MWT and FEV_1 and planed loss rate of 10%, a total of up to 270 patients will be enrolled to achieve 246 patients (164 EBV, 82 Controls). A 5.0% Type I error will be used to allow for two co-primary endpoints (FEV1 and 6MWT) for two-sided hypothesis tests of the mean change from baseline; both must attain significance. A mean difference of 15% FEV_1 (with 33.7% standard deviation) or 17% 6MWT (with 41.5% standard deviation) between the two study arms can be detected with 80% overall power.

The Sponsor believes the primary safety endpoint should be considered a success if the upper 95% confidence bound on the Major Complication Composite (MCC) rate delta does not exceed 30%. For example, if the MCC rate for the EBV arm is 20.5% for 112 patients, and the MCC rate is 8.9% for the Control arm of 56 patients, the MCC rate delta would equal 11.6%. The upper 95% confidence bound for this 11.6% delta would be 24.8% based on a study of 168 total patients. 24.8% is less than or equal to 30%, thus success for safety would be declared.

The sample size is also adequate to accommodate 40 centers; no center will be allowed to enroll more than 50 patients. Results will be displayed separately for U.S. and non-U.S. sites; any sites with more than 10 patients will be displayed as well; sites with fewer than 6 patients will be pooled together separately for U.S. and for non-U.S. sites.

10.0 STUDY DATA REPORTING AND PROCESSING

10.1 Study Data Collection

The final Case Report Form is designed to accommodate the specific features of the trial design. Modification of the CRF will only be made if deemed necessary. Significant modifications will be reviewed and approved by the Operations Committee.

All forms and other study related materials should be submitted according to the schedule reflected in Table 14.

Table 14: Schedule for Case Report Form and Test Report Submission

Event	CRF's & Test Reports	Submission Schedule
Pre-screening	Screening Assessment Forms HRCT Scan to Core Lab	Within 1 week Within 1 week
Enrollment	Screening Assessment 1 & 2 Forms Post Rehab / Pre-procedure Baseline Form V/Q Scan Images and Report Chest X-ray	Within 1 week Within 1 week Within 2 weeks Within 2 weeks
Randomization	Randomization Assignment Form	Within 24 hours
Treatment Arm: Procedure	EBV Procedure through Discharge Forms	Within 1 week
Control Arm: Office Visit	Control Arm Office Visit Form	Within 1 week
Follow-up Forms	24 Hour, 2/3, 7/10, 30, 90, 180 and 365-day Follow-up Form	Within 1 week
Study Exit	Study Exit Form	Within 1 week
Other Forms	Narrative Summaries, Report of Protocol Deviation, etc.	Within 1 week
UAE / SAE Reports	UAE / SAE Report Form	Within 24 hours

10.2 Site Data Monitoring and Quality Control

Primary data collection based on source-documented hospital chart reviews will be performed by study coordinators or investigators at each clinical site. Case Report Forms will be completed and forwarded 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 site needs will be communicated regularly. In addition, regularly scheduled teleconference between the study coordinator(s) for each site and the Sponsor may occur.

All clinical sites will be audited periodically by the sponsor's personnel, or sponsor's designee, for protocol adherence, accuracy of CRF completion, and compliance to applicable regulations. Any evident pattern of non-compliance with respect to these standards will be cause for the site to be put on probation for a period of one month, unless otherwise determined. If corrective actions are not subsequently undertaken, the clinical site will be asked to withdraw from the study.

Communication

In the initial phase of the 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, study 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 will be consulted.

Recruitment tracking

A weekly recruitment status report generated by the master tracking system will 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.

10.3 Data Processing and Quality Control

The Sponsor will employ a full-featured relational database on a central server to store the data. Conventional data verification sub-routines will be programmed to test entry and logical errors, while all individual (patient based) case report forms will be linked for cross-reference. Periodic analysis of each data field (across cases) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data mistakes. Specifically:

10.3.1 Data Cleaning

All CRF's will be subjected to initial inspection for omitted data, gross data inconsistencies, and timeliness of reporting. Any deficiencies will be resolved using electronic tracking and revision of errant forms at the clinical site.

10.3.2 Data Entry

All data entry screens are similar to the corresponding CRF's, in order to reduce transcription error by data entry personnel. During data entry, each field is interactively subjected to data type verification and range checking. The operator is notified of any error that may occur, and that error should be resolved before moving to the next entry field.

10.3.3 Second Data Entry

Once the first data entry is completed, the forms are entered again. The two entries are checked for parity after the second entry, and any discrepancies resolved by senior level data entry personnel.

10.3.4 Data Editing

Each data record is evaluated with an extensive electronic intra-form and inter-form edit checking on a regular interval. Any discovered error is then referred to the clinical site for review and correction by either the Study Coordinator or Investigator. A copy of the completed query form will be provided to the Sponsor and the corrected query response entered into the database by senior level data entry personnel.

10.3.5 Data Update

The cycle of data edit will be ongoing until all the data are clean. Such data transfer may occur by mail or fax depending on the clinical site facilities. The sponsor or designee will monitor the clinical site for source documentation verification. If further data entry or source documentation errors are discovered during the site visit the corrections will be made at that time and a final transfer of the corrected copy of the case report form will be sent to the Sponsor, with a copy remaining at the clinical site.

10.3.6 Final Data Analyses

All exported datasets for analyses will undergo a final data cleaning procedure using programmed logical routines unique to each exported dataset.

10.3.7 Data Form Inventory

A data form inventory system will be utilized to assure accurate record keeping and constant tracking of these items. Sites will be notified as necessary of all forms that are delinquent.

10.3.8 Data Back-up

Incremental computer data back up is performed daily using network tape backup systems, while a full database back up is performed on a weekly basis. All hard copies of CRF's will be locked in a secure location, while all media back-up will be stored at two locations: on-site in a fire-proof cabinet, and off site.

10.3.9 Report Generation and Summary Statistics

A customized report is generated for record keeping and scheduling, serving as an overview of the current database and revealing the backlog in data processing. In addition, recruitment status, patients' baseline characteristics, and summary statistics of non-endpoint data can be easily scanned for outliers, and protocol compliance by clinical site may be determined for immediate feedback.

10.4 Confidentiality and Protection of Study Files

Passwords will be issued to appropriate personnel to insure confidentiality and protection of the data by allowing variable levels of access to the computer system. For example, only the data entry person or Project Manager enters and/or verifies data. All other personnel may only read the data on-screen or print out patient listings. The hard copies of the CRF's are kept in a locked, secure location when not in use for data entry.

11.0 STUDY MANAGEMENT

11.1 Operations Committee

The Operations Committee will approve the final trial design and protocol issued to the Data and Safety Monitoring Board (DSMB) and the clinical sites. 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 patient 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.

The Operations Committee includes:

Frank Sciurba, M.D.	VENT Primary Investigator
Rich Ferrick	Director, Regulatory and Quality Assurance- Sponsor
Greg Bakan	Vice President, Sales and Marketing - Sponsor
Jennifer Hebert	Director, Clinical Affairs - Sponsor
John McCutcheon	President/CEO - Sponsor

11.2 Data and Safety Monitoring Board

The DSMB will be responsible for making recommendations to the Operations Committee regarding endpoint analysis and any potential problems. The frequency of DSMB meetings will be determined prior to study commencement; however; DSMB may call a meeting at any time if there is reason to suspect that safety is an issue. The DSMB chairperson will notify Emphasys, by confidential memo, of any safety or compliance issues. They will also provide confidential recommendations, when necessary, of study continuation or termination based on the safety stopping rules determined at study onset, or because a statistically significant result was established.

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 applicable regulatory guidelines.

The DSMB will consist of at least one statistician, one pulmonologists and one thoracic surgeon with LVRS experience. 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.

11.3 Clinical Events Committee

The Clinical Events Committee (CEC) will consist of Pulmonologists, Thoracic Surgeons or Pulmonary Nurse Practitioners who are not otherwise participating in the study (Note: The CEC will be a separate group from the DSMB.). The CEC will meet regularly to review and adjudicate, in a blinded fashion, all serious and/or device related Adverse Events.

11.4 Core Radiology Lab

A core radiology lab (CRL) will be identified prior to patient enrollment. The CRL will be responsible for screening all baseline HRCT's for patient eligibility. For eligible patients, the CRL will score the degree and distribution of emphysema. These scores will be used in the algorithm to determine proper valve targeting.

11.5 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 meeting. A multi-center publication will also be prepared for publication in a reputable scientific journal. **The publication of results from any single center experience**

within the trial is not 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 by members of the Steering Committee will require the approval of the Operations Committee. We anticipate 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.

12.0 ADVERSE EVENT REPORTING

Adverse Event information will be collected throughout the study. The Investigator or Research Coordinator will record all Adverse Events on the appropriate CRF. The applicable CRF will capture the date of onset, severity, duration and relationship to the device or protocol.

A key used to accurately code all observations and Adverse Events is provided as **Appendix B**. Any event considered unexpected in nature, degree or severity MUST be reported to Emphasys within 24 hours of knowledge of the event. All reported observations and Adverse Events will be adjudicated by the Clinical Events Committee.

12.1 Duration of Follow-up after Adverse Events

All Adverse Events must be followed until resolution or until a stable clinical endpoint is reached. All required treatments and outcomes of the Adverse Event must be recorded as stated in Section 12.0.

12.2 Device Failures and Malfunctions

All investigational device failures and malfunctions will be documented on the CRF and reported in the clinical results.

12.2.1 Device Failure

A device has failed if it does not perform according to labeling and negatively impacts the treatment while used according to the labeling.

12.2.2 Valve Removal

The number of valves removed, the bronchus that the valve was removed from, and the reasons for device removals will be recorded.

12.2.3 Device Malfunction

A device malfunction is an unexpected change to the device that is contradictory to the labeling and may or may not affect device performance.

All devices considered to have malfunctioned or failed must be returned to Emphasys after appropriate decontamination per hospital guidelines.

13.0 REGULATORY RESPONSIBILITIES

13.1 Investigator Responsibilities

The investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol and the code of federal regulations. This section describes these responsibilities at his/her site.

13.1.1 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. The investigator is also responsible for fulfilling any conditions of approval imposed by the IRB, such as regular reporting, study timing, etc.

13.1.2 Informed Consent

Part of the IRB approval must include approval of an Informed Consent text specific to the trial. The investigator must administer this approved Informed Consent text to each prospective study patient, and obtain the patient's signature on the text, prior to enrollment in the study. A sample Informed Consent text will be provided. This may be modified to suit the requirements of the individual site. A copy of the informed consent that has been approved by the reviewing IRB will be provided to the study sponsor.

13.1.3 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.

13.1.4 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.

13.1.4.1 Correspondence

Records of all correspondence with another investigator, an IRB, a Core Laboratory, the sponsor, a monitor, or FDA, including required reports

13.1.4.2 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 sponsor or otherwise disposed of.

13.1.4.3 Patient Records

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

13.1.5 Reports

Table 15 displays a list of the reports that are the investigator's responsibility to generate. The table also shows to whom the report is to be sent, and with what frequency or time constraints. While some of these reports will be developed by or with the assistance of Emphasys the final responsibility for them rests with the investigator.

Table 15: Reports Required from Clinical Investigators

Type of Report	Prepared by Investigator For:	Time Constraints of Notification
Patient Death	Sponsor/ CEC/DSMB	Within 2 calendar days.
Unanticipated Adverse Effect	Sponsor/ CEC/DSMB	If serious or life-threatening, within 2 calendar days; otherwise within 10 working days.
Report of Patient Enrollment	Sponsor	Within 5 working days.
Patient Withdrawal	Sponsor	Within 5 working days.
Withdrawal of IRB Approval	Sponsor	Within 5 working days.
Annual Progress Report	Sponsor / IRB / EC	Submitted annually.
Significant Protocol Deviations	Sponsor	Within 5 working days.
Informed Consent Not Obtained	Sponsor / IRB / EC	Within 5 working days.
Final Summary Report	Sponsor / IRB / EC	Within 3 months.

13.2 Sponsor Responsibilities

Emphasys is the manufacturer of the study device and the sponsor of the clinical trial. Emphasys' responsibilities in the study include:

a. Provide study device to participating study sites, in quantities sufficient to support study activities, per agreements executed with the study sites.

b. Provide training to Principal Investigator(s) and Study Coordinator(s).

c. Select the clinical investigators and study sites, and other consultants who participate in the study.

d. Provide financial support to each study site and the core laboratories per individual contracts with each site.

e. Ensure that the study is conducted according to ISO 14155, Good Clinical Practice Guidelines 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.

f. Perform site monitoring of clinical data at clinical study sites

g. Emphasys retains ownership of all clinical data generated in this study, and controls the use of the data for purposes of regulatory submissions to the U.S. and/or other governments. Emphasys will exercise no veto over publication of study results in the medical literature but will be provided with advance copies of manuscripts and abstracts to review for technical accuracy.

h. Make an Investigator's Brochure available upon request to all investigators participating in the study.

13.3 Training

The training of appropriate clinical site personnel will be the responsibility of the sponsor. To insure uniform data collection and protocol compliance, a formal educational session will be provided to study site personnel which will review the Investigational Plan, techniques for the identification of eligible patients, instructions on in-hospital data collection, methods for soliciting data from alternative sources, schedules for follow-up with the study site coordinators, and regulatory requirements. Detailed telephone and fax feedback regarding completion of forms will be provided by the Sponsor, and through regular site monitoring.

13.4 Sponsor Monitoring on Site

Sponsor personnel or their designees will perform study site monitoring. Each site will be monitored according to 21 CFR 812 and Emphasys Medical'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 patient enrollment, patient selection, informed consent,

randomization, required clinical data and record keeping, etc. 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 the following documents are received by Emphasys:

1. Written IRB approval for conduct of the study
2. Text of the site's approved written study-specific patient consent document
3. Signed Clinical Trial Agreement
4. Investigators' and Co-investigators' current curriculum vitae

The Emphasys study monitor or designee will maintain personal contact with the investigator and staff throughout the study by phone, mail, and on-site visits. The monitor will compile and file an observation report at each visit. Monitoring will ensure continued protocol compliance, adequate patient enrollment, accurate data reporting, and adequate accounting of shipments of the study device.

At the close of the study at an investigational site, the clinical monitor will make a final on-site visit. The purpose of this visit is to collect all outstanding study data documents, ensure that the investigator's files are accurate and complete, review record retention requirements with the investigator, make a final accounting of all study supplies shipped to the investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study. The observations and actions made at this visit will be documented as a final report for investigator and sponsor acceptance.

13.5 Other Institutions

A complete list of participating study centers will be housed at Emphasys Medical, Inc.

14.0 GLOSSARY OF TERMS

6MWT – The six-minute walk 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 complication whether considered major or minor and whether or not associated directly with the Emphasys Endobronchial Valve procedure. Anticipated AE's are listed as endpoints, but unanticipated events are documented as well.

BODE Index – Body Mass Index, Airflow Obstruction, Dyspnea and Exercise Capacity index

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.

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 (DL_{CO}).

DL_{CO} – a measure of diffusing capacity (see above)

Dyspnea – Shortness of breath.

EBV – Emphasys Endobronchial Valve

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

Emphasys 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.

FEV_1 – Forced expiratory volume in one second is the minimum volume of gas that can be forcefully exhaled in one second after a maximal inspiration.

$FEF_{25\text{-}75\%}$ – Forced expiratory flow 25-75% is the average flow rate measured over the middle half (by volume) of the expiration.

FRC – Functional residual capacity is the volume of gas in the lung after a normal expiration.

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.

MMRC Survey – Modified Medical Research Council (MRC) dyspnea scale

NETT – acronym for National Emphysema Treatment Trial

$PaCO_2$ – Partial pressure of carbon dioxide in arterial blood.

PaO_2 – Partial pressure of oxygen in arterial blood.

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

QWB – a standardized, general quality of life assessment tool.

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.

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.

REFERENCES

[1] Celli BR, Cote CG, Marin JM, *et al*. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. N Engl J Med 2004;350;10
[2] Sciurba FC, Rogers RM, Keenan RJ, *et al*. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. N Engl J Med 1996;334:1095-1099.
[3] Martinez FJ. Montes de Oca M, Whyte RI, *et al*. Lung-volume reduction improves Dyspnea, dynamic hyperinflation, and respiratory muscle function. Am J Respir Crit Care Med 1997;155:1984-1990.
[4] Sabanathan A, Sabanathan S, Shah R., Richardson J. Lung volume reduction surgery for emphysema. J Cardiovasc Surg 1998;39:237-43.
[5] Geddes D, Davies M, Koyama H. Effect of Lung-Volume-Reduction Surgery in Patients with Severe Emphysema. N Engl J Med 2000;343:239-245.
[6] Gelb AF, et al. Lung Function 4 Years After Lung Volume Reduction Surgery for Emphysema. CHEST 1999;116,1608-1615.
[7] Gierada DS, et al. Patient Selection for Lung Volume Reduction Surgery, An Objective Model Based on Prior Clinical Decisions and Quantitative CT Analysis. CHEST 2000;117,991-998.
[8] Russi EW, Bloch KE, Weder W. Functional and morphological heterogenicity of emphysema and its implication for selection of patients for lung volume reduction surgery. Eur Resp J 1999;14,230-236.
[9] Rogers RM, et al. Preoperative Severity of Emphysema Predictive of Improvement After Lung Volume Reduction Surgery. CHEST 2000;118,1240-47.
[10] Gelb AF, Zamel Z, McKenna RJ Jr, et al. Mechanism of short-term improvement in lung function after emphysema resection. Am J Respir Crit Care Med 1996;154:945-951.
[11] Swanson SJ, Mentzer SJ, DeCamp MM Jr, *et al*. No-cut thoracoscopic lung plication: a new technique for lung volume reduction surgery. J Am Coll Surg 1997;185:25-32.
[12] Hoppin FG Jr. Theoretical basis for improvement following reduction pneumoplasty in emphysema. Am J Respir Crit Care Med 1997;155:520-525.
[13] Iwasaki M, Nishiumi N, Kaga K, et al. Application of the Fold Plication Method for Unilateral Lung Volume Reduction in Pulmonary Emphysema. Ann Thorac Surg 1999; 67:815-817
[14] Kuwahari I, Iwasaki M, Kaga K et al. Effectiveness of the Fold Plication Method in LVRS. Internal Medicine 2000; Vol. 39, 5:381-384.
[15] National Emphysema Treatment Trial Research Group. A Randomized Trial Comparing Lung-Volume-Reduction Surgery with Medical Therapy for Severe Emphysema. N Engl J Med 348:21:2059-2073.
[16] Toma TP et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. Lancet 2003; 361:931-33.
[17] Joyce CJ and Williams AB. Kinetics of absorption atelectasis during anesthesia: a mathematical model. J Appl Physiol 1999; 86:1116-1125.
[18] Woodring JH, Baker MD, and Stark P. Pneumothorax *ex-vacuo*. CHEST 1996; 110:1102-1105.
[19] Hoppin FG. Theoretical Basis for Improvement Following Reduction Pneumoplasty in Emphysema. Am J Respir Crit Care Med 1997;155:520-525.
[20] Sciurba et al. Improvement in Pulmonary Function and Elastic Recoil After Lung-Reduction Surgery for Diffuse Emphysema. NEJM 1996;334:1095-1099.
[21] Gelb AF et al. Mechanism of Short-term Improvement in Lung Function after Emphysema Resection. Am J Respir Crit Care Med 1996; 154:945-951.
[22] Fessler HE and Permutt S. Lung Volume Reduction Surgery and Airflow Limitation. Am J Respir Crit Care Med 1998; 157:715-722.
[23] Gelb AF et al. Serial Lung Function and Elastic Recoil 2 Years After Lung Volume Reduction Surgery for Emphysema. CHEST 1998; 113:1497-1506.
[24] O'Donnell, Denise E., Revill, Susan M., and Webb, Katherine A. Dynamic Hyperinflation and Exercise Intolerance in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med; 2001; Vol 164. pp770-777.
[25] Goddard PR, Nicholson EM, Laszlo G, Watt I. Computed tomography in pulmonary emphysema. Clin Radiol 1982; 33:379-387.
[26] Bergin C, Müller NL, Nichols DM, et al. The diagnosis of emphysema: a computed tomographic-pathologic correlation. Am Rev Respir Dis. 1986; 133:541-546.

[27] Bankier AA, Maertelaer VD, Keyzer C, Gevenois PA. Pulmonary Emphysema: Subjective Visual Grading versus Objective Quantification with Macroscopic Morphometry and Thin-Section CT Densitometry.
[28] Global Initiative for Chronic Obstructive Lung Disease, NHLBI/WHO Workshop Report, April 2001, NIH Publication #2701.
[29] Exercise program adapted from The National Emphysema Treatment Trial (NETT) Pulmonary Rehabilitation Protocol, courtesy of The University of Pittsburgh NETT Center.
[30] Joyce CJ and Williams AB. Kinetics of absorption atelectasis during anesthesia: a mathematical model. J Appl Physiol 1999; 86:1116-1125.
[31] Woodring JH, Baker MD, and Stark P. Pneumothorax *ex-vacuo*. CHEST 1996; 110:1102-1105.
[32] Starck P and Leung A. Effects of Lobar Atelectasis on the Distribution of Pleural Effusion and Pneumothorax. Journal of Thoracic Imaging 1996; 11:145-149.
[33] Gurney JW. Atypical Manifestations of Pulmonary Atelectasis. Journal of Thoracic Imaging 1996; 11:165-175.
[34] ATS Standardization of Spirometry. Am J Resp Crit Care med. 1994; 152:1110-1123 Update
[35] AARC Clinical Practive Guideline, Body Plethysmography: 2001 Revision and Update. Repspir Care 2001; 46 (5): 506-513
[36] ATS Standard for Single-breath Carbon Monoxide Diffusing Capacity (Transfer Factor). Am J Respir Crit Care Med. 1995; 152: 2185-2198
[37] Hankinson, JL, Odencrantz JR, Fedan KB. Spirometric Reference Values from a Sample of the General U.S. Population Am J Respir Crit Care Med 1999;159:179-187
[38] Silverman M, Barry J, Hellerstein H, et al. Variability of the perceived sense of effort in breathing during exercise in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1988;137 (1):206-9.
[39] Dyspnea: Mechanisms, Assessment, and Management: A Consensus Statement, Official Statement of the American Thoracic Society, Adopted July 1998. Am J Crit Care Med 1999; 159:321-340.
[40] ATS Statement: Guidelines for the Six-Minute Walk Test, Official Statement of the American Thoracic Society, Approved March 2002. Am J Crit Care Med 2002; 166:111-117.
[41] Lung Function Testing: Selection of Reference Values and Interpretive Strategies, Official Statement of the ATS. Am Rev Respir Dis 1991; 144:1202-1218.
[42] Redelmeier DA, Bayoumi AM, Goldstein RS, and Guyatt GH. Interpreting Small Differences in Functional Status: The Six Minute Walk Test in Chronic Lung Disease Patients. Am J Respir Crit Care Med 1997; 155:1278-1282.