**The IBV Valve Trial: a Multicenter, Randomized, Double-blind Trial of Endobronchial Therapy for Severe Emphysema**

Running head: Bronchial valve treatment for severe COPD with emphysema

Douglas E Wood MD1, Daniel A Nader DO2, Steven C Springmeyer MD3, Mark R Elstad MD4, Harvey O Coxson PhD5, Andrew Chan MD6, Navdeep S Rai MD7, Richard A Mularski MD8, Christopher Cooper MD9, Robert A Wise MD10, Paul W Jones MD11, Atul C Mehta MD12, Xavier Gonzalez MD3, Daniel H Sterman MD13 for the IBV Valve Trial Research Team

1University of Washington, Seattle, WA

2Oklahoma State University, Tulsa, OK, USA

3Spiration Inc, Redmond, WA, USA

4George E. Whalen DVA Medical Center, Salt Lake City, UT, USA

5Department of Radiology, Vancouver General Hospital, Vancouver, Canada

6University of California at Davis, Davis, CA, USA

7St. Joseph Medical Center, Tacoma, WA, USA

8The Center for Health Research, Kaiser Permanente Northwest, Portland, OR, USA

9University of California Los Angeles, Los Angeles, CA, USA

10Johns Hopkins University, Baltimore, MD, USA

11St. George’s Hospital Medical School, London, UK

12Cleveland Clinic Main Campus, Cleveland, OH, USA

 13University of Pennsylvania Medical Center, Philadelphia, PA, USA

Corresponding author: Douglas E Wood MD, Department of Cardiothoracic Surgery, 1959 N.E. Pacific, AA-115, Box 356310, Seattle, WA 98195-6310 dewood@u.washington.edu

Summary conflict of interest statements: SCS and XG are employees of Spiration. DEW, DAN, MRE, HOC, AC, NSR, RAM, CC and ACM received support for conducting research. DEW, CC, RAW, PWJ, ACM, and DHS received reimbursement for expenses and time as steering committee members)

Funding: Spiration, Inc.

Prior abstract publication/presentation: American Thoracic Society, May 2012, San Francisco, CA

***e-Appendix materials***

**Inclusion and Exclusion Criteria**

Inclusion Criteria

* Subject is between 40 and 74 years of age
* Subject has predominantly upper lobe emphysema and severe dyspnea
* Subject is certified to satisfy the criteria of the ATS/ERS Guidelines for Management of Stable COPD as documented by the Medical Management and Pulmonary Rehabilitation (MMPR) report form. If pulmonary rehabilitation is obtained to meet this criterion, then entry to the study will be within 6 weeks following completion of pulmonary rehabilitation.
* Subject must be able to demonstrate physical ability to participate in the study by performing a 6-minute walk distance of ≥ 140 m.
* Subject has abstained from cigarette smoking for 4 months, as confirmed by urine or serum cotinine test, and is willing to abstain throughout the study
* Subject’s obstructive disease is severe as defined by:
	+ FEV1 ≤45% of predicted
* Subject’s hyperinflation is defined by:
	+ TLC ≥ 100% of predicted
	+ RV ≥ 150% of predicted
* If eligible for LVRS or lung transplant, the subject has been counseled about the benefits and risks of surgery and has declined to proceed with surgery
* Subject is willing to participate in a blinded, controlled study, complete the required follow-up visits, and maintain consistent nutrition and exercise habits during the study period
* Investigator has confirmed by 2 independent subject evaluations that medical management is within standard of care and subject has been stable and without a COPD exacerbation for 6 weeks or more.

### Exclusion Criteria

* Subjects with FEV1 and DLCO < 20% of predicted
* Subjects over 70 years of age and an FEV1 or DLCO < 20% of predicted
* Subject has severe gas exchange abnormalities as defined by:
	+ PCO2 > 50 mm Hg
	+ PaO2 < 45 mm Hg on room air (Denver criterion: PaO2 < 30 mm Hg)
* Subject has co-existing major medical disease that will limit evaluation, participation, or follow-up in the study
* Subject is in poor nutritional health and requires specific intervention (see ATS/ERS Guidelines)
* A female subject, of childbearing potential, has a positive HCG pregnancy test. This test must be obtained within 7 days prior to the procedure.
* Subject is unable to provide informed consent
* Subject is not an appropriate candidate for or is unable to tolerate, flexible bronchoscopy procedures
* Subject has dysrhythmia or cardiovascular disease that poses a risk during exercise
* Subject has history of exercise-related syncope
* Subject has history of 2 or more hospitalizations for COPD exacerbation or respiratory infections in the past year.
* Subject has bronchitis with sputum production > 4 Tablespoons per day.
* Subject has an active asthma component to their disease or requires more than 15 mg of prednisone daily.
* Subject has giant bulla (> 1/3 volume of lung)
* Subject has severe pulmonary hypertension
* Subject has requirement for > 6 L O2 to keep saturation ≥ 90% with daily exercise
* Subject has evidence of systemic disease or neoplasia expected to compromise survival during the 6-month study period
* Subject has any disease or condition that interferes with completion of initial or follow-up assessments of the primary effectiveness measure. This would include neurological or musculoskeletal conditions that may interfere with testing.
* Subject has had prior lung volume reduction surgery or major lung procedures
* Subject has a lung nodule anticipated to require evaluation or intervention during the study period
* Subject has demonstrated unwillingness or inability to complete screening or baseline data collection procedures.
* Subject has a diffuse emphysema pattern or α1-Antitrypsin deficiency.
* Subject is classified as ASA Class greater than P4 including presence of co-morbidity that could significantly increase the risk of a bronchoscopy procedure.

|  |  |
| --- | --- |
| Short acting beta-agonist  | 94.0%  |
| Long acting beta-agonist  | 88.8%  |
| Short acting anticholinergic  | 24.8%  |
| Long acting anticholinergic  | 84.9%  |
| Inhaled corticosteroid  | 84.5%  |
| Oral corticosteroid  | 19.8%  |
| Methylxanthine  | 17.1%  |
| Prior pulmonary rehabilitation  | 53.4%  |
| Prescribed O2  at rest | 53.6%  |

* Subject participated in a study of an investigational drug or device within the past 30 days prior to participation in this study, or is currently participating in another clinical study

**e-Table 1**. Subject population medication use, prior pulmonary rehabilitation and oxygen use

**Initial 37 Subjects and a Protocol Revision**: The treatment algorithm was initially complete occlusion of the right upper lobe paired with the inclusion criteria for TLC being ≥ 125% of predicted. This was because a retrospective analysis of Pilot Study data indicated a higher TLC was associated with reduced pneumothorax presumably because of more collateral ventilation associated with more hyperinflation. After 3 episodes of pneumothorax in the first 37 randomized subjects (3 of 18 treatment patients or 16.6%) with surgical intervention in one and prolonged air leaks in two (21 and 16 day hospitalizations), the protocol was modified to bilateral-partial lobe occlusion and a TLC of ≥ 100% of predicted.

**Imaging Procedural Instructions**

A. CT Scanning for Quantitative Analysis

Image acquisition (non-contrast)

1. Must be a multi-slice CT scanner (8 detectors or more). GE, Siemens and Phillips equipment is preferred for this study.
	1. 1 or 1.25 mm volumetric acquisition with contiguous slices
	2. 120 kVp
	3. 130 mAs ("Care Dose"/"Smart Dose" off)
	4. CT scan at full suspended inspiration
	5. Smallest field of view that includes both lungs
2. Image Reconstruction:
	1. High spatial frequency reconstruction algorithm (GE – bone, Siemens – b60f)
	2. Low spatial frequency reconstruction algorithm (GE – standard, Siemens – b35f)
	3. Images reconstructed and archived with a 512 x 512 matrix

The images in digital format will be processed by the imaging core laboratory and then forwarded to the image analysis center for volumetric analyses.

B. Lung Scan with Quantitative Regional Perfusion Mapping:

Ventilation Scanningis not part of the protocol. The investigator uses a perfusion scan with quantitation for confirmation of upper lobe predominance and patient selection.

Perfusion Scanning Technique

• Patient Preparation: None

• Standard Dose: 4 mCi 99m Tc-MAA by IV administered with the patient supine.

• Standard Views: acquire at least 2 views; anterior and posterior.

The standard anterior and posterior views are used for this assessment. For the anterior view, the height of the right or left lung is divided into thirds. The counts from these three regions are measured from appropriate regions of interest for both the anterior and posterior images. Geometric mean for each of the three zones is calculated by multiplying the posterior counts by the anterior counts and then finding the square root of the product.

This process is then repeated for the other lung. The comparative perfusion value for each of the three right and three left zones relative to the total bilateral perfusion is given by summing the six geometric means for the R and L lungs. The geometric mean of each of the six zones is divided by the six geometric means for the six zones to give the percent of total perfusion that is contributed by each zone.

**e-Table 2.** Serious Adverse Events in the Primary Safety Measure

|  |
| --- |
| Acute asthma or bronchospasm requiring admission to an intensive or critical care unit  |
| Acute exacerbation of COPD that requires hospitalization |
| Airway injury from valve placement or bronchoscopic procedure requiring surgical intervention |
| Adult respiratory distress syndrome (ARDS) |
| Death from any cause |
| Hemoptysis estimated over 200 ml or requiring transfusion, surgery, or arterial embolization |
| Infection at any site requiring hospitalization and IV antibiotics  |
| Pneumonia requiring hospitalization and IV antibiotics. |
| Pneumothorax requiring surgical intervention |
| Prolonged air leak > 7 days defined as the time from chest tube insertion to the time the air leak is not persistent. |
| Respiratory failure that requires mechanical ventilatory support for > 24 hours |
| Stenosis or tissue reaction in an airway treated with a valve requiring intervention |
| Valve migration resulting in blockage of a non-targeted airway |

**e-Table 3.** Mean change (baseline to 6 months) for tests and questionnaires for treatment group by subset into those with or without a serious or severe adverse event in Days 0-7 after the procedure.

This Table shows that the 30 subjects that had adverse events within 7 days of the procedure have greater changes. This suggests the adverse values seen in the treatment group are due to procedure complications rather than the device.



**e-Figure 1.** Effect of sham-bronchoscopy procedure and optimal medical management on quality of life

****

**Description of Statistical Plan**

The IBV**®** Valve Trial is a prospective, randomized, blinded, controlled, adaptive, multicenter clinical trial to evaluate the safety and effectiveness of the IBV**®** Valve System for the treatment of severe emphysema. Subjects were randomized in a 1:1 ratio to receive the IBV**®** Valve System or undergo a sham control procedure. Adverse events were adjudicated by a clinical events committee and study outcomes reviewed by a data safety monitoring board.

The primary objective of the study was to demonstrate that the proportion of responders is statistically higher in the IBV group than in the control group. A responder was defined as a subject who met all of the following criteria:

* Improvement in St. George's Respiratory Questionnaire (SGRQ) Total score by at least 4 points (from baseline to 6 months)
* Increase in non-upper lobe (NUL) lung volume of at least 10% (from baseline to 6 months)
* Decrease in upper-lobe (UL) lung volume (from baseline to 6 months)

A major secondary objective related to efficacy was to demonstrate that the mean change (baseline to 6 months) in distance walked in a Six-Minute Walk Test (6MWT) was statistically higher in the IBV group than the control group. In both objectives, the standard for being "statistically higher" was that the posterior probability of superiority exceeded 95%. As part of the FDA submission process, the study design was extensively simulated under varying conditions, and the type I error rate (alpha) of the design was verified to be at most 0.05.

The primary safety objective was to compare the incidence of a composite of all serious adverse events between the treatment and control groups. This objective had no pre-specified pass/fail criterion.

Interim Analyses and Adaptive Sample Size Determination

The IBV**®** Valve Trial was designed with several pre-specified interim analyses, timed to occur when n=200, 250, 300, ..., 450 subjects had been accrued. At each interim analysis, the trial could stop enrolling either because current trends indicated futility or because current trends indicated that eventual success was likely with the current sample size. This determination was made using Bayesian predictive probability calculations and a model that included outcomes measured at 3 months for those who had not yet provided 6-month outcomes. If eventual success was likely on the primary objective (above 0.95 for the N=200 analysis, above 0.90 for the N=250 analysis, above 0.85 for the N=300 analysis, and above 0.80 for all subsequent interim analyses), the predictive probability of eventual success on the 6MWT (secondary) objective was to be calculated, and enrollment was to be stopped only if this predictive probability was sufficiently high (above a pre-specified threshold of 0.80) or sufficiently low (below a pre-specified threshold of 0.25). If enrollment did not stop at an interim analysis, accrual was to continue to the next pre-specified sample size increment, up to a maximum of 500 randomized subjects.

At the point of enrollment stop, an "interim win" analysis was to be conducted immediately; the standard for a win was that the predictive probability of eventual success was > 0.99. If this standard was not met, a second interim win analysis was to be conducted three months later, using the same standard. If that standard was not met, subjects were to be followed through 6 months, at which time a final analysis was to occur.

Prior Distributions

Bayesian analyses require specification of prior distributions for the parameters of interest. All priors are flat or minimally informative. For the primary objective, the probability of a subject being a responder was assigned a Beta(1,1) (i.e., uniform) prior distribution, separately for each treatment group. For adverse event summaries and comparisons, the probability of a subject having the event was assigned a Beta(0.1,0.1) prior distribution. Means (μ) and variances (σ2) of continuous variables were assigned a standard reference prior that is uniform on the (μ, log(σ)) scale.