

PHP_7.01.128		Bronchial Valves	
Original Policy Date:	December 1, 2025	Effective Date:	June 1, 2026
Section:	7.0 Surgery	Page:	Page 1 of 31

### State Guidelines

As of the publication of this policy, there are no applicable Medi-Cal guidelines (Provider Manual or All Plan Letter). Please refer to the Policy Statement section below.

### Policy Statement

In the absence of any State Guidelines, please refer to the criteria below.

- I. Bronchial valves are considered **investigational** in **all** situations including, but not limited to:
  - A. Treatment of prolonged air leaks
  - B. Treatment for individuals with chronic obstructive pulmonary disease or emphysema

### Policy Guidelines

#### Coding

See the [Codes table](#) for details.

### Description

Bronchial valves are synthetic devices deployed with bronchoscopy into ventilatory airways of the lung to control airflow. They have been investigated for use in individuals who have prolonged bronchopleural air leaks and in individuals with lobar hyperinflation from severe or advanced emphysema.

#### Summary of Evidence

For individuals who have pulmonary air leaks who receive bronchial valves, the evidence includes a systematic review, case series, and a prospective cohort observational study related to the Humanitarian Device Exemption for the Spiration IBV Valve device. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. Other reports are small series of heterogeneous patients, including a systematic review of these data. There are no comparative data with alternatives. This evidence is inadequate to determine the impact of this technology on the net health outcome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have severe or advanced emphysema with little or no collateral ventilation between target and ipsilateral lobe who receive bronchial valves, the evidence includes multiple randomized controlled trials (RCTs) comparing bronchial valves to usual care at 6 or 12 months, 1 RCT comparing bronchial valves to lung volume reduction surgery (LVRS) through 12 months, systematic reviews, a single center prospective cohort study with patient-reported outcomes, and a prospective cohort study comparing 2 different one-way valve devices. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The RCTs provide evidence of clinically meaningful benefit for bronchial valves compared to standard medical management on measures of lung function, exercise tolerance, and quality of life. However,

confidence in these results is low due to study limitations, including a lack of blinding and wide confidence intervals around the estimates of effect. Across studies, there was an increased risk of serious procedure-related adverse events compared to usual care, including pneumothorax occurring in up to 27% of patients. Results at 24 months have been published from one RCT (EMPROVE), with evaluable data from 114 of 172 participants (66.3%). Between the 12-month visit and 24-month visit, 10 participants died (8 intervention and 2 control). Change from baseline in FEV1 remained significantly improved in the treatment group compared to control group through 24 months, but the FEV1 responder rate (15% or greater improvement from baseline) at 24 months did not differ between groups (19.7% treatment vs 13.3% control;  $P = .57$ ). Acute exacerbations of COPD at the 24-month follow-up occurred in 13.7% (14 of 102) and 15.6% (7 of 45) of individuals in the treatment and control groups, respectively ( $P = .80$ ). Significant improvements were maintained through 24 months on some, but not all, measures of quality of life. A RCT (CELEB) that compared bronchial valves to LVRS in 80 individuals found no statistically significant difference between treatment groups on the primary outcome (change from baseline to 12 months on the iBODE instrument,  $-0.27$  ( $-0.62$  to  $1.17$ ;  $P = .54$ ). Notably, the magnitude of change from baseline for both groups on the i-BODE was below the 1.5-point difference considered by the study investigators to be sufficiently clinically important. The trial was limited by lack of participant blinding, high loss to follow-up, choice of a composite primary outcome, and evidence of selective outcome reporting. More participants in the bronchial valve group required additional procedures post-intervention, including 4 (8.5%) who went on to LVRS. In a prospective cohort study of patient-reported outcomes 1 year following treatment, 74.8% were satisfied with the treatment, 52.6% were satisfied with the reduction in their symptoms after treatment, and 91.4% said they would recommend the treatment to others. Confidence in these findings is limited by the study's uncontrolled design and high loss to follow-up (29.9%). The potential benefits of the procedure do not outweigh the demonstrated harms. In another prospective cohort study, there were no statistically significant differences between the Zephyr and Spiration one-way valve devices with regards to lung function, symptom burden, quality of life, or adverse events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

#### Additional Information

Not applicable

#### Related Policies

- N/A

#### Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

## Regulatory Status

In October 2008, the Spiration® IBV Valve System (Spiration) was approved by the U.S. Food and Drug Administration (FDA) through the humanitarian device exemption (H060002) process for use in controlling prolonged air leaks of the lung or significant air leaks that are likely to become prolonged air leaks following lobectomy, segmentectomy, or lung volume reduction surgery. An air leak present on postoperative day 7 is considered prolonged unless present only during forced exhalation or cough. An air leak present on day 5 should be considered for treatment if it is: (1) continuous, (2) present during the normal inhalation phase of inspiration, or (3) present on normal expiration and accompanied by subcutaneous emphysema or respiratory compromise. Use of the Intrabronchial Valve System is limited to 6 weeks per prolonged air leak. FDA product code: OAZ.

Two bronchial valve systems are FDA approved for treatment of patients with severe emphysema. In June 2018, FDA granted the Zephyr Valve system breakthrough device status with expedited approval for the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little to no collateral ventilation. In December 2018, the FDA approved the Spiration Valve System for adult patients with shortness of breath and hyperinflation associated with severe emphysema in regions of the lung that have evidence of low collateral ventilation. FDA product code: NJK.

**Table 1. Bronchial Valve Systems Approved by FDA**

Device	Indication	Manufacturer	Location	Date Approved	HDE/PMA No.
IBV® Valve System	To control prolonged air leaks of the lung, or significant air leaks that are likely to become prolonged air leaks, following lobectomy, segmentectomy, or lung volume reduction surgery	Spiration, Inc	Redmond, WA	10/24/08	H060002
Spiration® Valve System	For adult patients with shortness of breath and hyperinflation associated with severe emphysema in regions of the lung that have evidence of low collateral ventilation	Spiration, Inc	Redmond, WA	12/03/18	P180007
Zephyr® Endobronchial Valve System	For the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little to no collateral ventilation	Pulmonx Corporation	Redwood City, CA	06/29/18	P180002

FDA: Food and Drug Administration, HDE: human device exemption; PMA: premarket approval application.

## Health Equity Statement

Blue Shield of California Promise Health Plan’s mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan’s mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons

or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

**Rationale**

**Background**

**Pulmonary Air Leaks**

Proper lung functioning depends on the separation between the air-containing parts of the lung and the small vacuum-containing space around the lung called the pleural space. When air leaks into the pleural space, the lung is unable to inflate, resulting in hypoventilation and hypoxemia; this condition is known as a pneumothorax. A pneumothorax can result from trauma, high airway pressures induced during mechanical ventilation, lung surgery, and rupture of lung blebs or bullae, which may be congenital or a result of chronic obstructive pulmonary disease (COPD).

**Emphysema**

Emphysema, a form of COPD, is a progressive, debilitating disease characterized by irreversible destruction of alveolar tissue. This destruction results in reduced elastic recoil, progressive hyperinflation, and gas trapping, with patients experiencing chronic dyspnea, limited exercise tolerance, and poor health-related quality of life. In emphysematous COPD, diseased portions of the lung ventilate poorly, cause air trapping, and hyperinflate, compressing relatively normal lung tissue. The patterns and degree of emphysema heterogeneity (i.e., the extent and distribution of air space enlargements) can be measured using computed tomography (CT) density as an indicator for tissue destruction. The most diseased portions of lung can then potentially be targeted for lung volume reduction procedures. In homogeneous emphysema, there is minor or no regional difference in disease within or between lobes of the lung.

In the United States, the prevalence of COPD varies widely by state, with the estimated prevalence in 2021 ranging from <4.5% in California, the District of Columbia, Hawaii, and Utah to >9% in Kentucky, Mississippi, Tennessee, and West Virginia.<sup>1</sup> In 2018, chronic lower respiratory disease, primarily COPD, was the fourth leading cause of death in the United States.<sup>2</sup> COPD mortality has decreased among Americans overall, but this decline has not been observed in all sociodemographic groups. An analysis of COPD mortality between 2004 and 2018 found that African American women were the only sociodemographic group to have had an increase in COPD mortality, with an annual percent change (APC) of 1.3% (95% confidence interval [CI], 0.9% to 1.6%), compared to a decrease in men (APC -1.2%; 95% CI, -1.5% to -0.9%), and no change for women overall.<sup>3</sup>

The Global Initiative for Chronic Obstructive Lung Disease, or GOLD, system is commonly used to categorize patients with emphysema according to severity.<sup>4</sup> Stages of airflow limitation are based on the forced expiratory volume in 1 second (FEV1), or the amount of air a person can force out in 1 second after taking a deep breath. Patients with an FEV1 of less than 50% of their predicted value are considered to have severe airflow limitation. Patients are also grouped in the GOLD system using the ABE assessment tool according to categories of risk of having an exacerbation. These groups are based on the number and type of exacerbations per year and self-reported symptoms such as breathlessness. Of note, group E was previously divided into 2 separate groups, but was merged in 2023 to highlight the clinical significance of exacerbations.

**Table 2. Classification of Disease Severity**

Stages of Airflow Limitation	Severity Grouping
<ul style="list-style-type: none"> <li>• GOLD 1 (mild): FEV1 ≥80% predicted</li> <li>• GOLD 2 (moderate): 50% ≤ FEV1 &lt;80% predicted</li> <li>• GOLD 3 (severe):                             <ul style="list-style-type: none"> <li>○ 30% ≤ FEV1 &lt;50% predicted</li> </ul> </li> </ul>	<p><b>Group A:</b> 0 to 1 exacerbation per year, not requiring hospitalization, fewer symptoms</p> <p><b>Group B:</b> 0 to 1 exacerbation per year, not requiring hospitalization, more symptoms</p>

Stages of Airflow Limitation	Severity Grouping
<ul style="list-style-type: none"> <li>GOLD 4 (very severe): FEV1 &lt;30% predicted</li> </ul>	<b>Group E:</b> ≥2 exacerbations per year, or 1 or more requiring hospitalization

FEV1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

### Bronchial Valves

Bronchial valves are synthetic devices deployed with bronchoscopy into ventilatory airways of the lung to control airflow. During inhalation, the valve is closed, preventing air flow into the diseased area of the lung. The valve opens during exhalation to allow air to escape from the diseased area of the lung. They have been investigated for use in patients who have prolonged bronchopleural air leaks and in patients with lobar hyperinflation from severe or advanced emphysema.

When used to treat persistent air leaks from the lung into the pleural space, the bronchial valve theoretically permits less air flow across the diseased portion of the lung during inhalation, aiding in air leak closure. The valve may be placed, and subsequently removed, by bronchoscopy.

The use of bronchial valves to treat emphysema is based on the improvement observed in patients who have undergone lung volume reduction surgery. Lung volume reduction surgery involves excision of peripheral emphysematous lung tissue, generally from the upper lobes. The precise mechanism of clinical improvement for patients undergoing lung volume reduction has not been firmly established. However, it is believed that elastic recoil and diaphragmatic function are improved by reducing the volume of the diseased lung. Currently, and at the time the clinical trials were designed, very few lung volume reduction procedures were performed. The procedure is designed to relieve dyspnea and improve functional lung capacity and quality of life; it is not curative. Medical management remains the most common treatment for a majority of patients with severe emphysema.

In early trials of bronchial valves for treatment of emphysema, absence of collateral ventilation (pathways that bypass the normal bronchial airways) was associated with better outcomes, presumably because patients with collateral ventilation did not develop lobar atelectasis (collapse). In subsequent trials, patients were selected for absence of collateral ventilation, and it is current practice for patients to be assessed for the presence of collateral ventilation prior to undergoing the procedure. Collateral ventilation is measured by the Chartis System, which requires bronchoscopy, or as a surrogate, CT scanning to assess the completeness of fissures. After 45 days post-procedure, residual volume can provide information on whether lung volume reduction has been achieved successfully.

### Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects.

Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

## **Treatment of Pulmonary Air Leaks**

### **Clinical Context and Therapy Purpose**

The purpose of placing bronchial valves in individuals who have pulmonary air leaks is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is individuals with pulmonary air leaks.

### ***Interventions***

The therapy being considered is the placement of bronchial valves. A bronchial valve is a device that permits one-way air movement. During inhalation, the valve is closed, preventing air flow into the diseased area of the lung. The valve opens during exhalation to allow air to escape from the diseased area of the lung. When used to treat persistent air leak from the lung into the pleural space, the bronchial valve theoretically permits less air flow across the diseased portion of the lung during inhalation, aiding in air leak closure. The valve may be placed, and subsequently removed, by bronchoscopy.

### ***Comparators***

The following practices are currently being used:

- Inserting a chest tube (tube thoracostomy) and employing a water seal or one-way valve to evacuate air collected in the pleural space and prevent it from reaccumulating;
- Lowering airway pressures by adjusting the mechanical ventilator;
- Using autologous blood patches; and
- Performing a thoracotomy with mechanical or chemical pleurodesis.

### ***Outcomes***

The general outcomes of interest, in addition to overall survival, are a reduction in symptoms (e.g., pneumothorax) and improvements in functional outcomes. Placement of bronchial valves requires an inpatient surgical procedure. Bronchial valves can be utilized for up to 6 weeks to effect resolution of a persistent pulmonary leak.

## **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

## **Review of Evidence**

### **Systematic Reviews**

No RCTs or comparative observational studies were identified. Only case series and case reports, and a systematic review of this data, are available.

Damaraju et al (2024) published a systematic review of observational data evaluating the efficacy and safety of bronchial valves for pulmonary air leak.<sup>5</sup> The review included 28 studies comprising a total of 2472 patients and assessed the use of endobronchial valves, intrabronchial valves, or both. A

crosswalk of included studies and characteristics of the review are provided in Tables 3 and 4, respectively. Results of the analysis are presented in Table 4. The pooled success rate of bronchial valves for treating persistent air leak was 82% (95% confidence interval [CI], 75 to 88). Studies that used intrabronchial valves reported a numerically higher success rate compared to those using endobronchial valves (84% vs. 72%). Similarly, studies with more than 50 participants showed a numerically greater success rate than smaller studies (93% vs. 77%). However, none of these factors significantly influenced success rates in multivariable meta-regression analysis. The overall complication rate was 9.1% (48 out of 527 cases). The most common complications were granulation tissue (n=19), valve migration (n=5), and hypoxemia (n=5).

**Table 3. Comparison of Trials/Studies Included in SR & M-A**

Study	Damaraju et al (2024) <sup>5</sup>
Travaline et al (2009)	●
Gillespie et al (2011)	●
Firlinger et al (2013)	●
Dooms et al (2014)	●
Cordovilla et al (2015)	●
Hance et al (2015)	●
Podgaetz et al (2015)	●
Reed et al (2015)	●
Bakhos et al (2016)	●
Fiorelli et al (2016)	●
Gilbert et al (2016)	●
Cornwell et al (2016)	●
Gaspard et al (2017)	●
Fiorelli et al (2018)	●
Huang et al (2018)	●
Yu et al (2018)	●
Abu-Hiljeh et al (2019)	●
Bermea et al (2019)	●
Majid et al (2019)	●
Mukhtar et al (2019)	●
Flora et al (2021)	●
Keenan et al (2021)	●
Valentin et al (2021)	●
Singh et al (2022)	●
Song et al (2022)	●
Wang et al (2022)	●
Ficial et al (2023)	●
Omballi et al (2023)	●

M-A: meta-analysis; SR: systematic review.

**Table 4. SR & M-A Characteristics**

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Damaraju et al (2024) <sup>5</sup>	Through July 2023	28	Studies where ≥5 patients underwent bronchial valve placement for PAL	2472 (5 to 1185)	Observational	3 to 37 months

M-A: meta-analysis; PAL: pulmonary air leak; SR: systematic review;

**Table 5. SR & M-A Results**

Study	Success rate	Adverse events
Damaraju et al (2024) <sup>5</sup>		
Total N	2472	NR

Study	Success rate	Adverse events
Pooled effect (95% CI)	82.3% (75.4 to 88.2)	NR
		Granulation tissue (n=19) Valve migration (n=5) Hypoxemia (n=5) Pneumonia (n=3)

CI: confidence interval; M-A: meta-analysis; PAL: pulmonary air leak; SR: systematic review.

### Case Series

A review of selected case series is provided below.

In the largest United States-based case series to date, Mukhtar et al (2019) analyzed discharge data from the Agency for Healthcare Research and Quality-Nationwide Inpatient Sample between 2012 and 2016.<sup>6</sup> The analysis included adults diagnosed with pneumothorax who underwent endobronchial valve insertion either 3 or more days after chest tube placement or following an invasive thoracic procedure. All-cause mortality remained around 10% throughout the study period, with no statistically significant variation across study years (p=.713). Similarly, the average length of hospital stay was approximately 21 days, with no statistically significant variation across study years (p=.992).

Travaline et al (2009) reported on 40 patients treated at 17 sites in the United States and Europe.<sup>7</sup> The Zephyr Endobronchial Valve (EBV) was used. All patients in the series had prolonged pulmonary air leak (mean duration, 119 days; median, 20 days). The most common comorbidities were cancer and chronic obstructive pulmonary disease (COPD). After valve placement, 19 (47.5%) patients had complete resolution of the acute air leak, 18 (45%) had a reduction in air leak, 2 (5%) had no change, and no data were available for 1 patient. The mean time from valve placement to chest tube removal was 21 days (median time, 7.5 days). Six patients experienced adverse events related to valve placement, including valve expectoration, moderate oxygen desaturation, initial malpositioning of a valve, pneumonia, and *Staphylococcus aureus* colonization. The length of follow-up varied, ranging from 5 to 1109 days. At last follow-up, 16 patients had died, though none of the deaths was attributed to the valve or the implantation procedure.

Firlinger et al (2013) studied 13 patients with persistent, continuous air leak (i.e., having an intrathoracic chest tube for >7 days despite conservative and/or surgical therapy) in Austria.<sup>8</sup> Spiration valves were used in 9 patients and Zephyr valves in 4 patients. Ten (77%) of 13 patients were considered responders, defined as successful chest tube removal without need for further intervention. The Spiration IBV (intra-bronchial valve) was used in 6 of 10 responders and all 3 nonresponders.

Gillespie et al (2011) reported on a case series of 7 patients with pulmonary air leaks treated with Spiration IBV.<sup>9</sup> The median duration of air leaks in the 7 patients before valve placement was 4 weeks (range, 2 weeks to 5 months). One patient had a second valve implanted due to an additional air leak. Complete air leak cessation occurred in 6 of 8 procedures after a mean duration of 5.2 days. The other 2 procedures resulted in a reduction of air leak. There were no operative or postoperative complications attributed to the bronchial valves. The valves were removed in 5 of the 7 patients at a mean of 37 days after placement (range, 14 to 55 days). Valves were not removed from a patient who entered hospice care or the patient who underwent 2 procedures because the patient declined removal.

The Humanitarian Device Exemption approval of the IBV Valve required a post-approval study (PAS). The PAS was a prospective observational study to collect safety information about the IBV Valve System for the treatment of prolonged air leak. Eligible subjects were enrolled into the study on the day of valve treatment. The subjects were monitored after treatment until discharge from the hospital (a minimum of 1 night stay after the procedure). After discharge, the subjects were seen by

the investigator for assessment of air leak status as clinically indicated. Valves were to be removed after the air leak was resolved. If the air leak was not resolved, the valves were to be removed no longer than 6 weeks after device placement and other options were to be considered. A summary of the U.S. Food and Drug Administration (FDA) PAS is provided in Table 6.

**Table 6. Summary of IBV Valve PAS**

Study	Countries	Sites	Dates	Participants	SAEs	Findings Regarding Air Leak Resolution
H060002 / PAS001 Prospective Cohort Study	US	11	2009-2014	39 post IBV valve placement for prolonged air leak	2 <sup>1</sup>	32/39 per protocol follow-up: 2/32: no response 30/32: positive response 11/30: complete resolution 19/30: improvement

Source: [https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma\\_pas.cfm?c\\_id=249&t\\_id=367937](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?c_id=249&t_id=367937)

IBV: Intrabronchial valve; PAS: Post-Approval Study; SAE: serious adverse event.

<sup>1</sup> AE: One systolic arrest secondary to hypercapnia resolved prior to IBV placement and one mucus impaction of a bronchial valve

**Section Summary: Treatment of Pulmonary Air Leaks**

Data on the Spiration IBV are limited to reports of the first patients submitted to the Food and Drug Administration for the Humanitarian Device Exemption for use for prolonged air leaks, as well as the results of the PAS completed in 2014. Other reports are small series of heterogeneous patients, including a systematic review of this data. There are no comparative data with alternatives. This evidence is inadequate to determine the impact of this technology on the net health outcome.

**Treatment of Severe or Advanced Emphysema**

**Clinical Context and Therapy Purpose**

The purpose of placing bronchial valves in individuals who have severe or advanced emphysema with little or no collateral ventilation between target and ipsilateral lobe is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

**Populations**

The relevant population of interest is individuals with severe/advanced emphysema with little or no collateral ventilation between target and ipsilateral lobe who remain symptomatic despite optimal medical management.

Emphysema, a form of COPD, is a progressive, debilitating disease characterized by irreversible destruction of alveolar tissue. This destruction results in reduced elastic recoil, progressive hyperinflation, and gas trapping with patients experiencing chronic dyspnea, limited exercise tolerance, and poor health-related quality of life.

Bronchial valves would be considered for patients at Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3 or 4 (severe or very severe).

**Interventions**

The therapy being considered is the placement of bronchial valves. Bronchial valves are synthetic devices deployed with a flexible bronchoscope into the airways of the lung. The devices use a one-way valve to achieve an atelectasis (collapse) of the lobe, allowing air to escape while blocking airflow into the treated lobe. Valves are designed to prevent air inflow during inspiration but to allow air and mucus to exit during expiration. This is intended to result in a reduction in lung volume and hyperinflation in the targeted area. Endobronchial valve insertion is done with the patient under sedation or general anesthesia. Several valves may be needed. Bronchial valves can be removed or replaced using bronchoscopy.

**Comparators**

Alternatives for the treatment of severe emphysema include medical management, lung volume reduction surgery, and lung transplantation.

GOLD lists the following components of optimal medical management for severe emphysema:<sup>4</sup>

- Smoking cessation;
- Individualized pharmacological therapy;
- Assessment of inhaler technique;
- Pulmonary rehabilitation (exercise training, health education, breathing techniques);
- Influenza and pneumococcal vaccinations;
- Oxygen therapy;
- Palliative approaches to symptom control (treat dyspnea, support nutrition, address panic, anxiety, depression, and fatigue).

**Outcomes**

The general outcomes of interest, in addition to overall survival, are a reduction in symptoms, functional outcomes, quality of life, and treatment-related morbidity.

Relevant health outcomes include COPD exacerbations, mortality, and adverse events (e.g., pneumothorax, pneumonia, and respiratory failure). Efficacy outcomes include measures of lung function, physical function, and quality of life (Table 7).

Improvement in lung function after use of bronchial valves as part of multimodality pulmonary care should be assessed at 6 months after insertion.

**Table 7. Efficacy Outcome Measures**

Measure	Description	Clinically Meaningful Difference
FEV1	<ul style="list-style-type: none"> <li>• Volume of air a person can force out in 1 second after taking a deep breath</li> <li>• Not an objective of COPD management, but frequently used by regulatory authorities to interpret treatment efficacy in COPD trials</li> <li>• Used to categorize severity of airflow limitation</li> </ul>	15% improvement <ul style="list-style-type: none"> <li>• 100 to 140 mL increase</li> </ul>
SGRQ	<ul style="list-style-type: none"> <li>• Measures quality of life in patients with emphysema</li> <li>• Scores range from 0 to 100, with higher scores indicating a worse quality of life</li> </ul>	4-point decrease (improvement)
6-Minute Walk Test	<ul style="list-style-type: none"> <li>• Distance a person can walk in 6 minutes</li> <li>• Measures physical function</li> <li>• Healthy subjects can walk 400 to 700 meters</li> </ul>	Increase of 25 to 30 meters

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; SGRQ: St. George Respiratory Questionnaire.

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

**Review of Evidence**

**Zephyr Valve**

**Randomized Controlled Trials**

Seven RCTs have evaluated the Zephyr valve in patients with severe emphysema (Table 8). Only a single trial (BELIEVER) used a sham procedure as a comparator; the rest were open-label and compared the Zephyr valve to standard medical care, typically optimal medical care as described in the GOLD guidelines. The VENT trial included patients with collateral ventilation, but subgroup analyses of patients with collateral ventilation were reported. The IMPACT (A Multicentre, Prospective, Randomized, Controlled, One-way Crossover Investigation of Endobronchial Valve (EBV) Therapy vs. Standard of Care (SoC) in Homogeneous Emphysema) trial included patients with homogeneous emphysema distribution and the other trials were limited to those with heterogeneous emphysema. The BELIEVER trial was limited in that it only had a 3-month follow-up duration. The other trials followed patients for 6 or 12 months. In IMPACT, participants in the standard of care arm were crossed over to the Zephyr valve arm if eligible after completing 6 months of follow-up. Eberhardt et al (2021) reported randomized results up to 6 months and single-arm results at 12 months.<sup>10</sup>

A post hoc analysis of the 2 earliest trials (Endobronchial Valve for Emphysema Palliation Trial (VENT) EU 2012 and VENT US 2010) showed better response rates in participants who had intact fissures. As a result, the newer trials altered their inclusion criteria to only select participants with intact fissures, thereby lowering the chance of selecting participants who had collateral ventilation, which resulted in better functional outcomes.<sup>11</sup>

The trials showed statistically and clinically significant improvements in FEV1 (Table 9). Both response and mean change were significantly higher in the valve group in all the trials that measured this outcome. This was consistent and clinically meaningful, but there was some imprecision, with wide confidence intervals in some of the trials. On the St. George Respiratory Questionnaire (SGRQ), there was no significant difference in the sham-controlled study, while the open-label trials consistently showed a better outcome in the valve group.

The incidence of COPD exacerbations requiring hospitalization reported in the trials is shown in Table 10. In the immediate post-procedure period, more patients who received the intervention experienced a COPD exacerbation. However, at later time points, the incidence was lower among patients who received the valve. For example, in the LIBERATE (Lung Function Improvement After Bronchoscopic Lung Volume Reduction With Pulmonx Endobronchial Valves Used in Treatment of Emphysema) trial, the mean difference up to 45 days was 3.0% (95% confidence interval [CI], -4.1% to 10.1%), compared to 7.69% (95% CI, -5.99% to 21.38%) from day 46 up to 12 months.

Mortality and adverse event results are detailed in Table 11. The number of deaths was low, and studies were not powered to detect a difference in events between groups. The most common serious adverse event was pneumothorax, which occurred in up to 27% of patients.

**Table 8. Summary of Key RCT Characteristics- Zephyr Valve**

Trial	Countries	Sites	Dates	Participants	Interventions	Duration
LIBERATE, Criner et al (2018) <sup>12,13</sup>	US and other	31	2013-2016	Heterogeneous emphysema and little to no collateral	Zephyr valve (n=128) Standard care (n=62)	12 months
NCT01796392						

Trial	Countries	Sites	Dates	Participants	Interventions	Duration
				ventilation  91.6% White, 5.8% Black, 2.6% other race 46.8% male		
TRANSFORM, Kemp et al (2017) <sup>14</sup>  NCT02022683	Europe	17	2014-2016	Heterogeneous emphysema and no collateral ventilation  Race and ethnicity not reported 59.8% male	Zephyr valve (n=65)	Standard care (n=32)  6 months
IMPACT, Valipour et al (2016) <sup>15</sup> Eberhardt et al (2021) <sup>10</sup>  NCT02025205	Austria, Germany, Netherlands	15	2014-2016	Homogenous emphysema and no collateral ventilation  Race and ethnicity not reported 38.7% male	Zephyr valve (n=43)	Standard care (n=50)  6 months
STELVIO, Klooster et al (2015) <sup>16</sup>  NTR2876 (Netherlands)	Netherlands	1	NR	Severe emphysema and no collateral ventilation  Race not reported 32.4% male	Zephyr valve (n=34)	Standard care (n=34)  6 months
BELIEVER HI-FI, Davey et al (2015) <sup>17</sup>  ISRCTN04761234	England	1	2012-2013	Heterogeneous emphysema and intact interlobar fissures  Race and ethnicity not reported 62.0% male	Zephyr valve (n=25)	Sham procedure (n=25)  3 months
VENT EUROPE, Herth et al (2012) <sup>18</sup>  NCT00129584	Multiple European	23	2005-2009	Severe heterogenous emphysema  99.4% White 71.9% male	Zephyr valve (n=111, 44 with complete fissure)	Standard care (n=60, 19 with complete fissure)  12 months
VENT US, Scirba et al (2010) <sup>19</sup>  NCT00129584	US	31	2004-2006	Severe heterogenous emphysema  97.2% White 82.4% male	Zephyr valve (n=220)	Standard care (n=101)  6 months

NCT: National Clinical Trial; NR: Not reported; RCT: randomized controlled trial.

**Table 9. RCTs of the Zephyr Valve- Efficacy Results**

Study (Publication Date)	FEVI Responders (>15% Increase from Baseline <sup>1</sup> )	FEVI - Mean Change	SGRQ Responders (>4-point decrease from baseline)	SGRQ - Mean Change	6-Minute Walk Distance - Responders (>25 meters increase from baseline)	6-Minute Walk Distance - mean change, meters
<b>LIBERATE (2018)</b>						
Number analyzed	190	190	190	190	190	190
Zephyr valve	47.7%	17.2%	56.2%		41.8%	
Standard care	16.8%	-0.8%	30.2%		19.6%	
Difference (95% CI)	31.5% (18.9% to 44.1%)	17.96% (9.84% to 26.09%)	25.6% (11.3% to 39.9%)	-7.05 (-11.84 to -2.27)	22.8% (9.8% to 35.9%)	39.31 (14.64 to 63.98)
p-value	<.001	<.001	NR	.004	NR	<.002
<b>TRANSFORM (2017)</b>						
Total N	97	97	97	97	97	97
Zephyr valve	56.3%		61.7%		52.4%	36.2
Standard care	3.2%		34.4%		12.9%	-42.5
Difference (95% CI)	53.1% (NR)	0.23 L ( 0.14 to 0.32)	27.3% (NR)	-6.5 (-12.4 to -0.6)	39.5% (NR)	78.7 (46.3 to 111.0)
P-value	<.001	<.001	.042	.031	.001	<.001
<b>IMPACT (2016 and 2021)</b>						
Total N	93	93	84	84	92	92
Zephyr valve	30.2%	11.54%	63.9%	-6.84	45.2%	21.3
Standard care	10.0%	-4.73%	31.3%	0.63	22.0%	-7.1
Difference (95% CI)	20.2% (NR)	16.3% (NR)	32.8% (NR)	-7.51 (NR)	23.2% (NR)	28.3 (NR)
P-value	.014	<.0001	.003	<.0001	.018	.016
<b>STELVIO (2015)</b>						
Total N	68	NR	68	NR	68	68
Zephyr valve	59.0%	NR	79%	NR	59%	60 (35 to 85)
Standard care	24.0%	NR	33%	NR	6%	-14 (-25 to -3)
Difference (95% CI)	35.0% (NR)	NR	46% (NR)	NR	49% (NR)	74 (47 to 100)
P-value	0.001	NR	NR	NR	<.001	.001
<b>BELIEVER HI-FI (2015)</b>						
Total N	43	43	43	43	NR	43
Zephyr valve	47%	24.8%	58%		NR	Median, IQR: 25 (7 to 64)
Sham	4%	3.9%	46%		NR	Median, IQR: 3 (-14 to 20)
Difference (95% CI)	43.2% (19.4% to 67.0%)	20.9% (4.3% to 37.5%);	12.1% (-17.8% to 41.9%)	-9.64 (-14.09 to -5.20)	NR	NR
p-value	.0022	.033	NR	.36	NR	.0119
<b>VENT Europe</b>						
Total N	NR	63	NR	63	NR	63
Zephyr valve	NR	15%	NR	-6.0	NR	13%
Standard care	NR	-2%	NR	3.0	NR	10%
Difference (95% CI)	NR	17% (NR)	NR	3.0 (NR)	NR	3% (NR)
p-value	NR	.04	NR	.09	NR	.80
<b>VENT US<sup>2</sup></b>						
Total N	321	NR	321	NR	321	NR
Zephyr valve	23.5%	NR	23.5%	NR	25.3%	NR
Standard care	10.7%	NR	10.7%	NR	17.8%	NR
Difference (95% CI)	6.8 (NR)	NR	12.8%	NR	7.5% (NR)	NR

Study (Publication Date)	FEV1 Responders (>15% Increase from Baseline <sup>1</sup> )	FEV1 - Mean Change	SGRQ Responders (>4-point decrease from baseline)	SGRQ - Mean Change	6-Minute Walk Distance - Responders (>25 meters increase from baseline)	6-Minute Walk Distance - mean change, meters
p-value	.02	NR	.02	NR	.25	NR

<sup>1</sup>Responder definition was >10% in STELVIO and >12% in IMPACT and TRANSFORM.

CI: confidence interval; FEV1: forced expiratory volume in 1 second; IQR: interquartile range; NR: not reported; RCT: randomized controlled trial; SGRQ: St. George Respiratory Questionnaire.

**Table 10. COPD Exacerbations in RCTs of the Zephyr Valve**

Study	Time Point	Zephyr vs Control
LIBERATE	0 days to 46 days	7.8% vs. 4.8% Difference 3.0% (95% CI -4.1% to 10.1%)
	> 46 days to 12 months	23.0% vs. 30.6% Difference 7.69% (95% CI -5.99% to 21.38%)
TRANSFORM	0 days to 30 days	4.6% vs. 0%
	> 30 days to 6 months	4.6% vs. 6.3%
IMPACT	0 days to 30 days	14.0% vs. 1.0% p=.046
	31 days to 6 months	18.6% vs. 20.0%; p=1.00
STELVIO	0 days to 6 months	12% vs. 6%; p=.67
BELIEVER	0 days to 3 months	20.0% vs. 12.0%; p=.70
VENT EU	0 days to 3 months	11.7% vs. 10.0%; p=.80
	> 3 months to 12 months	Data NR (NS)
VENT US	0 days to 90 days	7.9% vs. 1.1%; p=.03
	3 months to 12 months	10.3% vs. 9.2%; p=.84

CI: confidence interval; COPD: chronic obstructive pulmonary disease; NR: not reported; NS: nonsignificant; RCT: randomized controlled trial.

**Table 11. Mortality and Serious Adverse Events in RCTs of the Zephyr Valve**

Study	Time Point	Mortality (Zephyr vs Control)	Serious Adverse Events (Zephyr vs Control)
LIBERATE	0 days to 46 days	3.1% vs. 0% Difference 3.1% (95% CI 0.11% to 6.1%)	39.8% vs. 4.8%
	>46 days to 12 months	0.8% vs. 1.6%	38.5% vs. 50.0%
TRANSFORM	0 days to 30 days	1.5% vs. 0%	38.5% vs. 3.1%
	>30 days to 6 months	0% vs. 0%	15.4% vs. 9.4%
IMPACT	0 days to 30 days	0 vs. 0	44.2% vs. 1.0%; p<.001
	31 days to 6 months	0 vs. 2 (4.0%)	34.9% vs. 26.0%; p=.269
STELVIO	0 days to 6 months	1 vs. 0	67.6% vs. 14.7%
BELIEVER	0 days to 3 months	2 vs. 0	% patients NR
VENT EU	0 days to 3 months	1 (0.9%) vs. 1 (1.7%); p=1.00	% patients NR
	>3 months to 12 months	5 (4.5%) vs. 3 (5.0%)	% patients NR
VENT US	0 days to 12 months	6 (5%) vs. 4 (7%)	% patients NR
	0 to 90 days	2 (0.9%) vs. 0 (0%)	4.2% vs. 0%
VENT US	3 months to 12 months	6 (2.8%) vs. 3 (3.4%); p=.72	6.1% vs. 4.6%
	0 days to 6 months	6 (2.8%) vs. 0 (0%); p=.19	6.1% vs. 1.2%; p=.08
	0 days to 12 months	3.7% vs. 3.5%; p=.88	10.3% vs. 4.6%; p=.17

CI: confidence interval; NR: not reported; RCT: randomized controlled trial.

Tables 12 and 13 summarize the design and conduct limitations of the Zephyr valve RCTs. Because they included patients with collateral ventilation, the VENT trials are no longer representative of the

intended use of the device. BELIEVER is limited by its 3-month follow-up duration. A major limitation in most of the trials was a lack of blinding, which could have influenced performance on measures of lung function, exercise tolerance (e.g., it might have affected clinicians' coaching of patients and/or the degree of effort exerted by patients), and patient-reported measures of symptoms and quality of life. Most studies were too small to detect differences between groups on important health outcomes such as mortality and COPD exacerbations. Five of 7 trials were conducted outside of the U.S. Three of 7 trials did not report race or ethnicity data on participants. In the 3 trials that reported race, 91.7% to 99.4% of participants were White. Therefore, it is uncertain if their results would be generalizable to the U.S. population.

**Table 12. RCTs of the Zephyr Valve- Relevance Limitations**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
LIBERATE					
TRANSFORM	4. unable to determine; race of participants not reported			6. Used >12% in FEV for response	
IMPACT	4. unable to determine; race of participants not reported				
STELVIO	4. unable to determine; race of participants not reported			6. Used >10% for FEV1 response	
BELIEVER HI-FI	4. unable to determine; race of participants not reported				1,2 three months only
VENT Europe	3. included patients with collateral ventilation; 4. 97.2% white				
VENT US	3. included patients with collateral ventilation; 4. 99.4% White				

FEV1: forced expiratory volume in 1 second.

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 13. RCTs of the Zephyr Valve- Study Design and Conduct Limitations**

Study	Allocation <sup>a</sup> Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
LIBERATE	1, 2 not blinded				

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
TRANSFORM		1, 2 not blinded				
IMPACT		1, 2 not blinded				
STELVIO		1, 2 not blinded		6 Not ITT for some outcomes		3. confidence intervals not reported for some outcomes
BELIEVER HI-FI						
VENT Europe		1, 2 not blinded			3 smaller than the a priori estimate	3. confidence intervals not reported for some outcomes
VENT US		1, 2 not blinded				

ITT: intent to treat.

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Systematic Reviews

Multiple systematic reviews with meta-analyses have assessed the use of the Zephyr valve system for patients with severe emphysema.<sup>11,20,21,22</sup> Authors of all of these reviews came to similar conclusions: In patients with severe emphysema and low collateral ventilation, RCTs provide evidence of clinically meaningful benefit for bronchial valves compared to standard medical management on short-term measures of lung function, exercise tolerance, and quality of life, but these benefits should be measured against the greater risk of serious adverse events compared to usual care.

A recent and relevant good methodological quality meta-analysis was conducted by LaBarca et al in 2019.<sup>22</sup> The remainder of this section focuses on this review. La Barca et al (2019) included all 7 RCTs of the Zephyr valve, but excluded from quantitative meta-analyses the 2 RCTs that included patients with collateral ventilation (VENT EU and VENT US) (Table 14). Two independent reviewers assessed the risk of bias of the included studies, and the quality of the overall body of evidence was ranked using the GRADE approach. Prespecified efficacy outcomes were change in FEV1, change in SGRQ, change in 6-minute walk test distance, and change in residual volume. The safety analysis included assessment of all-cause mortality and pneumothorax. The reviewers also conducted subgroup analyses based on length of follow-up (3 months vs. 6 months or longer), heterogeneous versus homogeneous emphysema distribution, and study comparator (standard of care vs. sham valve). Results are summarized in Table 15. Meta-analyses found statistically and clinically significant improvements with the Zephyr valve in FEV1, residual volume, 6-minute walk distance, and SGRQ,

but with an increased risk of adverse events. The certainty of evidence was rated high only for SGRQ and risk of pneumothorax. Certainty of the evidence for the other efficacy outcomes was downgraded due to risk of bias from lack of blinding, and non-primary outcomes. Certainty of the evidence was rated low for overall mortality because it was not a primary outcome and the estimate had wide confidence intervals.

**Table 14. Systematic Review and Meta-Analysis of the Zephyr Valve-Characteristics**

Study	Search end date	RCTs	Participants	N (Range)	Duration
LaBarca et al (2020) <sup>22</sup>	Oct 2018	7 (5 included in meta-analyses; excluded studies in patients with collateral ventilation)	Adult patients (mean age range 59.7 to 65.3 years); mostly COPD stage IV; without collateral ventilation measured by the Chartis system; optimal medical management according to GOLD recommendations;	498 (50 to 190)	3 to 12 months

COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; RCT: randomized controlled trial.

**Table 15. Meta-analysis of RCTs of the Zephyr Valve- Results<sup>22</sup>**

Outcome	Pooled Result (95% CI)	Heterogeneity	Certainty of the Evidence (reasons for downgrading)
<i>Change in Residual Volume, mL (mean difference)</i>	-0.57 (-0.76 to -0.39)	$I^2 = 37\%$ ; $p = .18$	Not assessed
<i>Change in FEV1, mL (mean difference)</i>	20.74% (15.68 to 25.79)	$I^2 = 25\%$ ; $p = .25$	Moderate (risk of bias regarding blinding of participants and personnel in most studies)
<i>Change in 6-min walk distance, meters (mean difference)</i>	53.10 (34.72 to 71.49)	$I^2 = 54\%$ ; $p = .07$	Low (high heterogeneity between studies despite subgroup analysis, non-primary outcome) Note: An erratum published in 2021 with corrected data found heterogeneity was no longer significant for this outcome, but the Certainty of Evidence rating was not changed
<i>Change in SGRQ score (mean difference)</i>	-8.42 (-10.86 to -5.97)	$I^2 = 6\%$ ; $p = .37$	High
<i>Pneumothorax (relative risk)</i>	6.32 (3.74 to 10.67)	$I^2 = 25\%$ ; $p = .25$	High
<i>Overall Mortality (relative risk)</i>	1.26 (0.50 to 3.15)	$I^2 = 25\%$ ; $p = .25$	Low (non-primary outcome, wide CI)

CI: confidence interval; FEV1: forced expiratory volume in 1 second; RCT: randomized controlled trial; SGRQ: St. George Respiratory Questionnaire.

**Randomized Controlled Trial of Zephyr Valve Compared to Lung Volume Reduction Surgery**

The CELEB study was an RCT comparing the Zephyr valve to LVRS in individuals with severe emphysema at 5 centers in the UK (Table 16). The primary outcome was the between group difference in the i-BODE index from baseline to 12 months post-procedure. i-BODE is a composite measure of disease severity made up of 4 components: the incremental shuttle walk test, body mass index, FEV1, and the Medical Research Council (MRC) dyspnea score. The instrument is scored from 0 to 10, with 10 indicating greater severity. The study authors do not cite a MCID threshold for the i-BODE, but calculated the sample size to detect a 1.5-point difference between groups, based on a previous study that reported an association between change in BODE score 3 months post-LVRS and survival at 5 years. Secondary outcomes were health status as assessed by the COPD Assessment Test (CAT) score, patient experience of physical activity assessed using the clinic visit PROactive Physical Activity in COPD (c-PPAC) score, change in residual volume, and change in fat-free mass index.

Of 163 individuals screened, 88 were eligible and randomized. The most common reason for ineligibility was evidence of collateral ventilation. A total of 80 individuals received treatment (34 LVRS, 46 BV). Six who were randomized to LVRS, and 1 who was randomized to the BV group decided against having the procedure post-randomization and exited the trial prior to treatment.

There was no statistically significant difference between groups on the primary outcome (Table 17), or on any of the 4 individual components of the composite measure (Table 15). Notably, the magnitude of change from baseline for both groups on the i-BODE was below the 1.5-point difference considered by the study investigators to be sufficiently clinically important. Of 4 secondary outcomes reported, only the CAT differed significantly between groups, and favored the LVRS arm with a magnitude of difference above the MCID threshold of 2 points (mean difference from baseline -6 [2 to 9]).

Other health outcomes are shown in Table 19. More participants in the BV group required additional procedures post-intervention, including 4 (8.5%) who went on to LVRS. There were 2 additional procedures required in the LVRS group; 1 participant returned to surgery for BV insertion due to a prolonged air leak, and 1 had a redo thoracotomy and wash out of a hemothorax. There were 7 repeat procedures in the BV group requiring the participant to undergo a further bronchoscopy; 4 related to pneumothoraces, with 2 requiring surgical chest drains and 2 undergoing blood pleurodesis. Two participants had valves removed and 1 participant had valves removed and replaced before undergoing a LVRS. Three further participants in the BV arm crossed over into the LVRS arm due to no symptomatic benefit. There was 1 death in the BV group (procedure-related) and 1 death in the LVRS group (not considered procedure-related). Participants undergoing BV placement were required to remain as inpatients for a minimum of 3 days post-procedure in case of pneumothorax. Of those who had a pneumothorax, 9 (81.8%) occurred while still an inpatient post procedure, median (IQR) time to onset was 2 (30) days, and the drain was removed after a median (IQR) 10 (12) days. The median (IQR) number of days with a chest drain post LVRS was 8.0 (11.0).

The study had several limitations that decrease confidence in its results (Tables 20 and 21). Lack of blinding of participants increases the potential for bias on outcomes requiring participant effort or self-reported experience of symptoms, although outcome assessors were blinded and participants were instructed not to reveal their allocation. Because it was designed to assess comparative effectiveness of bronchial valves and LVRS, the trial does not address existing gaps in the evidence on bronchial valves compared to medical management, the comparison of interest for this evidence review. The use of an endpoint not used in previous BV trials and the absence of outcomes that were primary endpoints in previous trials (such as the 6-minute walk test and the SGRQ) limits comparisons of the trial's results to the existing body of evidence. Additionally, the rationale for the choice of a composite endpoint was not clear. There is evidence of selective reporting of outcomes in that the published protocol lists the EQ-5D-5L as a secondary endpoint to be assessed, but this measure is not mentioned in the results publication and the reason for its absence is not addressed.<sup>23</sup> Given that the CAT score (a measure of health status) showed a statistically and clinically significant benefit for LVRS over BVs, additional comparative information on quality of life, if measured, would help to inform the assessment of whether the benefits of bronchial valves outweigh its demonstrated risks. Bronchial valves are proposed as a less invasive, and therefore safer, alternative to LVRS. However, participants who receive bronchial valves in the CELEB trial had more repeat procedures (including subsequent LVRS) than those who received LVRS and there was 1 procedure-related death in the BV group. Finally, the trial was limited by a high loss to follow-up: only 21 of 34 (61.8%) participants who received LVRS and 28 of 46 who received BVs (60.9%) had complete data on the primary outcome. The authors note that follow-up was interrupted due to the COVID-19 pandemic and some in-person research visits were missed as they were not possible or considered unsafe in this vulnerable group.

**Table 16. RCT of Bronchial Valves Compared to Lung Volume Reduction Surgery (CELEB) - Study Characteristics**

Trial	Countries	Sites	Dates	Participants	Interventions	Duration of Follow-up
Buttery et al (2023) <sup>24</sup>	UK	5	2016-2019	N = 8848% female, mean (SD) age 64.6 (7.7) years  All participants were required to have undergone a course of Pulmonary Rehabilitation within the 12 months preceding trial enrollment and underwent bronchoscopy to confirm absence of collateral ventilation. 87 (98.9%) White, 1 (1.1%) Middle Eastern	LVRS N = 41 randomized 34 received treatment  randomized 46 received treatment	12 months

LVRS: lung volume reduction surgery; RCT: randomized controlled trial; SD: standard deviation.

**Table 17. RCT of Bronchial Valves Compared to Lung Volume Reduction Surgery- Efficacy Results (Primary and Secondary Outcomes)**

	Secondary Outcomes, Mean Change from Baseline to 12 months					
	Primary Outcome	Health Status (CAT Score, 95% CI)	Health Related Quality of Life (EQ-5D-5L)	Residual Volume % predicted (95% CI)	Fat-free Mass (kg/m <sup>2</sup> )	Patient experience of Physical activity (PROactive Physical Activity in COPD instrument,(95% CI))
Buttery et al (2023) <sup>24</sup>	i-BODE mean change from baseline to 12 months (95% CI)					
N analyzed	49 (21 LVRS/28 BV)		Not reported			
LVRS	-1.10 (1.44)	-7 (-11 to -1)		-36.1 (-54.1, to -10)	-0.79 (-3.67 to 1.44)	+18.3 (17.3)
Bronchial Valves	-0.82 (1.61)	-1 (-3 to 3)		-30.1 (-53.7 to 9)	0.46 (-1.84 to 1.89)	+16.1 (16.9)
Difference (95% CI)	-0.27 (-0.62 to 1.17)	-6 (2 to 9)		2.7 (-25.4 to 19.1)	0.98 (-1.25 to 3.20)	-2.2 (-15.8 to 11.4)
p-value	.54	.005		.81	.39	.74

CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; CI: confidence interval. LVRS: lung volume reduction surgery.

**Table 18. RCT of Bronchial Valves Compared to Lung Volume Reduction Surgery- Efficacy Results- Components of Composite Primary Outcome**

	Mean Change from Baseline to 12 Months			
	BMI (kg/m <sup>2</sup> )	FEV1 % predicted	MRC Dyspnea score	ISWT (m)
Buttery et al (2023) <sup>24</sup>				
LVRS	0.10 (SD 1.83)	1.1 (SD 9.1)	-0.65 (SD 0.89)	27.9 (SD 60.7)
Bronchial Valves	0.74 (SD 1.57)	4.5 (SD 6.8)	-0.33 (SD 0.97)	-4.8 (SD 73.8)
Difference (95% CI)	0.64 (-0.27 to 1.56)	3.4 (CI -0.8 to 7.6)	-0.32 (-0.80 to 0.16)	-32.7 (-71.0 to 5.5)
P-value	.16	.11	.19	.09

BMI: body mass index; CI: confidence interval; FEV1: forced expiratory volume in 1 second; ISWT: incremental shuttle walk test; LVRS: lung volume reduction surgery; MRC: medical Research Council; RCT: randomized controlled trial.

**Table 19. RCT of Bronchial Valves Compared to Lung Volume Reduction Surgery- Other Health Outcomes and Adverse Events**

Study	Mortality at 12 months	COPD exacerbations requiring hospitalization at 3 months	Adverse Events
Buttery et al (2023) <sup>24</sup>			
LVRS	1 death 44 days post-procedure, complications related to the procedure	3/34 (8.8%)	Most common complication was subcutaneous emphysema (29.3%) 2 individuals required at least 1 further bronchoscopy or procedure 1 individual crossed over to bronchial valves
Bronchial Valves	1 death 5 months post-procedure, acute COPD exacerbation, not procedure related	5/46 (10.9%)	Most common complication was pneumothorax (30.4%) 8 individuals required at least 1 further bronchoscopy or procedure 4 individuals crossed over to LVRS

COPD: chronic obstructive pulmonary disease; RCT: randomized controlled trial.

**Table 20. RCT of Bronchial Valves Compared to Lung Volume Reduction Surgery- Study Relevance Limitations**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Buttery et al (2023) <sup>24</sup>			Comparator was LVRS	Rationale for choice of composite primary outcome measure unclear	

LVRS: lung volume reduction surgery.

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 21. RCT of Bronchial Valves Compared to Lung Volume Reduction Surgery - Study Design and Conduct Limitations**

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Buttery et al (2023) <sup>24</sup>		1. participants not blinded, outcome assessment blinded	2. Quality of life on EQ-5L was measured but not reported.	1. high loss to follow-up: 21/34 (61.8%) who received LVRS and 28/46 (60.9%) who received BV had data on the primary outcome (i-BODE at 12 months)		

BV: bronchial valve; LVRS: lung volume reduction surgery.

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment

unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

## Spiration Valve

### Randomized Controlled Trials

Three RCTs of the Spiration valve in patients with emphysema have been published.<sup>25,26,27</sup> One used a sham control, and 2 were open-label. Tables 22 to 25 summarize the characteristics and results of these trials.

EMPROVE (A Prospective, Randomized, Controlled Multicenter Clinical Study to Evaluate the Safety and Effectiveness of the Spiration<sup>®</sup> Valve System for the Single Lobe Treatment of Severe Emphysema) was an open-label trial of 172 patients with severe emphysema and no collateral ventilation. Twelve-month results were published in a peer-reviewed journal in 2019;<sup>27</sup> results were previously available as part of the Spiration Premarket Approval (PMA) application.<sup>28</sup> Efficacy results at 6 months (the timepoint for the primary endpoint, change in FEV1) are summarized in Table 23. Patients who received the Spiration valve had improvements in lung function and quality of life compared to usual care, but there was no significant difference between groups in exercise capacity. Thoracic serious adverse events, the primary safety outcome, were more frequent in the Spiration group (31.0% vs. 11.9%), primarily due to a 12.4% incidence of serious pneumothorax (Table 25). Criner et al reported 24-month results from EMPROVE in 2023.<sup>29</sup> Of the 172 participants enrolled, 114 were evaluable at 24 months: 80 (81.6%) of the treatment group and 34 (77.3%) of the control group. Between the 12-month visit and 24-month visit, 10 participants died (8 intervention and 2 control) and 15 additional withdrew (7 intervention, 8 control). Change from baseline in FEV1 remained significantly improved in the treatment group compared to control group through 24 months ( $P=.01$ ; data reported graphically only). The FEV1 responder rate (15% or greater improvement from baseline) at 24 months did not differ between groups (19.7% treatment vs 13.3% control;  $P=.57$ ). Acute exacerbations of COPD at the 24-month follow-up occurred in 13.7% (14 of 102) and 15.6% (7 of 45) of individuals in the treatment and control groups, respectively ( $P=.80$ ). One individual in the intervention group and none in the control group experienced a pneumothorax during the 12- to 24-month follow-up period. Significant improvements were maintained through 24 months on some, but not all, measures of quality of life; however confidence in these results is limited due to the study's lack of blinding. Significant differences were maintained on the SGRQ ( $P=.03$ ) and the mMRC dyspnea scale ( $P=.001$ ), but mean SF-36 PCS scores were not significantly different between groups ( $P=.06$ ).

The REACH (The Spiration Valve System for the Treatment of Severe Emphysema) trial found improvements in FEV1, 6-minute walk test, and SGRQ. The sham-controlled IBV Valve (A Prospective, Randomized, Controlled Multicenter Clinical Trial to Evaluate the Safety and Effectiveness of the IBV<sup>®</sup> Valve System for the Treatment of Severe Emphysema) trial showed statistically significant results favoring the Spiration valve, but confidence intervals were wide and the study authors concluded that the trial did not obtain clinically meaningful results.<sup>25</sup>

**Table 22. Summary of Key RCT Characteristics- Spiration Valve**

Trial	Countries	Sites	Dates	Participants	Interventions	Comparator	Duration
EMPROVE <sup>27,28</sup> NCT01812447 <sup>29</sup>	US and Canada	31	2013-2017	Severe emphysema without collateral ventilation  Race not reported 53.5% male	Spiration valve (n=113)	Standard care (n=59)	24 months  Primary outcome was FEV1 change at 6 months
REACH, Li et al (2018) <sup>26</sup> NCT01989182	China	12	2013-2017	Severe emphysema and intact interlobular fissures  100% Asian 99% male	Spiration valve (n=72)	Standard care (n=35)	6 months
IBV Valve, Wood et al (2014) <sup>25</sup> NCT00475007	US	36	2007-2017	Emphysema, airflow obstruction, hyperinflation, and severe dyspnea  Race not reported 57% male	Spiration valve (n=142)	Sham procedure (n=135)	6 months

IDE: Investigational Device Exemption; NCT: National Clinical Trial; NR: Not reported; RCT: randomized controlled trial.

**Table 23. RCTs of the Spiration Valve- Efficacy Results**

Study	FEV1 Responders (>15% Increase from Baseline)	FEV1 Mean Change, liters	SGRQ Responders (>4-point decrease from baseline)	SGRQ Score Mean Change	6-Minute Walk Distance- Responders (>25 meters increase from baseline)	6-Minute Walk Distance- Mean change, meters
<b>EMPROVE<sup>27,28</sup></b>						
Total N	156	156	136	136	150	150
Spiration valve	36.8%	NR	50.5%	-5.8	32.4%	NR
Standard care	10.0%	NR	22.0%	3.7	22.9%	NR
Difference (95% CI)	25.7% (12.7% to 38.7%)	0.101 (0.060 to 0.141)	28.6% (12.4% to 44.8%)	-9.5 (-14.4 to -4.7)	9.4% (-5.5% to 24.4%)	Difference 6.9 (-14.2 to 28.2)
p-value	NR	NR	NR	NR	NR	NR
<b>REACH<sup>26</sup></b>						
Total N	NR	NR	NR	NR	NR	NR
Spiration valve	48%	0.09 (95% CI 0.16 to 0.05)	NR	-8.39 (95% CI -12.69 to -4.08)	NR	20.82 (95% CI -0.58, 42.22)
Standard Care	13%	-0.24 (95% CI -0.14, -0.07)	NR	2.11 (95% CI -3.87, 8.08)	NR	-15.58 (95% CI -40.12, 8.96)
Difference (95% CI)	35% (NR)	NR	NR	NR	NR	NR
p-value	.001	.001	NR	.007	NR	NR

Study	FEVI Responders (>15% Increase from Baseline)	FEVI Mean Change, liters	SGRQ Responders (>4-point decrease from baseline)	SGRQ Score Mean Change	6-Minute Walk Distance- Responders (>25 meters increase from baseline)	6-Minute Walk Distance- Mean change, meters
IBV Valve <sup>25</sup>						
Total N	NR	250	254	277	NR	NR
Spiration valve	NR	-0.07 (SD 0.17)	32.2%	2.15 (16.36)	NR	-24.02
Sham	NR	0.00 (SD 0.16)	39.8%	-1.41 (11.26)	NR	-3.0
Difference	NR	(-0.11, -0.02)	7.6% (-4.15% to 19.39%)	(0.04, 7.07)	NR	-21.02 (-38.84 to -2.44)
p-value	NR	NR	NR	NR	NR	NR

CI: confidence interval; FEVI: forced expiratory volume in 1 second; NR: not reported; RCT: randomized controlled trial; SGRQ: St. George Respiratory Questionnaire.

**Table 24. COPD Exacerbations in RCTs of the Spiration Valve**

Study	Time Point	Spiration vs Control
EMPROVE	0 to 6 months	16.8% vs. 10.2% Difference 6.6% (95% CI -5.1% to 16.0%)
	>6 to 12 months	13.6% vs. 8.5% Difference 5.1% (95% CI -7.4% to 14.2%)
	>12 months to 24 months	13.7% vs 15.6%; P =.80
REACH	0 to 6 months	19.7% vs. 24.2%
IBV Valve	0 to 6 months	4.9% vs. 1.5% Difference 3.4% (95% CI -0.5 to 7.9%)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; RCT: randomized controlled trial.

**Table 25. Mortality and Serious Adverse Events in RCTs of the Spiration Valve**

Study	Time Point	Mortality Spiration vs Control	Serious Adverse Events Spiration vs Control
EMPROVE	0 to 6 months	5.3% vs. 1.7%; Difference 3.6% (95% CI -1.7% to 8.9%)	31.0% vs. 11.8%; 19.1% (95% CI 5.9% to 29.7%)
	>6 to 12 months	3.9% vs. 6.4%	21.4% vs. 10.6%; 10.7% (95% CI 3.0% to 21.2%)
	>12 months to 24 months	7.8% vs 4.4%; P =.72	27.5% vs 15.6%; P =.41
REACH	0 to 6 months	0% vs. 3.0%	44.3% vs. 24.2%
IBV Valve	0 to 6 months	4.2% vs. 0.7%; Difference 3.5% (95% CI 0.2% to 7.5%)	14.1% vs. 3.7%; 10.4% (95% CI 4.0% to 17.1%)

CI: confidence interval; RCT: randomized controlled trial.

Tables 26 and 27 summarize the design and conduct limitations of the Spiration valve RCTs. A major limitation was a lack of blinding, which could have influenced performance on measures of lung function, exercise tolerance (e.g., it might have affected clinicians' coaching of patients and/or the degree of effort exerted by patients), and patient-reported measures of symptoms and quality of life. One trial was conducted in China and the 2 trials conducted in the U.S. did not report data on race. Therefore, it is uncertain if the study results would be generalizable to the U.S. population.

**Table 26. RCTs of the Spiration Valve- Study Relevance Limitations**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
EMPROVE	4. unable to determine; race of participants not reported				
REACH	4. 100% male				
IBV Valve	4. unable to determine; race of participants not reported				

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 27. RCTs of the Spiration Valve- Study Design and Conduct Limitations**

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
EMPROVE		1, 2 not blinded				
REACH		1, 2 not blinded				
IBV Valve						

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

**Prospective Cohort Study**

Hartman et al (2021) conducted a prospective cohort study to investigate patient satisfaction and patient-specific treatment goals among individuals who received bronchial valves for the treatment of severe emphysema at 1 hospital in the Netherlands.<sup>30</sup> Patient satisfaction was measured by a questionnaire administered 1 year after valve placement. Patient-specific goals were measured using the Dutch patient-specific complaint (PSC) questionnaire. In this questionnaire, patients reported their 3 most personally desired post-treatment goals and used a numeric rating scale (0 to 10) to score the level of disability per goal before and 1 year after treatment. Lung function, exercise capacity, dyspnea severity, and quality of life were also measured before treatment and at 1-year follow-up. Of 134 patients who underwent bronchial valve placement prior to January 1, 2019, 109 (81.3%) completed the patient-satisfaction questionnaire, 88 (65.7%) completed the PSC questionnaire at baseline and follow-up, and 94 (70.1%) returned to the hospital for a follow-up visit at 1 year. Reasons for loss to follow-up in 40 patients were bronchial valve removed (16 patients), died (n=5), comorbidity (n=5), revision at that time (n=3), lung volume reduction surgery (LVRS) or lung transplant (n=2), and other (n=9). The PSC-questionnaire score significantly improved 1 year after bronchial valve treatment, from 23.7 to 17.1 points (mean decrease of 6.5 points; p=.001) and an improvement in the PSC-questionnaire sum score was significantly associated with a larger improvement in FEV1, residual volume, exercise capacity, dyspnea severity, and quality of life. Seventy-five percent of the patients who completed the questionnaire were satisfied or very satisfied with the treatment and 11% were unsatisfied or very unsatisfied. Just over half of the questionnaire respondents (52.6%) were satisfied or very satisfied with the reduction in their symptoms after treatment, and 24.9% were unsatisfied or very unsatisfied. For the question of whether the treatment

satisfied their expectations (range 1 to 5), the mean score was 3.29 (standard deviation 1.43). Most of those who completed the questionnaire (91.4%) would recommend the treatment to other patients.

This study was limited by its uncontrolled design and relatively high loss to follow-up (29.9%), but it provides information on outcomes important to patients that could be used to guide future research.

Sgarbossa et al (2024) conducted a prospective observational study across 3 emphysema centers in Germany to compare the efficacy and safety of Zephyr and Spiration valve devices in patients with severe lung emphysema.<sup>31</sup> Eligible patients (FEV1  $\leq$ 45% predicted) were included and evaluated at baseline and 3 to 6 months post-endoscopic LVRS. A total of 153 patients were analyzed (Spiration, n=54; Zephyr, n=99). Both groups showed significant improvements in lung function, symptom burden, and quality of life. From baseline to follow-up, FEV1 increased from 0.81 to 0.96 L with Spiration and from 0.72 to 0.79 L with Zephyr ( $p < .001$  for both). Changes in the SGRQ score demonstrated improvements from baseline, from 67.45 to 57.18 points with Spiration ( $p = .042$ ) and from 65.72 to 60.03 points with Zephyr ( $p < .001$  for both). Likewise, changes in 6-minute walk distance improved from 225 to 285 meters with Spiration and from 242 to 295 meters with Zephyr ( $p < .001$  for both). No significant differences were observed between groups in the median changes of these parameters or in adverse event rates, including pneumothorax (Spiration: 9%, Zephyr: 12%;  $p = .601$ ), valve explantation (Spiration: 4%, EBV: 1%;  $p = .284$ ), or mortality (1 in each group).

### Section Summary: Severe or Advanced Emphysema

In individuals with severe or advanced emphysema with little or no collateral ventilation between target and ipsilateral lobe, RCTs provide evidence of clinically meaningful benefit for bronchial valves compared to standard medical management on measures of lung function, exercise tolerance, and quality of life. However, confidence in these results is low due to study limitations, including a lack of blinding and wide confidence intervals around estimates of effect. Across studies, there was an increased risk of serious procedure-related adverse events compared to usual care, including pneumothorax occurring in up to 27% of patients. Results at 24 months have been published from one RCT (EMPROVE), with evaluable data from 114 of 172 participants (66.3%). Between the 12-month and 24-month visits, 10 participants died (8 intervention and 2 control). Change from baseline in FEV1 remained significantly improved in the treatment group compared to control group through 24 months, but the FEV1 responder rate (15% or greater improvement from baseline) at 24 months did not differ between groups (19.7% treatment vs 13.3% control;  $P = .57$ ). Acute exacerbations of COPD at the 24-month follow-up occurred in 13.7% (14 of 102) and 15.6% (7 of 45) of individuals in the treatment and control groups, respectively ( $P = .80$ ). Significant improvements were maintained through 24 months on some, but not all, measures of quality of life. A RCT (CELEb) that compared bronchial valves to LVRS in 80 individuals found no statistically significant difference between treatment groups on the primary outcome (change from baseline to 12 months on the iBODE instrument, -0.27 (-0.62 to 1.17;  $P = .54$ ). Notably, the magnitude of change from baseline for both groups on the i-BODE was below the 1.5-point difference considered by the study investigators to be sufficiently clinically important. The trial was limited by a lack of participant blinding, high loss to follow-up, choice of a composite primary outcome, and evidence of selective outcome reporting. More participants in the bronchial valve group required additional procedures post-intervention, including 4 (8.5%) who went on to LVRS. In a prospective cohort study of patient-reported outcomes 1 year following treatment, 74.8% were satisfied with the treatment, 52.6% were satisfied with the reduction in their symptoms after treatment, and 91.4% said they would recommend the treatment to others. Confidence in these findings is limited by the study's uncontrolled design and high loss to follow-up (29.9%). The potential benefits of the procedure do not outweigh the demonstrated harms. In another prospective cohort study, there were no statistically significant differences between the Zephyr and Spiration one-way valve devices with regard to lung function, symptom burden, quality of life, or adverse events.

### Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a U.S. professional society, an international society with U.S. representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### Global Initiative for Chronic Obstructive Lung Disease (GOLD)

The 2025 GOLD publication makes the following recommendations and statements on lung volume reduction interventions (see Figure 3.27 in the GOLD publication):<sup>4</sup>

- "In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, health status, and lung function at 6 to 12 months following treatment. Endobronchial valves (Evidence A); lung coils (Evidence B); vapor ablations (Evidence B)." Per the guideline, Evidence category A includes data from: "well-designed randomized controlled trials that provide consistent findings in the population for which the recommendation is made without any important limitations...or high quality evidence from 2 or more clinical trials involving a substantial number of subjects, or a single high quality randomized controlled trial involving substantial numbers of patient without any bias."
- "In selected patients with heterogeneous or homogenous emphysema and significant hyperinflation refractory to optimized medical care, surgical or bronchoscopic modes of lung volume reduction (e.g., endobronchial one-way valves, lung coils or thermal ablation) may be considered."
- "In select patients with advanced emphysema refractory to optimized medical care, surgical or bronchoscopic interventional treatments may be beneficial."

### National Institute for Health and Care Excellence (NICE)

In December 2017, NICE issued the following recommendations on endobronchial valve insertion to reduce lung volume in emphysema:<sup>32</sup>

1.1 Current evidence on the safety and efficacy of endobronchial valve insertion to reduce lung volume in emphysema is adequate in quantity and quality to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit.

1.2 Patient selection should be done by a multidisciplinary team experienced in managing emphysema, which should typically include a chest physician, a radiologist, a thoracic surgeon and a respiratory nurse.

1.3 Patients selected for treatment should have had pulmonary rehabilitation.

1.4 The procedure should only be done to occlude volumes of the lung where there is no collateral ventilation, by clinicians with specific training in doing the procedure.

NICE guidance on the diagnosis and management of COPD (2018, updated 2019) included the following recommendations on lung volume reduction procedures:<sup>20</sup>

Offer a respiratory review to assess whether a lung volume reduction procedure is a possibility for people with COPD when they complete pulmonary rehabilitation and at other subsequent reviews, if all of the following apply:

- they have severe COPD, with FEV1 less than 50% and breathlessness that affects their quality of life despite optimal medical treatment
- they do not smoke

- they can complete a 6-minute walk distance of at least 140 m (if limited by breathlessness).

At the respiratory review, refer the person with COPD to a lung volume reduction multidisciplinary team to assess whether lung volume reduction surgery or endobronchial valves are suitable if they have:

- hyperinflation, assessed by lung function testing with body plethysmography **and**
- emphysema on unenhanced CT chest scan **and**
- optimised treatment for other comorbidities.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**

Some ongoing and unpublished trials that might influence this review are listed in Table 28.

**Table 28. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT01796392 <sup>a</sup>	Lung Function Improvement After Bronchoscopic Lung Volume Reduction With Pulmonx Endobronchial Valves Used in Treatment of Emphysema (LIBERATE)	190	Apr 2024 (post approval study, 5-year extension)
NCT04186546 <sup>a</sup>	Zephyr Valve Registry (ZEVr)	150	Dec 2026
NCT04302272 <sup>a</sup>	The Spiration Valve System (SVS) Post-Market Registry Study for Severe Emphysema	150	Apr 2028

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

**References**

1. Centers for Disease Control and Prevention. Chronic Obstructive Pulmonary Disease (COPD). Data and Statistics. 2024. <https://www.cdc.gov/nchs/fastats/copd.htm> Accessed April 24, 2025.
2. Xu JQ, Murphy SL, Kochanek KD, Arias E. Mortality in the United States, 2018. NCHS Data Brief, Number 355. Hyattsville, MD: National Center for Health Statistics; 2020. <https://www.cdc.gov/nchs/data/databriefs/db355-h.pdf>. Accessed April 24, 2025.
3. Zarrabian B, Mirsaeidi M. A Trend Analysis of Chronic Obstructive Pulmonary Disease Mortality in the United States by Race and Sex. *Ann Am Thorac Soc*. Jul 2021; 18(7): 1138-1146. PMID 33347376
4. Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2025 Global Strategy for Prevention, Diagnosis, and Management of COPD. <https://goldcopd.org/2025-gold-report/>. Accessed April 24, 2025.
5. Damaraju V, Sehgal IS, Muthu V, et al. Bronchial Valves for Persistent Air Leak: A Systematic Review and Meta-analysis. *J Bronchology Interv Pulmonol*. Jul 01 2024; 31(3). PMID 38716831
6. Mukhtar O, Khalid M, Shrestha B, et al. Endobronchial valves for persistent air leak all-cause mortality and financial impact: US trend from 2012-2016. *J Community Hosp Intern Med Perspect*. 2019; 9(5): 397-402. PMID 31723383
7. Travaline JM, McKenna RJ, De Giacomo T, et al. Treatment of persistent pulmonary air leaks using endobronchial valves. *Chest*. Aug 2009; 136(2): 355-360. PMID 19349382

8. Firlinger I, Stubenberger E, Müller MR, et al. Endoscopic one-way valve implantation in patients with prolonged air leak and the use of digital air leak monitoring. *Ann Thorac Surg*. Apr 2013; 95(4): 1243-9. PMID 23434254
9. Gillespie CT, Sterman DH, Cerfolio RJ, et al. Endobronchial valve treatment for prolonged air leaks of the lung: a case series. *Ann Thorac Surg*. Jan 2011; 91(1): 270-3. PMID 21172529
10. Eberhardt R, Slebos DJ, Herth FJF, et al. Endobronchial Valve (Zephyr) Treatment in Homogeneous Emphysema: One-Year Results from the IMPACT Randomized Clinical Trial. *Respiration*. 2021; 100(12): 1174-1185. PMID 34350884
11. van Agteren JE, Hnin K, Grosser D, et al. Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. Feb 23 2017; 2(2): CD012158. PMID 28230230
12. Criner GJ, Sue R, Wright S, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE). *Am J Respir Crit Care Med*. Nov 01 2018; 198(9): 1151-1164. PMID 29787288
13. Dransfield MT, Garner JL, Bhatt SP, et al. Effect of Zephyr Endobronchial Valves on Dyspnea, Activity Levels, and Quality of Life at One Year. Results from a Randomized Clinical Trial. *Ann Am Thorac Soc*. Jul 2020; 17(7): 829-838. PMID 32223724
14. Kemp SV, Slebos DJ, Kirk A, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM). *Am J Respir Crit Care Med*. Dec 15 2017; 196(12): 1535-1543. PMID 28885054
15. Valipour A, Slebos DJ, Herth F, et al. Endobronchial Valve Therapy in Patients with Homogeneous Emphysema. Results from the IMPACT Study. *Am J Respir Crit Care Med*. Nov 01 2016; 194(9): 1073-1082. PMID 27580428
16. Klooster K, ten Hacken NH, Hartman JE, et al. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. *N Engl J Med*. Dec 10 2015; 373(24): 2325-35. PMID 26650153
17. Davey C, Zoumot Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HiFi study): a randomised controlled trial. *Lancet*. Sep 12 2015; 386(9998): 1066-73. PMID 26116485
18. Herth FJ, Noppen M, Valipour A, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. *Eur Respir J*. Jun 2012; 39(6): 1334-42. PMID 22282552
19. Sciruba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med*. Sep 23 2010; 363(13): 1233-44. PMID 20860505
20. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: Diagnosis and management. Available at: <https://www.nice.org.uk/guidance/ng115/chapter/Recommendations#managing-stable-copd>. Accessed April 24, 2025.
21. van Geffen WH, Slebos DJ, Herth FJ, et al. Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis. *Lancet Respir Med*. Apr 2019; 7(4): 313-324. PMID 30744937
22. Labarca G, Uribe JP, Pacheco C, et al. Bronchoscopic Lung Volume Reduction with Endobronchial Zephyr Valves for Severe Emphysema: A Systematic Review and Meta-Analysis. *Respiration*. 2019; 98(3): 268-278. PMID 31117102
23. Buttery S, Kemp SV, Shah PL, et al. CELEB trial: Comparative Effectiveness of Lung volume reduction surgery for Emphysema and Bronchoscopic lung volume reduction with valve placement: a protocol for a randomised controlled trial. *BMJ Open*. Oct 17 2018; 8(10): e021368. PMID 30337307
24. Buttery SC, Banya W, Bilancia R, et al. Lung volume reduction surgery versus endobronchial valves: a randomised controlled trial. *Eur Respir J*. Apr 2023; 61(4). PMID 36796833
25. Wood DE, Nader DA, Springmeyer SC, et al. The IBV Valve trial: a multicenter, randomized, double-blind trial of endobronchial therapy for severe emphysema. *J Bronchology Interv Pulmonol*. Oct 2014; 21(4): 288-97. PMID 25321447

26. Li S, Wang G, Wang C, et al. The REACH Trial: A Randomized Controlled Trial Assessing the Safety and Effectiveness of the Spiration® Valve System in the Treatment of Severe Emphysema. *Respiration*. 2019; 97(5): 416–427. PMID 30554211
27. Criner GJ, Delage A, Voelker K, et al. Improving Lung Function in Severe Heterogenous Emphysema with the Spiration Valve System (EMPROVE). A Multicenter, Open-Label Randomized Controlled Clinical Trial. *Am J Respir Crit Care Med*. Dec 01 2019; 200(11): 1354-1362. PMID 31365298
28. U.S. Food & Drug Administration. Spiration Valve System. Summary of Safety and Effectiveness Data. Available at: [https://www.accessdata.fda.gov/cdrh\\_docs/pdf18/P180007B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180007B.pdf). Accessed April 23, 2025.
29. Criner GJ, Mallea JM, Abu-Hijleh M, et al. Sustained Clinical Benefits of Spiration Valve System in Patients with Severe Emphysema: 24-Month Follow-Up of EMPROVE. *Ann Am Thorac Soc*. Feb 2024; 21(2): 251-260. PMID 37948704
30. Hartman JE, Klooster K, Ten Hacken NHT, et al. Patient Satisfaction and Attainment of Patient-Specific Goals after Endobronchial Valve Treatment. *Ann Am Thorac Soc*. Jan 2021; 18(1): 68-74. PMID 32881586
31. Sgarbossa T, Borchers P, Saccomanno J, et al. Comparison of Efficacy and Safety of Different Types of One-Way Valves in Endoscopic Lung Volume Reduction in Patients with Severe Lung Emphysema. *Respiration*. 2025; 104(4): 281-289. PMID 39586268
32. National Institute for Health and Care Excellence. Endobronchial valve insertion to reduce lung volume in emphysema (2017). Available at: <https://www.nice.org.uk/guidance/IPG600/chapter/1-Recommendations>. Accessed April 23, 2025.

## Documentation for Clinical Review

### Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Reason for endobronchial valve use
  - Documentation of the FDA Humanitarian Device Exemption (HDE) process and approval
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results
  - Prior conservative treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results

### Post Service (in addition to the above, please include the following):

- Operative report(s)

## Coding

*The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.*

Type	Code	Description
CPT®	31647	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), initial lobe
	31648	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), initial lobe
	31649	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), each additional lobe (List separately in addition to code for primary procedure)
	31651	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), each additional lobe (List separately in addition to code for primary procedure[s])
HCPCS	None	

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/01/2025	New policy.
06/01/2026	Administrative update. Definitions of Decision Determinations section updated.

### Definitions of Decision Determinations

**Healthcare Services:** For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

**Medically Necessary or Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

#### Criteria Determining Experimental/Investigational Status

Below is an excerpt of the language taken from California Children’s Services Numbered Letter 05-1020.\*

\*Department of Healthcare Services Numbered Letter 05-1020. Accessed April 21, 2026, from <https://www.dhcs.ca.gov/services/ccs/Documents/CCS-NL-05-1020-Experimental-and-Investigational-Services.pdf>

## Policy

- A. The California Children's Services (CCS) Program and the Genetically Handicapped Persons Program (GHPP) will not provide coverage for experimental services unless specifically authorized by law.
- B. The CCS Program and GHPP may provide coverage for an investigational service if:
  1. It is approved by the FDA under any Investigational New Drug (IND) Application; or
  2. It is authorized for use under the State of California's Right to Try Act; and
  3. Its use is consistent with its FDA-approved IND Application or the State of California's Right to Try Act;
- C. Additional criteria that will be considered in the adjudication process include:
  1. Conventional therapy will not adequately treat the intended patient's condition;
  2. Conventional therapy will not prevent progressive disability or premature death;
  3. The provider of the proposed service has a record of safety and success with it or equivalent to that of other providers of the investigational services;
  4. Other criteria (e.g., cost and availability) may be considered in the adjudication of a given request in cases in which more than one investigational service is available;
  5. There is reasonable expectation that the investigational service will significantly prolong the patient's life or will maintain or restore a range of physical and social function suited to activities of daily living; and
  6. The service is not being performed as part of a research study protocol. For a beneficiary with cancer who participates in a clinical trial for cancer, California Health and Safety Code (HSC) §1370.6 requires that all routine patient care costs related to the clinical trial be covered if the beneficiary's CCS-paneled treating physician recommends participation in the clinical trial after determining that participation in the clinical trial has a meaningful potential to benefit the enrollee. The coverage does not include investigational services that have not been approved by the FDA and that are associated with the clinical trial.

## Feedback

Blue Shield of California Promise Health Plan is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at [www.blueshieldca.com/en/bsp/providers](http://www.blueshieldca.com/en/bsp/providers).

For medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at [www.blueshieldca.com/en/bsp/providers](http://www.blueshieldca.com/en/bsp/providers).

*Disclaimer: Blue Shield of California Promise Health Plan may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.*