Policy Number	**SUR706.015**
Policy Effective Date	**12/15/2024**

Bronchial Valves

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History

Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

The use of a U.S. Food and Drug Administration (FDA) approved bronchial valve (Zephyr® Endobronchial Valve System or Spiration® Valve System) **may be considered medically necessary** for the treatment of emphysema when **ALL** of the following criteria are met:

- Confirmed diagnosis of emphysema; AND
- Age 40 to 75 years; AND
- Body mass index (BMI) less than 35kg/m^2; AND
- Stable with ≤20mg prednisone (or equivalent) daily; AND
- Forced expiratory volume (FEV_1) between 15% and 45% of predicted value at initial evaluation; AND
- 6-minute walking distance (6MWD) ≥100m and <500m; AND
- Non-smoking for 4 consecutive months prior to initial evaluation, and throughout the evaluation for the procedure.

NOTE 1: Because assessments may be performed immediately prior to the placement of valves, final coverage determination may be based on verification of little to no collateral ventilation as determined using the Chartis (Zephyr) or SeleCT (Spiration) systems.

The use of a U.S. Food and Drug Administration (FDA) approved bronchial valve (Zephyr® Endobronchial Valve System or Spiration® Valve System) **is considered experimental, investigational and/or unproven** for all other indications, including but not limited to the following:

- Treatment of air leaks;
- Patients who have had a prior lung transplant, lung volume reduction surgery (LVRS), median sternotomy or lobectomy;
- Patients with congestive heart failure, left ventricular ejection fraction <45%, unstable cardiac arrhythmia, myocardial infarction or stroke;
- Patients with severe hypercapnia ($PaCO_2$ >60mmHg on room air) and/or severe hypoxemia (PaO_2 <45mm Hg on room air);
- Patients with known allergies to nitinol, nickel, titanium or silicone;
- Patients with large bullae >30% of either lung;
- Patients with contraindications for bronchoscopic procedures;
- Homogeneous emphysema;
- Two or more chronic obstructive pulmonary disease (COPD) exacerbations or two or more episodes of pneumonia within last 90 days;
- Evidence of active pulmonary infection;
- Unable to safely discontinue anticoagulants or platelet activity inhibitors for 7 days;
- Uncontrolled pulmonary hypertension (systolic pulmonary arterial pressure greater than 45 mm HG) or evidence or history of cor pulmonale as determined by recent echocardiogram (completed within last 90 days)
- High resolution computed tomography (HRCT) obtained within the last 90 days demonstrates:
    - Parenchymal destruction score of greater than 75% in all three right lobes or both left lobes; or
    - Emphysema heterogeneity score less than 15%; or
    - Large bullae encompassing greater than 30% of either lung; or
    - Insufficient landmarks to evaluate the CT study using the software as it is intended;
- Resting bradycardia (less than 50 beats/min), frequent multifocal premature ventricular contractions (PVCs), complex ventricular arrhythmia, sustained supraventricular tachycardia (SVT);
- Post-bronchodilator FEV1 less than 15% or greater than 45% of predicted value at initial evaluation;
- Total lung capacity (TLC) less than 100% predicted (determined by body plethysmography) at initial evaluation;
- Residual volume (RV) less than 175% predicted (determined by body plethysmography) at initial evaluation;
- Diffusion capacity for carbon monoxide (DLCO) less than 20% predicted value at initial evaluation;
- 6-minute walk distance (6MWD) less than 100 meters or greater than 450 meters at initial evaluation;

- Presence of alpha-1 anti-trypsin deficiency;
- Plasma cotinine level greater than 13.7 ng/ml (or arterial carboxyhemoglobin >2.5% if using nicotine products) at initial evaluation.

Policy Guidelines

None.

Description

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, prevalence of COPD varies widely by state, with the estimated prevalence in 2019 ranging from <4.5% in California, Colorado, Hawaii, Massachusetts, Minnesota, and Utah to >9% in Alabama, Arkansas, Kentucky, and West Virginia. (1) In 2018, chronic lower respiratory disease, primarily COPD, was the fourth leading cause of death in the United States. (2) 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. (3)

The Global Initiative for Chronic Obstructive Lung Disease, or GOLD, system is commonly used to categorize patients with emphysema according to severity. (4) 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 according to categories of risk of having an exacerbation. These groups are based on number and type of exacerbations per year and self-reported symptoms such as breathlessness.

Table 1: Classification of Disease Severity

Stages of Airflow Limitation	Severity Grouping
GOLD 1 (mild): FEV1 ≥80% predicted	Group A: low risk 0 to 1 exacerbations per year, not requiring hospitalization, fewer symptoms
GOLD 2 (moderate): 50% ≤FEV1 <80% predicted	Group B: low risk 0 to 1 exacerbations per year, not requiring hospitalization, more symptoms
GOLD 3 (severe): 30% ≤FEV1 <50% predicted	Group C: high risk ≥2 exacerbations per year, or one or more requiring hospitalizations, fewer symptoms
GOLD 4 (very severe): FEV1 <30% predicted	Group D: high risk ≥2 exacerbations per year, or one or more requiring hospitalizations, more symptoms

FEV1: forced expiratory volume; 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.

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, 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 2. Bronchial Valve Systems Approved by the 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	Spiration, Inc.	Redmond, WA	10/24/08	H060002

	air leaks, following lobectomy, segmentectomy, or lung volume reduction surgery				
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.

Rationale

Medical policies 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, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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 is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials (RCTs) 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 question addressed in this medical policy is: Does placement of bronchial valves improve the net health outcome in individuals with pulmonary air leaks?

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

Patients

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

Case Series

No RCTs or comparative observational studies were identified. Only case series and case report data are available.

In the largest case series, Travaline et al. (2009), reported on 40 patients treated at 17 sites in the United States (U.S.) and Europe. (5) The Zephyr Endobronchial Valve 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 patients (47.5%) had complete resolution of acute air leak, 18 (45%) had a reduction in air leak, 2 (5%) had no change, and data were not available for 1 patient. The mean time from valve placement to chest tube removal was 21 days, and the median time was 7.5 days. Six patients experienced adverse effects related to valve placement including valve expectoration, moderate oxygen desaturation, initial mal-positioning of a valve, pneumonia, and *Staphylococcus aureus* colonization. The length of follow-up was varied, ranging from 5 to 1109 days. At last follow-up, 16 patients had died, though none of the deaths were attributed to the valve or the valve implantation procedure.

Firlinger (2013) et al. 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. (6) 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 (intrabronchial valve) was used in 6 of 10 responders and all 3 non-responders.

Gillespie et al. (2011) reported on a case series of 7 patients with pulmonary air leaks treated with Spiration IBV. (7) 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, 14-55 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 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 FDA PAS is provided in Table 3.

Table 3. Summary of IBV Valve PAS

Study	Countries	Sites	Dates	Participants	SAEs	Finding Regarding Air Leak Resolution
H060002/PAS001 Prospective Cohort Study	U.S.	11	2009-2014	39 post IBV valve placement for prolonged air leak.	2[1]	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

PAS: Post-Approval Study; SAE: serious adverse event

[1] AE: One systolic arrest secondary to hypercapnia resolved prior to IBV placement and one mucus impaction of a bronchial valve.

Section Summary: Treatment of Air Leaks

Data on the Spiration IBV are limited to reports of the first patients submitted to the FDA 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 heterogenous patients. 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 is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this medical policy is: Does placement of bronchial valves improve the net health outcome in individuals with severe or advanced emphysema?

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

Populations
The relevant population of interest is individuals with severe/advanced emphysema with little or no collateral ventilation between target ad 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 in 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 synthetic devices deployed with a flexible bronchoscope into the airways of the lungs. 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 (LVRS), and lung transplantation.

GOLD lists the following components of optimal medical management for severe emphysema: (4)

- 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, fatigue).

Outcomes
The general outcomes of interest, in addition to overall survival, are a reduction in symptoms, improvements in 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 4).

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

Table 4. Efficacy Outcome Measures

Measure	Description	Clinically Meaningful Difference
FEV1	• Volume of air a person can force out in one second after taking a deep breath • Not an objective of COPD management, but frequently used by regulatory authorities to interpret treatment efficacy in COPD trials • Used to categorize severity of airflow limitation	15% improvement • 100-140mL increase
SGRQ	• Measures quality of life in patients with emphysema • Scores range from 0 to 100, with higher scores indicating a worse quality of life	4-point decrease (improvement)
6-Minute Walk Test	• Distance a person can walk in 6 minutes • Measures physical function • Healthy subjects can walk 400-700 meters	Increase of 25-30 meters

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

<u>Study Selection Criteria</u>
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.

Zephyr Valve

Randomized Controlled Trials (RCTs)

Seven RCTs have evaluated the Zephyr valve in patients with severe emphysema (Table 5). 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. (8)

A post hoc analysis of the two 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. (9)

The trials showed statistically and clinically significant improvements in FEV1 (Table 6). Both response and mean change were significantly higher in the valve group in all the trials that measured this. 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 significance 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 are shown in Table 7. 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% 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 8. 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 5. Summary of Key RCT Characteristics – Zephyr Valve

Trial	Countries	Sites	Dates	Participants	Interventions	Duration

LIBERATE, Criner et al. (2018) (10, 11) NCT01796392	U.S. and other	31	2013-2016	Heterogeneous emphysema and little to no collateral ventilation 91.6% White 5.8% Black 2.6% other race 46.8% male	Zephyr valve (n=128)	Standard care (n=62)	12 months
TRANSFORM, Kemp et al. (2017) (12) 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) (13) Eberhardt et al. (2021) (8) 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) (14) 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) (15) ISRCTN04761234	England	1	2012-2013	Heterogeneous emphysema and intact interlobar fissures Race and ethnicity not	Zephyr valve (n=25)	Sham procedure (n=25)	3 months

				reported 62.0% male			
VENT EUROPE, Herth et al. (2012) (16) 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, Sciurba et al. (2010) (17) NCT00129584	U.S.	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; n:sample size; RCT: randomized controlled trial.

Table 6. RCTs of the Zephyr Valve – Efficacy Results

Study	FEV1 Responders (>15% Increase from Baseline[1])	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
LIBERATE (2018)						
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 (14.6 to 63.98)
p-value	<0.001	<0.001	NR	0.004	NR	<0.002
TRANSFORM (2017)						
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 (95% CI	27.3% (NR)	-6.5 (-12.4 to -0.6)	39.5% (NR)	78.7 (46.3 to 111.0)

		0.14 to 0.32)				
p-value	<0.001	<0.001	0.042	0.031	0.001	<0.001
IMPACT (2016 and 2021)						
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	0.014	<0.0001	0.003	<0.0001	0.018	0.016
STELVIO (2015)						
Total N	68	NR	68	NR	68	68
Zephyr Valve	59.0%	NR	79%	NR	59%	60 (35.85)
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 400)
p-value	0.001	NR	NR	NR	<0.001	0.001
BELIEVER HI-FI (2015)						
Total N	43	43	43	43	NR	43
Zephyr Valve	47%	24.8%	58%		NR	*Median, IQR*: 25 (7 to 64)
Standard care	4%	3.9%	46%		NR	*Median IQR*: 3 (-14 to 20)
Difference (95% CI)	43.2% (19.4% to 67.1%)	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	0.0022	0.033	NR	0.36	NR	0.0119
VENT Europe						
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	0.04	NR	0.09	NR	0.80
VENT U.S.						

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
p-value	0.02	NR	0.02	NR	0.25	NR

[1]Responder definition was >10% in STELVIO and >12% in TRANSFORM.
CI: confidence interval; FEV1: forced expiratory volume in 1 second; IQR: interquartile range; N: sample size; NR: not reported; RCT: randomized controlled trial; SD: standard deviation. SGRQ: St. George Respiratory Questionnaire.

Table 7. COPD Exacerbations in RCTs of the Zephyr Valve

Study	Time Point	Zephyr vs. Control
LIBERATE	0 – 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 – 30 days	4.6% vs. 0%
	>30 days to 6 months	4.6% vs. 6.3%
IMPACT	0 days to 3 months	16.3% vs. 12.0%
	31 days to 6 months	18.6% vs. 20.0%; p=1.00
STELVIO	0 days to 6 months	12% vs. 6%; P =0.67
BELIEVER	0 days to 3 months	20.0% vs. 12.0%; P =0.70
VENT EU	0 days to 3 months	11.7% vs. 10.0%; P =0.80
	>3 months to 12 months	Data NR (NS)
VENT U.S.	0 to 90 days	7.9% vs. 1.1%; P =0.03
	3 months to 12 months	10.3% vs. 9.2%; p=.84

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

Table 8. 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 – 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 – 30 days	4.6% vs. 0%	44.6% vs. 0%
	>30 days to 6 months	4.6% vs. 6.3%	20.0% vs. 9.3%
IMPACT	0 days to 3 months	1 vs. 0	44.2% vs. 12.0%
	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	NR	% patients NR
	>3 months to 12 months	5 (4.5%) vs. 3 (5.0%)	% patients NR
	0 days to 12 months	6 (5%) vs. 4 (7%)	% patients NR
VENT U.S.	0 to 90 days	1% vs. 0%	4.2% vs. 0%
	0 days to 12 months	3.7% vs. 3.5%	10.3% 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; RCT: randomized controlled trial; NR: not reported.

Tables 9 and 10 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 9. RCTs of the Zephyr Valve Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
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 U.S.	3. Included patients with collateral ventilation. 4. 99.4% White				

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

[a] 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.

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

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

[d] 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. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 10. RCTs of the Zephyr Valve Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
LIBERATE		1, 2 not blinded				

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 U.S.		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.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] 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).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

[f] 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 (SR) with meta-analyses have assessed the use of the Zephyr valve system for patients with severe emphysema. (9, 18, 19, 20) 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 (up to 12 months) 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. (2019) (Table 11). (20) The remainder of this section focuses on this review. LaBarca et al. 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). 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 safely 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 vs. homogeneous emphysema distribution, and study comparator (standard of care vs. sham valve).

Results are summarized in Table 12. Meta-analyses found statistically and clinically significant improvements with the Zephyr valve in FEV1, residual volume, 6-minute walk distance, and SGRQ, but with 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, heterogeneity between studies, 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 11. Systematic Review and Meta-Analysis of the Zephyr Valve Characteristics

Study	Search end-date	RCTs	Participants	N (Range)	Duration
LaBarca et al. (2020) (20)	Oct. 2018	7 (5 included in meta-analysis; excluded studies in patients with collateral ventilation	Adult patients (mean age 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 (50-190)	3 months to 12 months

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

Table 12. Meta-analysis of RCTs of the Zephyr Valve Results (20)

Outcome	Pooled Results (95% CI)	Heterogeneity	Certainty of the Evidence (reasons for downgrading)
Change in Residual Volume, mL (mean difference)	-0.57 (-0.76 to -0.39)	I^2= 37%; p =.18	Not assessed
Change in FEV1, mL (mean difference)	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)
Change in 6-min walk distance, meters (mean difference)	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.
Change in SGRQ score (mean difference)	-8.42 (-10.86 to -5.97)	I^2= 6%; p =.37	High
Pneumothorax (relative risk)	6.32 (3.74 to 10.67)	I^2= 25%; p =.25	High
Overall Mortality (relative risk)	1.26 (0.50 to 3.15)	I^2= 25%; p =.25	Low (non-primary outcome, wide confidence interval)

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

Randomized Controlled Trial (RCT) of Zephyr Valve Compared to Lung Volume Reduction Surgery (LVRS)

The CELEB study was an RCT comparing the Zephyr valve to LVRS in individuals with severe emphysema at 5 centers in the U.K. (Table 13). 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 14), 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 16. 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 1participant had valves removed and re-placed 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 2 (30) days and 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 17 and 18). 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 medical policy. 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. (21) 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 13. RCT of Bronchial Valves Compared to Lung Reduction Volume Surgery (CELEB) – Study Characteristics

Trial	Buttery et al. (2023) (22)
Countries	United Kingdom
Sites	5
Dates	2016-2019
Participants	N = 88 48% 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
Interventions	LVRS N=41 randomized; 34 received treatment
	Bronchial valves (Zephyr) N=47 randomized; 46 received treatment
Duration of Follow-up	12 months

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

Table 14. RCT of Bronchial Valves Compared to Lung Volume Reduction Surgery – Efficacy Results (Primary and Secondary Outcomes)

	Primary Outcome	**Secondary Outcomes, Mean Change from Baseline to 12 Months**

Buttery et al. (2023) (22)	*i-Bode Mean Change from Baseline to 12 Months (95% CI)*	*Health Status (CAT Score, 95% CI)*	*Health Related Quality of Life (EQ-5D-5L)*	*Residual Volume % Predicted (95% CI)*	*Fat-free Mass (kg/m^2)*	*Patient Experience of Physical Activity (PROactive Physical Activity in COPD Instrument, [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

RCT: randomized controlled trial; CI: confidence interval; LVRS: lung volume reduction surgery; BV: bronchial valves; COPD: chronic obstructive pulmonary disease.

Table 15. RCT of Bronchial Valves Compared to Lung Volume Reduction Surgery – Efficacy Results – Components of Composite Primary Outcome

	Mean Change from Baseline to 12 Months			
Buttery et al. (2023) (22)	*BMI (kg/m^2)*	*FEV1 % predicted*	*MRC Dyspnea Score*	*ISWT (m)*
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

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

Table 16. RCT of Bronchial Valves Compared to Lung Volume Reduction Surgery – Other Health Outcomes and Adverse Events

Study	**Mortality at 12 Months**	**COPD Exacerbations Requiring**	**Adverse Events**

		Hospitalization at 3 Months	
Buttery et al. (2023) (22)			
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; LVRS: lung volume reduction surgery; RCT: randomized controlled trial.

Table 17. RCT of Bronchial Valves Compared to Lung Volume Reduction Surgery – Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Buttery et al. (2023) (22)			Comparator was LVRS	Rationale for choice of composite primary outcome measure unclear	

LVRS: lung volume reduction surgery; RCT: randomized controlled trial.
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] 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.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] 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. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 18. RCT of Bronchial Valves Compared to Lung Volume Reduction Surgery – Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Buttery et al. (2023) (22)		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 valves; LVRS: lung volume reduction surgery; RCT: randomized controlled trial.
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] 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).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] 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

Review of Evidence

Randomized Controlled Trials (RCTs)

Three RCTs of the Spiration valve in patients with emphysema have been published. (23,24,25) One used a sham control and two were open-label. Tables 19-22 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® 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. Trial results were published in a peer-reviewed journal in 2019; (25) results were previously available as part of the Spiration PMA application. (26) 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 serous pneumothorax. The REACH (The Spiration Valve System for the Treatment of Severe Emphysema) trial found improvements in FEV1, 6MWT, and SGRQ, The sham-controlled IBV Valve (A Prospective, Randomized, Controlled Multicenter Clinical Trial to Evaluate the Safety and Effectiveness of the IBV® 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. (23)

Table 19. Summary of Key RCT Characteristics – Spiration Valve

Trial	Countries	Sites	Dates	Participants	Interventions		Duration
					Active	Comparator	
EMPROVE (25,26), IDE# G 120192	U.S and Canada	31	2013-2017	Severe emphysema without interlobular collateral ventilation Race not reported 53.5% male	Spiration valve (n = 113)	Standard care (n = 59)	12 months
REACH, Li et al. (2018) (24) NCT01989192	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) (23) NCT00475007	U.S.	36	2007-2017	Emphysema, airflow obstruction, hyperinflation, and sever dyspnea Race not reported 57% male	Spiration valve (n = 142)	Sham procedure (n = 135)	6 months

RCT: randomized controlled trial; NCT: national clinical trial; IDE: Investigational Device Exemption; NR: Not reported; n: sample size.

Table 20. RCTs of the Spiration Valve Efficacy Results

Study	FEV1 Responders (>15% Increase from Baseline[1])	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
EMPROVE (25,26)						
Total N	156	156	156	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
REACH (24)						
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%	-0.25 (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	35% (NR)	NR	NR	NR	NR	NR

p-value	0.001	0.001	NR	0.007	NR	NR
IBV Valve (23)						
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; SD: standard deviation; FEV1: forced expiratory volume in 1 second; SGRQ: St. George Respiratory Questionnaire; N: sample size; NR: not reported; RCT: randomized controlled trial.

Table 21. COPD Exacerbations in RCTs of the Spiration Valve

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

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

Table 22. 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	0-6 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%)
	>6-12 months	3.9% vs 6.4%	21.4% vs 10.6%10.7% (95% CI 3.0% to 21.2%)
REACH	0-6 months	0% vs 3.0%	44.3% vs 24.2%
IBV Valve	0-6 months	4.2% vs 0.7%Difference 3.5% (95% CI 0.2%, 7.5%)	14.1% vs 3.7%10.4% (95% CI 4.0% to 17.1%)

CI: confidence interval; RCT: randomized controlled trial

Tables 23 and 24 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 23. RCTs of the Spiration Valve Study Relevance Limitations

Study	Population[a]	Intevention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
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.

[a] 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.

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

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

[d] 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. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 24. RCTs of the Spiration Valve Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
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.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] 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).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] 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 treatment of severe emphysema at 1 hospital in The Netherlands. (27) 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 aftertreatment, 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.

<u>Section Summary: Severe or Advanced Emphysema</u>

In individuals with severe emphysema and low 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, but there was a greater risk of serious adverse events compared to usual care. Despite limitations in study designs, including a lack of blinding, significant heterogeneity across studies on some measures, and a higher risk of serious adverse events, with up to 27% of patients experiencing pneumothorax, which can be a commonly occurring side effect of the procedure, the evidence is sufficient to determine that the technology improves the net health outcome.

Summary of Evidence

For individuals who have pulmonary air leaks who receive bronchial valves, the evidence includes the 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. There are no comparative data with alternatives. This evidence is inadequate to determine the impact of this technology in the net health outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 a prospective cohort study with patient-reported outcomes, randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. 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 measures of lung function, exercise tolerance, and quality of life. Despite limitations in study designs, including a lack of blinding and a higher risk of serious adverse events, with up to 27% of patients experiencing pneumothorax, a commonly occurring side effect of the procedure, the evidence is sufficient to determine that the technology improves the net health outcome.

Practice Guidelines and Position Statements

Global Initiative for Chronic Obstructive Lung Disease (GOLD)

The 2023 GOLD publication makes the following statements on lung volume reduction interventions: (4)

- "In selected patients with heterogeneous or homogeneous 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 Care and Excellence (NICE)

In December 2017, NICE issued the following recommendations on endobronchial valve insertion to reduce lung volume in emphysema: (28)

> 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: (18)

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.

Ongoing and Unpublished Clinical Trials

Some ongoing and unpublished trials that might influence this policy are listed in Table 25.

Table 25. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT01796392[a]	Lung Function Improvement After Bronchoscopic Lung Volume Reduction With Pulmonx Endobronchial Valves Used in Treatment of Emphysema (LIBERATE)	190	Feb 2023 (post approval study, 5-year extension)
NCT01812447[a]	A Prospective, Randomized, Controlled Multicenter Clinical Study to Evaluate the Safety and Effectiveness of the Spiration® Valve System for the Single Lobe Treatment of Severe Emphysema (EMPROVE)	172	Aug 2022 (planned longer-term follow-up, 5 and 2 years for the treatment and control groups, respectively)
NCT04185646[a]	Zephyr Valve Registry (ZEVR)	150	Dec 2025
NCT04302272[a]	The Spiration Valve System (SVS) Post-Market Registry Study for Severe Emphysema	150	Apr 2028

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	31647, 31648, 31649, 31651
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. Centers for Disease Control and Prevention. Chronic Obstructive Pulmonary Disease (COPD). Data and Statistics. 2021. Available at: <https://www.cdc.gov> (accessed April 25, 2023).
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. Available at: <https://www.cdc.gov> (accessed April 28, 2023).

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). 2023 Global Strategy for Prevention, Diagnosis, and Management of COPD. Available at: <https://goldcopd.org> (accessed April 24, 2023).
5. Travaline JM, McKenna RJ, Jr., De Giacomo T, et al. Treatment of persistent pulmonary air leaks using endobronchial valves. Chest. Aug 2009; 136(2):355-360. PMID 19349382
6. Firlinger I, Stubenberger E, Muller 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):1243-1249. PMID 23434254
7. 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):270-273. PMID 21172529
8. 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
9. 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: CD012158. PMID 28230230
10. 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 2018; 198(9):1151-1164. PMID 29787288
11. Dransfield MT, Garner JL, Bhatt SP, et al. Effect of Zephyr Endobronchial Valves on Dyspnea, Activity Levels and Quality of Life at One Year. Ann Am Thorac Soc. Mar 30 2020. PMID 32223724
12. 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 2017; 196(12):1535-1543. PMID 28885054
13. Valipour A, Slebos D-J, Herth F, et al. Endobronchial Valve Therapy in Patients with Homogeneous Emphysema. Results from the IMPACT Study. Am J Respir Crit Care Med. Nov 2016; 194(9):1073-1082. PMID 27580428
14. Klooster K, ten Hacken NH, Hartman JE, et al. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. N Engl J Med. Dec 2015; 373(24):2325-2335. PMID 26650153
15. 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):1066-1073. PMID 26116485
16. 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):1334-1342. PMID 22282552
17. Sciurba 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):1233-1244. PMID 20860505

18. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: Diagnosis and management. Available at: <https://www.nice.org.uk> (accessed April 24, 2023).
19. van Geffen WH, Slebos DJ, Herbos 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
20. 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. NA. 2019; 98(3):268-278. PMID 31117102
21. 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 fora randomised controlled trial. BMJ Open. Oct 17 2018; 8(10):e021368. PMID 30337307
22. 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):2202063. PMID 36796833
23. 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):288-297. PMID 25321447
24. 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
25. 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
26. U.S. Food & Drug Administration. Spiration Valve System. Summary of Safety and Effectiveness Data. Available at: <https://www.accessdata.fda.gov> (accessed April 23, 2023).
27. 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
28. National Institute for Health and Care Excellence. Endobronchial valve insertion to reduce lung volume in emphysema (2017). Available at: <https://www.nice.org.uk> (accessed April 22, 2023).
29. U.S. Food & Drug Administration. Spiration IBV Valve System Approval Letter. October 24, 2008. Available at: <https://www.accessdata.fda.gov> (accessed December 27, 2023).
30. U.S. Food & Drug Administration. Zephyr Endobronchial Valve Approval Letter. June 29, 2018. Available at: <https://www.accessdata.fda.gov> (accessed December 27, 2023).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
12/15/2024	Reviewed. No changes.
02/01/2024	Document updated with literature review. Coverage unchanged. References 1-3, 8, 21, 22, 27 added; other revised.
4/15/2022	Document updated. The following change was made to the Coverage: Little to no collateral ventilation as determined using the Chartis (Zephyr) or SeleCT (Spiration) systems was removed from the medically necessary statement criteria and added as NOTE 1. No new references added.
1/1/2022	Reviewed. No changes.
11/1/2020	Document updated with literature review. Coverage revised to consider the use of a U.S. Food and Drug Administration (FDA) approved bronchial valve (Zephyr® Endobronchial Valve System or Spiration® Valve System) may be considered medically necessary for the treatment of emphysema when ALL of the following criteria are met: confirmed diagnosis of emphysema; AND age 40 to 75 years; AND body mass index (BMI) less than 35kg/m2 ; AND stable with ≤20mg prednisone (or equivalent) daily; AND FEV1 between 15% and 45% of predicted value at initial evaluation; AND 6 minute walking distance (6MWD) ≥100m and <500m; AND non-smoking for 4 consecutive months prior to initial evaluation, and throughout the evaluation for the procedure; AND little to no collateral ventilation as determined using the Chartis (Zephyr) or SeleCT (Spiration) systems. The use of a U.S. Food and Drug Administration (FDA) approved bronchial valve (Zephyr® Endobronchial Valve System or Spiration® Valve System) is considered experimental, investigational and/or unproven for all other indications (see list of exclusions in coverage). References revised; new references 1, 7, 16, and 19 added.
2/15/2020	Document updated with literature review. Coverage unchanged but clarified to indicate endobronchial valves changed to bronchial valves. Title changed from Endobronchial Valves. References revised; new references 1-3, 8-13, 18, and 20 added.
10/15/2017	Document updated with literature review. Coverage unchanged.
10/1/2016	Reviewed. No changes.

2/1/2015	Document updated with literature review. Coverage unchanged; however all other sections were completely revised and updated.
1/1/2011	New medical document. Endobronchial valves are considered experimental, investigational and unproven for all indications, including but not limited to treatment of patients with prolonged air leaks, COPD or emphysema.