NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endobronchial valve insertion to reduce lung volume in emphysema

Emphysema is a chronic lung disease that causes the walls of the smaller airways in the lungs to break down. This creates abnormally large spaces that fill with air, reducing the amount of air that reaches the healthy parts of the lung. In this procedure, a thin flexible tube with a camera on the end (bronchoscope) is moved through the nose or mouth into the lungs, and small one-way valves are then placed in the airways leading to the damaged parts of the lungs. The aim is to reduce the airflow to the damaged parts, allowing more air to reach the healthy areas.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in August 2017.

Procedure name

- Endobronchial valve insertion to reduce lung volume in emphysema

Specialist societies

- British Thoracic Society
- Royal College of Surgeons of England.

Description

Indications and current treatment

Emphysema is a chronic lung disease in which the walls of the air sacs (alveoli) in the lungs weaken and disintegrate. This leaves behind abnormally large air spaces that stay filled with air even when the patient breathes out. The most common symptoms of emphysema are shortness of breath, coughing, fatigue and weight loss. Recurrent illnesses (such as chest infections) often lead to exacerbations, for which patients may need hospitalisation. Emphysema is usually smoking related but may also be inherited.

Treatment options include pulmonary rehabilitation (exercise training, breathing retraining, and patient and carer education), smoking cessation, and the use of inhaled or oral bronchodilators and corticosteroids. Oxygen therapy may also be indicated in more severe cases. Lung volume reduction surgery is an option for patients who experience breathlessness, and whose pulmonary function test results show severe obstruction and enlarged lungs. Such surgery can be done thoracoscopically (using video-assisted thoracoscopy or thoracotomy) or using an open approach (using a sternotomy or thoracotomy). Lung transplantation surgery may also be an option. Certain therapies under clinical investigation such as coiling, use of sealants and thermal ablation may be used in regional lung disease.

What the procedure involves

The aim of insertion of endobronchial valves (also known as intrabronchial valves) to reduce lung volume in emphysema is to achieve atelectasis of selected lung segments. It uses an endoscopic approach, which is less invasive than open or thoracoscopic lung volume reduction surgery. Before the procedure, it is usual practice to assess the presence of collateral ventilation (when air enters a lobe of the lung through a passage that bypasses the normal airway). A surrogate for this is CT scanning to assess the completeness of fissures. A functional approach, specially developed for use before airway valve insertion, involves a specially designed balloon catheter with a flow sensor.

Endobronchial valve insertion is done with the patient under sedation or general anaesthesia. Using a delivery catheter passed through a bronchoscope, a synthetic valve is placed in the target location and fixed to the bronchial wall. The valve is designed to prevent air inflow during inspiration but to allow air and mucus to exit during expiration. Several valves may be needed (1 or more for each segment of the lung to be treated). Patients may sometimes be given antibiotics or corticosteroids. Two devices with different designs are available for interventional lung volume reduction – 1 is duckbill shaped and the other umbrella shaped.

Outcome measures

Pulmonary function tests and measures of lung volumes

FEV_1 (forced expiratory volume) – the volume of air that the patient is able to exhale in the first second of forced expiration.

FVC (forced vital capacity) – the total volume of air that one can forcibly exhale after a full inspiration.

TLC (total lung capacity) – maximum volume of air present in the lungs.

RV (residual volume) – volume of air remaining in the lungs after a full exhalation.

6MWD (6-minute walking distance test) – assesses distance walked over 6 minutes as a sub-maximal test of aerobic capacity or endurance.

Modified Medical Research Council dyspnoea scale

Measures perceived respiratory disability ranging from none (grade 0) to almost incomplete incapacity (grade 4)

Grade	Description of breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is designed to measure health impairment in patients with respiratory disease. Three component scores are calculated for the SGRQ:

1. Symptoms – concerned with the effect of respiratory symptoms, their frequency and severity.

2. Activity – concerned with activities that cause or are limited by breathlessness.

3. Impacts – covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease.

A total score is also calculated, which summarises the impact of the disease on overall health status. Scores are expressed as a percentage of overall impairment in which 100 represents the worst and 0 indicates the best possible health status.

COPD assessment test (CAT)

The CAT is a validated 8-question self-completed questionnaire designed to measure the health status of patients with chronic obstructive pulmonary disease (COPD) being responsive to change and to treatment. The CAT has a scoring range of 0 (low impact on daily activities) to 40 (very high impact on daily activities). A change of 2 units suggests a meaningful difference.

CAT score	Level of impact on daily activities
More than 30	Very high
More than 20	High
10 to 20	Medium
Less than10	Low
5	Healthy limit

BODE Index for COPD survival prediction

BODE stands for **B**ody mass index, airflow **O**bstruction, **D**yspnoea and **E**xercise capacity. It is a score that combines:

Variable	Points on BODE Index			
	0	1	2	3
FEV1 (% predicted)	≥65	50–64	36–49	≤35
6-Minute Walk Test (meters)	≥350	250–349	150–249	≤149
mMRC dyspnoea Scale	0–1	2	3	4
Body mass index	>21	≤21		

Interpretation of BODE

	Approximate 4-year survival rates
0 to 2 points	80%
3 to 4 points	67%
5 to 6 points	57%
7 to 10 points	18%

Clinical COPD questionnaire (CCQ)

This is a questionnaire with 10 questions that assesses COPD patients in 3 domains: symptoms (4 questions), functional state (4 questions) and mental state (2 questions). The total CCQ score, and the score on each of the three domains, varies between 0 (very good health status) to 6 (extremely poor health status).

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endobronchial valve insertion to reduce lung volume in emphysema. The following databases were searched covering the period from their start to 11 November 2016: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with emphysema.
Intervention/test	Endobronchial valve insertion to reduce lung volume in emphysema.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 1,673 patients from 1 systematic review and meta-analysis[1], 1 RCT[7] and 6 case series[2-4, 8].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on endobronchial valve insertion to reduce lung volume in emphysema

Study 1 van Agteren JEM (2017)

Details

Study type	**Systematic review and meta-analyses (Cochrane)**
Country	Australia
Recruitment period	Databases searched up to December 2016
Study population and number	n=703, 5 randomised controlled trials (RCTs) comparing patients treated by the 'Zephyr' valve to controls n=372, 3 RCTs comparing patients treated by the 'Spiration' valve to controls
Age and sex	Range 58 to 65 years, the majority of studies recruited more male than female patients, only STELVIO 20115, IMPACT 2016 and VENT US 2010 recruited a majority of female patients.
Patient selection criteria	The studies has similar inclusion criteria defining baseline values of lung function: - FEV_1 ranging between 23.2% and 33.8% predicted - RV ranging between 179.0% and 258% predicted - TLC ranging between 124.0% and 145.4% predicted. - Average scores on the SGRQ ranged between 54.0 units and 70.65 units - Average distances on 6MWD between 293.7 and 377.0 meters. In most studies controls were patients treated by optimal medical care consisting of combined inhaled corticosteroids, long-acting beta 2 agonist, and anti-cholinergic agents.
Technique	Best quality clinical trials reporting on the use of 2 different valves were included for quantitative and qualitative analysis. Results were reported separately for the 'duckbill' (Zephyr, Pulmonx Inc, Redwood City, California, US) and the 'umbrella' (IBV, Spiration Inc, Redwood, Washington, US)
Follow-up	**Postoperative to 12 months**
Conflict of interest/source of funding	Dion Grosser has received payment to attend workshops and to provide education and proctoring for placement of Zephyr (Pulmonx) and has received flights and accommodation to attend an education session on implantation of coils (PneumRx). The remaining authors declared having no conflicts of interest.

Analysis

Follow-up issues: None.

Study design issues: Two authors independently screened titles and abstracts for potentially relevant studies. Two authors independently screened full texts for inclusion in the synthesis. A PRISMA tool was used to classify the quality of the studies.

Study population issues: All included studies were RCTs.

Studies included:

Study	n	Valve group (Zephyr)	Controls	Disease distribution	FU
BeLieVer HIFi 2015	50	25	25 (sham)	Heterogeneous	3 months
IMPACT 2016	93	43	50	Homogeneous	12 months (only 3 months FU available)
STELVIO 2015	68	34	34	Both	6 months
VENT EU 2012	171	111	60	Both	12 months
VENT US 2010	321	220	101	Both	12 months

Study	n	Valve group (Spiration)	Controls	Disease distribution	FU
Eberhardt 2012	22	11 (unilateral valve)	11 (bilateral valves)	Heterogeneous	3 months
IBV trial 2014	277	142	135	Heterogeneous	6 months
Ninane 2012	73	37	36	Heterogeneous	6 months

The majority of studies were multicentre studies with exception of BeLieVeR HIFi 2015 (UK), STELVIO 2015 (Netherlands), Eberhardt 2012 (Germany).
The VENT EU 2012 and VENT US 2010 trials did not assess patients for collateral ventilation before inclusion in the study.

Two studies used the Spiration valve (IBV Valve trial 2014; Ninane 2012) and only targeted participants with upper-lobe heterogeneous disease, while the other, Eberhardt 2012, recruited participants with upper- or lower-lobe predominant emphysema.

Other issues: There where 2 studies allowing crossover from control to intervention after the initial follow-up was completed: STELVIO 2015 and IMPACT 2016.

ASPIRE 2015, BeLieVeR HIFi 2015, IMPACT 2016 and STELVIO 2015, were deemed to be at low risk of selection bias because of random sequence generation as they conducted random sequence generation via block randomisations. Eberhardt 2012, IBV trial 2014, Ninane 2012, VENT EU 2012 and VENT US 2010 did not provide sufficient information to permit an accurate judgement of the risk of selection bias.

Ninane 2012 did not reach the intended number of participants and was discontinued for logistical reasons, causing it to be at a high risk of bias. All other studies were deemed to be at a low risk of other biases.

Key efficacy and safety findings

Efficacy

Zephyr valve versus SMC (5 RCTs)

Lung function measures	Summary of evidence		Notes
FEV_1 (change from baseline)			
1% change in FEV_1[2]	MD 0.77, 95% CI 0.43 to 1.11, p<0.00001, I^2=0%	n=703 5 RCTs	low-quality evidence, favours EBV
2% change in FEV_1 stratified per follow-up			
90 days	MD 0.48 (95% CI 0.32 to 0.64, p<0,00001, I^2=42%	n=143 2 RCTs	favours EBV
6 months	MD 0.40, 95% CI 0.22 to 0.58, p<0.00001, I^2=41%	n=560 3 RCTs	
12 months[2]	MD 8.00%, 95%CI 1.00 to 15.00, p=0.04, I^2=NA	n=171 1 RCT	
FEV_1 per emphysema distribution	MD 16.36% (95% CI 9.02 to 23.71, p=0.00001, I^2=0%	n=137 2 RCTs	favours EBV in patients with heterogeneous emphysema
FEV_1 stratified per collateral ventilation	MD 18.15%, 95% CI 11.81 to 24.49, p=0.000001, I^2=0%	n=542 3 RCTs	favours EBV in patients with no collateral ventilation*
	MD 2.48%, 95% CI −2.63 to 7.59, p=0.34, I^2=0%	2 RCTs	in patients with collateral ventilation*
	MD 17.80% (95% CI 7.78 to 27.82)	n=68 1 RCT	favours EBV in patients with intact fissures
	MD 17.23% (95% CI 8.10 to 26.36)	n=93 1 RCT	favours EBV in patients with intact fissures
FEV_1 stratified per lobar occlusion status in patients with intact fissures (12 months)	MD 28% (SD 32) EBV in patients with complete lobar occlusion vs MD 2% (SD 10) in patients without complete lobar occlusion, p=0.005	n=171 1 RCT	favours EBV in patients with complete lobar occlusion
	MD 20.6% (SD 25.1) EBV in patients with complete lobar occlusion vs MD 5.2% (SD 17.4) in patients without complete lobar occlusion, p=0.006	n=321 1 RCT	favours EBV in patients with complete lobar occlusion
RV (change from baseline)			
MD −0.58, 95% CI −0.77 to −0.39, p<0.00001, I^2=56%		n=200 3 RCTs	low-quality evidence, favours EBV
EBV group mean −1.29% versus controls mean 0.69%, p=0.41		n=321 1 RCT	
MCID 0.35 litres between EBV group (n=11) and controls (n=7), p=0.24		n=50 1 RCT	
EBV group mean 44.2% versus controls mean 18%, MCID −430 ml , p=0.006		n=93 1 RCT	favours EBV
EBV group mean 71% versus controls mean 3%, MCID −430 ml , p=0.001		n=68 1 RCT	
TLC (change from baseline)			
MD −0.34 litres, 95%CI −0.46 to −0.23, p<0.00001, I^2=16%;		n=107 2 RCTs	moderate-quality evidence, favours EBV
MD 0.3 litres (SD 0.7) for participants with lobar occlusion and 0.2 litres (SD 1.2) for those without, compared to a 0.4 litres, p>0.05		n=171 1 RCT	
EBV group: MD −1.2% (SD10.6) versus controls: MD −0.4% (SD 13), p=0.29		n=321 1 RCT	
RV/TLC (change from baseline)			
MD −5.76, 95% CI −10.45 to −1.06, p<0.016, I^2=81		n=118 2 RCTs	low-quality evidence, favours EBV**
63% EBV group versus 9% controls, reached the MCID of 4% RV/TLC, p<0.001 MD −8.1% (SD 10.7)		n=68 1 RCT	favours EBV
MD −2.75% (SD1.6)		n=50 1 RCT	favours EBV
MD −14% (SD 11) EBV in patients with complete lobar occlusion versus 0% (SD 12) in EBV patients without complete lobar occlusion versus −2% (SD 10), p value not reported		n=171 1 RCT	
FVC (change from baseline)			
MD −14.4% (SD 27.8)		n=68 1 RCT	favours EBV
Gas transfer values (DLCO, change from baseline)			
EBV group improved by 0.30 mmol/min/kPa (IQR 0.03 to 0.43) versus controls 0 mmol/min/kPa (IQR −0.19 to 0.13), p=0.003		n=50 1 RCT	favours EBV
4 RCTs found no difference in gas exchange between EVB and controls			

**The difference between these 2 results was statistically significantly different p=0.0002*
** Using a random-effects model to adjust for heterogeneity

[1]The author highlights that some studies did not determine the presence of intact fissures (VENT EU 2012 and VENT US 2010), including patients with collateral ventilation which affected the response to treatment.

[2]Also mean FEV_1 changes had wide SD in the studies (22% to 41%) suggesting skewing in the data. The STELVIO 2015 study had better results that the remaining studies contributing to heterogeneity (due to patient monitoring and valve replacement during the trial).

Quality of life

SGRQ**	MD -7.29 units; 95% CI -11.12 to -3.45, p=0.0002, I^2=67%	n=695 5 RCTs	low-quality evidence, favours EBV
Reduction in at least 4 points in SGRQ (MCID)			
No difference between EBV and controls, p=1.0		n=50, 1 RCT	
79% of EBV versus 33% controls, p=0.001		n=68, 1 RCT	
57% of EBV versus 25% controls, p=0.003		n=93, 1 RCT	
45.9% EBV versus 8.3% controls, MCID reduction of 8 points; p<0.0001		n=93, 1 RCT	
SGRQ stratified per follow-up period			
90 days	MD -8.75, 95% CI -12.76 to -4.74, p=0.000019, I^2=0%;	n=136 2RCTs	favours EBV
6 months**	MD -7.09, 95% CI -12.59 to -1.60, p=0.01, I^2=79%;	n= 560 3 RCTs	
	MD -4.05, 95% CI -6.51 to -1.59, p=0.0012, I^2=52%; same comparison without the STELVIO study	n=492 2 RCTs	
SGRQ stratified by emphysema distribution			
Heterogeneous disease: MD -19 units , 95% CI −31 to −6), versus homogenous disease, MD −12 units, 95% CI −21 to −4; p=0.005		n=68 1 RCT	favours EBV in heterogeneous
Mean change −9.64 units (95% CI −14.09 to −5.20, p<0.0001		n=93 1 RCT	favours EBV
Absolute charge in SGRQ per collateral ventilation status			
Patients with intact fissures: MD −4.00 units, 95% CI −10.64 to 2.64 versus patients without intact fissures: MD 0.00 units, 95% CI −5.48 to 5.48, p= 0.36		n=171 1 RCT	favours EBV in patients with intact fissures
MD −9.03 units, 95% CI −12.07 to −5.98, p<0.00001, I^2=49%		n= 266 4 RCTs	
MD −3.40, 95% CI −6.43 to -0.37, p=0.0028, I^2=NA		n=321 1 RCT	Could not tell if fissures intact
Absolute change in SGRQ per lobar occlusion status (12 months)			
Patients with complete lobar occlusion MD −4 units (SD 16) versus patients without complete lobar occlusion +2 units (SD 10), p=0.4		n=171 1 RCT	
Patients with complete lobar occlusion MD −5.4 units (SD 11.2) versus patients without complete lobar occlusion −0.3 units (SD 12.8), p=0.12		n=321 1 RCT	
Other quality of life questionnaires (single RCTs)			
CAT	EBV group: median −2, IQR −7 to 3) versus controls median 0, IQR −2 to 2, p=0.23	n=50	
mMRC	No difference in QoL EBV patients versus controls		
CAT	EBV group versus controls: MD −0.9, 95%CI −2.9 to 1.1	n=93	
mMRC	EBV group versus controls: MD −0.57, 95% CI −0.98 to −0.16)		favours EBV
CCQ	EBV group versus controls, MD −0.74 points, p=0.002	n=68	favours EBV
mMRC	EBV group versus controls, MD −0.3 units, 95%CI −0.50 to −0.01	n=321	favours EBV

**Using a random-effects model to adjust for heterogeneity

Exercise capacity

6MWD by follow-up		
MD 38.12 meters, 95% CI 8.68 to 67.56, p=0.011, I^2=78%	n=379 4 RCTs	wide SD may indicate skewness**
MD 19.1 m, 9.3 m in the EBV group versus −10.7 m in the controls, p=0.002	n=321 1 RCT	
Ability to walk 26 m or more (MCID) (single RCTs)		
n=12 EBV group versus n=4 controls, p=0.001	n=50	
88% EBV group versus 6% controls, p<0.001	n=68	
50% EBV group versus 14% controls, p=0.002	n=93	
1 RCT found no difference in the number of patients able to walk more than 26 meters, p=0.28	n=321	
Exercise capacity stratified for collateral ventilation status		

1 RCT found no significant difference in exercise tolerance in the EBV group with collateral ventilation when compared to controls (p=0.8) and in the EBV group without collateral ventilation when compared to controls (p=0.5). This was also true for patients with intact fissures.	n=171	
1 RCT found no significant difference in 6MWD in the EBV group with collateral ventilation when compared to controls (p=0.25) and in the EBV group without collateral ventilation when compared to controls (p=0.08) at 12 months follow-up.	n=321	

**Using a random-effects model to adjust for heterogeneity

Hospital utilisation

Median post-treatment hospital stay 1 day (range1 to 13) and that median procedure time was 18 minutes (range 6 to 51) (STELVIO 2015)

Mean procedure time of 33.8 minutes (SD 20.5) (VENT US 2010)

Mean procedure time of 27 minutes (SD 18) (VENT EU 2012)

Spiration valve versus SMC

Lung function tests			
FEV_1 at end of follow-up			
3 months	MD 0.90 litres (SD 0.34) Spiration valve group versus controls 0.87 litres (SD 0.3), p=0.065	n=73 1 RCT	high-quality evidence, favours controls
6 months	MD −2.11% Spiration valve group versus 0.04% controls, p=0.001; 6 months	n=277 1 RCT	favours controls
Unilateral versus bilateral	Significant increase in FEV_1 for the unilateral group (21.4%, SD 10.7%), but not for the bilateral group (−3.1%, SD 15.0). MD 24.50%; 95% CI 13.61 to 35.39	n=22 1 RCT	favours unilateral group
RV, TLC and RV/TLC (change from baseline)			
RV	MD 0.38 litres, 95% CI 0.12 to 0.65, p=0.005, I^2=0%	n=322 2 RCTs	high-quality evidence, favours controls
	Unilateral group RV reduction at 90 days −872 ml (SD 796) or as percentage change from baseline -14.7% (SD 13.4), p=0.005 versus bilateral group +85 ml at 90 days (SD 446) and as a percentage change from baseline 1.5% (SD 7.7), p=0.7. MD -16.20; 95% CI −25.33 to −7.07	n=22 1 RCT	
TLC	MD 0.14; 95% CI −0.12 to 0.39, p=0.29, I^2=0%	n=322 2 RCTs	high-quality evidence
	not significantly reduced in either unilateral (% change -4.1, SD 10.1) or bilateral (+1.5%, SD 7.7) and there was no significant MD between groups, p=0.47	n=22 1 RCT	
RV/TLC	1 RCT found a statistically significantly MD from baseline, p=0.01, MD value not reported		favours controls
Gas exchange values			
PaO_2	MD 1.95 mm Hg; 95% CI −4.20 to 8.10, p=0.53, I^2=69%	n=308 2 RCTs	
$PaCO_2$	MD 1.33 mm Hg; 95%CI 0.27 to 2.39, p=0.014, I^2=16%	n=315 2 RCTs	favours controls
DLCO	1 RCT did not find a significant difference between comparators in change from baseline, p=0.53	n=73	
Exercise capacity (change from baseline)			
MD −19.54 meters; 95% CI −37.11 to −1.98, p=0.029, I^2=0%		n=326 2 RCTs	moderate-quality evidence, favours controls
Unilateral group improvement 48.9 meters (SD 53, p=0.024), versus bilateral group -52.3 meters, (SD 81.2), p=0.08).		n=22 1 RCT	favour unilateral group
Quality of life			
SGRQ	MD 2.64 units, 95% CI −0.28 to 5.56, p=0.076, I^2=28%	n=350 2 RCTs	high-quality evidence
	Significant decrease from baseline in total score of SGRQ (−11.8 units, SD 10.6) for the unilateral group, and found a non-significant increase in the bilateral group (2.12 units, SD 8.5); MD −13.92; 95% CI −21.95 to −5.89	n=22 1 RCT	favours unilateral group
mMRC	MD −0.10, 95%CI −0.34 to 0.14	n=252 1 RCT	
	MD −0.20; 95%CI −0.76 to 0.36 (3 months)	n=73 1 RCT	
	MD −1.0, p=0.05	n=22 1 RCT	favours unilateral group
SF-36	MD −0.62, 95% CI −2.59 to 1.35	n=240	

(physical component)		1 RCT	
No statistically significantly difference from baseline to 3 months follow-up on mMRC score (p=0.64) and 2 components of the SF-36 (mental component [p=0.83] and physical component [p=0.73])		n=73 1 RCT	
BODE index	−3.0, p=0.003	n=22 1 RCT	favours unilateral group
Hospital utilisation			
Procedure time	Mean 2.2 days (SD 6) for the Spiration valve group versus 1 day (SD 0) for the controls	n=277 1 RCT	
	Mean 62 min (SD 17) for EBV group versus 23 min (SD 14) in controls, p< 0.0001	n=73 1 RCT	
Days in hospital	Days in hospital for both groups: 1.1 days (SD 0.3), p=0.26		

Safety

Zephyr valve versus SMC

Mortality	OR 1.07, 95%CI 0.47 to 2.43; I^2=0%, p=0.86	n=703; 5 RCTs	moderate-quality evidence
Mortality stratified per follow-up			
Postoperative	OR 3.12, 95% CI 0.12 to 80.39, p=0.49, I^2=NA	n= 50; 1 RCT	
90 days	OR 2.17, 95% CI 0.67 to 7.02, p=0.20, I^2=0%	n=703, 5 RCTs	
6 months	OR 2.04, 95% CI 0.32 to 13.16, p=0.45, I^2=0%	n= 239; 2 RCTs	
12 months	OR 0.85, 95% CI 0.33 to 2.22, p=0.74, I^2=0%	n= 492; 2 RCTs	
Mortality stratified for presence of collateral ventilation and lobar occlusion strategy			
RCTS that tested for collateral ventilation OR 1.93, 95%CI 0.40 to 9.3, versus trials that did not OR 0.85, 95% CI 0.33 to 2.22, p=0.38			
Adverse event rate	OR 5.85, 95% CI 2.16 to 15.84	n=482; 3 RCTs	favours controls

Safety events by individual studies

	EBV group	Controls	p
BeLieVeR HIFi 2015 (n=50)	**n=25**	**n=25**	
COPD exacerbations	64% (16/25)	80% (20/25)	0.42
Pneumonia	2	0	0.49
Pneumothorax	2	1	1.0
Expectorated valves	4	NA	NA
Valve removal	2	NA	NA
IMPACT 2016 (n=93)	**n=43**	**n=50**	
% of serious adverse events leading to death or hospitalisation	44% (19/43)	12% (6/50)	<0.001
Pneumothorax	26% (11/43)	0	<0.001
COPD exacerbation	77% (33/43)	40% (20/50)	NR
% of COPD exacerbation requiring hospitalisation	16% (7/43)	12% (6/50)	NR
Pneumonia	0	1/50	NR
Valve removal	12% (5/43)	NA	NA
Valve replacement	7% (3/43)	NA	NA
STELVIO 2015 (n=68)	**n=34**	**n=34**	
Serious adverse events	23	5	<0.001
Non-serious adverse events	59	35	NR
Pneumothorax	18% (6/34)	0	0.02
Pneumonia	6% (2/34)	3% (1/34)	1.0
COPD exacerbation requiring hospitalisation	12% (4/34)	6% (2/35)	0.67
VENT EU 2012 (n=171)[1]	**n=111**	**n=60**	
Valve expectoration, migration or aspiration (episodes)	14	NA	NA
VENT US 2010 (n=321)	**n=220**	**n=101**	

Adverse events (6 months)	6% (13/220)	1% (1/101)	0.08
Adverse events (12 months)	10% (22/220)	5% (5/101)	0.7
Pneumonia (distal to valves)	4% (9/220)	NA	NA
Exacerbation requiring hospitalisation (6 months)	8% (17/220)	1% (1/101)	0.03
Exacerbation requiring hospitalisation (12 months)	NR	NR	0.84
Valve removal	14% (31/220)	NA	NA
Placement in incorrect lobe	1% (3/220)	NR	NA
Haemoptysis	Less than 1%(1/220)	NR	NA

Spiration valve versus SMC

Mortality

OR 4.95, 95% CI 0.85 to 28.94, p=0.076, I^2=0%; n=350 2 RCTs (moderate-quality evidence) (IBV trial 2014 and Ninane 2012)

Adverse event rate

OR 3.41, 95% CI 1.48 to 7.84; n=350; 2 RCTs; high-quality evidence [favours controls]

	EBV group	Controls	p
IBV trial 2014 (n=277)	**n=142**	**n=135**	**-**
Serious adverse events (including death)	22	6	NR
COPD exacerbations	7	2	NR
Respiratory failure	4	NR	NR
Pneumothorax	3	NR	NR
Pneumonia	1	NR	NR
Bronchospasm	1	NR	NR
Ninane 2012 (n=73)[2]	**n=37**	**n=36**	
Serious adverse events	NR	NR	0.52
Adverse events in general	NR	NR	0.21
COPD exacerbations	11	8	NR

Unilateral versus Bilateral valve (Eberhardt 2012)

	Unilateral group	Bilateral group	p
Eberhardt 2012 (n=22)	**n=11**	**n=11**	**-**
COPD exacerbation	2	2	
Respiratory failure requiring invasive or non-invasive ventilation	NR	2	NR
Pneumothorax	NR	1	NR

[1]No overall differences in occurrence of pneumothorax, however pneumothoraces lasting more than 7 days occurred in patients who had a high volume reduction and showed a more positive clinical response.

[2]Procedural adverse events were predominantly bronchospasm and dyspnoea.

Abbreviations used: 6MWD, 6-minute walking distance test; BODE, body mass index, airflow obstruction, dyspnoea and exercise index; CAT, COPD assessment test; CCQ, clinical COPD questionnaire; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DLCO, differences in diffusing capacity of the lung for carbon monoxide; EBV, endobronchial valves; FEV_1, forced expiratory volume in 1 second; IBV, intrabronchial valve; IQR, interquartile range, MCID, minimal clinically important differences; MD, mean difference; mMRC, modified Medical Research Council score; NA, not applicable; NR, not reported; OR, odds ratio; $PaCO_2$; arterial partial pressure or carbon dioxide; PaO_2; arterial partial pressure of oxygen; PRISMA, preferred reporting items for systematic reviews and meta-analyses; QoL, quality of life; RCTs, Randomised controlled trial; RV, residual volume; SD, standard deviation; SGRQ, St George's respiratory questionnaire, SMC, standard medical care, SMD, standardized mean difference.

Study 2 Gompelmann D (2014)

Details

Study type	**Case series**
Country	Europe and US
Recruitment period	Not reported
Study population and number	**n=421** (**n=26 that developed pneumothorax**) patients with severe emphysema treated by EBV and reported in 3 prospective clinical trials (the US and European cohorts of VENT and the multicentre Chartis study)
Age and sex	Pneumothorax group - mean 63±7.1 years, 77% males
Patient selection criteria	In VENT, FEV_1 between 15 and 45% and RV >150% were requirements for study inclusion. In the multicentre Chartis trial, FEV_1 between 15 and 50% was an inclusion criterion. VENT was a clinical controlled trial in which patients were randomly assigned to either an EBV group or a standard medical care group, whereas the Chartis trial was a single-arm study. The patients assigned to the EBV arm received unilateral complete occlusion of the targeted lobe by EBV.
Technique	Data from 3 prospective clinical trials (the US and European cohorts of VENT and the multicentre Chartis study) was retrieved for the analysis to evaluate the impact of pneumothorax on outcome following EBV treatment
Follow-up	**180 days (VENT trial)** **30 days (Chartis trial)**
Conflict of interest/source of funding	None declared.

Analysis

Follow-up issues: None

Study design issues: Functional data was not available for all patients that had pneumothorax.

Study population issues: in the US VENT, 220 patients were randomly assigned to the EBV group and 214 of the 220 patients were treated. In the Euro-VENT, 111 patients received EBV placement. In the multicentre Chartis study, 96 patients ha CV measurement with the Chartis Pulmonary Assessment System followed by EBV treatment.

Other issues: None.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
TLVR % in patients who experienced pneumothorax following EBV[1]
<table>
<tr><th>Trial</th><th>Mean ± SD</th><th>Median</th></tr>
<tr><td>VENT/Euro-VENT (6-month follow-up; n = 14)</td><td>60.2 ± 38.1</td><td>71.1</td></tr>
<tr><td>Chartis trial (3-month follow-up; n = 6)</td><td>74.5 ± 30.0</td><td>82.3</td></tr>
<tr><td>VENT/Euro-VENT/ Chartis trial (n = 20)</td><td>64.5 ± 35.7</td><td>78.8</td></tr>
</table>
FEV1 (n=20)[1]
45% (11/25) of patients that had pneumothorax had >15% improvement in FEV_1 at 6 months follow-up

6MWD (n=19)[1]
Of the patients who had a pneumothorax, 18% (5/25) experienced a >15% improvement in 6MWD at 6 months follow-up.

SGRQ (n=12)[1]
58% of patients who developed a pneumothorax had a > 4-point improvement in SGRQ

[1]HRCT for TLVR was available in 20 patients, 6MWD score in 19 and SGRQ results in 12.
</td><td>
n=421
Incidence of pneumothorax
VENT trial: 6% (18/325)[1]
Chartis trial: 8% (8/96)
Overall: 6% (25/421)[1]
The median duration of pneumothorax was 11 days (2 to 73 days).

Median time for onset of pneumothorax was 2 days after EBV. Fifteen patients experienced pneumothorax within 48 hours and 2 within 74 hours.

Incidence of pneumothorax with respect to treatment lobe
<table>
<tr><th>Target lobe</th><th>Total patient population</th><th>Patients with pneumothorax</th></tr>
<tr><td>Right upper</td><td>205</td><td>3%(6/205)</td></tr>
<tr><td>Left upper</td><td>104</td><td>9% (9/104)</td></tr>
<tr><td>Left lower</td><td>64</td><td>10% (7/64)</td></tr>
<tr><td>Right lower</td><td>45</td><td>7% (3/45)</td></tr>
<tr><td>Right middle/right lower</td><td>1</td><td>0</td></tr>
<tr><td>Right middle</td><td>2</td><td>0</td></tr>
</table>
Incidence of pneumothorax by tissue integrity
<table>
<tr><th>Fissure integrity</th><th>Total patient population, n</th><th>Patients with pneumothorax, n</th></tr>
<tr><td>Complete</td><td>161</td><td>11% (17/161)</td></tr>
<tr><td>Incomplete</td><td>234</td><td>3% (7/234)</td></tr>
<tr><td>Unknown</td><td>26</td><td>1/26</td></tr>
</table>
68% (17/25) of patients who developed pneumothorax had a complete interlobar fissure and thus low CV

Twenty one of the 25 pneumothoraces resolved with observation or chest drain insertion. One patient required chest drain and 2 additional ipsilateral EBVs that were removed after resolution of the pneumothorax. In 2 patient chest drain was not sufficient and thoracotomy was required in 1 and thoracoscopy and thoracotomy were required. In 1 patient admitted with pneumothorax and pneumonia required prolonged mechanical ventilation and died 85 days post EBV.

[1]In the US VENT 1 patient had a left-sided pneumothorax 203 days following EBV in the right upper lobe. The reason for this contralateral pneumothorax was a lung biopsy.
</td></tr>
<tr><td colspan="2">Abbreviations used: 6MWD, 6-minute walking distance test; CV, collateral ventilation; EBV, endobronchial valve; FEV_1,forced expiratory volume in 1 second; HRCT, high resolution computerised tomography; RV, residual volume; SD, standard deviation; SGRQ, St. George's respiratory questionnaire; TLVR, total lung volume reduction.</td></tr>
</table>

Study 3 Skowasch D (2016)

Details

Study type	**Case series (prospective, interim analysis)**
Country	Germany
Recruitment period	2012 and 2015
Study population and number	**n=321** emphysema patients treated by EBV (Zephyr valve)
Age and sex	Mean 65 years (±7.7), 56% (181/321) males
Patient selection criteria	The patients were recruited by 144 pulmonology centres that referred patients to treatment centres (51 sites). The patients would then have further examinations to exclude CV and confirm they were suitable candidates as per local protocol. Inclusion criteria: 18 years of age or older, ability to consent, FEV_1>15 and <45% of predicted, RV>180% of predicted and diagnosis of emphysema with evidence of hyperinflation. Exclusion criteria: Pulmonary infection, collateral ventilation
Technique	Interim analysis of an observational study done in the context of daily clinical practice. A minimum of 5 patients were enrolled from each recruitment centre. The presence of CV was assessed using the Chartis system, Pulmonx
Follow-up	**6 months**
Conflict of interest/source of funding	The study was supported by Pulmonx.

Analysis

Follow-up issues: Follow-up assessments occurred at 3, 6, 9 and 12 months after initial EBV treatment, up to a maximum of 5 years. Adverse events were collected from the moment the patients received EBV treatment to hospital discharge. After discharge adverse events were reported using the usual vigilance system for commercial products.

At the time of publication, 498 patients were treated, complete efficacy data was available for 321 patients and safety data was available from 343 patients, 5 patients died and 2 patients had missing data.

Study design issues: A sample size of 2,000 was considered necessary to achieve statistically significantly 95% CI of a relative mean change of FEV_1 at 2 years follow-up, assuming a mean ±SD change of 16±22% with a power of 99%. All patients remained in the study regardless of other care being received.

Study population issues: From the 321 patients in the efficacy population 265 were CV negative, 46 were rated 'inconclusive', 4 were CV positive and 4 were 'not done'.

Other issues: In average each patient was treated with 4 valves.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Efficacy data (reported to 6 months follow-up) not extracted as randomised trial efficacy data available from 7 RCT reported in paper 1 (Cochrane systematic review and meta-analysis). This study included for safety findings.</td><td>n=343
Death (during initial hospital stay): 5/498
These patients were not included in the safety population

<table>
<tr><th></th><th>AE or SAE*</th></tr>
<tr><td>Death</td><td>0/343</td></tr>
<tr><td>Pneumothorax</td><td>10% (35/343)</td></tr>
<tr><td>COPD exacerbation</td><td>1% (5/343)</td></tr>
<tr><td>Pneumonia distal to valve</td><td>1% (4/343)</td></tr>
<tr><td>Hypoxia</td><td>1% (4/343)</td></tr>
<tr><td>Valve migration</td><td><1% (3/343)</td></tr>
<tr><td>Fistula</td><td><1% (2/343)</td></tr>
<tr><td>Pleural effusion</td><td><1% (2/343)</td></tr>
<tr><td>Respiratory failure</td><td>1/343</td></tr>
<tr><td>Mild haemoptysis</td><td>1/343</td></tr>
<tr><td>Pleuritis</td><td>1/343</td></tr>
<tr><td>Increased sputum</td><td>1/343</td></tr>
<tr><td>Other</td><td>1/343</td></tr>
</table>

Among 343 patients 55 experienced 66 AE. According to physicians 26% (17/66) were device related and 68% (45/66) were procedure related.

*Percentages calculated by the NICE interventional procedures analyst</td></tr>
<tr><td colspan="2">Abbreviations used: AE, adverse events; SAE, severe adverse events.</td></tr>
</table>

Study 4 Sterman DH (2010)

Details

Study type	**Case series (prospective)**
Country	US
Recruitment period	2004 to 2006
Study population and number	**n=91**, patients with severe emphysema
Age and sex	mean 65 years (range 42 to 79), 56% (51/91) male
Patient selection criteria	Patient selection criteria: heterogeneous, upper-lobe predominant emphysema. Patients with a significant bronchospastic component to their emphysema, chronic bronchitis, or significant bronchiectasis were not included. Patients already accepted and listed for lung volume reduction surgery or lung transplantation were also excluded.
Technique	The EBV (Spiration) was used for bilateral upper lobe placement.
Follow-up	**12 months**
Conflict of interest/source of funding	Funded by Spiration Inc., USA.

Analysis

Follow-up issues: No patients were lost to follow-up. During the 12-month study, 26 patients withdrew (10 associated with an adverse event).

Study design issues: The primary outcome was safety (the rate of observed migration, erosion or infection associated with valves within the first 3 months after placement).

Study population issues:

Other issues: Mean of 7 valves was used per patient.

This paper was included in table 2 of the previous version of the guidance.

Key efficacy and safety findings

Efficacy	Safety
Efficacy data (reported to 12 months follow-up) not extracted as randomised trial efficacy data available from 7 RCT reported in paper 1 (Cochrane systematic review and meta-analysis). This study included for safety findings.	**Procedure-related complications** • Pneumonia associated with valves within 3 months of procedure = 1.1% (1/91) • Bacterial bronchitis associated with valves within 3 months of procedure = 1.1% (1/91) • Bronchospasm (within 3 days of procedure) = 8.8% (8/91) (1 was described as serious and associated with respiratory failure and myocardial infarction that began the evening after an uneventful procedure. The patient had further episodes of bronchospasm and the valves were removed on day 21. A second patient had valve removal on day 3 because the bronchospasm did not resolve). • Myocardial infarction on day 3 = 1.1%(1/91) • Injury to bronchi = 3.3% (3/91) • Transient hypercarbia = 2.2% (2/91) (1 patient needed overnight ventilator support) There were no occurrences of valve migration or erosion. Complications within 12 months • Pneumothorax = 12.1% (11/91) (5 were judged to be serious and definitely device-related. • Pneumonia distal to valves = 6.6% (6/91) • Valve removal = 17.6% (16/91) (between 97 and 358 days after device placement for pneumonia, bronchospasm, recurrent COPD exacerbations, or pneumothorax) *Deaths (n=3, 3.3%)* 1 patient died from tension pneumothorax 4 days after the procedure; 1 patient died on day 113 from respiratory failure and pneumonia; 1 patient died on day 33 related to respiratory failure and pneumonia after placing an endotracheal tube for surgical repair of a prolonged air leak.
Abbreviations used: None.	

Study 5 Fiorelli A (2016)

Details

Study type	**Case series (retrospective)**
Country	Italy
Recruitment period	2011 to 2014
Study population and number	n=49 (35 unilateral EBV, 14 bilateral EBV) consecutive patients with bilateral heterogeneous emphysema treated by EBV
Age and sex	Bilateral group - Mean 62 ± 5.6 years Unilateral group - Mean 61 ± 7.3 years Gender frequencies not reported
Patient selection criteria	Inclusion criteria Aged 40 to 75 tears, heterogeneous emphysema at HRCT scan, FEV_1 < 45% of predicted value, TLV > 100% of predicted, RV > 150% of predicted, $PaCO_2$ < 50mmHg, PaO_2 > 45mmHg, 6MWD test ≥ 140 m Exclusion criteria Homogeneous emphysema at HRCT and lung perfusion scan, current smoking, listed for other treatments (lung volume reduction, bullectomy, lung transplantation), FEV_1 <15% of predicted, DLCO < 20% of predicted.
Technique	Patients were split into 2 groups depending of treatment (unilateral or bilateral). Contralateral treatment using EBV was provided in some patients due to loss of clinical benefit after the first intervention (Bilateral group). All patients were treated using EBV (Zephyr valve, Pulmonx).
Follow-up	**Bilateral group – Median 36 months** **Unilateral group – Median 23 months**
Conflict of interest/source of funding	One invited commentator disclosed a financial relationship with Spiration. No other reported.

Analysis

Follow-up issues: Patients were reassessed from a functional status and quality of life at 3, 6 months and yearly thereafter.

Study design issues: The different timing of the second EBV treatment makes the assessment of efficacy more prone to bias. Retrospective study, subject of bias related to the speed of functional decline in patients having the second treatment. There was no assessment of CV. Completeness of fissures was reported based on radiological findings.

No statistically significantly baseline differences were found between unilateral and bilateral groups.

Study population issues: There were 29% (14/49) patients having a second EBV treatment after a median interval of 18 months (range, 2 to 25) after the initial treatment.

Other issues: In all, 74 valves were deployed (34 during the first procedure and 40 during the second), with a median of 5 valves (range, 5 to 8) per patient.

Key efficacy and safety findings

Efficacy

n=49

Mean hospital stay – 8.2 ± 2.0 days (3 days after the first procedure and 5 days after the second)

Treatment failure

There were 2 patients that did not have any benefit from the initial treatment and had contralateral procedure done 2 and 5 months later.

Functional and quality of life outcomes

	Baseline	1 Year	4 years	p
Bilateral group				
O_2 saturation, %	92 ± 4.1	93 ± 6.4	93 ± 5.7	0.3
PaO2	67 ± 12	73 ± 9	72 ± 12	0.1
PaCO2	41 ± 6.2	40 ± 3.9	39 ± 3.8	0.5
FEV_1	32 ± 6.8	40 ± 4.9	41 ± 2.8	0.02
FVC	30 ± 3.0	44 ± 1.4	42 ± 0.8	0.02
RV	247 ± 27	158 ± 8.3	125 ± 4.2	0.004
TLV, %	129 ± 26	110 ± 20	103 ± 39	0.1
6MWD	216 ± 17	430 ± 38	410 ± 31	0.02
DLCO	52 ± 12	56 ± 11	53 ± 10	0.7
SGRQ	55 ± 2.8	46 ± 1.5	45 ± 0.7	0.01
Unilateral group				
O_2 saturation, %	93 ± 5.4	93 ± 7.4	93 ± 9.7	0.4
PaO2	68 ± 14	74 ± 7.5	73 ± 9.1	0.3
PaCO2	40 ± 6.2	40 ± 9.2	40 ± 5.9	0.7
FEV_1	34 ±1.7	45 ± 2.4	43 ± 2.5	0.02
FVC	35 ± 1.7	44 ± 0.7	43 ± 0.7	0.01
RV	261 ± 17	141 ± 15	142 ± 9.5	0.006
TLV, %	119 ± 21	110 ± 12	108 ± 19	0.3
6MWD	172 ± 12	376 ± 36	355 ± 28	0.02
DLCO	53 ± 9	57 ± 10	54 ± 7	0.6
SGRQ	54 ± 2.4	43 ±1.4	43 ± 1.8	0.01

Survival rate – hazard ratio 1.24, 95% CI 0.46 to 3.32, p=0.6

Safety

	Bilateral group (n=14)	Unilateral group (n=35)
Pneumothorax	21% (3/14)	8% (3/35)
Pneumonia	1/14	0/35
Migration	14% (2/14)	0/35
Haemoptysis	14% (2/14)	0/35
Total Complications*	57% (8/14)	11% (4/35)

*p=0.0007

Bilateral group

Seven patients died: 4 of cancer, 2 of myocardial infarction, and 1 of end-stage respiratory failure.

Unilateral group

Nine patients died: 4 of cancer, 3 of myocardial infarction, 1 of intractable arrhythmia, and 1 of end-stage respiratory failure.

Abbreviations used: CI, confidence interval; DLCO, differences in diffusing capacity of the lung for carbon monoxide; EBV, endobronchial valve; FEV_1,forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high resolution computerised tomography; $PaCO_2$; arterial partial pressure or carbon dioxide; PaO_2, arterial partial pressure of oxygen; RV, residual volume; SGRQ, St George's respiratory questionnaire; TLC, total lung capacity.

Study 6 Venuta F (2011)

Details

Study type	**Case series (Prospective)**
Country	Italy
Recruitment period	Not reported
Study population and number	**n=40**, patients with heterogeneous emphysema treated unilaterally with EBV
Age and sex	Mean 61 ± 9.8, 93% (37/40) males
Patient selection criteria	Inclusion criteria - Heterogeneous emphysema at HRCT and lung perfusion scan, FEV_1 <35%, RV >180%, aged 35 to75 years Exclusion criteria - Homogeneous emphysema at HRCT and lung perfusion scan, currently smoking, presence of isolated bulla, $PaCO_2$ >50 mmHg DLCO <20%, productive cough, small airway disease.
Technique	Heterogeneity was subjectively assessed by at least two members of the team using HRCT. The presence of interlobar fissures was retrospectively blindly determined by a radiologist. All patients were treated with EBV (Zephyr valves, Pulmonx). Only patients treated unilaterally were included.
Follow-up	**Median 32 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Thirty three patients were evaluated after 1 years, 18 after 3 years and 9 after 5 years. Only 82.5% (33/40) of patients had a follow-up longer than 12 months

Study design issues: One patients had the valves removed in a different centre 3 months after procedure and was excluded from the survival analysis. All patients received optimal medical therapy at the time of evaluation.

The MRC dyspnoea scale ranges from 1 to 5, with higher scores indication more severe symptoms.

Study population issues: There were 2 patients receiving single lung transplantation and 1 double lung transplantation at mean 6 months after valve placement. Two of these patients died.

Other issues: Each patient was treated with an average of 4 EBV. Patients were not assessed for the presence of collateral ventilation.

This paper was included in table 2 of the previous version of the guidance.

Key efficacy and safety findings

Efficacy

n=40

Mean hospital stay - 5 days (range 2 to 32)

	Baseline (n=40)	**1 Year (n=33)**	**3 years (n=18)**	**5 years (n=9)**	**p**
Supplementary O_2, litres/min	1.87 ± 1.2	0.8 ± 0.8	0.8 ± 0.8	1.0 ± 1.0	<0.001
O_2 saturation	94.9 ± 3.1	94.7 ± 1.9	94.4 ± 1.9	95.7 ± 2.4	0.2
PaO2, mmHg	72.7 ± 11.3	74.6 ± 6.7	71.9 ± 6.3	72.9 ± 10.3	0.7
PaCO2 , mmHg	41.2 ± 4.5	39.5 ± 3.4	39.3 ± 2.6	39.7 ±2.9	0.2
FEV_1, litres/min	0.88 ± 0.3	1.09 ± 0.4	1.08 ± 0.4	1.2 ± 0.5	0.004
FVC, litres	2.0 ± 0.6	2.4 ± 0.6	2.4 ± 0.5	2.5 ± 0.6	0.06
RV, litres	5.2 ± 0.9	4.4 ±1.2	4.4 ± 1.2	3.98 ± 1.2	0.03
TLC, litres	7.45 ± 1.1	7.28 ± 1.0	7.29 ± 1.1	7.3 ± 1.3	0.7
ITGV, litres	6.0 ± 1.1	5.3 ± 1.1	5.2 ± 1.3	5.3 ±1.2	0.1
DLCO	2.95 ± 1.9	2.88 ± 1.5	3.35 ± 1.3	3.86 ± 1.2	0.2
6MWD	286 ± 97	349 ± 105	355 ± 90	402 ± 113	0.003
MRC score	3.9 ± 0.8	2.4 ± 0.6	2.6 ± 0.6	2.6 ± 0.7	<0.001

The improvements for FEV_1, 6-minute walk test and MRC score were statistically significant at all time points. The results for supplemental oxygen were statistically significant up to the third year.

Mean survival – 36 ± 4.3 months

1-year survival – 82%,

3-year survival – 47%,

5-year survival – 22%

Safety

Mortality

40% (16/40) patients died during follow-up (lung cancer in 25% (4/16) myocardial infarction with intractable arrhythmia in 19% (3/16), end-stage respiratory failure in 44% (7/16) and post-transplant in 13% (2/16).

Pneumothorax[1]	1/40
Pneumonia distal to valve	5% (2/40)
Mild haemoptysis[2]	1/40
Granulation into the valve[3]	5% (2/40)
Valve removal[4]	1/40

[1]Contralateral, happened 15 days after procedure

[2]Happened 3 years after procedure in a patient anticoagulated after coronary artery disease revascularisation

[3]Not compromising valve functionality

[4]Three months after EBV

Abbreviations used: DLCO, differences in diffusing capacity of the lung for carbon monoxide; EBV, endobronchial valve; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high resolution computerised tomography; ITGV, intrathoracic gas volume; MRC, Medical Research Council score; $PaCO_2$; arterial partial pressure or carbon dioxide; PaO_2; arterial partial pressure of oxygen; RV, residual volume.

Study 7 Kemp SV (2017)

Details

Study type	**RCT**
Country	European multicentre (17 centres) - TRANSFORM study
Recruitment period	2014 to 2016
Study population and number	**n=97 (65 EBV, 32 SMC)** ex-smokers older than 40 with severe emphysema
Age and sex	**EBV** – 64.9±8.0, 57% (37/67) males **SMC** – 63.0±6.0, 66% (21/32) males
Patient selection criteria	Inclusion criteria: • post-bronchodilator FEV1 of between 15% and 45% predicted despite optimal medical management, • total lung capacity (TLC) >100% predicted, • residual volume (RV) ≥180% predicted, and a • 6MWD of between 150m and 450m Exclusion criteria • Presence of CV
Technique	Heterogeneous emphysema was defined as an over 10% difference in destruction scores between target and ipsilateral lobes, assessed by HRCT imaging. CV was assessed using the Chartis system (Pulmonx, US). If there was more than 1 potential target lobe, the lobe with the highest destruction score and lowest perfusion as determined by scintigraphy was assessed for CV first. Subjects randomized to SMC were discharged after standard post bronchoscopy recovery, unless the treating physician deemed an admission necessary. Subjects randomized to EBVs were hospitalized for at least 1 day and discharged following a chest X-ray if there were no complications SAEs. TLVR was assessed with HRCT at 45 days and if necessary, a repeat bronchoscopy and valve revision or replacement were done. Patients were treated with Zephyr EBVs.
Follow-up	**6 months**
Conflict of interest/source of funding	The study was sponsored and funded by Pulmonx, US

Analysis

Follow-up issues: Patients were followed-up at 3 months after the last valve revision or insertion procedure. After 6 months, patients in the SMC group were given the options of exiting the study if they wanted to receive EBV, or to continue in follow-up for 12 months. EBV group follow-up is planned to last 24 months.

Study design issues: Prospective, multicentre 2:1 RCT of EBVs plus SMC or SMC alone. Primary outcome was the 3-month percentage of subjects with a FEV_1 improvement from baseline greater than 12% (protocol defined MCID). Secondary endpoints included comparison between EBV and SMC groups for the absolute and percent changes and responder rates achieving the MCID at 3 and 6 months for FEV1 (≥12%), RV (≤-430 mL), SGRQ score (≤-4 points), 6MWD (≥26 meters), mMRC dyspnoea score (≤-1 point), and for the EBV group only, the absolute and percent change in TLVR at 45 days post-procedure and the percent of subjects meeting the TLVR MCID of ≥350mL (12) relative to baseline.

The sample size calculation of 78 subjects was based on the primary endpoints, 80% power, alpha = 0.05, a two-sided Chi-Square test, and 15% drop-out rate.
For the ITT analysis missing data were imputed using the last observation carried forward method.

Study population issues: The median of randomised subjects per centre was 5 (range 1 to 14). Baseline characteristic were similar although EBV group reported a worse respiratory related QoL (p=0.042), and absolute but not percent predicted FEV_1 (p=0.008).

A median of 4 valves (range 2 to 8) were implanted by patient. Treatment distributions were 52% left upper lobe, 22% left lower lobe, 15% right upper lobe, 8% right upper and right middle lobe combined, and 3% right lower lobe.

Other issues: None.

Key efficacy and safety findings

Efficacy

n=97 (65 EBV, 32 SMC)

Median hospital stay

EBV - 4 days (range 1 to 49)

SMC – 1 day (range 1 to 3)

TLVR ≥350ml - 90%, mean of 1.09 ± 0.62L (p<0.001, 45 days follow-up)

MCID responders for key outcome measures in the ITT population at 6 months

Variable	EBV	SMC	p-value*
FEV_1 (L): (MCID ≥ +12%)	56% (36/64)	3% (1/31)	<0.001
RV (ml): (MCID ≤ -430 mL)	58% (37/64)	26% (8/31)	0.003
SGRQ: (MCID ≤ -4 points)	62% (35/62)	34% (11/32)	0.042
6MWD: (MCID≥ +26 meters)	52% (33/63)	13% (4/31)	<0.001
mMRC: (MCID ≤ -1 point)	44% (29/64)	23% (7/31)	0.032

*Chi-squared test

Safety

Patients affected by serious adverse events

At 6 months there were 78% (35/65) of patients having SAE in the EBV group and 9% (4/32) in the SMC group, p<0.001.

Event	EBV, n=65		SMC, n=32**
	≤ 30 days	**≥30 days**	**≥30 days**
Pneumothorax	20% (13/65)	3% (2/65)	0
Dyspnoea	8% (5/65)	3% (2/65)	0
Pneumonia	5% (3/65)	5% (3/65)	3% (1/32)
COPD exacerbation	5% (3/65)	5% (3/65)	6% (2/32)
Subcutaneous emphysema	2% (1/65)	0	0
Haemoptysis	2% (1/65)	0	0
Inhaled foreign body	2% (1/65)	0	0
Lower respiratory tract infection	2% (1/65)	0	0
Death	2% (1/65)[1]	0	0
Bronchospasm	0	2% (1/65)	0
Influenza	0	2% (1/65)	0
EBV removal	0	2% (1/65)	0

Revision procedure – 28% (18/65)

** There were no SAE occurring before day 30 in the SMC group.

[1]Cardiac arrest occurring as consequence of pneumothorax.

Abbreviations used: 6MWD, 6-minute walking distance test; CI, confidence interval; EBV, endobronchial valves; FEV_1, forced expiratory volume in 1 second; HRCT, high resolution computed tomography; ITT, intention-to-treat; MCID, minimal clinically important differences; mMRC, modified Medical Research Council score; QoL, quality of life; RCTs, Randomised controlled trial; RV, residual volume; SAD, serious adverse events; SD, standard deviation; SGRQ, St George's respiratory questionnaire, SMC, standard medical care.

Study 8 Gompelmann D (2016)

Details

Study type	**Case series**
Country	Germany
Recruitment period	2009 to 2013
Study population and number	**n=381 patients with severe emphysema treated by EBV** (70 developing pneumothorax)
Age and sex	Mean 64 years (41 to 81), 52% males
Patient selection criteria	All patients who had pneumothorax during follow-up after insertion of EBV at the Thoraxklinik (University of Heidlberg). Patients had severe emphysema confirmed by baseline lung function tests demonstrating a significant FEV_1 reduction and severe hyperinflation.
Technique	Retrospective evaluation of pneumothorax management and impact of pneumothorax on clinical outcomes in 70 patients following valve therapy in 381 consecutive patients enrolled in several prospective trials. Patients were treated with Zephyr or the Spiration valves, or both. The most emphysematous lobe was identified using a multi-detector CT and perfusion scan.
Follow-up	**1 year**
Conflict of interest/source of funding	Some authors disclosed having received fees from different device manufacturers of pharmaceutical companies.

Analysis

Follow-up issues:

Study design issues: Reviewed data were clinical (VC, FEV_1, RV, TLV, 6MWD, TLC and mMRC dyspnoea score) and radiological outcomes of patients that developed pneumothorax after EBV, at 1 year follow-up. The prevalence, onset, duration and management of pneumothorax following valve treatment were assessed.

Study population issues: The patients were divided into two subgroups depending on whether a complete lobar atelectasis could be observed. The patients with complete lobar atelectasis as the maximum radiological result following valve placement belonged to the atelectasis group, whereas the other subgroup consisted of patients with partial atelectasis, dystelectasis or no change in volume.

The mean FEV1 was 0.8 litres and the mean RV was 262±21% predicted. The left lower lobe was the most common target lobe.

Other issues: None

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>n=381 treated by EBV (70 pneumothorax)

<u>Valve reimplantation 3 months after explantation</u> – 16% (5/31)
<u>Failure to develop complete atelectasis</u> – 60% (42/70)

<u>Change from baseline by parameter</u>
<table>
<tr><th rowspan="2">Clinical outcome measure</th><th colspan="3">Atelectasis</th><th colspan="3">No atelectasis</th></tr>
<tr><th>n</th><th>Mean±SD</th><th>p</th><th>n</th><th>Mean±SD</th><th>p</th></tr>
<tr><td>VC, mL</td><td>53</td><td>28±494</td><td>0.676</td><td>34</td><td>−51±493</td><td>0.598</td></tr>
<tr><td>VC (% predicted)</td><td>53</td><td>1.7±14.7</td><td>0.414</td><td>34</td><td>−1.1±14.1</td><td>0.449</td></tr>
<tr><td>FEV1 (mL)</td><td>53</td><td>55±148</td><td>0.009</td><td>34</td><td>39±142</td><td>0.115</td></tr>
<tr><td>FEV1 (% predicted)</td><td>53</td><td>2.0±5.3</td><td>0.007</td><td>34</td><td>1.3±4.9</td><td>0.119</td></tr>
<tr><td>RV, mL</td><td>50</td><td>−390±964</td><td>0.006</td><td>32</td><td>−203±835</td><td>0.179</td></tr>
<tr><td>RV (% predicted)</td><td>50</td><td>−23.0±43.3</td><td>0.001</td><td>32</td><td>−15.9±34.0</td><td>0.013</td></tr>
<tr><td>TLC, mL</td><td>51</td><td>−348±876</td><td>0.007</td><td>32</td><td>−237±805</td><td>0.107</td></tr>
<tr><td>TLC (% predicted)</td><td>51</td><td>−7.1±15.8</td><td>0.002</td><td>32</td><td>5.1±12.8</td><td>0.032</td></tr>
<tr><td>6MWT, m</td><td>42</td><td>13.9±72.9</td><td>0.223</td><td>26</td><td>5.4±75.5</td><td>0.308</td></tr>
<tr><td>mMRC, points</td><td>38</td><td>−0.2±1.3</td><td>0.400</td><td>24</td><td>−0.4±1.0</td><td>0.846</td></tr>
</table>
At 3 month follow-up EBV was associated with significant improvement of all lung parameters except VC.</td><td>Pneumothorax rate – 18% (70/381)
• 13% (9/70) resolved under observation only
• 87% (61/70) required chest tube insertion;
• 51% (31/61) of these pneumothorax did not resolve and valve removal was necessary.
• Persistent fistula (despite chest drain and valve removal) was present in 45% (14/31) of patients. This was corrected by talc slurry (1/14) or surgical resolution: video-assisted thoracoscopy (77% [10/13]), thoracotomy (15% [2/13]) or both (8% [1/13])

Median time to pneumothorax – 1 day (range 0 to 125)
Pneumothorax within 3 days of EBV – 73% (51/70)</td></tr>
<tr><td colspan="2">Abbreviations used: 6MWD, 6-minute walking distance test; EBV, endobronchial valves; FEV_1, forced expiratory volume in 1 second; CT, computed tomography; ITT, intention-to-treat; MCID, minimal clinically important differences; mMRC, modified Medical Research Council score; RCTs, Randomised controlled trial; RV, residual volume; SD, standard deviation; SGRQ, St George’s respiratory questionnaire; VC, vital capacity.</td></tr>
</table>

Efficacy

Forced expiratory volume

A systematic review (SR) and meta-analysis included 5 randomised controlled trials (RCTs) of patients treated by a duckbill-shaped endobronchial valve (EBV) insertion and 3 RCTs of patients (n=372) treated by an umbrella-shaped EBV insertion, both compared with standard medical care (SMC). These 2 groups were analysed separately. In a meta-analysis of the 5 RCTs of duckbill EBV insertion compared with SMC, there was a statistically significant difference in 1% change from baseline in forced expiratory volume in 1 second (FEV_1) in favour of duckbill EBV insertion (mean difference [MD] 0.48, 95% confidence interval [CI] 0.32 to 0.64, p<0.00001, I^2=42). In 2 RCTs (n=143) from the same meta-analysis, a 2% increase in FEV_1 was statistically significantly more frequent in patients treated by duckbill EBV than in those treated by SMC at 90-day follow-up (MD 0.77, 95% CI 0.43 to 1.11, p<0.00001, I^2=0%). In the other 3 RCTs (n=560) from the same meta-analysis, a 2% increase in FEV_1 was statistically significantly more frequent in patients treated by duckbill EBV than in those treated by SMC at 6-month follow-up (MD 0.40, 95% CI 0.22 to 0.58, p<0.00001, I^2=41%). In 1 RCT of the same systematic review, a 2% increase in FEV_1 was statistically significantly more frequent in patients treated by duckbill EBV insertion than patients treated by SMC at 12 months follow-up (MD 8.00%, 95%CI 1.00 to 15.00; p=0.04, I^2=NA; n=171). One RCT (n=277) included in the SR reported a statistically significantly lower percentage change in FEV_1 in the patients treated by umbrella EBV (MD −2.11%) when compared with SMC patients (0.04%, p=0.001), at 6 months follow-up. One RCT (n=73), which studied patients treated by the umbrella EBV, reported no statistically significant difference in FEV_1 measurements at 3-month follow-up (MD 0.90 litres, standard deviation [SD] 0.34) compared with patients having SMC (0.87 litres, SD 0.34, p=0.065). A second RCT (n=22) of the umbrella EBV reported statistically significantly improved FEV_1 measurements in patients treated unilaterally (21.4%, SD 10.7%) but not in patients treated bilaterally (−3.1%, SD 15.0; MD 24.50%, 95% CI 13.61 to 35.39).[1]

In a case series of 49 patients treated by duckbill EBV, FEV_1 was statistically significantly increased from baseline values in patients in the groups treated unilaterally and bilaterally, p=0.02.[5]

In a case series of 40 patients treated by duckbill EBV, FEV_1 was statistically significantly increased from baseline values at 5 years follow-up, p=0.004.[6]

In a case series of 381, FEV_1 was statistically significantly increased from baseline values in patients treated by EBV who developed atelectasis (using duckbill or umbrella shaped valves, 55 mL ±148, p=0.009) but not in patients who did not develop atelectasis (39 ml ±142, p=0.115).[8]

FEV_1 changes by emphysema distribution

The SR reported a statistically significantly larger change in FEV_1 from baseline in patients with heterogeneous emphysema treated by duckbill EBV than in patients with homogeneous emphysema having the same treatment (MD 16.36%, 95% CI 9.02 to 23.71, p=0.00001, I^2=0%, n=137, 2 RCTs).[1]

FEV_1 charges by collateral ventilation status and interlobar fissures patency

In 3 RCTs (n=542) included in the SR there was a statistically significant increase in FEV_1 from baseline in patients without collateral ventilation treated by duckbill EBV (MD 18.15%, 95% CI 11.81 to 24.49; p=0.000001, I^2=0%). Three RCTs (n=542) reported no statistically significant increase in FEV_1 after duckbill EBV treatment in patients with collateral ventilation (MD 2.48%, 95% CI −2.63 to 7.59, p=0.34, I^2=0%). The SR reported that 2 RCTs showed statistically significant increases in FEV_1 in patients with intact interlobar fissures as a surrogate for the absence of collateral ventilation (MD 17.80%, 95% CI 7.78 to 27.82, n=68; and MD 17.23%, 95% CI 8.10 to 26.36, n=93).

One RCT (n=171) of the SR reported a statistically significantly higher change in FEV_1 in patients with intact fissures treated by duckbill EBV achieving complete lobar occlusion (MD 28% [standard deviation, SD 32]), in opposition to partial lobar occlusion (MD 2% [SD 10]), p=0.005. Similarly, as reported by another RCT (n=321) in the same SR, FEV_1 increase was statistically significantly higher in patients with intact fissures treated by duckbill EBV achieving complete lobar occlusion (MD 20.6% [SD 25.1]) than in patients with intact fissures and incomplete lobar occlusion after duckbill EBV (MD 5.2% [SD 17.4]), p=0.006.[1]

In an RCT of 97 patients without CV, an increase in FEV_1 of greater than 12% from baseline values was statistically significantly more frequent in patients treated by duckbill EBV (56% [36/64]) than in patients treated by SMC (3% [1/31], p<0.001) at 6 months follow-up.[7]

Lung function other than FEV_1

Residual volume (RV)

The SR included a meta-analysis of 3 RCTs (n=200) reporting a statistically significant reduction in RV from baseline measurements in patients treated by duckbill EBV compared with SMC patients (MD −0.58, 95% CI −0.77 to −0.39, p<0.00001, I^2=56%, low-quality evidence). One RCT (n=321) in the same SR found no statistically significant difference in RV reduction between patients treated by duckbill EBV (−1%) and SMC controls (less than 1%, p=0.41). One RCT in the same systematic review found no statistically significant minimally clinically important difference (MCID) in RV (defined as 0.35 litres) between the Zephyr EBV group (n=11) and sham controls (p=0.24). Two RCTs from the same

SR found a statistically significantly larger reduction of RV in patients treated by duckbill EBV than in patients receiving SMC (44% duckbill EBV group, 18% SMC group, MCID −430 ml, p=0.006, n=93) (71% duckbill EBV group, 3% controls, MCID −430 ml, p=0.001, n=68). A meta-analysis of 2 RCTs (n=322) in the same SR reported a statistically significant RV reduction favouring SMC patients over patients treated by umbrella EBV (MD 0.38 litres, 95% CI 0.12 to 0.65, p=0.005, I^2=0%, high-quality evidence).

One RCT (n=22) included in the SR reported statistically significant RV reduction in patients treated unilaterally with the umbrella EBV (−872 ml [SD 796]; percentage change from baseline −14.7% [SD 13.4], p=0.005) but not in the group of patients treated bilaterally (85 ml [SD 446]; percentage change from baseline 1.5% [SD 7.7], p=0.7).[1]

In the case series of 49 patients treated by duckbill EBV, RV was statistically significantly decreased from baseline values in patients in the groups treated unilaterally (p=0.006) and bilaterally p=0.004.[5]

In the case series of 40 patients treated by duckbill EBV, RV was statistically significantly reduced from baseline values at 5 years' follow-up, p=0.03.[6]

In the RCT of 97 patients without CV, a reduction in RV greater than 430 ml from baseline values was statistically significantly more frequent in patients treated by duckbill EBV (58% [37/64]) than in patients treated by SMC (26% [8/31], p<0.003) at 6 months follow-up.[7]

In the case series of 381 patients, RV was statistically significantly reduced from baseline values in patients treated by EBV who developed atelectasis (using duckbill or umbrella shaped valves, −390 ml ±964, p=0.006) but not in patients who did not develop atelectasis (−203 ml ±835, p=0.179).[8]

Total lung capacity (TLC)

A meta-analysis of 2 RCTs (n=107) reported a statistically significant increase in TLC from baseline measurements in patients treated by duckbill EBV over SMC patients (MD −0.34 litres, 95%CI −0.46 to −0.23, p<0.00001, I^2=16%; moderate-quality evidence). One RCT from the same SR reported a non-statistically significant difference in TLC between patients treated by duckbill EBV achieving complete lobar occlusion (MD 0.3 litres [SD 0.7]) and patients with incomplete lobar occlusion after duckbill EBV (0.2 litres [SD 1.2]) compared with SMC patients 0.4 litres, p>0.05. Similarly, 2 RCTs reported in the same SR found no difference in TLC reduction between patients treated by duckbill EBV and SMC patients (duckbill EBV group: MD -1.2% [SD10.6], SMC patients: MD -0.4% [SD 13], p=0.29, n=322; duckbill EBV group [n=11] and SMC patients [n=7], MCID 0.35 litres, p=0.24). The SR reported a meta-analysis of 2 RCTs (n=322) that suggested no statistically significant difference in TLC between patients treated

by umbrella EBV and SMC patients (MD 0.14; 95% CI −0.12 to 0.39, p=0.29, I^2=0%, high-quality evidence). One RCT (n=22) included in the SR found no statistically significant improvement in TLC in patients treated either unilaterally with umbrella EBV (percentage change −4.1 [SD 10.1]) or bilaterally (1.5% [SD 7.7]) and there was no statistically significant MD between groups, p=0.47.[1]

In the case series of 49 patients treated by duckbill EBV, TLC was not statistically significantly different from baseline values in patients in the unilateral or bilateral groups.[5]

In the case series of 40 patients treated by duckbill EBV, TLC was not statistically significantly different from baseline values at 5 years follow-up.[6]

In an RCT of 97 patients without CV, total lung volume reduction from baseline values of greater than 350 mL was reported in 90% of patients treated by duckbill EBV (mean of 1.09 ± 0.62L, p<0.001) at 45 days follow-up.[7]

In the case series of 381 patients, TLC was statistically significantly reduced from baseline values in patients treated by EBV who developed atelectasis (using duckbill or umbrella shaped valves, −348 mL ±876, p=0.007) but not in patients who did not develop atelectasis (−237 mL ±805, p=0.107).[8]

RV/TLC

The SR reported a meta-analysis of 2 RCTs (n=118) that suggested a statistically significantly larger RV/TVL change from baseline in patients treated by duckbill EBV over those treated with SMC (MD −5.76, 95% CI −10.45 to −1.06, p<0.016, I^2=81%, low quality evidence). One RCT (n=68) from the same SR reported a statistically significant MCID of 4% in RV/TLC favouring 63% of the patients treated by duckbill EBV in comparison with 9% of controls, p<0.001. The same RCT found a statistically significant difference in RV/TLC in patients treated by duckbill EBV over the SMC group (MD −8.1% [SD 10.7]). Similarly, 1 RCT (n=50) from the same SR reported statistically significantly different RV/TLC in patients treated by duckbill EBV over the patients having sham treatment (MD −2.75% [SD1.6]). One RCT included in the SR reported changes in RV/TLC to be larger in patients treated by duckbill EBV with complete lobar occlusion (MD −14% [SD 11]) than in duckbill EBV patients without complete lobar occlusion (0% [SD 12]) or SMC patients (−2% [SD 10]), p value not reported. One RCT (n=73) included in the SR reported a statistically significantly better RV/TLC at follow-up in patients treated by umbrella EBV over SMC patients (p=0.01), MD value not reported.[1]

Functional vital capacity (FVC)

One RCT included in the SR reported a variation in FVC from baseline measurements favouring patients treated with duckbill EBV over SMC controls (MD −14.4% [SD 27.8]), p value not reported.[1]

In the case series of 49 patients treated by duckbill EBV, FVC was statistically significantly increased from baseline values in patients in the groups treated unilaterally (p=0.01) and bilaterally (p=0.02).[5]

In the case series of 40 patients treated by duckbill EBV, FVC was not statistically significantly different from baseline values at 5 years' follow-up.[6]

In the case series of 381 patients, FVC was not statistically significantly increased from baseline values in patients treated by EBV who developed atelectasis (using duckbill or umbrella shaped valves, 28 mL ±494, p=0.676) or in patients who did not develop atelectasis −51 mL ±493, p=0.598).[8]

Exercise capacity

The SR reported a meta-analysis of 4 of the RCTs (n=379) of patients treated with duckbill EBV in whom the 6-minute walking distance (6MWD) test was used to assess exercise capacity. The analysis showed a statistically significant increase in exercise capacity from baseline compared with SMC (MD 38.12 m, 95% CI 8.68 to 67.56, p=0.011, I^2=78%). There was high variability between studies. One RCT (n=171) of the same SR reported a statistically significant increase in 6MWD results at follow-up in patients treated by duckbill EBV (9.3 m), compared with medically treated controls (−10.7 m; MD 19.1 m, p=0.002). Three RCTs included in the systematic review reported a statistically significantly higher frequency of patients able to walk 26 m or more in the duckbill EBV group (n=12) compared with (n=4) SMC patients, p=0.001; (n=68) 88% in the duckbill EBV group compared with 6% SMC patients, p<0.001; and (n=93) 50% in the duckbill EBV group versus 14% SMC patients, p=0.002. One RCT (n=321) found no statistically significant difference in the number of patients able to walk more than 26 m between the duckbill EBV and SMC groups (p=0.28). The SR reported a meta-analysis of 2 RCTs (n=326) that showed a statistically significant difference in exercise capacity from baseline favouring patients having SMC compared with patients treated by umbrella EBV (MD −19.54 m, 95% CI −37.11 to −1.98, p=0.029, I^2=0%, moderate-quality evidence). One RCT (n=22) included in the SR reported statistically significantly improved 6MWD results in patients treated by umbrella EBV unilaterally (48.9 meters [SD 53], p= 0.024), but not in the group treated bilaterally (−52.3 meters [SD 81.2], p=0.08).[1]

<u>Exercise capacity by CV status</u>

One RCT (n=171) included in the SR reported no statistically significantly difference in exercise tolerance in the umbrella EBV group with collateral ventilation when compared with SMC patients (p=0.8) and in the umbrella EBV

group without collateral ventilation when compared with SMC patients (p=0.5). This was also true for patients with intact fissures. Another RCT (n=321) included in the same SR found no statistically significant difference in 6MWD measurements in the duckbill EBV group with collateral ventilation when compared with controls (p=0.25) and in the duckbill EBV group without collateral ventilation when compared with SMC patients (p=0.08) at the 12-month follow-up.[1]

In the case series of 40 patients treated by duckbill EBV, 6MWD was statistically significantly increased from baseline values at 5 years follow-up, p=0.003.[6]

In the RCT of 97 patients without CV, an increase in 6MWD of greater than 26 meters from baseline values was statistically significantly more frequent in patients treated by duckbill EBV (52% [33/63]) than in patients treated by SMC (13% [4/31], p<0.001) at 6 months follow-up.[7]

Hospital utilisation

One RCT (n=68) included in the SR and meta-analysis reported that median post-treatment hospital stay was 1 day (range 1 to 13) and that median procedure time was 18 minutes (range 6 to 51). Two RCTs from the same SR reported a mean procedure time of 33.8 minutes (SD 20.5, n=321) and 27 minutes (SD 18, n=171). One RCT (n=277) included in the SR reported a mean hospital stay of 2.2 days (SD 6) for the umbrella EBV group and 1 day (SD 0) for the controls. One RCT (n=73) in the same SR reported mean procedure time of 62 minutes (SD 17) in the umbrella EBV group compared with 23 minutes (SD 14) in controls (p< 0.0001) and days in hospital were no different in both groups: 1.1 days (SD 0.3), p=0.26.[1]

Quality of life

Five RCTs (n=695) included in the SR reported on quality of life measured by the St. George's respiratory questionnaire (SGRQ, 100 being the worst and 0 the best possible health status). In this analysis, there was statistically significantly better quality of life in patients treated by duckbill EBV compared with those having SMC (MD −7.29 units, 95% CI −11.12 to −3.45, p=0.0002, I^2=67%) at a maximum follow-up of 12 months. One RCT (n=50) of the SR review found no statistically significant difference in greater than 4-point reduction in SGRQ (defined as MCID) in patients treated by duckbill EBV compared with patients having sham treatment, p=1.0. In opposition, 1 RCT (n=68) of the same SR reported a statistically significant over 4-point reduction in SGRQ in patients treated by duckbill EBV (79%) compared with patients having SMC (33%, p=0.001). One RCT (n=93) reported that an over 4-point reduction in SGRQ was statistically significantly more frequent in patients treated by duckbill EBV (57%) than in patients having SMC (25%, p=0.003); and a statistically significant 8-point reduction in SGRQ was more frequent in the duckbill EBV group (46%) than in

medically treated controls (8%, p<0.0001). One RCT (n=50) of the same SR reported no statistically significant difference in quality of life measured by reduction in the COPD assessment test score (CAT, range 0 = low impact on daily activities to 40 = very high impact on daily activities) between patients treated by duckbill EBV (median -2, interquartile range [IQR] −7 to 3) and patients receiving SMC (median 0, IQR −2 to 2, p=0.23). The same RCT reported no statistically significant difference in changes on the modified Medical Research Council score (mMRC, ranging from none = grade 0 to almost incomplete incapacity = grade 4) when comparing patients treated by duckbill EBV with SMC patients. Similarly, another RCT (n=93) in the same SR found no statistically significant difference in CAT between patients treated by duckbill EBV and SMC patients (MD −0.9, 95%CI −2.9 to 1.1) but found a statistically significantly larger reduction in mMRC scores in patients treated by duckbill EBV over SMC patients (MD −0.57, 95% CI −0.98 to −0.16). One RCT (n=68) also included in the SR and meta-analysis reported a statistically significant reduction in the clinical COPD questionnaire (CCQ, 0 = very good health status to 6 = extremely poor health status) favouring patients treated by duckbill EBV over patients treated by SMC (MD −0.74 points, p=0.002). One RCT (n=321) in the same SR reported a small but statistically significant reduction in mMRC score favouring patients treated by duckbill EBV over patients treated by SMC (MD −0.3 units, 95%CI −0.50 to −0.01).[1]

The SR reported a meta-analysis of 2 RCTs (n=350) that showed no statistically significant difference in SGRQ score between patients treated by umbrella EBV and those having SMC (MD 2.64 units, 95% CI −0.28 to 5.56, p=0.076, I^2=28%, high-quality evidence). One RCT included in the SR reported no statistically significant differences in mMRC score between patients treated by umbrella EBV and controls (MD −0.10, 95%CI −0.34 to 0.14, n=252). The same study found no differences in the physical component score on the short form 36 questionnaire (SF-36) between the umbrella EBV group and controls (MD −0.62, 95% CI −2.59 to 1.35; n=240). One RCT (n=73) reported in the SR found no statistically significant difference from baseline to 3 months follow-up in mMRC score (p=0.64) and 2 components of the SF-36 (mental component [p=0.83] and physical component [p=0.73]) when comparing patients treated by umbrella EBV with SMC patients.[1]

One RCT (n=22) included in the SR found a statistically significant improvement in SGRQ scores from baseline in patients treated by umbrella EBV unilaterally (−11.8 units, SD 10.6) but not in patients treated bilaterally (2.12 units SD 8.5). The between group difference favoured unilateral treatment (MD −13.92; 95% CI −21.95 to −5.89). Similarly, the same study reported on statistically significantly better mMRC score (MD −1.0, p=0.05) and body mass index, airflow obstruction, dyspnoea and exercise capacity index (BODE, range 0 = better survival to 10 = worse survival; −3.0, p=0.003) favouring the unilateral group over the bilateral group in patients treated with umbrella EBV.[1]

In the case series of 40 patients treated by duckbill EBV, MRC score was statistically significantly decreased from baseline values at 5 years follow-up, $p<0.001$.[6]

Quality of life by follow-up period

Two RCTs (n=136) included in the SR and meta-analysis reported a larger reduction in SRGQ score at 90 days in patients treated by duckbill EBV than in SMC patients (MD −8.75, 95% CI −12.76 to −4.74, p=0.000019, I^2=0%). The same remained true at 6-month follow-up as reported by 2 meta-analysed RCTs (n=492, MD −4.05, 95% CI −6.51 to −1.59, p=0.0012, I^2=52%) in the same SR.[1]

Quality of life by emphysema distribution and CV status

One RCT (n=68) of the SR and meta-analysis reported a statistically significantly greater reduction in SGRQ score in patients with heterogeneous emphysema treated by duckbill EBV (MD −19 units, 95% CI −31 to −6) than in patients with homogeneous emphysema treated by duckbill EBV (MD −12 units, 95% CI −21 to −4; p=0.005). Another RCT (n=93) in the same SR reported a statistically significant reduction in SGRQ in patients with heterogeneous disease treated by duckbill EBV (MD −9.64 units (95% CI −14.09 to −5.20, p<0.0001).[1]

One RCT (n=171) of the same SR reported no statistically significant difference in SGRQ score in patients with intact fissures treated by duckbill EBV (MD −4.00 units, 95% CI −10.64 to 2.64) compared with patients without intact fissures treated by duckbill EBV (MD 0.00 units, 95% CI −5.48 to 5.48, p=0.36). The meta-analysis of 4 RCTs (n=266) from the SR reported a statistically significantly greater reduction in SGRQ scores from baseline assessment in patients with intact fissures treated by duckbill EBV compared with controls (MD −9.03 units, 95% CI −12.07 to −5.98, p<0.00001, I^2=49). One RCT (n=321) in the same SR reported a statistically significant reduction in SGRQ score in patients treated by duckbill EBV compared with controls (MD −3.40, 95% CI −6.43 to −0.37, p=0.0028), but could not differentiate if patients had collateral ventilation or not. One RCT (n=171) of the SR and meta-analysis reported no statistically significant change in SGRQ score in patients treated by duckbill EBV resulting in complete lobar occlusion (MD −4 units [SD 16]) compared with patients not developing complete lobar occlusion (MD +2 units [SD 10], p=0.4). This was similar in another RCT (n=321) reported in the same SR (patients with complete lobar occlusion MD −5.4 units [SD 11.2] and patients without complete lobar occlusion −0.3 units [SD 12.8], p=0.12).[1]

In the RCT of 97 patients without CV, a reduction in SGRQ of greater than 4 points from baseline values was statistically significantly more frequent in patients treated by duckbill EBV (62% [35/62]) than in patients treated by SMC (34% [11/32], p<0.042) at 6 months follow-up. In the same RCT, a reduction in mMRC dyspnoea score of greater than 1 point from baseline values was

statistically significantly more frequent in patients treated by duckbill EBV (44% [29/64]) than in patients treated by SMC (23% [7/31], p<0.032) at 6 months follow-up.[7]

Safety

Mortality

Mortality was not statistically significantly different in patients treated by duckbill EBV compared with patients having SMC (OR 1.07, 95% CI 0.47 to 2.43, I^2=0) in a meta-analysis of 5 RCTs (n=703) included in a SR; moderate-quality evidence. Postoperative mortality was not statistically significantly different in patients treated by duckbill EBV when compared with sham controls (OR 3.12, 95% CI 0.12 to 80.39, p=0.49) in 1 RCT (n=50) included in the same SR. Similarly, 90-day mortality was not statistically significantly different between patients treated by duckbill EBV or controls (OR 2.17, 95% CI 0.67 to 7.02, p=0.20, I^2=0%) in a meta-analysis of 5 RCTs (n=703) included in the SR. Six-month mortality was not statistically significantly different between patients treated by duckbill EBV or SMC controls (OR 2.04, 95% CI 0.32 to 13.16, p=0.45, I^2=0%) in a meta-analysis of 2 RCTs (n=239) included in the same SR. One year mortality was not statistically significantly different between patients treated by duckbill EBV and controls (OR 0.85, 95% CI 0.33 to 2.22, p=0.74, I^2=0%) in a meta-analysis of 2 RCTs (n=429) included in the SR. Mortality was not statistically significantly different in patients treated by duckbill EBV in RCTs that tested for CV (OR 1.93, 95% CI 0.40 to 9.3) when compared with RCTs that did not (OR 0.85, 95% CI 0.33 to 2.22, p=0.38), in the SR and meta-analysis. Mortality was not statistically significantly different in patients treated by umbrella EBV compared with those having SMC (OR 4.95, 95% CI 0.85 to 28.94, p=0.076, I^2=0%) in a meta-analysis of 2 RCTs (n=350) in the SR.[1]

One patient died from tension pneumothorax 4 days after valve insertion in a case series of 91 patients.[4]

One patient died from pneumothorax-induced cardiac arrest within 30 days of duckbill EBV insertion in an RCT of 97 patients.[7]

Rate of adverse events

The rate of adverse events was statistically significantly higher in patients treated by duckbill EBV compared with those having SMC (OR 5.85, 95% CI 2.16 to 15.84) in a meta-analysis of 3 RCTs (n=482) in the SR. Serious adverse events leading to death or hospitalisation were statistically significantly more frequent in patients treated by duckbill EBV (44% (19/43) when compared with patients receiving SMC (12% (6/50) in 1 RCT included in the SR, p<0.001. Serious adverse events were statistically significantly more frequent in patients treated by duckbill EBV (23) than in controls (5) in 1 RCT included in the SR of 1,075

patients, p<0.001. Non-serious adverse events were fore frequent in patients treated by duckbill EBV (59 events) than in SMC patients (35 events) in the same RCT (n=93). The rate of adverse events was statistically significantly different in patients treated by duckbill EBV (6% [13/220]) when compared with SMC patients (1% [1/101]) at 6 months follow-up (p=0.08) but not at 12 months follow-up (10% [22/220] Zephyr EBV group, 5% [5/101] in controls, p=0.7) in 1 RCT reported in the SR of 1,075 patients. Serious adverse events were reported on 22 occasions in patients treated by umbrella EBV and in 6 patients having SMC in 1 RCT (n=277) included in the SR. The rate of adverse events was statistically significantly higher in patients treated by umbrella EBV than in those having SMC (OR 3.41, 95% CI 1.48 to 7.84) in a meta-analysis of 2 RCTs (n=350) in the SR.[1]

Total complications were statistically significantly more frequent in patients treated bilaterally by duckbill EBV (57% [8/14]) than unilaterally (11% [4/35]) in a case series of 49, p=0.0007. [5]

COPD exacerbations

COPD exacerbation episodes were not statistically significantly more frequent in patients treated by duckbill EBV (64%, 16/25) compared with those having SMC (80%; 20/25) in an RCT (n=50) reported in the SR (p=0.42). COPD exacerbations were reported in 77% (33/43) of patients treated by duckbill EBV and 40% (20/50) of SMC patients in 1 RCT reported in the SR of 1,075 patients. COPD exacerbation requiring hospitalisation occurred in 16% (7/43) of the patients treated by duckbill EBV and 12% (6/50) of the SMC patients in the same RCT (n=93). The rate of COPD exacerbations requiring hospitalisation was not statistically significantly different in patients treated by duckbill EBV (12% [4/34]) when compared with SMC patients (6% [2/35]) in 1 RCT reported in the SR of 1,075 patients, p=0.67. COPD exacerbation episodes were reported in patients treated with the umbrella valve in 2 RCTs included in the SR: 7 in the valve group and 2 in the SMC group in 1 RCT (n=277) and 2 in the valve group and 2 in the SMC group in another RCT (n=22).[1]

Pneumothorax occurred in 1% (5/343) of patients reported in a case series of patients without CV treated by duckbill EBV.[3]

COPD exacerbation happened in 5% (3/65) of patients treated by duckbill EBV within 30 days of treatment and in 5% (3/65) of patients thereafter, at 6 months follow-up. COPD exacerbation was reported in 6% (2/32) of patients receiving SMC only after 30 days of treatment, in the same RCT.[7]

Respiratory failure

Respiratory failure occurred on 4 occasions in patients treated by the umbrella valve in 1 RCT included in the SR.[1]

Respiratory failure was reported in 1 patient in a case series of 343 patients without CV treated by duckbill EBV.[3]

Pneumonia

Pneumonia episodes were not statistically significantly more frequent in patients treated by duckbill EBV (n=2) compared with patients having SMC (n=0) in an RCT (n=50) reported in the SR (p=0.49). The pneumonia rate was not statistically significantly different in patients treated by duckbill EBV (6% [2/34]) compared with those having SMC (3% [1/34]) in 1 RCT reported in the SR (p=1.0). Pneumonia distal to the valve was reported in 4% (9/220) of patients treated by duckbill EBV in 1 RCT included in the SR. Pneumonia was reported in 1 patient treated by umbrella EBV in 1 RCT included in the same SR. [1]

Pneumonia distal to the valve occurred in 1% (4/343) of patients reported in the case series of patients without CV treated by duckbill EBV.[3]

Pneumonia distal to the valve was reported in 7% (6/91) of patients and bacterial bronchitis in 1/91 patients in the case series of 91 patients treated by umbrella EBV at 12-month follow-up.[4]

Pneumonia was reported in 1/14 patients treated bilaterally by duckbill EBV in the case series of 49.[5]

Pneumonia distal to the valve was reported in 5% (2/40) of patients treated by duckbill EBV in a case series of 40.[6]

Pneumonia developed in 5% (3/65) of patients treated by duckbill EBV within 30 days of treatment and in 5% (3/65) patients thereafter in the RCT of 97 patients. Pneumonia was reported in 3% (1/32) of patients receiving SMC only after 30 days of treatment, in the same RCT. Lower respiratory tract infection developed in 1/65 patients treated by duckbill EBV within 30 days of treatment, and 1 influenza infection was reported in 1/65 patients 30 days after duckbill EBV treatment, in the RCT of 97 patients .[7]

Pneumothorax

Pneumothorax episodes were not statistically significantly more frequent in patients treated by duckbill EBV (n=2) compared with patients having SMC (n=1) in an RCT (n=50) reported in the SR (p=1.0). The pneumothorax rate was reported as 26% (11/43) and 18% (6/34) in patients treated by duckbill EBV in 2 RCTs included in the SR. Pneumothorax occurred on 3 occasions in patients treated by umbrella EBV in 1 RCT included in the SR.[1]

Pneumothorax rate was 6% (25/421) in a case series of 421 patients treated by duckbill EBV. The mean duration of pneumothorax was 11 days (range 2 to 73). The median time for onset of pneumothorax was 2 days after duckbill EBV; 15

patients experienced pneumothorax within 48 hours and 2 within 74 hours, in the same case series of 421. Pneumothorax was reported in 10% (7/64) of patients treated by duckbill EBV on the left lower lobe, 9% (9/104) on the left upper lobe, 7% (3/45) on the right lower lobe and 3%(6/205) on the right upper lobe. Pneumothorax was reported in 11% (17/161) of patients with complete interlobar fissures, 3% (7/234) with incomplete interlobar fissures and 1/26 patients with unknown fissure status, in the case series of 421 patients treated by duckbill EBV. Pneumothorax was reported more frequently in patients with complete interlobar fissures (68% [17/25]).[2]

Pneumothorax developed in 10% (35/343) of patients reported in the case series of patients without CV treated by duckbill EBV.[3]

Pneumothorax within 12 months of valve insertion was reported in 12% (11/91) of patients in a case series of 91 patients treated by umbrella EB; 5 of these were judged to be serious and definitely device-related.[4]

Pneumothorax was reported in 21% (3/14) of patients in the bilateral group and in 8% (3/35) of patients in the unilateral group in the case series of 49 patients treated by duckbill EBV.[5]

One patient had contralateral pneumothorax 15 days after duckbill EBV in a case series of 40 patients.[6]

Pneumothorax developed in 20% (13/65) of patients treated by duckbill EBV within 30 days of treatment and in 3% (2/65) of patients thereafter in the RCT of 97 patients, at 6 months follow-up.[7]

Pneumothorax was reported in 18% (70/381) patients treated by EBV with duckbill or umbrella shaped valves in the case series of 381 patients. In these 70 patients, pneumothorax resolved under observation in 13% (9/70), and 87% (61/70) needed chest tube insertion. In 51% (31/61) pneumothorax did not resolve and valve removal was necessary. Persistent fistula (despite chest drain and valve removal) was present in 45% (14/31) of patients. This was corrected by talc slurry (1/14) or surgical resolution: video-assisted thoracoscopy (77% [10/13]), thoracotomy (15% [2/13]) or both (8% [1/13]). In the same study 73% (51/70) of cases of pneumothorax developed within 3 days of EBV treatment.[8]

Valve expectoration, migration or replacement

Four episodes of valve expectoration were reported in 1 RCT (n=50) of the duckbill EBV included in the SR.[1]

Valve replacement was reported in 7% (3/43) of patients treated by duckbill EBV in 1 RCT (n=93) included in the SR. Valve expectoration, migration or aspiration were reported on 14 occasions in 1 RCT (n=171) of duckbill EBV reported in the SR.[1]

Valve replacement was needed in less than 1% (3/343) of patients reported in the case series of 343 patients.[3]

Valve migration was reported in 14% (2/14) of patients treated bilaterally by duckbill EBV in the case series of 49 patients.[5]

Valve removal

Valve removal (duckbill EBV) was needed in 2 cases in 1 RCT (n=50), in 12% (5/43) of patients in another RCT and in 14% (21/220) of patients in another RCT included in the SR.[1]

Valve removal was reported in 17.6% (16/91) of patients in the case series of 91 patients treated by duckbill EBV.[4]

Valve removal was reported in 1 patient treated by duckbill EBV in a case series of 40.[6]

EBV removal more than 30 days after duckbill EBV insertion was needed in 1/65 patients in the RCT of 95 patients.[7]

Haemoptysis

Haemoptysis was reported in less than 1% (1/220) of patients treated by duckbill EBV in 1 RCT included in the SR.[1]

Mild haemoptysis occurred in 1 of 343 patients in the case series of 343 patients.[3]

Haemoptysis was reported in 14% (2/14) of patients treated bilaterally by EBV in the case series of 49 patients.[5]

Haemoptysis developed in 1/65 patients treated by duckbill EBV within 30 days of treatment in the RCT of 97 patients.[7]

Bronchospasm

Bronchospasm was reported in 1 patient treated by umbrella EBV) in 1 RCT included in the SR.[1]

Bronchospasm within 3 days of the procedure was reported in 9% (8/91) of patients in the case series of 91 patients. One of these was described as serious, and associated with respiratory failure and myocardial infarction that began the evening after the procedure; the patient had further episodes of bronchospasm

and the valves were removed on day 21. A second patient had valve removal on day 3 because the bronchospasm did not resolve.[4]

Bronchospasm occurred in 1/65 patients treated by duckbill EBV 30 days after treatment in the RCT of 97 patients.[7]

Other

Placement of valve in the incorrect lobe was reported in 1% (3/220) of patients in 1 RCT included in the SR.[1]

Hypoxia was reported in 1% (4/343) of patients, fistula in less than 1% (2/343), pleural effusion in less than 1% (2/343) and increased sputum in 1/343 of patients in the case series of 343 patients without CV treated by duckbill EBV.[3]

Injury to bronchi was reported in 3% (3/91) of patients in a case series of 91 patients treated by umbrella EBV (not further described). In the same case series, 2% (2/91) of patients reported transient hypercarbia; 1 patient needed overnight ventilator support.[4]

Granulation into the valve that did not compromise valve function was reported in 5% (2/40) patients treated by duckbill EBV in a case series of 40.[6]

Dyspnoea occurred in 8% (5/65) of patients treated by duckbill EBV within 30 days of treatment and in 3% (2/65) of patients thereafter in the RCT of 97 patients. Inhaled foreign bodies were reported after more than 30 days after duckbill EBV insertion in 1/65 patients and subcutaneous emphysema within 30 days of duckbill EBV treatment was reported in 1/65 patients in the same RCT.[7]

Validity and generalisability of the studies

- Outcome measures and questionnaires used to assess patients treated by EBV were consistent in the literature.
- The treatment protocol varied between studies in terms of the number of valves used and whether treatment was bilateral or unilateral.
- Interlobar fissure integrity was used as a surrogate measure for the absence of collateral ventilation.
- The studies assessing long-term outcomes may not be powered to report meaningful data and are affected by loss to follow-up.

- The collaboration of the different manufacturers with research groups is frequent and evident in the published evidence.

Existing assessments of this procedure

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has released a consensus report: Global strategy for the diagnosis, management and prevention of COPD (2017 report, available from http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/) with the intention of contributing to the implementation of effective management programs in local healthcare systems worldwide. Non-surgical lung volume reduction techniques are considered a less invasive alternative to lung volume reduction surgery. Bronchoscopic interventions to reduce hyperinflation are considered more effective in patients with severe heterogeneous emphysema without interlobar collateral ventilation. Pneumothorax, valve removal or valve replacement are reported as recognised adverse events of the procedure.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Insertion of endobronchial nitinol coils to improve lung function in emphysema. NICE interventional procedures guidance 517 (2015). Available from: https://www.nice.org.uk/guidance/ipg517
- Lung volume reduction surgery for advanced emphysema. NICE interventional procedures guidance 114 (2005). Available from: https://www.nice.org.uk/guidance/ipg114

NICE guidelines

- Chronic obstructive pulmonary disease in over 16s: diagnosis and management. NICE clinical guideline 101 (2010). Available from: https://www.nice.org.uk/guidance/cg101

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Specialist Advisor Questionnaires for endobronchial valve insertion to reduce lung volume in emphysema were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 3 companies who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- Different studies used different types of endobronchial valves. Most of the evidence comes from one of the valves (Zephyr, Pulmonx). The devices do not seem to be equivalent in safety and efficacy.

Ongoing studies

- NCT02823223 - Endobronchial Valve in Patients with Heterogeneous Emphysema. Location, China; study type, RCT; estimated enrolment, n=72; follow-up, 6 months; start date, June 2016; estimated completion date, June 2018 (ongoing but no longer recruiting).

- NCT01969734 - Endobronchial Valves in Moderate COPD (REMODEL). Location, UK; study type, intervention efficacy study; estimated enrolment, n=72; follow-up, 3 months; start date, March 2014; estimated completion date, March 2015 (unknown current status).

- NCT02022683 - A Multi-center, Prospective, Randomized, Controlled Trial of Endobronchial Valve Therapy vs. Standard of Care in Heterogeneous Emphysema. Location, multi-centre (Belgium, France, Germany, Netherlands, Sweden, UK); study type, RCT; estimated enrolment, n=72; follow-up, 24 months; start date, December 2013; estimated completion date, September 2018 (ongoing not recruiting).

- NCT01580215 - Long Term Follow up Investigation of Endobronchial Valves in Emphysema. Location, Germany; study type, prospective cohort; estimated enrolment, n=2000; follow-up, 5 years; start date, July 2012; estimated completion date, December 2020 (ongoing not recruiting).

References

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2. Gompelmann D, Herth FJF, Slebos DJ et al. (2014) Pneumothorax following endobronchial valve therapy and its impact on clinical outcomes in severe emphysema. Respiration, and international review of thoracic diseases 87(6), 485-91.
3. Skowasch D, Fertl A, Schwick B et al. (2016) A long-term follow-up investigation of endobronchial valves in emphysema (the LIVE Study): study protocol and six-month interim analysis results of a prospective five-year observational study. Respiration, and international review of thoracic diseases 92(2), 118-26.
4. Sterman DH, Mehta AC, Wood DE et al. (2010) A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. Respiration 79: 222–33.
5. Fiorelli A, D'Andrilli A, Anile M et al. (2016) Sequential bilateral bronchoscopic lung volume reduction with one-way valves for heterogeneous emphysema. The Annals of thoracic surgery 102(1), 287-94.
6. Venuta F, Anile M, Diso D et al. (2012) Long-term follow-up after bronchoscopic lung volume reduction in patients with emphysema. European Respiratory Journal 39: 1084–9.
7. Kemp SV, Slebos DJ, Kirk A et al. (2017) A multicentre RCT of Zephyr endobronchial valve treatment in heterogeneous emphysema (TRANSFORM). American Journal of Respiratory and Critical Care Medicine, online.
8. Gompelmann D, Benjamin N, Kontogianni K et al. (2016) Clinical and radiological outcome following pneumothorax after endoscopic lung volume reduction with valves. International Journal of COPD 11: 3093-3099.

Appendix A: Additional papers on endobronchial valve insertion to reduce lung volume in emphysema

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Argula RG, Strange C, Ramakrishnan V et al. (2013) Baseline regional perfusion impacts exercise response to endobronchial valve therapy in advanced pulmonary emphysema. Chest 144(5): 1578-86.	Case series n=169 FU=6 months	Patients having heterogeneous emphysema with a low baseline target lobe regional perfusion benefit from EBV therapy, independent of the degree of target lobe destruction. This effect is attenuated if the EBV therapy is not occlusive.	Larger case series already included. Reports results of trial included in paper 1 in table 2.
Asai N, Ohkuni Y, and Kaneko N (2014) A case of giant bulla successfully treated by bronchoscopic lung volume reduction therapy. Journal of bronchology & interventional pulmonology 21(1): 101-2.	Case report n=1 FU=4 years	Report of a case of giant bullae in a patient who experienced significant and sustained subjective as well as objective improvement after bronchoscopic suction.	Larger case series already included.
Baldi S, Coni F, Limerutti G et al. (2016) Delayed functional improvement after near-fatal bleeding complication following endobronchial valve therapy for emphysema. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace 81(1-2): 748.	Case report n=1 FU=6 months	Case report of severe bleeding after EBV treatment.	Larger case series already included.
Bierach J, Maloney JD, and Ferguson JS (2013) Endobronchial valve placement for a giant bulla in a patient with hypercapnic respiratory failure. Annals of the American Thoracic Society 10(5): 521-4.	Case report n=1 FU=2 months	Giant bulla successfully treated by EBV.	Larger case series already included.
Brown MS, Kim HJ, Abtin et al. (2012) Emphysema lung lobe volume reduction: effects on the ipsilateral and contralateral lobes. European radiology 22(7), 1547-55	Non-randomised comparative study n=421 FU=6 months	Computed tomography allows assessment of the treatment of emphysema with endobronchial valves. Endobronchial valves can reduce the volume	Case series with larger follow-up included.

		of an emphysematous lung lobe. Compensatory expansion is greater in ipsilateral lobes than in the contralateral lung. Reduced air trapping is measurable by RV/TLC and smaller low attenuation area.	
Cetinkaya E, Ozgul M Akif, GS et al. (2015) Successful Treatment of Bulla with Endobronchial Valves. Case reports in pulmonology 2015, 947403.	Case report n=1 FU=7 months	Giant bulla successfully treated by EBV.	Larger case series already included.
Choi M, Lee WS, Lee M et al. (2015) Effectiveness of bronchoscopic lung volume reduction using unilateral endobronchial valve: a systematic review and meta-analysis. International journal of chronic obstructive pulmonary disease 10: 703-10.	Systematic review and meta-analysis n=15 studies FU=NA	BLVR may be an effective and safe procedure for the treatment of severe COPD patients with emphysema, based on existing studies.	Cochrane systematic review already included. No new efficacy data. Limited reporting of safety data.
Chung SCS, Peters MJ, Chen S et al. (2010) Effect of unilateral endobronchial valve insertion on pulmonary ventilation and perfusion: a pilot study. Respirology (Carlton, and Vic.) 15(7): 1079-83.	Case series n=8 FU=3 months	There appears to be redistribution of ventilation and perfusion to the contralateral lung following endobronchial valve placement. This may be of importance when assessing patients for unilateral BLVR. Selecting patients with heterogeneous disease is emphasized, taking into consideration not just comparison between upper and lower lobes, but between left and right lungs.	Larger case series already included.
Darwiche K, Karpf-Wissel R, Eisenmann S et al. (2016) Bronchoscopic Lung Volume Reduction with Endobronchial Valves in Low-FEV1 Patients. Respiration 92(6).	Case series n=20 FU=3 months	BLVR with valves can be safely performed in patients with FEV1 ≤20% predicted when close postprocedural monitoring is provided. Improvement in lung function and exercise capacity can be achieved.	Larger case series already included.
Davey C, Zoumot Z, Jordan S et al. (2015) Bronchoscopic lung volume reduction with endobronchial valves	Study protocol	Unilateral lobar occlusion with endobronchial valves in	Study report included in paper 1 in table 2.

for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. Lancet (London, and England) 386(9998): 1066-73.		patients with heterogeneous emphysema and intact interlobar fissures produces significant improvements in lung function. There is a risk of significant complications and further trials are needed that compare valve placement with lung volume reduction surgery.	
de Oliveira HG, de Oliveira S M, Rambo RR et al. (2016) Fissure Integrity and Volume Reduction in Emphysema: A Retrospective Study. Respiration, and international review of thoracic diseases 91(6): 471-9.	Case series n=38 FU=1 year	A target lobe volume reduction using EBVs is possible with lung fissure integrity >75%. For patients with fissure integrity between 75 and 90%, a further evaluation of interlobar ventilation should be performed. A clinically relevant volume reduction following treatment with EBVs is likely with any level of fissure integrity >90%.	Larger case series already included.
Destors M, Aniwidyaningsih W, Jankowski A et al. (2012) Endoscopic volume reduction before or after lung transplantation. European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery 42(5): 897-8.	Case series n=2 FU=2 months	Report of successful endobronchial valve treatments in two patients with severe emphysema	Larger case series already included.
Eberhardt R, Gompelmann D, Schuhmann M et al. (2012) Complete unilateral vs partial bilateral endoscopic lung volume reduction in patients with bilateral lung emphysema. Chest 142(4): 900-8.	RCT n=22 FU=3 months	Unilateral intrabronchial valve placement with complete occlusion appears superior to bilateral partial occlusion.	Included in paper 1 in table 2.
Eberhardt R, Gerovasili V, Kontogianni K et al. (2015) Endoscopic lung volume reduction with endobronchial valves in patients with severe emphysema and established pulmonary hypertension. Respiration, and international review of thoracic diseases 89(1): 41-8.	Case series n=6 FU=90 days	ELVR was feasible and resulted in an improvement of clinical and hemodynamic parameters in 5 out of 6 patients. These results have to be further confirmed in larger-scale controlled studies.	Larger case series already included.
Fiorelli A, Petrillo M, Vicidomini G et al. (2014) Quantitative assessment of emphysematous parenchyma	Case series n=25	The study showed that the volumetric quantification adds	Larger case series already included.

using multidetector-row computed tomography in patients scheduled for endobronchial treatment with one-way valves. Interactive cardiovascular and thoracic surgery 19(2): 246-55.	FU=3 months	further information to the routine evaluation for optimizing the selection of patients scheduled for endobronchial valve treatment.	
Galluccio G and Lucantoni G (2010) Bronchoscopic lung volume reduction for pulmonary emphysema: Preliminary experience with a new NOVATECH endobronchial silicone one-way valve. Interactive Cardiovascular and Thoracic Surgery 11(2): 213-215.	Case series n=1	Case of a patient with severe pulmonary emphysema that was successfully treated by the placement of a new, removable, unidirectional endobronchial silicone valve.	Larger case series already included.
Herth FJF, Eberhardt R, Gompelmann D et al. (2013) Radiological and clinical outcomes of using Chartis™ to plan endobronchial valve treatment. European Respiratory Journal 41: 302–8.	Case series n=96 FU=30 days	Of the 51 patients classified as having an absence of CV according to their Chartis reading, 36 showed a TLVR ≥350 ml. 29 patients were classified as having CV, and of these 24 did not meet this TLVR cut-off. Chartis showed an accuracy level of 75% in predicting whether or not the TLVR cut-off would be reached. Those predicted to respond showed significantly greater TLVR ($p<0.0001$) and FEV_1 improvement ($p=0.0013$) than those predicted not to respond. Chartis is a safe and effective method of predicting response to EBV treatment	Higher quality randomised efficacy evidence already included in Table 2. No new safety data.
Hillerdal G, and Mindus S (2014) One- to four-year follow-up of endobronchial lung volume reduction in alpha-1-antitrypsin deficiency patients: a case series. Respiration, and international review of thoracic diseases 88(4): 320-8.	Case series n=15 FU=4 years	In carefully selected AAT deficiency patients with severe emphysema, ELVR can be safely performed with encouraging long-lasting results.	Larger case series already included.
Hillerdal G (2015) Case Report: Bilateral Endoscopic Volume Reduction in a Woman with Severe Emphysema. Clin Respir J	Case report n=1 FU=NR	In conclusion, valve treatment in suitable patients can give substantial improvement in lung function and quality of	Larger case series already included.

		life and can be repeated on the other side if warranted some years later.	
Hopkinson NS, Kemp SV, Toma TP et al. (2011) Atelectasis and survival after bronchoscopic lung volume reduction for COPD. European Respiratory Journal 37: 1346–51.	Case report n=19 FU=6 years	The data in the present study suggest that atelectasis following BLVR is associated with a survival benefit that is not explained by baseline differences.	Higher quality randomised efficacy evidence already included in Table 2. No new safety data.
Iftikhar IH, McGuire FR and Musani AI (2014) Predictors of efficacy for endobronchial valves in bronchoscopic lung volume reduction: A meta-analysis. Chronic respiratory disease 11(4): 237-45.	Systematic review and meta-analysis n=5 studies FU=NA	The preliminary findings of our meta-analysis confirm that one-way valves perform better in a select group of patients who show intact fissures on lung imaging pre-treatment and in those who achieve lobar occlusion.	Cochrane systematic review already included. No new efficacy data. No new safety data.
Jenkins M, Vaughan P, Place D et al. (2011) Endobronchial valve migration. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 40(5): 1258-60.	Case report n=1 FU=5 months	Reports the treatment of a severe bullous emphysema and valve migration.	Larger case series already included.
Klooster K, Hartman JE, Ten Hacken et al. (2017) One-Year Follow-Up after Endobronchial Valve Treatment in Patients with Emphysema without Collateral Ventilation Treated in the STELVIO Trial. Respiration 93: 112-121	RCT n=40 FU=1 year	Pneumothorax is a frequent severe complication following valve therapy that requires further intervention. Nevertheless, the pneumothorax does not impair the clinical status in the majority of patients. Patients with lobar atelectasis benefit after recovering from pneumothorax in terms of lung function parameters.	Extended follow-up of paper already reported in table, paper 1. No new safety outcomes.
Klooster K, ten Hacken, Nick H T, et al. (2015) Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. The New England journal of medicine 373(24): 2325-35.	RCT n=84 FU=6 months	Endobronchial-valve treatment significantly improved pulmonary function and exercise capacity in patients with severe emphysema characterized by an absence of interlobar collateral ventilation.	Same as STELVIO study
Kotecha S, Westall GP, Holsworth L et al. (2011) Long-term outcomes from bronchoscopic lung volume reduction using a bronchial	Case series n=23 FU=5 years	BLVR with the Emphasys one-way valve has an acceptable safety profile and in select	Study with larger follow up already included.

prosthesis. Respirology (Carlton, and Vic.) 16(1): 167-73.		patients may achieve long-term sustained improvements in pulmonary function	
Kumar A, Dy R, Singh et al. (2017) Early Trends in Bronchoscopic Lung Volume Reduction: A Systematic Review and Meta-analysis of Efficacy Parameters. Lung 195: 19-28	Systematic review and meta-analysis n=18 studies (4 EBV) FU=6 months to 5 years	All three variables showed statistically significant PMDs but that for FEV1 was smaller than the MCID. BLVR offers early promise in the palliation of advanced emphysema. Better characterization of patients to identify phenotypes that will derive sustained benefit is needed.	Relevant papers already included in table 2, paper 1. No new safety outcomes.
Liu H, Xu M, Xie Y et al. (2015) Efficacy and safety of endobronchial valves for advanced emphysema: a meta-analysis. Journal of thoracic disease 7(3): 320-8.	Systematic review and meta-analysis n=3 RCTs FU=NA	EBV lung volume reduction for advanced emphysema showed superior efficacy and a good safety and tolerability compared with standard medications and sham EBV, further more randomized controlled trial (RCT) studies are needed to pay more attention to the long-term efficacy and safety of bronchoscopic lung volume reduction with EBV in advanced emphysema.	Cochrane systematic review already included. No new efficacy data. No new safety data.
Lovis A, Lahzami S, Gonzalez M et al. (2014) An unusual and unknown complication of endobronchial valves. The Annals of thoracic surgery 97(4): e117.	Case report n=1 FU=3 months	Report of a patients treated by EBV that required valve removal,	Larger case series already included.
Ninane V, Geltner C, Bezzi M et al. (2012) Multicentre European study for the treatment of advanced emphysema with bronchial valves. The European respiratory journal 39(6): 1319-25.	RCT n=73 FU=6 months	The procedure and devices were well tolerated and there were no differences in adverse events reported in the treatment and control groups. Treatment with bronchial valves without complete lobar occlusion in both upper lobes was safe, but not effective in the majority of patients.	Reported in paper 1 in table 2.
Park TS, Hong Y, Lee J S et al. (2015) Bronchoscopic lung volume reduction by endobronchial valve in	Case series n=43 FU=6 months	EBV therapy was as effective and safe in Korean patients as it	Larger case series already included.

advanced emphysema: the first Asian report. International journal of chronic obstructive pulmonary disease 10:1501-11.		has been shown to be in Western countries.	
Perch M, Riise GC, Hogarth K et al. (2015) Endoscopic treatment of native lung hyperinflation using endobronchial valves in single-lung transplant patients: a multinational experience. The clinical respiratory journal 9(1): 104-10.	Case series n=14 FU=2 months	Treating NLH with IBV endobronchial valves leads to clinical improvement in the majority of patients, and the treatment has an acceptable safety.	Larger case series already included.
Pizarro C, Ahmadzadehfar H, Essler M et al. (2015) Effect of endobronchial valve therapy on pulmonary perfusion and ventilation distribution. PloS one 10(3): e0118976.	Case series n=26 FU=1 month	ELVR induces a relevant decrease in perfusion and ventilation of the treated zone with compensatory perfusional and ventilatory redistribution to the contralateral lung, primarily to the non-concordant, contralateral zone	Larger case series already included.
Pizarro C, Schueler R, Hammerstingl C et al. (2015) Impact of endoscopic lung volume reduction on right ventricular myocardial function. PloS one 10(4): e0121377.	Case series n=32 FU=2 months	ELVR beneficially impacts RtV functional parameters. Speckle tracking-based RtV apical longitudinal strain analysis allows early determination of RtV contractile gain and identification of clinical responsiveness.	Larger case series already included.
Skowasch D, Pizarro C, Valipour A et al. (2013) Endobronchial valve-induced pneumatocele: a case report. Pneumologie (Stuttgart, and Germany) 67(11): 639-40.	Case report n=1 FU=hospital discharge	After endoscopic lung volume reduction with endobronchial valves (EBV), a huge pneumatocele has occured and resolved spontaneously within a few weeks	Larger case series already included.
Szlubowska S, Zalewska-PJ, Majda A et al. (2015) The influence of lung volume reduction with intrabronchial valves on the quality of life of patients with heterogeneous emphysema - a prospective study. Pneumonologia i alergologia polska 83(6): 418-23.	Case series n=20 FU=3 months	The presented study revealed a significant improvement of the quality in the life measured by SGRQ after IBV treatment for heterogeneous emphysema. For the first time our study showed the significant improvement of all three domains of SGRQ after IBV treatment.	Larger case series already included.
Thomsen C, Theilig D, Herzog D et al. (2016) Lung perfusion and emphysema distribution affect the	Case series n=57 FU=3 months	Patients with high perfusions in INL demonstrated greater	Larger case series already or with longer

outcome of endobronchial valve therapy. International journal of chronic obstructive pulmonary disease 11: 1245-59.		improvements in 6MWT, while patients with high HI were more likely to respond in FEV1.	follow-up already included.
Trudzinski FC, Hoink AJ, Leppert D et al. (2016) Endoscopic Lung Volume Reduction Using Endobronchial Valves in Patients with Severe Emphysema and Very Low FEV1. Respiration, and international review of thoracic diseases 92(4): 258-265.	Case series n=20 FU=30 day	The patients benefitted moderately from EBV treatment despite an initially low FEV1. Some patients improved remarkably. EBV treatment in patients with an FEV1 <20% of pred. is generally feasible and safe. The greatest risk is pneumothorax with prolonged chest tube duration.	Larger case series already included.
Tuleta I, Pizarro C, Molitor E et al. (2016) Recurrent Chronic Obstructive Pulmonary Disease Exacerbations after Endobronchial Valve Implantation Are Associated with the Presence of Pseudomonas aeruginosa. Respiration, and international review of thoracic diseases 91(6): 510-6.	Case series n=16 FU=6 months	Increased rates of COPD exacerbations after endobronchial valve implantation are associated with the presence of P. aeruginosa. The finding warrants further investigation.	Larger case series already included.
Tuohy MM, Remund KF, Hilfiker R et al. (2013) Endobronchial valve deployment in severe alpha-1 antitrypsin deficiency emphysema: a case series. The clinical respiratory journal 7(1): 45-52.	Case series n=51 FU=4 years	The data from this case series suggest that this intervention may provide bridging therapy to subsequent transplantation for younger AAT patients with end-stage emphysema.	Larger case series already included.
Valipour Ar, Slebos DJ, Herth F (2016) Endobronchial Valve Therapy in Patients with Homogeneous Emphysema. Results from the IMPACT Study. American journal of respiratory and critical care medicine 194(9): 1073-1082.	RCT n=93 FU=3 months	EBV in patients with homogeneous emphysema without collateral ventilation results in clinically meaningful benefits of improved lung function, exercise tolerance, and quality of life.	Same as IMPACT. Included in paper 1, table 2.
Van Geffen WH, Klooster K, Hartman JE et al. (2017) Pleural Adhesion Assessment as a Predictor for Pneumothorax after Endobronchial Valve Treatment. Respiration 94: 224-231	Case series n=64 FU=6 months	A threshold PAS of >=12 was associated with a higher risk of pneumothorax (OR 13.0, 95% CI 3.1-54.9). A score <12 did not rule out the occurrence of pneumothorax. A higher number of pleural adhesions on HRCT with a subsequent higher PAS in the	Further analysis of data from study already included in table 2, paper 1.

		treated lung is associated with a higher occurrence of pneumothorax after EBV treatment.	
Venuta F, Diso D, Anile M et al.(2011) Bronchoscopic lung volume reduction as a bridge to lung transplantation in patients with chronic obstructive pulmonary disease. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 39(3): 364-7.	Case series n=4 FU=6 months	BLVR allowed to improve the functional status and quality of life of these patients. In a selected group of COPD patients awaiting lung transplantation, the reported short- to medium-term objective improvement may play an important role to ameliorate the clinical status and reach the time of surgery.	Larger case series already included.
Votruba J, Collins J, and Herth FJF (2011) Successful treatment of ventilator dependent emphysema with Chartis treatment planning and endobronchial valves. International journal of surgery case reports 2(8): 285-7.	Case report n=1 FU=2 months	Endoscopic lung volume reduction assisted by Chartis to plan treatment resulted in a clinical and a health-economic benefit.	Larger case series already included.
Wang L, Hu Y, Wang X et al. (2015) Treating heterogeneous emphysema by lung volume reduction surgery using one-way valve stent implantation. International journal of clinical and experimental medicine 8(8): 14457-63.	Case series n=3 FU=6 months	No obvious improvements in the PFs of all the three patients were observed in the re-examination performed six months after surgery.	Larger case series already included.
Wood DE, Nader DA, Springmeyer SC etal. (2014) The IBV Valve trial: a multicenter, randomized, double-blind trial of endobronchial therapy for severe emphysema. Journal of bronchology & interventional pulmonology 21(4): 288-97.	RCT n=277 FU=6 months	This trial had technical and statistical success but partial-bilateral endobronchial valve occlusion did not obtain clinically meaningful results. Safety results were acceptable and compare favourably to lung volume reduction surgery and other bronchial valve studies.	Same as IBV trial, already reported in paper 1, table 2.
Yin Y, Hou G, Herth FJ et al. (2016) Significant lung volume reduction with endobronchial valves in a patient despite the presence of microcollaterals masked by low-flow Chartis phenotype. International Journal of COPD 11: 2913-2917	Case report n=1 FU=2 weeks	The Chartis system has proven to be useful for determining whether CV is present or absent, but this system can also erroneously indicate the absence of CV, which can lead to BLVR failure. It is described how the low-flow Chartis phenotype	Larger case series already included in table 2.

		in the target lobe resulted in difficult judgment of existence of CV. Consequently, BLVR with EBVs implanted into the right upper bronchus failed to reduce lung volume or induce atelectasis. Inserting another EBV into the right middle bronchus blocked the latent CV, which led to significant lung volume reduction in the right upper lobe (RUL) and right middle lobe (RML) and to improve the pulmonary function, 6-min walking distance, and St George respiratory questionnaire scores over a 2-week follow-up period.	
Zoumot Z, Davey C, Jordan S et al. (2015) Efficacy and Mechanism Evaluation. A randomised controlled study of Bronchoscopic Lung Volume Reduction with endobronchial valves for patients with Heterogeneous emphysema and Intact interlobar Fissures: the BeLieVeR-HIFi study.	RCT n=50 FU=3 months	With appropriate selection of patients through a multidisciplinary team it is possible to produce a significant improvement in lung function through lobar occlusion with endobronchial valves in heterogeneous emphysema.	Same as BeLieVer study trial, already reported in paper 1, table 2.
Zoumot Z, LoMauro A, Aliverti A et al. (2015) Lung Volume Reduction in Emphysema Improves Chest Wall Asynchrony. Chest 148(1): 185-95.	Case series n=26 FU=3 months	Successful LVR significantly reduces chest wall asynchrony in patients with emphysema.	Larger case series already included.

Appendix B: Related NICE guidance for endobronchial valve insertion to reduce lung volume in emphysema

Interventional procedures	**Insertion of endobronchial nitinol coils to improve lung function in emphysema. NICE interventional procedure guidance 517 (2015).** 1.1 Current evidence on the safety and efficacy of the insertion of endobronchial nitinol coils to improve lung function in emphysema is limited in quantity and quality. Therefore the procedure should only be used in the context of research. 1.2 Research studies would preferably include observational data collection and should describe patient selection in detail. Outcome measures should include lung function, dyspnoea score, exercise tolerance, quality of life and long-term safety. Studies should also report on the influence of the procedure on subsequent lung surgery. NICE may update the guidance on publication of further evidence. **Insertion of endobronchial valves for lung volume reduction in emphysema. NICE Interventional Procedures Guidance 114 (2013).** 1.1 Current evidence on the efficacy of insertion of endobronchial valves for lung volume reduction in emphysema shows some clinical and quality-of-life benefits. However, this evidence includes data from patients who have and those who have not had assessment of collateral ventilation, which specialists now advise as fundamental to selection for treatment. Evidence of safety in the short term is adequate but the evidence of safety in the longer term is inadequate in quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake insertion of endobronchial valves for lung volume reduction in emphysema should take the following actions. • Inform the clinical governance leads in their NHS trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended.

	• Audit and review clinical outcomes of all patients having insertion of endobronchial valves for lung volume reduction in emphysema (see section 7.1). 1.3 Patient selection should be done by a multidisciplinary team experienced in the management of emphysema including a chest physician, a chest radiologist and a thoracic surgeon. 1.4 This procedure should only be carried out by clinicians with specific training and expertise in interventional bronchoscopy (including provision of sedation), who should perform their initial procedures with an experienced mentor. 1.5 NICE encourages further research into insertion of endobronchial valves for lung volume reduction in emphysema. Research should take the form of studies that allow comparison of the procedure with the natural history of the disease and other treatment options including surgery. The studies should define the criteria and techniques used for patient selection. Outcome measures should include lung function, dyspnoea score, exercise tolerance, quality of life and long-term safety. **Lung volume reduction surgery for advanced emphysema. NICE interventional procedure guidance 114 (2005).** 1.1 Current evidence on the safety and efficacy of lung volume reduction surgery for advanced emphysema appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Clinicians wishing to use lung volume reduction surgery for advanced emphysema should ensure that patients are fully informed about the risks of the procedure and the likelihood of deterioration in the longer term. Use of the Institute's information for the public is recommended. 1.3 Patient selection is important because mortality is increased in patients with the most seriously compromised lung function. The Institute has issued a clinical guideline on chronic obstructive pulmonary disease. 1.4 The procedure should be undertaken by a multidisciplinary team that includes a respiratory physician, specialists in pulmonary rehabilitation and a thoracic surgeon.
Clinical guidelines	**Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in**

	primary and secondary care (partial update). NICE clinical guideline 101 (2010) ***1.2.10 Lung surgery*** 1.2.10.1 Patients who are breathless, and have a single large bulla on a CT scan and an FEV_1 less than 50% predicted should be referred for consideration of bullectomy. [2004] 1.2.10.2 Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living, despite maximal medical therapy (including rehabilitation), should be referred for consideration of lung volume reduction surgery if they meet all of the following criteria: • FEV_1 more than 20% predicted • $PaCO_2$ less than 7.3 kPa • upper lobe predominant emphysema • T_LCO more than 20% predicted. [2004] 1.2.10.3 Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living despite maximal medical therapy should be considered for referral for assessment for lung transplantation bearing in mind comorbidities and local surgical protocols. Considerations include: • age • FEV_1 • $PaCO_2$ • homogeneously distributed emphysema on CT scan • elevated pulmonary artery pressures with progressive deterioration. [2004] ***1.2.12 Multidisciplinary management*** 1.2.12.1 COPD care should be delivered by a multidisciplinary team. [2004] 1.2.12.3 It is recommended that respiratory nurse specialists form part of the multidisciplinary COPD team. [2004]

Appendix C: Literature search for endobronchial valve insertion to reduce lung volume in emphysema

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	30/08/2017	Issue 8 of 12, August 2017
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	30/08/2017	Issue 7 of 12, July 2017
HTA database (Cochrane Library)	30/08/2017	Issue 4 of 4, October 2016
MEDLINE (Ovid)	30/08/2017	1946 to August Week 3 2017
MEDLINE In-Process (Ovid)	30/08/2017	
EMBASE (Ovid)	30/08/2017	1974 to 2017 Week 35
PubMed	30/08/2017	n/a
JournalTOCS	30/08/2017	n/a

Trial sources searched on 15/11/2016

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 04/11/2016-11/11/2016

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 lung diseases/
2 Emphysema/
3 exp Pulmonary Emphysema/
4 (pulmonar* adj4 emphysem*).tw.
5 Pulmonary Disease, Chronic Obstructive/
6 (lung adj4 diseas*).ti,ab.

7 (chronic* adj4 obstruct* adj4 (pulmonar* or airway* or lung* or airflow*) adj4 disease).tw.
8 COPD.tw.
9 COAD.tw.
10 emphysema*.tw.
11 Lung Volume Measurements/
12 (Lung* adj4 volume* adj4 measur*).tw.
13 11 or 12
14 reduc*.tw.
15 13 and 14
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 15
17 Forced Expiratory Volume/
18 (force* adj4 expirator* ad4 volum*).tw.
19 or/16-18
20 (airway* adj4 valve*).tw.
21 (((one* adj4 way*) or undirect*) adj4 valve*).tw.
22 EBV.tw.
23 IBV.tw.
24 EMV.tw.
25 Bronchoscopy/
26 bronchoscopes/
27 Bronchoscop*.tw.
28 or/25-27
29 Pneumonectomy/
30 Pneumonectom*.tw.
31 (lung adj4 volum* adj4 reduc*).tw.
32 or/29-31
33 28 and 32
34 20 or 21 or 22 or 23 or 24 or 33
35 19 and 34
36 ((endobronchial* or bronchial or bronchoscopy) adj4 valve*).tw.
37 ((intrabronchial or intra bronchial or intra-bronchial) adj4 valve*).tw.
38 IBV Valve.tw.
39 (zephyr or spiration or repneu).tw.
40 or/35-39
41 (collateral adj4 ventilat*).tw.
42 chartis.tw.
43 or/40-42
44 Animals/ not Humans/
45 43 not 44
46 (201611* or 201612* or 2017*).ed.
47 45 and 46