Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Recommendation 02
November 2020

In response to an enquiry from Pulmonx International

Endobronchial valves for lung volume reduction in patients with severe or very severe emphysema

Recommendation for NHSScotland

All patients referred to secondary care who have severe or very severe emphysema, and significant disability despite optimal medical management, should undergo a detailed assessment by a multi-disciplinary team to determine eligibility for lung volume reduction.

Endobronchial valves should be available to all eligible patients, with procedures consolidated within a small number of centres via a unified national referral pathway to ensure equity of access. Patients should not be considered for endobronchial lung volume reduction if they have collateral ventilation or if they lack suitable target areas within the lungs.

Individual patient- and procedure-associated risk must be discussed with the patient as part of a shared decision on endobronchial lung volume reduction.

The cost effectiveness of endobronchial valve implantation remains uncertain for the Zephyr® valve and there are no cost effectiveness data for the Spiration® valve. Patient outcome data for all valve procedures should be collected and made available to inform future economic analyses.

NHSScotland is required to consider the Scottish Health Technologies Group (SHTG) recommendation.

What were we asked to look at?

A manufacturer of endobronchial valves (Pulmonx International) asked us to look at the evidence on the use of endobronchial valves to reduce lung volume in patients with severe or very severe emphysema who continue to experience significant emphysema-associated disability despite optimal medical management. Scottish consultant thoracic surgeons confirmed the relevance of this topic to NHSScotland.

Why is this important?

Emphysema and chronic obstructive pulmonary disease (COPD) are chronic, progressive, and ultimately fatal, diseases of the lungs. Emphysema is one of two conditions that are classed as COPD, the other being chronic bronchitis. Emphysema can exist without chronic bronchitis as a distinct respiratory condition. Patients with COPD can have predominantly emphysema, predominantly chronic bronchitis, or both. Chronic obstructive pulmonary disease is the second most common lung disease in the UK.

Treatments for emphysema/COPD include lifestyle modification, pulmonary rehabilitation, and medical therapies. A proportion of patients with severe or very severe emphysema/COPD that continues to worsen despite optimal medical management require surgical intervention to reduce the volume of their damaged lungs. Lung volume reduction surgery is an invasive, palliative procedure involving excision of 20-40% of the volume of each affected lung[1]. Endobronchial valve implantation offers a less invasive option for lung volume reduction.

What was our approach?

We produced SHTG Recommendations based on a review of the published evidence on the clinical effectiveness, cost effectiveness and safety of endobronchial valves for lung volume reduction in patients with severe or very severe emphysema. We also reviewed the literature relating to patient experiences and preferences for treatment of severe or very severe emphysema. Further information about the SHTG Recommendation development process is on this Healthcare Improvement Scotland webpage.

What next?

The SHTG Recommendation on endobronchial valves will be circulated to Scottish respiratory managed clinical networks, health boards, and the cross-party group on lung health at the Scottish Parliament.

Key points from the evidence

- Evidence was available on two types of endobronchial valve: the Zephyr® Endobronchial Valve System (Pulmonx International) and the Spiration® Valve System (Olympus Inc.).
- Three meta-analyses, based on the same seven randomised controlled trials (RCTs), compared the Zephyr® valve plus medical therapy with medical therapy alone or a sham procedure plus medical therapy. The results from the meta-analyses are summarised in table A. The findings for all clinical effectiveness outcomes favoured the intervention group. The Zephyr® valve was associated with a significantly increased risk of serious adverse events or a pneumothorax.

Table A: effectiveness and safety of the Zephyr® valve plus medical therapy compared with medical therapy alone or a sham control plus medical therapy in patients with severe or very severe heterogeneous or homogenous emphysema and little or no collateral ventilation

Outcome	n studies (n patients)	Findings (95% CI)	p-value	GRADE assessment
Clinical effectiveness outcomes				
FEV_1 % predicted	7 (879)	WMD 18.8% (14.2% to 23.5%)	<0.00001	High
SGRQ score	7 (871)	WMD -7.0 points (-9.9 points to -4.4 points)	<0.00001	High
6MWT	7 (876)	WMD 39.9m (18.4m to 61.3m)	0.0003	Moderate
Residual lung volume	5 (470)	MD -0.5L (-0.8L to -0.3L)	<0.00001	-
Safety outcomes				
Serious Adverse Events (prolonged hospitalisation, life-threatening events, mortality)	6 (819)	RR 3.1 (1.5 to 6.6)	0.003	High
Pneumothorax	5 (793)	RR 6.3 (3.7 to 10.7)	0.0001	High
Mortality	7 (990)	RR 1.1 (0.6 to 2.4)	0.72	Moderate
COPD exacerbation	9 (990)	RR 0.99 (0.8 to 1.99)	0.93	Moderate

FEV_1 = forced expiratory volume in 1 second, SGRQ = St George's respiratory questionnaire (lower scores indicate higher quality of life), 6MWT = 6 minute walk test, COPD = chronic obstructive pulmonary disease, CI = confidence interval, WMD = weighted mean difference, MD = mean difference, RR = relative risk, L = litres, m = metres, GRADE = Grading of Recommendations Assessment, Development and Evaluation

- A meta-analysis of four RCTs compared the Spiration® valve plus medical therapy with medical therapy alone or a sham procedure plus medical therapy in patients with severe or

very severe emphysema. A sub-group analysis assessed the effects of the Spiration® valve in patients with little or no collateral ventilation. Results from the meta-analyses are summarised in table B. All statistically significant results (effectiveness and safety) favoured the intervention group.

Table B: effectiveness and safety of the Spiration® valve plus medical therapy compared with medical therapy alone or a sham control plus medical therapy in patients with severe or very severe heterogeneous emphysema

Outcome	All patients (4 studies; n=629)	No collateral ventilation (2 studies; n=179)	GRADE assessment
	Findings (95% CI)		
Clinical effectiveness outcomes			
FEV_1 % predicted	MD 2.0% (-2.5% to 6.6%) NS	MD 4.2% (2.9% to 5.4%) p<0.05	Low
SGRQ score	MD -6.5 points (-16.1 points to 3.0 points) p=0.18	MD -12.3 points (-15.8 points to -8.7 points) p<0.00001	Low
6MWT	MD 4.6m (-21.9m to 31.0m) p=0.74	MD 19.0m (-9.4m to 47.5m) p=0.19	Very low
Residual lung volume	MD -0.01L (-0.5L to 0.5L) p=0.98	MD -0.4L (-0.6L to -0.2L) p=0.0005	Low
mMRC dyspnoea score	MD -0.3 points (-0.6 points to -0.05 points) p=0.02	MD -0.5 points (-0.7 points to -0.3 points) p<0.00001	Low
Safety outcomes			
Pneumothorax	RR 1.9 (0.4 to 8.7) p=0.41	RR 4.6 (0.8 to 26.2) p=0.08	Low

FEV_1 = forced expiratory volume in 1 second, SGRQ = St George's respiratory questionnaire (lower scores indicate higher quality of life), 6MWT = 6 minute walk test, mMRC = modified Medical Research Council, CI = confidence interval, MD = mean difference, RR = relative risk, NS = non-significant, L = litres, m = metres, GRADE = Grading of Recommendations Assessment, Development and Evaluation

- A network meta-analysis comparing the Zephyr® and Spiration® valves in patients with severe or very severe heterogeneous emphysema and no collateral ventilation, found no statistically significant differences between the valves for any outcome.
- Two qualitative studies found that patients had a strong desire to take action to improve their quality of life and breathlessness, despite procedure-associated risks, and valued both surgical and endobronchial valve procedures for lung volume reduction. A quantitative analysis (n=294) found that, on average, respondents preferred interventions (surgical or endobronchial) over current treatment, and favoured endobronchial valves over surgery.
- The results of a cost-utility analysis from the German healthcare system perspective indicated that over a 5- and 10-year time horizon, the Zephyr® valve was associated with

increased quality-adjusted-life-years (QALYs) and higher costs compared with medical therapy alone. The incremental cost effectiveness ratio (ICER) at five years was €46,322 (£41,401) and at 10 years was €25,142 (£22,471). The analysis had a number of limitations affecting the generalisability of results, including selection of patients who had a positive outcome from valve implantation, comparison only with medical therapy rather than other procedures, and costs data from a non-UK healthcare setting.

- No cost effectiveness evidence was identified for the Spiration® valve.

Scottish Health Technology Council considerations

The following points capture the Council's deliberations towards agreeing the final recommendations at the Council meeting on 2 October 2020.

- The Council recognised that for individual, highly selected patients endobronchial valves can be a very effective treatment, with clinically important effects on FEV_1, residual lung volume and quality of life.
- The Council discussed the lack of options available to specialists in secondary care when treating patients with worsening COPD who are receiving optimal medical therapies.
- The Council discussed the differing quantity and strength of evidence available for the Zephyr® and Spiration® valves, and the lack of cost effectiveness evidence. The Council agreed any recommendations should allow for clinical choice in valve selection and development of new valves.
- The Council noted the importance of a clear, nationally agreed patient pathway that involves primary, secondary, and tertiary care services to ensure equity of access to endobronchial valves for eligible patients.
- In order to promote consistency of patient selection, the Council stated that responsibility for patient selection for endobronchial valve insertion should be restricted to multi-disciplinary teams at national centres of excellence. Once consistent patient selection is established, clinicians with expertise in endobronchial procedures could offer endobronchial valves at regional centres, although consideration of required procedure volumes to maintain competency would be advisable.
- The Council noted that the ongoing UK-based CELEB trial will provide clinical and cost effectiveness evidence on endobronchial valves compared with surgical lung volume reduction.
- The Council discussed the relevance of the published economic modelling to the Scottish context, highlighting that the analyses were based on a sub-group of patients who had a successful procedure. The 10-year time horizon was considered optimistic based on the life expectancy of patients undergoing the procedure in Scotland.

Contents

Definitions

Forced expiratory volume (FEV): the volume of air that can be forcibly expelled from the lungs in a set unit of time following maximal inhalation. The most commonly reported FEV is the volume of air expelled in the first second of exhalation, denoted as FEV_1[2].

Pneumothorax: a collapsed lung; occurs when air leaks into the space between the lung and chest wall, pushing on the outside of the lung and causing it to collapse[3].

Heterogeneous and homogenous emphysema: when the pattern of emphysema-related lung damage is fairly even throughout the lung it is referred to as homogenous; where the pattern is uneven it is called heterogeneous emphysema[4].

Collateral ventilation: airflow into alveolar structures in the lung through passages or channels that bypass the normal airways. This phenomenon has implications for the effectiveness of endobronchial valves[5].

Surgical/subcutaneous emphysema: when air gets into subcutaneous tissues, often in the chest wall or neck[6].

Literature search

A systematic search of the secondary literature was carried out between 5 and 10 March 2020 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline, Embase, Web of Science, and the Cochrane Library were searched for systematic reviews and meta-analyses.

The primary literature was systematically searched between 5 and 10 March 2020 using the following databases: Medline, Embase, and Web of Science.

Key websites were searched for guidelines, policy documents, clinical summaries, and economic studies.

A separate search for patient and social aspects was undertaken. This involved a search of selected websites, and the Medline and PsycInfo databases using search filters to identify qualitative studies. Details of the search filters used are available on request.

All search results were limited to English language. Studies on clinical effectiveness and safety were limited to those published since 2017 (when the NICE Interventional Procedures Guidance (IPG) on endobronchial valves was published).

Concepts used in all searches included: emphysema, COPD, bronchial valves, endobronchial valves, intrabronchial valves, lung volume reduction. A full list of resources searched and terms used is available on request.

Research question

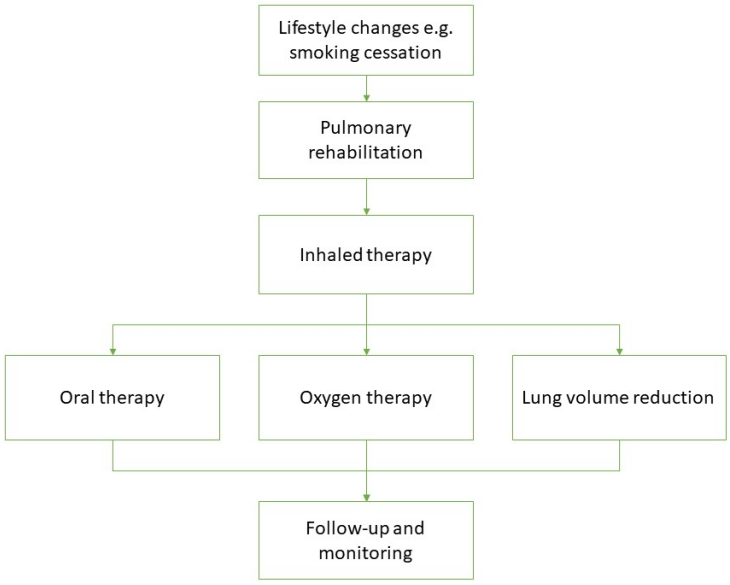
Are endobronchial valves clinically effective, cost effective and safe for lung volume reduction in patients with severe or very severe emphysema?

Introduction

Emphysema is a chronic, progressive lung condition resulting from damage to tiny air sacs (alveoli) in the lungs[4]. The main cause of emphysema is long-term exposure to airborne irritants such as cigarette smoke, air pollution, or chemical fumes[7]. These inhaled irritants cause the walls of the alveoli to lose their elasticity and degrade, merging alveoli together to form large, baggy sacs within the lung[4]. Old, stale air becomes trapped in these damaged regions of the lung resulting in hyper-inflation and a reduction in the available space within the chest for healthy sections of the lung to function[4, 7]. Consequently, less oxygen reaches the bloodstream through the lungs, which manifests as breathlessness. Other common symptoms of emphysema are a chronic chesty cough, regular chest infections, and wheezing[8].

Most people with emphysema also have chronic bronchitis[7]. When these two conditions occur together they are referred to as chronic obstructive pulmonary disease (COPD)[9]. People with COPD can have predominantly emphysema symptoms, predominantly chronic bronchitis symptoms, or a mixture of both[10]. Current treatment options for people with COPD or emphysema include lifestyle modification, pulmonary rehabilitation, pharmacotherapy and oxygen therapy (figure 1)[11]. These therapies have a limited effect on lung hyper-inflation and people with severe or very severe emphysema can remain significantly disabled despite optimal medical management.

Figure 1: simplified care pathway for management of COPD*



**based on NICE managing COPD pathway[12]*

Severity of emphysema and COPD are classified using the internationally recognised GOLD levels of airflow restriction severity defined based on FEV_1 (table 1)[13]. Throughout this document GOLD level 3 emphysema or COPD is referred to as severe and level 4 emphysema or COPD as very severe.

Table 1: GOLD classification of airflow restriction severity in patients with emphysema or COPD who have an FEV_1/forced vital capacity (FVC) <0.70[14]

GOLD level	Severity of airflow restriction	FEV_1
1	Mild	≥80% predicted
2	Moderate	50%≤ FEV_1 <80% predicted
3	Severe	30%≤ FEV_1 <50% predicted
4	Very severe	<30% predicted

A proportion of people with severe or very severe emphysema or COPD that progresses despite optimal medical management may be offered lung volume reduction surgery or a lung transplant. These operations carry substantial risks[8]. Endobronchial valves* have been proposed as a less invasive option for lung volume reduction.

Health technology description

Endobronchial valves are implanted into airways supplying diseased sections of the lungs in people with severe or very severe emphysema[4]. Endobronchial valve insertion is a minimally invasive procedure, normally performed under general anaesthesia. The valves prevent inhaled air from entering diseased sections of the lung while allowing trapped air to escape during exhalation. This one-way flow of air causes the damaged air sacs of the lung to collapse, reducing lung volume. Patients continue using any prescribed medical therapies for their emphysema after an endobronchial valve procedure[14, 15].

The Zephyr® Endobronchial Valve System (Pulmonx International) is a silicone duck-bill valve attached to a nickel-titanium self-expanding retainer covered by a silicone membrane[15]. On average three to five Zephyr® valves are implanted in each patient. A flexible bronchoscope and delivery catheter are used to place the valves in airways leading to affected sections of the lung.

The Spiration® Valve System (Olympus Inc.) is a flexible, umbrella-shaped valve, with a frame made of nickel-titanium covered in a polyurethane membrane[14]. An average of four valves are implanted in each patient. The Spiration® Valve System comes with a deployment catheter and a loader tool for inserting the appropriate sized valve into the catheter.

* The term endobronchial valve is medically synonymous with the term intrabronchial valve. In the published literature the term endobronchial is often used to refer to the Zephyr® valve, and intrabronchial to refer to the Spiration® valve. For the purposes of this review, endobronchial encompassed both valves.

Endobronchial valves are intended for use only when airflow to affected areas of the lung can be completely occluded; if air can enter affected areas through collateral ventilation the valves will be less effective. Careful patient selection is therefore a key consideration with this technology. The manufacturers of current valves have developed technologies/software to assist clinicians in identifying patients best suited to endobronchial valve implantation:

- The Chartis® Pulmonary Assessment System (Pulmonx International) and the Stratx® Quantitative Lung CT Analysis service (Pulmonx International) can be used alongside standard pulmonary tests and computed-tomography (CT) scans. The Chartis® and Stratx® tools enable clinicians to assess airflow from the target lung area and to assess degree of emphysema destruction and fissure completeness respectively. The Stratx® tool involves uploading patient CT images to a cloud-based platform for analysis by Pulmonx.
- The SeleCT® tool (VIDA Diagnostics Inc.) can be used alongside standard pulmonary tests and CT scans to identify patients most likely to benefit from the Spiration® valve.

The clinical expertise required for implanting endobronchial valves is currently available at the Golden Jubilee National Hospital and the Royal Infirmary of Edinburgh. To date, the Zephyr® valve is the only endobronchial valve used in Scotland (Mr M Will, Consultant Thoracic Surgeon, NHS Lothian. Personal communication, 09 June 2020).

Epidemiology

The main risk factor for developing emphysema is long-term cigarette smoking, which has a population attributable risk of 50-70%[9]. Additional risk factors include exposure to second-hand smoke, occupational exposure to chemical fumes or dust, and exposure to air pollution[7]. The risk of developing emphysema increases with age, with most smokers first experiencing symptoms between the ages of 40 and 60[7, 10].

National epidemiological data were only available for COPD, not emphysema as a separate entity. Most people with COPD have a combination of emphysema and chronic bronchitis, but it is not clear the extent to which the emphysema component will have contributed to this epidemiological data, as some people with COPD have only bronchitis.

The estimated UK population prevalence of COPD is approximately 2%[9, 16]. A proportion of these COPD patients will have emphysema-predominant disease (little or no chronic bronchitis) and others will have both emphysema and chronic bronchitis. Population prevalence estimates for COPD are likely to be underestimates since up to two-thirds of cases remain undiagnosed[9]. Even with under-diagnosis, COPD is still the second most common lung disease in the UK[10]. Scottish data on COPD incidence, mortality, and hospital admissions are provided in table 2.

Table 2: Scottish COPD data per 100,000 population 2018-19[9, 17]

	Age-standardised incidence	Age-standardised mortality	Number of hospital stays	Number of hospital bed-days
Male	35.4	63.4	279	1,652
Female	34.0	59.7	380	2,451
All persons	34.7	61.6	330	2,052

Approximately 10% of people with COPD have severe or very severe disease[1]. An estimated 15% of these patients may be suitable for lung volume reduction procedures (surgical or bronchoscopic) if they meet patient selection criteria. These figures lead to an estimated 1,444 people in Scotland with severe or very severe emphysema who could be eligible for lung volume reduction through surgery or a bronchoscopic procedure. Not all of these patients would meet the criteria for endobronchial valve implantation.

A retrospective study in the Netherlands analysed the outcomes for 1,500 patients with COPD referred to a specialist hospital facility over a 7-year period (2007-14)[18]. Only 12% (175/1,500) of the original referred population received an endobronchial valve after assessment by a respiratory physician. Applying these figures to the Scottish estimates above, results in approximately 160-170 patients in Scotland who would be eligible for an endobronchial valve procedure each year.

Minimum clinically important differences

In addition to the statistical significance of changes in clinical outcomes following endobronchial valve implantation, it is important to consider the clinical significance of the changes. In other words are the changes in outcomes due to endobronchial valves resulting in clinically important improvements in patient health. The determination of clinical importance for outcomes reported in the literature was based on the minimum clinically important difference for each outcome (table 3).

Table 3: minimum clinically important difference for clinical outcomes in patients with emphysema/COPD[19, 20]

Outcome	Minimum clinically important difference
FEV_1 (L)	0.1L to 0.14L increase
FEV_1 (% predicted)	5% to 10% increase
Residual lung volume (L)	0.31L to 0.43L reduction
6MWT (m)	26 ± 2m increase
SGRQ score (points)	4 point reduction

Clinical effectiveness

GOLD report 2020

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report provides recommendations on COPD management based on published literature[13]. In relation to endobronchial values, the 2020 GOLD report states:

"*In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, health status, and lung function at 6-12 months following treatment. Endobronchial valves (Evidence A).*"

Evidence A relates to the levels of evidence used in the report, indicating that this recommendation is based on RCTs without significant limitations or bias. All of the endobronchial valve trials cited in the GOLD report studied the Zephyr® valve.

Guidance

In 2017, NICE published Interventional Procedures Guidance (IPG 600) on the use of endobronchial valves for lung volume reduction in patients with emphysema[21]. The IPG makes the following recommendations:

- "*Current evidence on the safety and efficacy of endobronchial valve insertion to reduce lung volume in emphysema is adequate in quantity and quality to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit.*
- *Patient selection should be done by a multidisciplinary team experienced in managing emphysema, which should typically include a chest physician, a radiologist, a thoracic surgeon and a respiratory nurse.*
- *Patients selected for treatment should have had pulmonary rehabilitation.*
- *The procedure should only be done to occlude volumes of the lung where there is no collateral ventilation, by clinicians with specific training in doing the procedure.*"

The NICE IPG does not distinguish between the Zephyr® and Spiration® valves, even though the IPG committee noted that published evidence indicated the two devices may have different efficacy profiles.

Zephyr® endobronchial valve system

Three good quality meta-analyses reported on the effectiveness of the Zephyr® endobronchial valve for lung volume reduction in patients with severe or very severe emphysema[22-24]. The meta-analysis by Rustagi *et al* (2019) incorporated seven randomised controlled trials (n=990) comparing the Zephyr® valve plus medical therapy with standard medical care alone (six trials), or a sham valve procedure plus medical therapy (one trial), in patients with severe or very severe emphysema[23].

Results from the RCT that used a sham procedure in the comparator group appear similar to those of trials using medical therapy as the comparator (see appendix 2, table A). Two included trials (VENT US and VENT EU) incorporated a proportion of patients who had collateral ventilation/incomplete lobar fissures, which would have implications for effectiveness of endobronchial valves. The other trials incorporated patients with little or no collateral ventilation. The authors of the meta-analysis assessed the risk of bias in included trials using the Cochrane tool. Overall risk of bias was considered to be low for the majority of included trials. A high risk of performance bias was assigned to five trials due to a lack of blinding of study participants and/or outcome assessors. Most outcomes were objective measures of lung volume or function, which may mitigate this risk of bias.

Results from the meta-analysis by Rustagi *et al* (2019) are presented in table 4. Statistically significant and clinically important changes favouring the Zephyr® valve were reported for the outcomes of FEV_1 % predicted, quality of life (St George's Respiratory Questionnaire – SGRQ score) and metres walked in the 6-minute walking test (6MWT). The meta-analysis authors considered the evidence underpinning these outcomes to be of moderate or high quality based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework. The moderate or high heterogeneity in some analyses may be due to differences in RCT patient selection criteria.

Table 4: meta-analysis comparing the Zephyr® endobronchial valve plus medical therapy with standard medical care alone or a sham valve procedure plus medical therapy in patients with severe or very severe heterogeneous or homogenous emphysema and little or no collateral ventilation[23]

Outcome	n studies (n patients)	Findings (95% CI)	p-value	I^2	GRADE assessment
FEV_1 (% predicted)	7 (879)	WMD 18.82 (14.18 to 23.47)	<0.00001	35%	High
SGRQ score* (points)	7 (871)	WMD -7.00 (-9.85 to -4.14)	<0.00001	52%	High
6MWT (m)	7 (876)	WMD 39.86 (18.42 to 61.29)	0.0003	77%	Moderate
All serious adverse events	6 (819)	RR 3.13 (1.48 to 6.60)	0.003	83%	High
Mortality	7 (990)	RR 1.14 (0.55 to 2.39)	0.72	0%	Moderate
Respiratory failure requiring mechanical ventilation	7 (990)	RR 1.06 (0.38 to 2.95)	0.92	0%	Moderate
COPD exacerbation and lower	7 (990)	RR 0.99 (0.82 to 1.99)	0.93	0%	Moderate

respiratory tract infection					

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; WMD = weighted mean difference; SGRQ = St George's Respiratory Questionnaire; 6MWT = 6-minute walking test; COPD = chronic obstructive pulmonary disease; RR = risk ratio

*Lower SGRQ scores indicate a better quality of life

The meta-analysis by Labarca *et al* (2019) used the same set of RCTs to evaluate the Zephyr® valve, but excluded two studies (VENT US and VENT EU) from the quantitative analysis on the basis that patients in these trials were more likely to have collateral ventilation and had unclear emphysema distribution[22]. Despite the exclusion of two RCTs, the meta-analysis reported very similar findings to those presented in table 4 (see appendix 3). One additional outcome reported by Labarca *et al* (2019) was the change in residual lung volume. The Zephyr® endobronchial valve plus medical therapy was associated with statistically and clinically significant reductions in residual lung volume compared with the control group (medical therapy alone or a sham procedure plus medical therapy): mean difference (MD) -0.53L, 95% confidence interval (CI) -0.75L to -0.32L, p<0.00001, I^2=59%, five studies, n=498.

The third meta-analysis (van Geffen *et al*, 2019) used the same set of seven RCTs to evaluate the Zephyr® valve but took the additional step of contacting the VENT trial investigators to request data on patients within the trial who had no collateral ventilation[24]. The results of this meta-analysis were consistent with those reported in table 4 (see appendix 3). This meta-analysis reported on change in residual lung volume. Patients treated with the Zephyr® endobronchial valve plus medical therapy had a statistically and clinically significant reduction in residual lung volume compared with medical therapy alone or a sham procedure plus medical therapy: MD -0.57L, 95% CI -0.71L to -0.43L, p<0.0001, seven studies, n=600.

Spiration® valve system

A good quality meta-analysis of four RCTs (n=629) compared the Spiration® valve plus medical therapy with standard medical care alone (two trials) or a sham valve procedure plus medical therapy (two trials) in patients with severe or very severe heterogeneous emphysema[11]. The results of the trials incorporating a sham comparator appear similar in magnitude and direction of effect compared with the trials using medical therapy alone as the control (appendix 2, table B). The included trials were assessed for risk of bias by the meta-analysis authors, who reported high or unclear risk of performance bias in all studies due to a lack of blinding of patients and/or outcome assessors. Most outcomes were objective measures of lung volume or function, which may mitigate this risk of bias.

There are a number of underlying differences between the RCTs in this meta-analysis which may affect the results (see appendix 2, table B). Two of the included trials (IBV Valve Trial and Ninane *et al*, 2012) appear to have used an older version of the device. These older trials report using the valves for bilateral partial occlusion of affected areas of the lungs, while more recent studies (EMPROVE and REACH) report unilateral complete occlusion of affected lung tissue. The older trials

also incorporated some patients with collateral ventilation, who were excluded from more recent studies. The meta-analysis explored this in sub-group analyses.

Results of the Spiration® valve meta-analysis, including sub-group analyses, are presented in table 5. When the meta-analysis included all four RCTs, the only outcome that showed a statistically significant change was the modified Medical Research Council (mMRC) breathlessness score, and this change was unlikely to be clinically relevant. When the meta-analysis was limited to the two studies that enrolled patients with little or no collateral ventilation, there were statistically significant and clinically important improvements in FEV_1 (L), quality of life measured by the SGRQ score, and residual lung volume (L). Statistically significant improvements were also found for FEV_1 % predicted and mMRC breathlessness score, although these were not clinically important. Meta-analysis based on the two trials that included patients who had collateral ventilation found that results favoured the control group for the outcomes of FEV_1 (L and % predicted) and residual lung volume; there were no statistically significant differences for any other outcome.

In the main analysis incorporating all four trials, the meta-analysis authors considered the evidence quality for each outcome to be low or very low based on the GRADE criteria. There was also moderate or high heterogeneity in some analyses, potentially due to differences in patients recruited by the RCTs.

Table 5: meta-analysis comparing the Spiration® valve plus medical therapy with medical therapy alone or a sham valve procedure plus medical therapy, in patients with severe or very severe heterogeneous emphysema[11]

Outcome	All patients (4 studies; n=629)	With collateral ventilation (2 studies; n=350)	No collateral ventilation (2 studies; n=179)
FEV_1 (L)	MD 0.03 (95% CI -0.07 to 0.1) p=0.57 I^2=90%, GRADE: low	MD -0.07 (95% CI -0.11 to -0.03) p=0.0003 I^2=0%	MD 0.12 (95% CI 0.09 to 0.015) p<0.00001 I^2=0%
FEV_1 (% predicted)	MD 2.03 (95% CI -2.50 to 6.57) NS I^2=96%, GRADE: low	MD –2.15 (95% CI -3.47 to -0.83) p<0.05	MD 4.16 (95% CI 2.90 to 5.42) p<0.05 I^2=0%
SGRQ score (points)	MD -6.50 (95% CI -16.05 to 3.04) p=0.18 I^2=94%, GRADE: low	MD 0.85 (95% CI -5.93 to 7.63) p=0.81 I^2=65%	MD -12.27 (95% CI -15.84 to -8.75) p<0.00001 I^2=0%
6MWT (m)	MD 4.56 (95% CI –21.88 to 31.00) p=0.74	MD -19.64 (95% CI –36.52 to -2.76) p=0.02	MD 19.02 (95% CI –9.43 to 47.47) p=0.19

	I^2=73%, GRADE: very low	I^2=0%	I^2=60%
mMRC dyspnoea score (points)	MD -0.33 (95% CI -0.61 to -0.05) p=0.02 I^2=65%, GRADE: low	MD -0.11 (95% CI -0.33 to 0.10) p=0.31 I^2=0%	MD -0.54 (95% CI -0.74 to -0.33) p<0.00001 I^2=0%
Residual volume (L)	MD -0.01 (95% CI -0.50 to 0.49) p=0.98 I^2=85%, GRADE: low	MD 0.38 (95% CI 0.13 to 0.64) p=0.0004 I^2=0%	MD -0.36 (95% CI -0.56 to -0.16) p=0.0005 I^2=0%
Mortality	RR 2.54 (95% CI 0.81 to 7.96) NS I^2=0%, GRADE: low	NR	NR
Pneumothorax	RR 1.89 (95% CI 0.41 to 8.68) p=0.41 I^2=71%, GRADE: low	RR 0.61 (95% CI 0.15 to 2.47) p=0.49 I^2=0%	RR 4.64 (95% CI 0.82 to 26.16) p=0.08 I^2=71%
Acute COPD exacerbation*	RR 1.68 (95% CI 1.04 to 2.70) p=0.03 I^2=0%, GRADE: moderate	NR	NR

*Combined risk over 12 months follow-up, measured at 3 months, 6 months and 12 months in individual trials
CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; MD = mean difference; SGRQ = St George's Respiratory Questionnaire; 6MWT = 6-minute walking test; COPD = chronic obstructive pulmonary disease; RR = risk ratio; NR = not reported; NS = not significant; mMRC = modified Medical Research Council

Comparing the Zephyr® and Spiration® valves

There are no RCTs directly comparing the Zephyr® and Spiration® valves. A network meta-analysis (NMA) used indirect evidence from 10 RCTs to compare the two valves in patients with severe or very severe heterogeneous emphysema and little or no collateral ventilation[25]. The NMA incorporated two trials evaluating the Spiration® valve and four trials assessing the Zephyr® valve. Four trials described the use of a different intervention for lung volume reduction (endobronchial coils). Two Spiration® valve trials (IBV Valve Trial and Ninane *et al*, 2012) were excluded from the NMA because they included patients with collateral ventilation. One Zephyr® valve trial was excluded because it included only patients with homogenous emphysema (IMPACT) and another trial was excluded because the Chartis® system was not used to measure collateral ventilation in study participants (VENT).

The NMA conducted a frequentist analysis using a random effects model. The NMA authors did not report goodness of fit of the random effects model, nor do they address the transitivity assumption

(each patient is equally likely to have received any treatment in the network). Consistency was assessed using 'netsplit' analysis. There was no evidence of inconsistency between effect estimates derived from direct and indirect evidence in the network. The NMA authors used the Cochrane tool to assess risk of bias in included trials. The included studies had a low overall risk of bias, with unclear or high risk of bias relating to lack of blinding of outcome assessors and study participants. Most outcomes were objective measures of lung volume or function, which may mitigate this risk of bias.

Results from the NMA for comparisons between the Zephyr® and Spiration® valves are presented in table 6. Compared with medical therapy, both the Spiration® valve and the Zephyr® valve demonstrated statistically significant and clinically important improvements in FEV_1 (L) and SGRQ score. Only the Zephyr® valve demonstrated a statistically significant improvement in 6MWT distance compared with medical therapy alone. There were no statistically significant differences between valves for the outcomes of FEV_1, 6MWT or SGRQ score, suggesting both valves are equally superior to medical therapy alone. These results are in accord with the evidence from direct meta-analyses for each valve.

Table 6: network meta-analysis comparing Spiration® and Zephyr® valves in patients with severe or very severe heterogeneous emphysema and no collateral ventilation[25]

Outcome	Difference between Spiration® and Control (95% CI) 2 RCT, n=279	Difference between Zephyr® and Control* (95% CI) 4 RCT, n=405	Difference between Spiration® and Zephyr® valves (95% CI) 6 RCT, n=684
FEV_1 (L)	MD 0.11 (0.05 to 0.16)	MD 0.14 (0.08 to 0.19)	MD 0.03 (-0.05 to 0.11)
SGRQ score (points)	MD -9.32 (-14.18 to -4.45)	MD -8.14 (-11.94 to -4.35)	MD -1.17 (-7.35 to 5.00)
6MWT (m)	MD 18.54 (-18.20 to 55.27)	MD 52.23 (26.53 to 77.93)	MD 33.69 (-11.14 to 78.53)
Pneumothorax	OR 10.32 (1.35 to 79.13)	OR 11.47 (2.91 to 45.27)	OR 1.11 (0.09 to 12.9)
COPD exacerbation	OR 2.04 (0.88 to 4.74)	OR 1.56 (0.72 to 3.38)	OR 0.74 (0.24 to 2.40)

*Control = medical therapy alone or sham procedure plus medical therapy (1 trial)
CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; SGRQ = St George's Respiratory Questionnaire; 6MWT = 6-minute walking test; OR = odds ratio

Ongoing trials

An ongoing RCT was identified that involves five UK hospital sites, including one in Scotland (Golden Jubilee National Hospital)[26]. This trial compares lung volume reduction surgery with endobronchial valve placement (valve name not reported) in patients with COPD and heterogeneous emphysema. A

cost-utility study will be carried out from an NHS perspective using data from the trial. The trial is expected to publish late 2021.

Safety

Endobronchial valve device- or procedure-related adverse events include patient death, pneumothorax, bronchitis, COPD exacerbation, pneumonia, surgical emphysema, or migration of the implanted valve[27]. Safety outcomes were reported in the same secondary literature described in the clinical effectiveness section[11, 22, 23, 25].

Zephyr® endobronchial valve system

In the meta-analysis by Rustagi *et al* (2019), serious adverse events were defined as events that required or prolonged hospitalisation, events that were life-threatening, and patient mortality[23]. In patients with severe ore very severe emphysema but no collateral ventilation, the Zephyr® valve was associated with a statistically significant increase in the risk of having a serious adverse event compared with medical therapy alone or a sham valve procedure (table 4). There were no statistically significant differences in the risk of individual adverse events including death, respiratory failure requiring mechanical ventilation, or COPD exacerbation. The evidence quality for safety outcomes was judged by the meta-analysis authors to be moderate or high based on the GRADE criteria.

According to product instructions from the Zephyr® valve manufacturer, pneumothorax is a common adverse event following Zephyr® valve insertion[15]. The meta-analysis by Labarca *et al* (2019) reported pneumothorax as a safety outcome[22]. There was a statistically significant increased risk of developing a pneumothorax in patients treated with the Zephyr® valve plus medical therapy compared with patients treated with medical therapy alone or a sham control plus medical therapy: RR 6.32, 95% CI 3.74 to 10.67, p<0.0001, I^2=0%, five RCTs, n=498, GRADE high. Four out of seven RCTs evaluating the Zephyr® valve reported the number of patients who subsequently required removal of one or more valves due to pneumothoraces[22]. In the LIBERATE trial, 12/128 patients (9.4%) required valve removal due to pneumothorax formation (76% occurred within three days of the procedure[15]). In the IMPACT and TRANSFORM trials, five patients in each study required removal of one or more valves due to pneumothoraces (11.6% and 7.7% of patients respectively). In the STELVIO trial, 1/34 patients (2.9%) had temporary valve removal and 2/68 (2.9%) required permanent valve removal following a pneumothorax.

The meta-analysis by van Geffen *et al* (2019) reported similar results to Rustagi *et al* (2019) for the safety outcomes of any adverse event, 45-day mortality, and overall mortality (appendix 3)[24].

Spiration® valve system

The meta-analysis comparing the Spiration® valve plus medical therapy with medical therapy alone or a sham valve procedure plus medical therapy reported risk of mortality, pneumothorax, and acute

COPD exacerbation as safety outcomes (table 5)[11]. There was no statistically significant increase in the risk of developing a pneumothorax in patients treated with the Spiration® valve in this analysis, nor were there statistically significant increases in the risk of pneumothorax in sub-group analyses limited to patients with or without collateral ventilation. There was no statistically significant difference in risk of patient mortality. There was a statistically significant increase in the risk of acute COPD exacerbation following Spiration® valve implantation. Patient mortality and acute COPD exacerbation risk were only reported in the meta-analysis of all four RCTs, which included patients with and without collateral ventilation. The meta-analysis authors considered evidence quality for safety outcomes to be low or moderate based on the GRADE criteria.

In all four Spiration® valve trials, COPD exacerbation was the most frequently occurring adverse event in the intervention group[28-31]. Pneumothorax was the second most frequent adverse event in the treatment groups of the REACH and EMPROVE trials[28, 29]. In the EMPROVE trial, 11/16 patients (69%) with serious pneumothoraces had one or more valves removed; five of these patients subsequently had valves re-implanted once the pneumothorax had resolved.

Comparing the Zephyr® and Spiration® valves

In the NMA comparing Spiration® and Zephyr® valves in patients with severe or very severe emphysema and no collateral ventilation, both valves were associated with statistically significant increases in the odds of a pneumothorax compared with medical therapy alone (table 6). This is contrary to the results of the direct meta-analysis for the Spiration® valve that found no statistically significant increased risk of pneumothorax with this device. The differing results may be due to variation in the definitions of pneumothorax used. In the NMA, there were no statistically significant differences between the two valves in the risk of a pneumothorax. No statistically significant difference in the risk of COPD exacerbation was found across any comparison.

Patient and social aspects

Two qualitative studies[27, 32] and a quantitative analysis[33] explored patient preferences and experiences relating to treatments for emphysema. Quality of life (SGRQ score) was reported as an outcome in the clinical effectiveness literature and is therefore not addressed in this section.

The most recent qualitative study used semi-structured focus groups to explore the experiences of patients in England who had undergone lung volume reduction surgery or endobronchial valve placement (valve type not reported) for the treatment of emphysema[27]. Study participants were a convenience sample drawn from interventional procedure databases at two hospitals. It is not clear how many patients were invited to participate but declined, nor how patients were selected from the databases. Patients who agreed to participate in the study may have had more extreme experiences than those who declined. To minimise risk of bias the thematic analysis of focus group transcripts was performed independently by researchers not involved in the clinical care of study participants. One person from each focus group verified the results of the thematic analysis.

Mean age of study participants was 63, and half the participants were women. Only four out of 16 focus group participants (25%) had an endobronchial valve procedure, therefore data saturation for this procedure was not confirmed. Seven participants (44%) had undergone more than one procedure for lung volume reduction. The mean length of time since the first lung volume reduction procedure was 3.8 years. Overall, participants deemed both lung volume reduction surgery and endobronchial valves to be tolerable and successful interventions for treatment of emphysema.

The thematic analysis identified three over-arching themes: patient focus on declining health; consequences of the lung volume reduction procedure; vulnerability and lack of continuity in post-procedure care. Patients blamed themselves for their deteriorating health and felt they needed to fight for the opportunity to have lung volume reduction, often exploring treatment options for themselves due to a lack of specialist knowledge among general practitioners. Experiences of inpatient care were generally positive, although participants felt communication could be improved as they felt unprepared for chest infections and other complications many experienced after their procedure. One patient who had undergone both lung volume reduction surgery and endobronchial valve implantation described benefiting from both procedures, but feeling an immediate improvement after endobronchial valve implantation compared with a longer recovery period after surgery. Participants who required home oxygen therapy following their procedure felt this should have been more clearly explained as they felt unprepared and often equated home oxygen therapy with end-of-life. The lack of continuity of care once patients were discharged from hospital resulted in some participants feeling vulnerable at home where they had less support than in hospital. Many participants felt it was important to have a follow-up appointment with their surgical team, and that it would be beneficial to be offered pulmonary rehabilitation at this time.

The second qualitative study conducted semi-structured interviews with Australian patients and family members to understand their experiences of living with COPD and of having lung volume reduction surgery or an endobronchial valve procedure[32]. Patients in this study who underwent endobronchial valve implantation received the Emphasys EBV™ valve, a previous incarnation of the Zephyr® valve. Interviews were either face-to-face (n=18) or by telephone (n=40) and followed an interview guide to minimise interviewer bias. Data from the transcribed interviews were analysed using a philosophical framework and a phenomenological approach. Two couples from among the study participants, and one couple not involved in the study, provided validation of the interpretation of the transcripts.

Fifteen patients and 14 family members were interviewed 6 months and 12 months after a lung volume reduction procedure. Four eligible patients declined to participate in the study (reasons not given). Ten participants had an endobronchial valve procedure and five had lung volume reduction surgery. Twenty-eight out of 29 study participants had no regrets about the decision to have surgery or an endobronchial valve procedure, despite being aware of the associated risks and not always having experienced an improvement in their condition. Following endobronchial valve insertion, 50% of patients perceived no change in their condition, 40% felt they improved initially but went downhill over the subsequent 12 months, and one patient got worse. Following lung volume reduction, 60% of patients reported reduced breathlessness that made performing daily tasks easier and facilitated combining activities. Several patients also described improvements in social interactions and mood.

However, in one-third of patients for whom pre- and post-operative FEV_1 measurements were available, the change in FEV_1 did not reflect the person's perception of procedural success.

The urge to take a chance on a procedure to improve quality of life and reduce breathlessness, was central to the lived experience of patients in this study. Prior to lung volume reduction, participants had been consciously managing their body by pacing themselves, operating within known limits, and managing their environment and activities to deal with the challenges of constant breathlessness. Accepting palliative interventions seemed to be another expression of this conscious body management, and although procedures were described to patients as risk-laden or experimental, participants felt they had nothing to lose. Interventions to reduce lung volume seemed to help patients regain their sense of self, since someone had taken an active interest in their body, they were no longer an incurable case but a person in a body worth altering. Patients could perceive the possibility of a 'well self' who could act to improve their condition, which was particularly important to patients who felt they needed to do something to remedy what they viewed as a self-inflicted disease.

The quantitative study used a discrete choice experiment to quantify patient preferences for treatment of severe emphysema[33]. Study participants comprised a sample from the COPD Foundation Patient Powered Research Network (US), a voluntary register of patients with COPD or at risk of developing COPD. Patients on this register may not be representative of all COPD patients and the study only recruited patients who had an email address. All participants received a $25 (£20) gift token. Each participant had a self-reported diagnosis of emphysema, no prior history of lung volume reduction, and an mMRC breathlessness score >2. Patients were presented with a series of choices between hypothetical treatments with similar attributes to endobronchial valves, lung volume reduction surgery, and medical management. Thirty-six discrete choice questions were developed and grouped into four blocks of nine questions each. Participants were then randomly assigned to a block and the order of questions within each block were varied to mitigate bias. Eight patients pre-tested the questions. In each discrete choice question, the level of four attributes of the interventions could be varied to elicit patient preferences and determine the maximum acceptable risk for each outcome. The attributes tested in the study were improvements in breathlessness and daily activities, hospitalisation for COPD exacerbation, pneumothorax risk, and risk of death within three months of the procedure.

A total of 294 people (26%) out of 1,137 invited to participate in the study completed the discrete choice experiments. Study participants had an average age of 66, an average FEV_1 of 34% predicted, 64% were women, and the average time since diagnosis was 10 years. Participants described being breathless when doing routine tasks such as washing or dressing (83%), walking around the home (76%), and walking outside on level ground (96%). Participants also reported walking slower than other people their age (99%) and that household chores took longer because of breathlessness (97%). In this study, the maximum acceptable risk of death for a change from a 1-activity to a 3-activity improvement in breathlessness was 9.8%. The maximum acceptable risk of death for a reduction in frequency of hospitalisation for COPD exacerbations, from once every 6 months to once every 3 years, was 4.4%.

Respondents preferred the hypothetical interventions (endobronchial valves or surgery) over current treatment (medical therapy), and preferred endobronchial valves to surgery. Patients placed high relative value on avoiding a percentage point increase in treatment-related risk of death or pneumothorax, and on greater improvements in the number and range of activities they could do without experiencing breathlessness. Given a straight choice between endobronchial valves and current treatment, 76% of respondents chose endobronchial valves and 24% would continue their current treatment. In questions involving all three treatments, reducing the breathlessness benefit of endobronchial valves from a 3-activity improvement to a 2-activity improvement reduced the percentage of patients choosing this intervention from 71.4% to 64.6%, and increased the proportion choosing lung volume reduction surgery from 5.9% to 11.2%. Increasing the risk of death (5%) or pneumothorax (40%) did not substantially change patient preferences. About 20% of the study sample consistently chose current treatment over alternatives.

Organisational issues/context

An NHS England commissioning policy concluded that there was enough evidence to consider makingendobronchial valves available to patients with severe emphysema at centres with an experienced multi-disciplinary team (MDT)[1]. This policy is based on evidence from six of the seven trials now available for the Zephyr® valve and two of the four trials now available for the Spiration® valve. The evidence review behind the policy supports use of the Zephyr® valve but not the Spiration® valve based on the evidence available at the time.

The policy contains a list of criteria for the referral of patients to an MDT for lung volume reduction, and recommends against lung volume reduction in patients with limited life expectancy or multiple comorbidities. Once referred to the MDT patients are expected to undergo additional assessments, including imaging tests to determine emphysema distribution, assessment of exercise ability to determine fitness, calculation of individual procedural risk, bronchoscopic assessment of collateral ventilation (which would exclude endobronchial valve procedures), and measurement of baseline quality of life. The main reasons for refusing patients lung volume reduction were lack of a suitable target area in the lungs and excessive risk. To qualify specifically for an endobronchial valve procedure, patients should have upper or lower lobe heterogeneous emphysema without collateral ventilation, residual lung volume >180% predicted, carbon monoxide diffusion capacity >20%, and BMI >18.

The Zephyr® endobronchial valve manufacturer has stated that their valve is contraindicated in patients with an active lung infection, who are unable to undergo bronchoscopy, who have an allergy to nitinol, nickel, titanium or silicon, are current smokers, or who have air pockets that take up more than one-third of the lung[15]. Similar contraindications are likely to apply to the Spiration® valve, although this has not been confirmed by the manufacturer or reported in the literature.

Cost effectiveness

Two economic evaluations were identified, one from the perspective of the German healthcare system[34] and the other from a Dutch healthcare perspective[35]. Both evaluations used the Zephyr® valve.

The German cost-utility analysis compared the Zephyr® endobronchial valve plus medical therapy with medical therapy alone in patients with severe or very severe heterogeneous emphysema, no collateral ventilation, and successful lobar exclusion (a measure of procedure success)[34]. The results of the analysis indicate that over a 5- and 10-year time horizon, the Zephyr® valve is associated with increased quality-adjusted-life-years (QALYs) and higher costs compared with medical therapy alone. The incremental cost effectiveness ratio (ICER) at 5 years was €46,322 (£41,401) and at 10 years was €25,142 (£22,471). Endobronchial valve implantation provided patient benefits in terms of observed disease (re)staging at 12-month follow-up, which was associated with lower mortality risk, higher utility, and fewer COPD exacerbations: incremental QALYs at 5 years were 0.22 and at 10 years were 0.41. The incremental cost of endobronchial valve therapy was composed of procedure costs, valve purchase costs, and costs associated with treatment of excess adverse events during the first year: incremental cost at 5 years was €10,299 (£9,108) and at 10 years was €10,425 (£9,213). Incremental costs were partially offset by a smaller proportion of patients treated with the Zephyr® valve – compared with the comparator arm – developing severe or very severe emphysema and experiencing adverse events over years two to 10.

Clinical data on adverse events, disease (re)staging, and health-related quality-of-life (HRQoL) in the first year, were estimated from a sub-group of the VENT trial who had a successful outcome. Modelling for years 2 to 10 used a Markov model structure consistent with a previously published economic evaluation on smoking cessation versus usual care in patients with mild COPD. The model incorporated follow-up data from a lung health cohort study to estimate the probability of disease progression between GOLD stages of disease severity and German population mortality rates adjusted for age, disease severity, smoker status and risk of mortality following a COPD exacerbation, to estimate life expectancy. Utility values were estimated using the EuroQol 5-Dimension (EQ-5D) quality of life questionnaire, collected as part of a multi-national trial and valued using a UK tariff. Disutilities associated with COPD exacerbations were applied. Resource use was estimated from a German statutory health insurance perspective, with only direct healthcare costs included. The key clinical effectiveness inputs for this evaluation are summarised in table 7.

Table 7: baseline clinical effectiveness values used in German economic model[34]

Actual clinical events in year 1	Zephyr® valve	Medical therapy	Reference
Death	2.7%	2.8%	VENT sub-group data
COPD exacerbation with hospitalisation	35.1%	24.3%	
COPD exacerbation without hospitalisation	81.1%	97.2%	
Respiratory failure <24h on ventilation	2.7%	0%	
Respiratory failure >24h on ventilation	0%	0%	
Pneumonia (excluding distal to the valve)	21.6%	8.3%	
Pneumothorax/leak >7 days	5.4%	0%	
Stable pneumothorax	2.7%	0%	
Valve removal	8.1%	0%	
Pneumonia distal to an implanted valve	5.4%	0%	
GOLD staging at 12 months			
Stage 2 (moderate)	13.5%	0%	VENT sub-group data
Stage 3 (severe)	51.4%	44.4%	
Stage 4 (very severe)	35.1%	55.6%	
Disease progression and events in years 2 to 10	**Base case (range)**		**Reference**
Transition probabilities (3 months)			
GOLD stage 2 to 3 progression (moderate to severe)	0.3% (0.3% to 0.4%)		Menn *et al* (2012)
GOLD stage 3 to 4 progression (severe to very severe)	0.7% (0.6% to 0.8%)		
Event probabilities (3 months)			
Valve removal	3.7%		Sciurba *et al* (2010)
Mild exacerbation in GOLD stage 2 (moderate)	8.2% (7.2% to 9.2%)		Menn *et al* (2012)
Mild exacerbation in GOLD stage 3 (severe)	14.5% (13.1% to 16.0%)		
Mild exacerbation in GOLD stage 4 (very severe)	14.3% (13.3% to 15.4%)		
Moderate exacerbation in GOLD stage 2 (moderate)	18.4% (16.3% to 20.6%)		

Moderate exacerbation in GOLD stage 3 (severe)	26.8% (24.1% to 29.6%)	
Moderate exacerbation in GOLD stage 4 (very severe)	28.1% (26.2% to 29.9%)	
Severe exacerbation in GOLD stage 2 (moderate)	3.9% (3.4% to 4.4%)	
Severe exacerbation in GOLD stage 3 (severe)	3.8% (3.4% to 4.2%)	
Severe exacerbation in GOLD stage 4 (very severe)	4.9% (4.5% to 5.2%)	
Relative mortality risk in GOLD stage 2 (moderate)	4.0	1.15*relative risk in GOLD stage 2
Relative mortality risk in GOLD stage 3 (severe)	4.6	
Relative mortality risk in GOLD stage 4 (very severe)	9.5	

When considering the applicability of the German economic evaluation results to Scotland, the following issues should be taken into consideration:

- The cost-effectiveness estimates relate to a sub-group of patients in the VENT trial who achieved lobar exclusion following valve implantation. Patients who do not achieve lobar exclusion will likely incur similar or higher costs without the associated health benefits. The true ICER associated with the Zephyr® valve is likely to be higher than the findings of the German evaluation.

- The analysis results are only applicable to comparisons of the Zephyr® valve with standard medical therapy. Cost effectiveness relative to other lung volume reduction procedures, such as surgery or endobronchial coils, is unknown as there are no current published studies on these comparisons.

- Estimates of resource use and the information on costs used to value these resources is specific to the German health-care system and may not generalise to Scotland. Although German procedure-related costs were broadly applicable to Scotland (commercial in confidence).

- From a modelling perspective, the time horizon over which the base-case results were calculated appears to be too short to capture all the relevant costs and benefits associated with the intervention; the 10 year survival rates predicted for the endobronchial valve plus medical therapy and medical therapy alone cohorts in the model are approximately 40% and 34% respectively. However, clinical experts suggest the life expectancy of patients currently receiving endobronchial valves is closer to five years (Mr A Kirk, Consultant Thoracic Surgeon, Golden Jubilee National Hospital. Personal communication, 2 October 2020). This creates

uncertainty regarding the comparability of trial participants with patients in clinical practice and/or the appropriateness of mortality data used within the economic model.

An economic evaluation from the Dutch healthcare system perspective reached similar conclusions to the German analysis, estimating a 5- and 10-year ICER of €41,970 (£37,511) and €24,255 (£21,678), respectively for Zephyr® valve plus medical therapy compared with medical therapy alone in patients with severe or very severe emphysema and no collateral ventilation[35]. This study was less methodologically robust than the German analysis, for reasons including the assumption of no disease progression 6 months after valve implantation and exclusion of ongoing emphysema management costs. Further details have not been reported here.

Conclusion

Evidence from three good quality meta-analyses of seven RCTs indicates that the Zephyr® endobronchial valve plus medical therapy provides statistically significant and clinically important benefits to patients in terms of improvements in breathing, residual lung volume, quality of life, and activity levels. These benefits need to be balanced against a significant increase in the risk of serious adverse events or a pneumothorax with this device.

A good quality meta-analysis of four RCTs suggests that the Spiration® valve plus medical therapy has beneficial effects in patients with severe or very severe emphysema who have little or no collateral ventilation. In this patient sub-group, the Spiration® valve was associated with statistically and clinically significant improvements in breathing, quality of life and residual lung volume. There was no statistically significant increase in the risk of pneumothorax in patients treated with the Spiration® valve, although there was a significant increase in the risk of acute COPD exacerbation which needs to be balanced against the benefits to patients of this device.

The results of an NMA, which provides the only evidence comparing the Zephyr® and Spiration® valves, found no statistically significant differences in clinical effectiveness or safety outcomes between the two valves.

No analyses were identified that compared endobronchial valves with surgical lung volume reduction.

The majority of the trials of endobronchial valves had a risk of bias from lack of blinding. However, most outcomes were objective measures of lung volume or function, which should mitigate this risk of bias. Two Spiration® valve trials and one Zephyr® valve trial incorporated a sham bronchoscopy procedure within the control group. The results of these studies were comparable with trials using a medical therapy alone control, so the lack of blinding appears to have had little impact on study results. Trials for both the Zephyr® and Spiration® valves had a maximum follow-up of 12 months, limiting the conclusions that can be drawn about the long-term effectiveness and safety of the valves.

In addition to the variation in comparator procedures across the trials, there are a number of important factors to consider when weighing up the evidence on endobronchial valves. Firstly, the therapeutic approach in trials differed; the Zephyr® valve trials mainly used unilateral total occlusion of the affected lobe, whereas the Spiration® trials used unilateral total occlusion in two trials and bilateral partial occlusion in two trials. A study comparing outcomes for the Spiration® valve with a unilateral versus bilateral approach, found that outcomes were significantly better for unilateral total occlusion. Secondly, both valves appear to be more effective in patients who have little or no collateral ventilation. Thirdly, the Zephyr® trials tested the valve in patients with either homogenous or heterogeneous emphysema, whereas all the Spiration® valve trials recruited patients with heterogeneous emphysema.

No economic evaluations that were directly applicable to Scotland were identified. A cost-utility analysis from the German healthcare system perspective indicated that the Zephyr® valve was less likely to be cost-effective at 5 years (ICER £41,401) but increasingly cost-effective after 10 years (ICER £22,471). This study has a number of limitations and may not generalise to Scotland. No evidence on cost effectiveness was identified for the Spiration® valve.

A small number of studies found that patients valued both surgical and endobronchial valve interventions for lung volume reduction. They had a strong desire to act to improve their quality of life and reduce breathlessness, despite knowing the procedures carried risks. In a discrete choice experiment, it appeared that patients preferred active interventions over medical therapy, and favoured an endobronchial valve procedure over surgical lung volume reduction.

Identified research gaps

RCTs are required that directly compare the Zephyr® and Spiration® valves for lung volume reduction in patients with severe or very severe emphysema. Comparison of endobronchial valves with surgical lung volume reduction would also be useful and one such study is currently underway[26].

Economic evaluations from a UK NHS perspective are needed to assess the cost effectiveness of both the Zephyr® and Spiration® valves for treatment of patients with severe or very severe emphysema.

About SHTG Recommendations

SHTG Recommendations are produced to inform a decision at a particular point in time and therefore is not routinely updated. The Recommendations will however be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. Further information about SHTG Recommendations process is on this Healthcare Improvement Scotland webpage.

To propose a topic for SHTG consideration, email his.shtg@nhs.scot.

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

Acknowledgements

Reviewers

SHTG Executive would like to thank the following individuals who provided peer review comments on the draft review which were considered by the authors:

- Ms Brigitte Casteels-Rappagliosi, CEO & Founder, BC Consulting & Solutions Sàrl, Switzerland
- Dr Tom Fardon, Consultant Physician in Respiratory and General Internal Medicine, NHS Tayside
- Dr Samuel Kemp, Consultant Respiratory Physician, Royal Brompton Hospital NHS Foundation Trust
- Mr Alan Kirk, Consultant Thoracic Surgeon & Director of Education at Golden Jubilee National Hospital, NHS Greater Glasgow and Clyde
- Mr Malcom Will, Consultant Thoracic Surgeon, Royal Infirmary Edinburgh, NHS Lothian

SHTG Executive would like to thank the following individuals and organisations of the Evidence Review Team who provided comments on the draft review which were considered by the authors:

- Ms Maria Dimitrova, Health Economist, Healthcare Improvement Scotland
- Mr David Dunkley, Public Partner, Healthcare Improvement Scotland

- Dr Claudia Geue, Lecturer in Health Economics and Health Technology Assessment, University of Glasgow
- Dr Moray Nairn, Programme Manager, SIGN, Healthcare Improvement Scotland
- Professor Craig Ramsay, Director of Health Services Research Unit, University of Aberdeen
- Dr Neil Smart, SHTG Council Vice-Chair, Consultant Anaesthetist, NHS Greater Glasgow and Clyde
- Ms Susan Siegel, Public Partner, Healthcare Improvement Scotland
- Dr Hester Ward, Consultant in Public Health Medicine, NHS National Services Scotland

SHTG Executive would like to thank the following individuals and organisations who provided comments on the draft recommendation, which were considered by the SHTG Council:

- Dr Tom Fardon, Consultant Physician in Respiratory and General Internal Medicine, NHS Tayside
- Mr Alan Kirk, Consultant Thoracic Surgeon & Director of Education of Golden Jubilee National Hospital, NHS Greater Glasgow and Clyde
- Ms Sara Smith, Head of Medical Sciences, SHTG Consultation Group, NHS Lothian
- Mr Malcom Will, Consultant Thoracic Surgeon, Royal Infirmary Edinburgh, NHS Lothian

Declarations of interest were sought from all reviewers. Reviewers had no role in authorship or editorial control and the views expressed are those of HIS and the SHTG Council.

SHTG Council

SHTG Executive would like to thank the following individuals and organisations on the SHTG Council for developing this recommendation:

- Mr Ed Clifton, SHTG Unit Head, Healthcare Improvement Scotland
- Mr Mark Cook, Director Government Affairs, Assn. of British Healthcare Industries
- Dr Karen Facey, Senior Research Fellow, Usher Institute, University of Edinburgh
- Ms Claire Fernie, Public Partner, Healthcare Improvement Scotland
- Dr Rodolfo Hernandez, Research Fellow, Health Economics Research Unit (HERU), University of Aberdeen
- Mr Colin Marsland, Director of Finance, NHS Shetland
- Ms Anncris Roberts, Acting Unit Head, Planning & Quality – Health Technologies, Scottish Government
- Dr Iain Robertson, SHTG Council Chair, Consultant Interventional Radiologist, NHS Greater Glasgow and Clyde
- Dr Laura Ryan, Medical Director, NHS 24
- Dr Neil Smart, SHTG Council Vice-Chair, Consultant Anaesthetist, NHS Greater Glasgow and Clyde
- Mr Hugh Stewart, Public Partner, Healthcare Improvement Scotland

Healthcare Improvement Scotland development team

- Jenny Harbour, Lead Author/Health Services Researcher, SHTG, Healthcare Improvement Scotland
- Lynne Smith, Information Scientist, Knowledge Management Team, Healthcare Improvement Scotland
- Guy Berg, Health Economist, SHTG, Healthcare Improvement Scotland
- Tracey Mac Gann, Project Officer, SHTG, Healthcare Improvement Scotland

©Healthcare Improvement Scotland

Published November 2020

This document is licensed under the Creative Commons Attribution-Noncommercial-NoDerivatives 4.0 International License. This allows for the copy and redistribution of this document as long as Healthcare Improvement Scotland is fully acknowledged and given credit. The material must not be remixed, transformed or built upon in any way. To view a copy of this license, visit https://creativecommons.org/licenses/by-nc-nd/4.0/

References

1. NHS England. Clinical commissioning policy proposition: lung volume reduction by surgery or endobronchial valve for severe emphysema in adults. 2019 [cited 2020 Apr 10]; Available from: https://www.engage.england.nhs.uk/consultation/lung-volume-reduction/user_uploads/1622-lvr-policy-proposition.pdf.
2. David S, Edwards CW. StatPearls: forced expiratory volume. 2020 [cited 2020 Oct 15]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK540970/.
3. Mayo Clinic. Pneumothorax. 2019 [cited 2020 Apr 23]; Available from: https://www.mayoclinic.org/diseases-conditions/pneumothorax/symptoms-causes/syc-20350367.
4. British Lung Foundation. COPD (chronic obstructive pulmonary disease): emphysema. 2020 [cited 2020 Apr 23]; Available from: https://www.blf.org.uk/support-for-you/copd/emphysema.
5. Cetti EJ, Moore AJ, Geddes DM. Collateral ventilation. Thorax. 2006;61(5):371-3.
6. MedlinePlus. Subcutaneous emphysema. 2020 [cited 2020 May 07]; Available from: https://medlineplus.gov/ency/article/003286.htm.
7. Mayo Clinic. Emphysema. 2017 [cited 2020 Apr 24]; Available from: https://www.mayoclinic.org/diseases-conditions/emphysema/symptoms-causes/syc-20355555.
8. NRS Healthcare. Emphysema: everything you need to know about living well with emphysema. 2019 [cited 2020 Apr 24]; Available from: https://www.nrshealthcare.co.uk/articles/condition/emphysema.
9. Scottish Public Health Observatory. Chronic obstructive pulmonary disease (COPD). 2019 [cited 2020 Apr 24]; Available from: https://www.scotpho.org.uk/health-wellbeing-and-disease/chronic-obstructive-pulmonary-disease-copd/key-points/.
10. British Lung Foundation. Chronic obstructive pulmonary disease (COPD) statistics. [cited 2020 Apr 27]; Available from: https://statistics.blf.org.uk/copd.
11. Majid A, Labarca G, Uribe JP, Kheir F, Pacheco C, Folch E*, et al.* Efficacy of the Spiration valve system in patients with severe heterogeneous emphysema: a systematic review and meta-analysis. Respiration. 2020;99(1):62-72.
12. NICE. Managing COPD: NICE pathways. 2020 [cited 2020 Aug 28]; Available from: https://pathways.nice.org.uk/pathways/chronic-obstructive-pulmonary-disease#path=view%3A/pathways/chronic-obstructive-pulmonary-disease/managing-copd.xml&content=view-node%3Anodes-self-management.
13. Global Initiative for Chronic Obstructive Lung Disease Inc. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: 2020 report. 2020 [cited 09 Mar 2020]; Available from: https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.0wms.pdf.
14. ECRI. Spiration valve system (Olympus America) for treating severe emphysema symptoms. Plymouth Meeting, PA; ECRI: 2019.

15. ECRI. Zephyr endobronchial valve system (Pulmonx Corp) for treating respiratory symptoms of emphysema. Plymouth Meeting, PA; ECRI: 2019.

16. BMJ Best Practice. Chronic obstructive pulmonary disease. 2019 [cited 2020 Apr 27]; Available from: https://bestpractice-bmj-com.knowledge.idm.oclc.org/topics/en-gb/7/pdf/7/COPD.pdf.

17. Public Health Scotland. Diagnoses: hospital care - long-term conditions. 2019 [cited 2020 Apr 27]; Available from: https://www.isdscotland.org/Health-Topics/Hospital-Care/Diagnoses/.

18. Welling JBA, Hartman JE, Augustijn SWS, Kerstjens HAM, Vanfleteren LEGW, Klooster K*, et al.* Patient selection for bronchoscopic lung volume reduction. Int J Chron Obstruct Pulmon Dis. 2020;15:871-81.

19. Hartman JE, Ten Hacken NHT, Klooster K, Boezen HM, de Greef MHG, Slebos DJ. The minimal important difference for residual volume in patients with severe emphysema. Eur Respir J. 2012;40(5):1137-41.

20. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. Am J Respir Crit Care Med. 2014;189(3):250-5.

21. NICE. Endobronchial valve insertion to reduce lung volume in emphysema. Interventional procedures guidance, IPG600. 2017 [cited 2020 Mar 09]; Available from: https://www.nice.org.uk/guidance/ipg600.

22. Labarca G, Uribe JP, Pacheco C, Folch E, Kheir F, Majid A*, et al.* Bronchoscopic lung volume reduction with endobronchial Zephyr Valves for severe emphysema: a systematic review and meta-analysis. Respiration. 2019;98(3):268-78.

23. Rustagi N, Singh S, Dutt N, Kuwal A, Chaudhry K, Shekhar S*, et al.* Efficacy and safety of stent, valves, vapour ablation, coils and sealant therapies in advanced emphysema: a meta-analysis. Turk Thorac J. 2019;20(1):43-60.

24. van Geffen WH, Slebos DJ, Herth FJ, Kemp SV, Weder W, Shah PL. Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis. Lancet Respir Med. 2019;7(4):313-24.

25. Iftikhar IH, Schimmel M, Sardi A, Mehta I, Gonzalez E, Musani AI. Bronchoscopic lung volume reduction with valves and coils: a network meta-analysis. Ann Am Thorac Soc. 2020 [in press].

26. Buttery S. The CELEB trial: comparative effectiveness of lung volume reduction surgery for emphysema and bronchoscopic lung volume reduction with valve placement. 2020 [cited 2020 May 06]; Available from: http://www.isrctn.com/ISRCTN19684749?q=&filters=conditionCategory:Respiratory&sort=&offset=9&totalResults=657&page=1&pageSize=10&searchType=basic-search.

27. Buttery S, Lewis A, Oey I, Hargrave J, Waller D, Steiner M*, et al.* Patient experience of lung volume reduction procedures for emphysema: a qualitative service improvement project. ERJ Open Res. 2017;3(3):00031-2017.

28. Criner GJ, Delage A, Voelker K, Hogarth DK, Majid A, Zgoda M*, et al.* Improving lung function in severe heterogenous emphysema with the Spiration Valve System (EMPROVE): a multicenter, open-label randomized controlled clinical trial. Am J Respir Care Med. 2019;200(11):1354-62.

29. Li S, Wang G, Wang C, Gao X, Jin F, Yang H*, et al.* The REACH trial: a randomized controlled trial assessing the safety and effectiveness of the Spiration® Valve System in the treatment of severe emphysema. Respiration. 2019;97(5):416-27.

30. Ninane V, Geltner C, Bezzi M, Foccoli P, Gottlieb J, Welte T*, et al.* Multicentre European study for the treatment of advanced emphysema with bronchial valves. Eur Respir J. 2012;39(6):1319-25.

31. Wood DE, Nader DA, Springmeyer SC, Elstad MR, Coxson HO, Chan A*, et al.* The IBV Valve trial: a multicenter, randomized, double-blind trial of endobronchial therapy for severe emphysema. J Bronchol Interv Pulmonol. 2014;21(4):288-97.

32. Gullick JG, Colleen Stainton M. Taking a chance: the experience of lung volume reduction procedures for chronic obstructive pulmonary disease. Chronic Illn. 2009;5(4):293-304.

33. Mansfield C, Sutphin J, Shriner K, Criner GJ, Celli BR. Patient preferences for endobronchial valve treatment of severe emphysema. Chronic Obstr Pulm Dis. 2018;6(1):51-63.

34. Pietzsch JB, Garner A, Herth FJ. Cost-effectiveness of endobronchial valve therapy for severe emphysema: a model-based projection based on the VENT study. Respiration. 2014;88(5):389-98.

35. Hartman JE, Klooster K, Groen H, Ten Hacken NHT, Slebos DJ. Cost-effectiveness of endobronchial valve treatment in patients with severe emphysema compared to standard medical care. Respirology. 2018;23(9):835-41.

36. Criner GJ, Sue R, Wright S, Dransfield M, Rivas-Perez H, Wiese T*, et al.* A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). Am J Respir Crit Care Med. 2018;198(9):1154-64.

37. Kemp SV, Slebos DJ, Kirk A, Kornaszewska M, Carron K, Ek L*, et al.* A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (TRANSFORM). Am J Respir Crit Care Med. 2017;196(12):1535-43.

38. Valipour A, Slebos DJ, Herth F, Darwiche K, Wagner M, Ficker JH*, et al.* Endobronchial valve therapy in patients with homogeneous emphysema results from the IMPACT study. Am J Respir Crit Care Med. 2016;194(9):1073-82.

39. Davey C, Zoumot Z, Jordan S, McNulty WH, Carr DH, Hind MD*, et al.* Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. Lancet. 2015;386(9998):1066-73.

40. Klooster K, Ten Hacken NHT, Hartman JE, Kerstjens HAM, van Rikxoort EM, Slebos DJ. Endobronchial valves for emphysema without interlobar collateral ventilation. New Engl J Med. 2015;373(24):2325-35.

41. Herth FJF, Noppen M, Valipour A, Leroy S, Vergnon JM, Ficker JH*, et al.* Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J. 2012;39(6):1334-42.

42. Sciurba FC, Ernst A, Herth FJF, Strange C, Criner GJ, Marquette CH*, et al.* A randomized study of endobronchial valves for advanced emphysema. New Engl J Med. 2010;363(13):1233-44.

Appendix 1: abbreviations

6MWT	6 minute walk test
BMI	body mass index
BOLD	Burden of Obstructive Lung Disease Initiative
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CT	computed tomography
FEV	forced expiratory volume
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
IPG	interventional procedure guidance
MCID	minimum clinically important difference
MD	mean difference
MDT	multi-disciplinary team
mMRC	modified Medical Research Council
NMA	network meta-analysis
NR	not reported
NS	not significant
OR	odds ratio
QALY	quality adjusted life-years
RCT	randomised controlled trial
RR	relative risk/risk ratio
SGRQ	Saint George's Respiratory Questionnaire
SMD	standardised mean difference
WMD	weighted mean difference

Appendix 2: RCTs evaluating the Zephyr® or Spiration® endobronchial valves

Table A: RCTs evaluating the Zephyr® endobronchial valve system

Trial	n patients	Intervention	Comparator	Patient characteristics	Follow-up (months)	Results Between group differences: intervention – comparator (95% CI)
LIBERATE (2018)[36]	190	Zephyr® valve + standard medical therapy	Standard medical therapy	Heterogeneous severe or very severe emphysema (mean FEV_1 % predicted 28.0% ± 7.45% vs. control 26.2% ± 6.28%) Little or no collateral ventilation	12	Significant differences favouring Zephyr® for mean FEV_1, 6MWT, SGRQ score and residual volume at 12 months: ■ FEV_1 0.106L (0.047 to 0.165), p<0.001 ■ 6MWT 39.31m (14.64 to 63.98), p=0.002 ■ SGRQ score -7.05 points (-11.84 to -2.27), p=0.004 ■ Residual volume -0.52L (-0.77 to -0.27), p<0.001 ■ mMRC -0.8 points (-1.1 to -0.4), p<0.001
TRANSFORM (2017)[37]	97	Zephyr® valve + standard medical therapy	Standard medical therapy	Heterogeneous severe or very severe emphysema (mean FEV_1 % predicted 29.75% ± 9.18% vs.	6	Significant differences favouring Zephyr® for mean FEV_1, residual volume, 6MWT, and SGRQ score at 6 months: ■ FEV_1 0.23L (0.14 to 0.32), p<0.001 ■ Residual volume -0.67L (-1.09 to -0.25), p=0.002

				control 32.16% ± 8.35%) Little or no collateral ventilation		■ 6MWT 78.7m (46.3 to 111.0), p<0.001 ■ SGRQ score -6.5 points (-12.4 to -0.6), p=0.031 ■ mMRC score -0.56 points (-0.99 to -0.14), p=0.01
IMPACT (2016)[38]	93	Zephyr® valve + standard medical therapy	Standard medical therapy	Homogenous severe or very severe emphysema (mean FEV_1 % predicted 28.4% ± 6.3% vs. control 29.9% ± 6.3%)	3	Significant differences favouring Zephyr® for mean FEV_1, SGRQ score, 6MWT, and residual volume at 3 months: ■ FEV_1 0.12L (0.06 to 0.18), p<0.0001 ■ SGRQ score -9.64 points (-14.09 to -5.2), p<0.0001 ■ 6MWT 40.0m (15.0 to 65.0), p=0.002 ■ mMRC -0.57 points (-0.98 to -0.16), p=0.007 ■ Residual volume -0.48L (-0.84 to -0.11), p=0.0113 All serious adverse events (respiratory): 44.2% vs. 12.0%, p<0.001 Pneumothorax: 25.6% vs. 0%, p<0.001
BeLieVeR-HIFi (2015)[39]	50	Zephyr® valve	Sham intervention	Heterogeneous severe or very severe emphysema	12	Significant differences favouring Zephyr® for median FEV_1 and 6MWT: ■ FEV_1 0.06L (IQR 0.02 to 0.38) vs. 0.03L (IQR 0 to 0.06), p=0.03

				(Mean FEV_1 % predicted 31.6% ± 10.5% vs. control 31.8% ± 10.5%) Little or no collateral ventilation		■ Residual volume -0.26L (IQR -1.07 to -0.16) vs. -0.08L (IQR -0.39 to -0.08), p=0.08 ■ mMRC 0 (IQR -1 to 0) vs. 0 (IQR -1 to 0), p=0.4 ■ SGRQ score -4.40 points (IQR -16.93 to 6.76) vs. -3.57 (IQR -7.67 to 2.55), p=0.3 ■ 6MWT 25m (IQR 7 to 64) vs. 3m (IQR -14 to 20), p=0.01
STELVIO (2015)[40]	68	Zephyr® valve	Standard medical therapy	Heterogeneous or homogenous severe or very severe emphysema (mean FEV_1 % predicted 29.0% ± 7.0% vs. control 29.0% ± 8.0%)	6	Significant differences favouring Zephyr® for mean FEV_1 and 6MWT at 6 months: ■ FEV_1 140ml (55 to 225), p=0.002 ■ 6MWT 74m (47 to 100), p<0.001 Serious adverse events: 23 vs. 5, p<0.01 Pneumothorax: 6 vs. 0, p=0.02
VENT EU (2012)[41]	171	Zephyr® valve + standard medical therapy	Standard medical therapy	Heterogeneous or homogenous severe or very severe emphysema (mean FEV_1 % predicted 29.0% ±	12	No significant differences in FEV_1 or SGRQ score at 6 months: ■ FEV_1 (% predicted) 7 ± 20% vs. 0.5 ± 19%, p = 0.067

				8.0% vs. control 30.0% ± 8.0%) With or without collateral ventilation		■ SGRQ score -5 ± 14 vs. 0.3 ± 13, p=0.047
VENT US (2010)[42]	321	Zephyr® valve + standard medical therapy	Standard medical therapy	Heterogeneous or homogenous severe or very severe emphysema (mean FEV_1 % predicted 30.0% ± 8.0% vs. control 30.0% ± 8.0%) With or without collateral ventilation	12	Significant differences favouring Zephyr® for mean FEV_1, 6MWT, and SGRQ score at 6 months: ■ FEV_1 60.0ml (21.5 to 98.4), p=0.002 ■ 6MWT 19.1m (1.3 to 36.8), p=0.02 ■ SGRQ score -3.4 points (-6.7 to 0.2), p=0.04 ■ mMRC -0.3 points (-0.50 to -0.01), p=0.04

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; SGRQ = St George's Respiratory Questionnaire; 6MWT = 6-minute walking test; mMRC = modified Medical Research Council

*Lower SGRQ scores indicate a better quality of life

Table B: RCTs evaluating the Spiration® valve system

Trial	n patients	Intervention	Comparator	Patient characteristics	Follow-up (months)	Results Between group differences: intervention – comparator (95% CI)
EMPROVE (2019)[28]	172	Spiration® valve + standard medical therapy	Standard medical therapy	Heterogeneous severe or very severe emphysema (mean FEV_1 % predicted treatment group 30.8% ± 8.1%) No collateral ventilation	12	Significant differences favouring Spiration® for mean FEV_1, residual volume, and SGRQ score at 6 months: ■ FEV_1 0.10L (0.06 to 0.14) ■ Residual volume -0.36L (-0.59 to -0.13) ■ SGRQ score -13.0 points (-17.4 to -8.5) ■ mMRC -0.6 points (-0.9 to -0.3) ■ 6MWT 6.9m (-14.2 to 28.2) Serious adverse events: 31.0% vs. 11.9%
REACH (2019)[29]	107	Spiration® valve + standard medical therapy	Standard medical therapy	Heterogeneous severe or very severe emphysema (mean FEV_1 % predicted treatment group 27.3% ± 6.7%) No collateral ventilation	6	Significant differences favouring Spiration® for mean FEV_1, SGRQ score and 6MWT at 6 months: ■ FEV_1 0.09 ± 0.16L vs. -0.02 ± 0.14L, p < 0.001 ■ SGRQ score -8.39 ± 17.43 points vs. 2.11 ± 17.24 points, p=0.007 ■ mMRC -0.73 ± 0.92 points vs. -0.36 ± 1.03 points, p=0.09

						■ 6MWT 20.82 ± 86.65m vs. -15.58 ± 71.91m, p=0.042 ■ Residual volume -0.42 ± 1.84L vs. -0.05 ± 1.33L, p=0.114 Serious adverse events: 33% vs. 24.2%
IBV Valve Trial (2014)[31]	277	IBV system + standard medical therapy	Sham intervention + standard medical therapy	Heterogeneous severe or very severe emphysema (mean FEV_1 % predicted 29.8% ± 7.5% vs. control 29.7% ± 7.9%) With or without collateral ventilation	6	Significant differences favouring Spiration® for mean FEV_1, residual volume and 6MWT at 6 months: ■ FEV_1 -0.07 ± 0.17L vs. 0.00 ± 0.16L ■ Residual volume 0.31 ± 1.00L vs. -0.07 ± 1.29L ■ SGRQ score 2.15 ± 16.36 points vs. -1.41 ± 11.26 points ■ 6MWT -24.02 ± 69.81m vs. -3.40 ± 76.63m ■ mMRC -0.24 ± 1.02 points vs. -0.14 ± 1.00 points Serious adverse events: 14.1% vs. 3.7%
Ninane *et al.* (2012)[30]	73	IBV system	Sham intervention	Heterogeneous severe or very severe emphysema (mean FEV_1 % predicted 35.0%	3	Significant difference favouring Spiration® for residual volume at 3 months: ■ FEV_1 0.90 ± 0.34L vs. 0.87 ± 0.34L, p=0.07 ■ Residual volume 4.86 ± 1.35L vs. 5.05 ± 1.19L, p=0.012

				± 10.0% vs. control 32.0% ± 7.0%) With or without collateral ventilation		■ mMRC 2.5 ± 1.0 points vs. 2.7 ± 0.9 points, p=0.64 ■ 6MWT 33 ± 8m vs. 34 ± 8m, p=0.73 Any adverse event: 6 vs. 3, p=0.49

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; SGRQ = St George's Respiratory Questionnaire; 6MWT = 6-minute walking test; mMRC = modified Medical Research Council

*Lower SGRQ scores indicate a better quality of life

Appendix 3: meta-analyses evaluating the Zephyr® valve

Table A: findings from the meta-analysis by Labarca *et al* (2019)[22]

Outcome	n studies (n patients)	Findings (95% CI)	p-value	I^2
Change in FEV_1 (% predicted)	5 (498)	17.36% (9.28% to 25.45%)	0.001	78%
Residual lung volume (L)	5 (471)	-0.53 (-0.75 to -0.32)	<0.00001	59%
SGRQ score* (points)	5 (498)	-8.42 (-10.86 to -5.97)	<0.00001	6%
6MWT (m)	5 (498)	49.75 (28.75 to 70.75)	<0.00001	70%
Pneumothorax	5 (793)	RR 6.32 (3.74 to 10.67)	<0.00001	0%
Overall mortality (within max. 12 months follow-up)	5 (495)	RR 2.30 (0.66 to 8.02)	0.19	0%

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; MD = mean difference; SGRQ = St George's Respiratory Questionnaire; 6MWT = 6-minute walking test; OR = odds ratio
*Lower SGRQ scores indicate a better quality of life

Table B: findings from the meta-analysis by van Geffen et al (2019)[24]

Outcome	n studies (n patients)	Findings (95% CI)	p-value	I^2
FEV_1 (L)	6 (620)	MD 21.77 (17.63 to 25.90)	<0.0001	20%
Residual lung volume (L)	6 (600)	MD –0.57 (–0.71 to –0.43)	<0.0001	23%
SGRQ score* (points)	6 (609)	MD –9.13 (–12.37 to –5.89)	<0.0001	52%
6MWT (m)	6 (620)	MD 49.00 (31.89 to 66.10)	<0.0001	56%
All adverse events	6 (620)	OR 9.58 (5.56 to 16.50)	<0.00001	0%
45-day mortality	6 (620)	OR 3.04 (0.51 to 18.16)	0.22	0%

Overall mortality (within max. 12 months follow-up)	6 (620)	OR 1.84 (0.62 to 5.42)	0.27	0%

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; MD = mean difference; SGRQ = St George's Respiratory Questionnaire; 6MWT = 6-minute walking test; OR = odds ratio

*Lower SGRQ scores indicate a better quality of life