



## Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Zephyr endobronchial valve (EBV) system for patients with severe or very severe emphysema
Topic exploration report number:	TER118

### Introduction and aims

Zephyr endobronchial valve (EBV) system is used to treat patients with severe or very severe **emphysema** (one of the lung conditions included in the overall term of chronic obstructive pulmonary disease (COPD)). Emphysema is a progressive disease, causing an irreversible destruction of alveolar tissue and results in reduced elastic recoil, progressive hyperinflation and gas trapping within the lung lobe (lung hyperinflation). Patients have symptoms including: chronic dyspnea, limited tolerance to exercise, and poor health-related quality of life. Breathlessness worsens with disease progression. Depression, fear, anxiety and social isolation can occur with an increase in severity of symptoms. The disease can have a significant negative effect on the families and caregivers of patients.

The system consists of an implantable Zephyr EBV (including Endobronchial Loader System) and Zephyr Endobronchial Delivery Catheter. The valve is implanted during bronchoscopy and aims to block the inspiratory airflow into the hyperinflated lung lobe. The system is used during an endobronchial lung volume reduction procedure in patients with little or no collateral ventilation; the system can be used in patients with co-morbidities who are usually not candidates for lung volume reduction surgery (excision of the hyperinflated area).

The Zephyr EBVs have CE mark and FDA approval.

### Summary of findings

The use of Zephyr EBVs was evaluated in 6 randomised controlled trials and compared with sham EBV or usual care. A published meta-analysis of these trials suggests that Zephyr EBVs provide clinically meaningful improvement in patient outcomes over a short period of follow-up (3-12 months) but with an increase in adverse events.

Cost-effectiveness analysis is available from only one RCT which included patients with and without collateral ventilation (van Agteren et al. 2017).

## Evidence

One NICE Interventional Procedure Guidance (IPG600) and National Guideline (NG115) related to the intervention of interest were identified.

Three systematic reviews were identified which reported results of RCTs and observational studies focused on endobronchial valves. Labarca et al. (2019) and van Geffen et al. (2019) reported the evidence for Zephyr EBVs evaluated in 6 RCTs (BELIEVER-HIFI, IMPACT, STELVIO, LIBERATE, TRANSFORM and VENT US and EU). Labarca et al. (2019) does not include VENT US and EU RCT which evaluates patients with and without collateral ventilation (those patients were excluded in other RCTs). Choi et al. (2015) includes results from other observational studies. One Cochrane review included evidence from four RCTs included in other systematic reviews (BELIEVER-HIFI, IMPACT, STELVIO, VENT US and EU).

The follow-up of included RCTs varied from 3 to 12 months. Meta-analysis (Labarca et al. 2019) showed that Zephyr EBVs, compared to control (sham EBV or standard of care), improve:

- FEV1, for both homogenous and heterogeneous distribution, with a mean difference (MD) of 17.36% (95% CI 9.28-24.45, I<sup>2</sup> = 78%; 5 RCTs)
- SGRO (decrease of MD equal to -8.42 points (95% CI -10.86 to -5.97, I<sup>2</sup> = 6%); 5 RCTs)
- 6MWT (improvement of MD = 49.57 m (95% CI 28.75 - 70.75, I<sup>2</sup> = 70%); 5 RCTs)
- RV (improvement of MD = 530 mL (95% CI 750 - 320, I<sup>2</sup> = 59%); 5 RCTs)

The risk of mortality was 2.30 (95%CI 0.66 - 8.02, I<sup>2</sup> = 0%). The risk of pneumothorax increased in all trials (RR=6.32 (95% CI 3.74 - 10.67, I<sup>2</sup> = 0%)).

The only cost-effectiveness analyses were performed for patients with high heterogeneity in disease (VENT US and EU study)(van Agteren et al. 2017).

## Areas of uncertainty

We did not identify any cost-effectiveness evidence for patients with the Zephyr EBVs and without collateral ventilation.

## Conclusions

High quality studies are now published which summarise the evidence for Zephyr EBVs, however, there is no cost-effectiveness evidence for patients without collateral ventilation undergoing this intervention. No other RCTs are now ongoing and only one post-market evaluation of Zephyr EBVs is enrolling by invitation.

## Brief literature search results

Resource	Results
HTA organisations	
<a href="#">Healthcare Improvement Scotland</a>	We did not identify any relevant guidance/advice from this source.
<a href="#">Health Technology Assessment Group</a>	We did not identify any relevant guidance/advice from this source.
<a href="#">Health Information and Quality Authority</a>	We did not identify any relevant guidance/advice from this source.
UK guidelines and guidance	
<a href="#">SIGN</a>	We did not identify any relevant guidance/advice from this source.
<a href="#">NICE</a>	<p>NICE 2017. Endobronchial valve insertion to reduce lung volume in emphysema. Interventional Procedure Guidance 600. Available at: <a href="https://www.nice.org.uk/guidance/ipg600">https://www.nice.org.uk/guidance/ipg600</a></p> <p>NICE 2019. Chronic obstructive pulmonary disease in over 16s: diagnosis and management NICE Guideline 115. Available at: <a href="https://www.nice.org.uk/guidance/ng115">https://www.nice.org.uk/guidance/ng115</a></p>
Secondary literature and economic evaluations	
<a href="#">EUnetHTA</a>	We did not identify any relevant guidance/advice from this source.
<a href="#">Cochrane library</a>	<p>van Agteren JEM, Hnin K, Grosser D, Carson KV, Smith BJ. Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD012158. DOI: 10.1002/14651858.CD012158.pub2</p> <p>Includes five studies looking at endobronchial valves versus control (optimal medical care) in patients with COPD.</p>
Medline	<p>van Geffen, Slebos, Herth et al, Surgical and endoscopic interventions that reduce lung volume for emphysema : a systematic review and meta-analysis; Lancet Respir. 2019 7(4): 313-324 <a href="http://dx.doi.org/10.1016/S2213-2600(18)30431-4">http://dx.doi.org/10.1016/S2213-2600(18)30431-4</a> (RCTs only; includes evidence of Zephyr valves only)</p> <p>Choi M, Lee WS, Lee M, Jeon K, Sheen SS, Jheon S, Kim YS. Effectiveness of bronchoscopic lung volume reduction using unilateral endobronchial valve: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 10:703-10, 2015. DOI <a href="https://doi.org/10.2147/COPD.S75314">https://doi.org/10.2147/COPD.S75314</a> (RCTs and observational studies; includes studies with Zephyr and Emphasys valves)</p>
Ongoing primary or secondary research	

<a href="#">PROSPERO database</a>	<p>Ongoing review which list Zephyr EBVs:</p> <p>Measures for assessing outcomes after endobronchial valve (EBV) interventions for lung volume reduction in people with obstructive pulmonary conditions: systematic review [CRD42018114638]</p>
<a href="#">Clinicaltrials.gov</a>	<p>Zephyr EBVs only:</p> <p>NCT04161235 Post-Market Clinical Evaluation of the Zephyr Valve 5.5-LP EBV (enrolling by invitation)</p> <p>NCT04018729 Cell Therapy Associated With Endobronchial Valve (CEL&amp;VAL) (not yet recruiting)</p>
<b>Other</b>	
	<p>Other listed by the topic proposer:</p> <p><b>Clinical Commissioning Policy</b>  NHS England : Clinical Commissioning Policy Proposition : Lung volume reduction by surgery or endobronchial valve for severe emphysema in adults ; Reference : NHS England 1622</p> <p><b>Systematic review:</b>  Labarca, Uribe, Pacheco et al, Bronchoscopic Lung Volume Reduction with Endobronchial Zephyr Valves for Severe Emphysema: A Systematic Review and Meta-Analysis, Respiration, May 2019, DOI: 10.1159/000499508 (RCTs of Zephyr valves only)</p> <p><b>Patient preference study</b>  C. Mansfield et al, Patient preferences for endobronchial valve treatment of severe emphysema; Chronic Obstr Pulm Dis. 2019;6(1):In press. doi: <a href="https://doi.org/10.15326/jcopdf.6.1.2018.0147">https://doi.org/10.15326/jcopdf.6.1.2018.0147</a></p>
<b>Date of search:</b>	November 2019
<b>Concepts used:</b>	Endobronchial valve; zephyr; emphysema