South Australian Policy Advisory Committee on Technology (SAPACT)

Health Technology Assessment (HTA) Decision Summary Update

Government of South Australia

SA Health

Endobronchial valves for patients with chronic obstructive pulmonary disease and severe emphysema

SAPACT MEETING DATES	24th SAPACT meeting (20 November 2020), 25th SAPACT meeting (19 February 2021)
APPLICATION #	2022 (refer to 1401 for previous decision)
TECHNOLOGY	Zephyr endobronchial 'duckbill' valve (PulmonX Australia Pty Ltd)
TECHNOLOGY CLASSIFICATION	TGA class IIb
PATIENT INDICATION (Therapeutic Goods Administration (TGA))	The Zephyr endobronchial valve is an implantable bronchial valve intended to control airflow in order to improve lung function in patients with hyperinflation associated with emphysema and or reduce air leaks.

SAPACT DECISION

☒ Restricted recommendation for clinical use with financial/operational restrictions and under audit conditions.

SAPACT Advisory Recommendations

Based on evidence for clinical safety, effectiveness and cost effectiveness, SAPACT advises restricted use of the Zephyr endobronchial valve (EBV) under audit conditions. The Zephyr EBV provides clinical benefits to certain patients, although there is a risk of serious adverse events including pneumothorax, and with an expected increase in costs compared to standard care. The device should be used under the following criteria:

Patient selection:

- Clinical review:
  - Smoking status
  - Exacerbation frequency
  - Known bacterial colonisation
  - Rehabilitation status
  - Co-morbidities in particular unexplained nodules, pulmonary hypertension, IHD/recent MI
- Investigations:
  - Full PFTs, 6MWT, ABG
  - Quantitative CT
  - VQ differential index scan
  - Consideration to echo
- Multi-disciplinary team discussion
- Patient selection:
  - Inclusion:
    - Age 40 to 80 years
    - Fissure integrity
    - QCT
    - Chartis
    - Preferably both
    - TLC > 100%, RV ≥ 175%
    - Completed rehab program or equivalent
    - Consider both heterogeneous and homogeneous disease
    - If homogeneous need RV preferably > 200%
  - Exclusion:
    - FEV1 < 15% or > 50%
    - DLCO < 20%
    - Caution with CO_2 > 50mmHg
    - 6MWD < 140 metres
    - Nodules
    - Significant sputum
    - Unexplained weight loss last 3 months
    - MI or severe LV failure (LVEF < 35%) in the last 6 months
    - Uncontrolled pulmonary hypertension (>50 mmHg)

Proctoring

Patient selection and care in this chronically ill population can be complex. SAPACT recommends that initial procedures for interventionists who are unfamiliar with the use of endobronchial valves be proctored by experienced clinicians (e.g. from CALHN) to develop their local expertise. This will assist the learning curve, including valve placement, management of complications, patient recovery and also benefit nursing and anaesthetic staff.

Coordinated state-wide review and reporting

SA Health

SAPACT recommends that patient selection and patient outcomes be discussed at regular state-wide MDT meetings.

SAPACT requests that patient reports be provided to the relevant local health network new technologies committee (annual reporting of patient numbers, two-yearly report of clinical outcomes, with adverse events reported in line with local processes).

The following objective measures should be reported:

- Patient baseline characteristics, including imaging results
- Number of valves used and removed
- Rehospitalisation
- Pneumothorax and other adverse events
- Volume reduction and other technical outcomes (e.g. FEV1, 6MWD)
- The use of validated health-related quality of life measures (such as the SGRQ) is highly desirable

SAPACT notes that long-term data (>12 months) is valuable to determine patients outcomes. Shared reporting of state-wide outcomes will inform patient selection, patient care and outcomes in SA Health, and may assist to further refine the characteristics of patient who may best benefit from this procedure.

Background

This is a new submission from SALHN for the expanded use of Zephyr endobronchial one-way valves (EBV) in SA Health.

SAPACT previously reviewed an application to the CALHN New Clinical Procedures, Services or Other Interventions Committee (NCPSOI) in 2014 on the use of EBV in this population. At this time, the SAPACT recommended participation in a clinical trial, and for the use of EBVs could be considered on a case by case basis for difficult to treat, highly selected patients with emphysema.

The current application from SALHN is for up to 10 patients per year to be treated with the Zephyr EBV. Specifically, patients with severe chronic obstructive pulmonary disease (COPD; Gold stages 3 and 4) with severe emphysema and hyperinflation who are on maximal medical therapy and who have undergone pulmonary rehabilitation, with all patients to be reviewed by a multidisciplinary team (MDT).

An alternative valve, the Spiration Valve System, is not used in SA Health (personal communication). Therefore this summary is focused on the Zephyr EBV.

Summary of evidence

The body of evidence has improved since the previous SAPACT review in 2014, although long-term outcomes were still not available. Clinical evidence from seven randomised control trials showed inferior safety and superior clinical effectiveness of EBV compared with optimal medical care. The trials were consistent in terms of study design, outcomes reporting and overall results.

Local use of EBV shows evidence of appropriate patient outcomes and low rates of pneumothorax.

International and local guidelines support the use of EBV in selected COPD patients with emphysema, following careful assessment by a multidisciplinary team.

REGULATORY APPROVALS

1. Zephyr® endobronchial 'duckbill' valve

☒ **ARTG**: 165980, 12/10/2009 Prosthesis, internal, stent, bronchial.[1]

☒ **US FDA**: 28/06/2018, Zephyr® Endobronchial Valve System (Investigational device exemption (IDE) was provided in 2003)[2, 3]

☒ **EU CE mark**: 01/2012 Zephyr® endobronchial valve (EBV)[4]

2. Spiration endobronchial 'umbrella' valve (Olympus Australia Pty Ltd)

☒ **ARTG**: 188455, 23/8/2011 Endobronchial valve[1]

☒ **US FDA**: 03/12/2018, Spiration® Valve System (Humanitarian Device Exemption (HDE) was provided in 2008)[5, 6]

☒ **EU CE mark**: 2008, Spiration IBV® Valve System[7]

QUALITY OF EVIDENCE

Quality of Evidence	Systematic searches were conducted in 21 databases and grey literature sources. A number of recent systematic reviews and HTAs were identified.[8-20] A total of 7 randomised controlled trials (RCTs) are available on the Zephyr valve: • LIBERATE (Criner 2018) (n=190 randomised)[21] • BeLieVeR-HIFi (Davey 2015) (n=50)[22] • TRANSFORM (Kemp 2017) (n=97)[23] • STELVIO (Klooster 2015) (n=68)[24] • IMPACT (Valipour 2016) (n=93)[25] • VENT US (Scuriba 2010) (n=321)[26] and VENT EU (Herth 2012) (n=171)[27] Van Geffen 2019 is a recent high quality systematic review and meta-analysis (quality appraisal using the AMSTAR checklist for systematic reviews).[17] This review is supplemented by information from a separate recent high quality meta-analysis (Labarca 2019).[12]

	A total of 990 patients were randomised to valve placement or standard medical care (with sham valve placement in Davey 2015). Patients were similar in baseline characteristics, with many studies including both homogeneous and heterogeneous emphysema. For most domains, the RCTs were at low risk of bias, although there was a high risk of detection bias due to a lack of investigator blinding. One study was at high risk for performance bias as participants were not masked to treatment. There was no publication bias. Follow-up was to 12 months. All patients had COPD and severe emphysema, although trial inclusion varied according to emphysema distribution (Labarca 2019 excluded the VENT trials as they did not report the distribution of emphysema). There was consistency in study design and outcomes reporting and low heterogeneity in outcomes data. In summary, the use of EBV improved patient outcomes including quality of life (measured by the SGRQ), lung function (FEV_1) and physical ability (6MWT). However, this procedure is also associated with increased rates of adverse events including pneumothorax. There is a lack of evidence of long-term follow-up.[28] There are two ongoing trials of post-market evaluation of the Zephyr valve which may provide longer-term outcomes.[29, 30] There is one published protocol for the CELEB trial of LVR comparing surgery and valves for COPD patients with emphysema (Buttery 2018).[31] The trial end date is September 2020; no published results were identified.
CLINICAL NEED	
Burden of Illness	Across Australia, in 2018-19 there were 49,056 separations of COPD with acute lower respiratory infection (J44.0) of which 20,536 had an acute exacerbation (J44.1, AIHW Principal Diagnosis).[32] There were 336 principal diagnoses of emphysema. During this time period there were 31 procedures of lung volume reduction surgery (90170-00, procedures data cube).[33] Epidemiological analyses show that the prevalence of COPD is around 7.5% for people aged over 40 in Australia.[34]
Need	Chronic obstructive pulmonary disease (COPD) is a progressive disease which includes emphysema, chronic bronchitis and chronic asthma. The most important cause of COPD is cigarette smoking, followed by occupational dust exposure.[35] Over time, inflammation leads to lung damage with symptoms including breathlessness, repetitive coughing, fatigue, and frequent chest infections. COPD with emphysema is characterised by the destruction of lung tissue resulting in trapped air and hyperinflation of the lungs.[17] There is a significant impact on quality of life. COPD was the 5th leading cause of death in 2018,[36] and is associated with high rates of hospitalisation.[37] Based on data from the United Kingdom, up to a third of COPD patients would be considered severe or very severe based on spirometry results (FEV_1).[38] In Australia, the COPD-X Plan provides clinical guidelines for managing patients with COPD.[35] Standard care includes preventative vaccinations, pulmonary rehabilitation, medications (oral and inhaled) and domiciliary oxygen. Lung volume reduction (LVR) is an option in cases of severe heterogeneous emphysema (that is, where areas of damage are focused to one lobe, rather than being broadly distributed). LVR may improve endurance and symptoms of breathlessness by reducing hyperinflation, and improving respiratory function and gas exchange.[17] Traditionally, LVR has been achieved through surgery. LVR surgery is not currently provided in South Australia, and is rarely offered as an option to patients due to significant risks of morbidity and mortality.[39] More recently, less invasive endobronchial alternatives have become available including the use of vapour, coils, bypass tract airway stenting, transpleural ventilation or one-way valves. Of these, only valves are in regular clinical use in Australia.[35]
CLINICAL BENEFIT The clinical evidence found inferior safety and superior clinical effectiveness of EBV compared with optimal medical care.	
Safety	<u>Overall mortality</u> There was no significant difference in overall (all cause) mortality (7 RCTs, odds ratio 1.84 [85% confidence interval [CI]) 0.62 to 5.42], p=0.27) (van Geffen 2019). <u>All adverse events</u> There was an increased rate of adverse events in patients treated with valves compared to those who received standard medical care (7 RCTs, odds ratio 9.58 [95% CI 5.56 to 16.50], p<0.00001) (van Geffen 2019). Common adverse events were pneumothorax and COPD exacerbations. <u>Pneumothorax</u> There was an increased rate of pneumothorax in patients treated with valves (5 RCTs, risk ratio 6.32 [95% CI 3.74 to 10.67], p<0.00001) (Labarca 2019). There was no significant difference in the rate of pneumothorax in patients based on the distribution of emphysema (heterogeneous or homogeneous). The rate of pneumothorax in EBV patients varied across trials, from approximately 5 per cent (VENT) to 25-29 per cent (LIBERATE, TRANSFORM, IMPACT). In a separate post-hoc review of two trials, all patients with pneumothorax still benefitted from EBV with improvements in SGRQ, FEV1 and residual lobe volume (Gompelmann 2014). There is a lack of long-term data, with all trials restricted to 1 year follow-up. One retrospective observational study showed an improvement in survival at 10 years for patients who had successful lung reduction from a group of 19 patients treated with the Emphasys valve between 2002-04 (Garner 2016).
Effectiveness	<u>St George Respiratory Questionnaire (SGRQ)</u> The SGRQ is a disease specific quality of life assessment tool has been validated for COPD.[40] There was a significant improvement in SGRQ scores in patients treated with the Zephyr EBV (7 RCTs, weighted mean difference -9.13 [95% CI -12.37 to -5.89], p<0.001) (Van Geffen 2019). <u>Forced expiratory volume 1 second (FEV_1)</u> There was a significant improvement in patients who received EBV (7 RCTs, weighted mean difference 21.77 [95% CI 17.63 to

	25.90], p<0.0001) (Van Geffen 2019). Outcomes were similarly improved regardless of emphysema distribution (homogeneous or heterogeneous) (Labarca 2019). SA Health Six minute walk test (6MWT) There was a significant improvement in the 6MWT in patients with EBV (7 RCTs, weighted mean difference 49.00 [95% CI 31.89 to 66.10], p<0.0001) (van Geffen 2019). Residual volume Residual lung volume was significantly reduced in patients with EBV (7 RCTs, weighted mean difference -0.57 [95%CI -0.71 to -0.43], p<0.001) (van Geffen 2019). All improvements are consistent across primary studies and across separate meta-analyses. In terms of overall outcomes, results appeared slightly poorer in the BeLieVeR-HIFi and VENT trials. While the identified reviews did not provide an explicit statement on this, reasons for inferior outcomes may include study design (the BeLieVeR-HIFi study compared with sham valve placement), and the inclusion of patients with collateral ventilation (the VENT studies did not exclude patients with this presentation).
SUITABILITY OF PATIENT GROUP	
Suitability of Patient Group	SA Health • SAPACT undertook an evaluation summary of EBV in 2014, as a result of a query from the CALHN New Clinical Procedures, Services or Other Interventions Committee (NCPSOI). Three RCTs were available. SAPACT concluded that the evidence was inconclusive, with concerns regarding valve migration, pneumothorax and device removal, and gaps in the evidence concerning long-term outcomes and uncertainty regarding hospital readmission. There was a recognition that a small number of patients may benefit from the use of endobronchial valves. The SAPACT recommendation was to participate in a clinical trial, and that endobronchial valves could be used on a case-by-case basis for difficult to treat, highly selected patients with emphysema. CALHN patient selection: • Clinical review: o Smoking status o Exacerbation frequency o Known bacterial colonisation? o Rehabilitation status o Co-morbidities in particular unexplained nodules, pulmonary hypertension, IHD/recent MI • Investigations: o Full PFTs, 6MWT, ABG o Quantitative CT o VQ differential index scan o Consideration to echo • Multi-disciplinary team discussion • Patient selection: o Inclusion: ▪ Age 40 to 80 years ▪ Fissure integrity ▪ QCT ▪ Chartis ▪ Preferably both ▪ TLC > 100%, RV ≥ 175% ▪ Completed rehab program or equivalent ▪ Both heterogeneous and homogeneous disease now treated ▪ If homogeneous need RV preferably > 200% o Exclusion: ▪ FEV1 < 15% or > 50% ▪ DLCO < 20% ▪ Caution with CO_2 > 50mmHg ▪ 6MWD < 140 metres ▪ Nodules ▪ Significant sputum ▪ Unexplained weight loss last 3 months ▪ MI or severe LV failure (LVEF < 35%) in the last 6 months ▪ Uncontrolled pulmonary hypertension (>50 mmHg) NALHN patient eligibility: 1) Emphysema patients who have significant hyperinflation (Residual Volume >175%) 2) Non resolving pneumothorax patients who are not suitable for surgery

SALHN proposed patient selection criteria:

Inclusion criteria:

- Adult patients (>18 years of age)
- COPD stages III and IV with severe emphysema with hyperinflation
- Optimal medical management according to GOLD recommendations
- Intact fissures (determined by wither CT scan or Chartis assessment)

Exclusion criteria:

- Patients for whom bronchoscopic procedures are contraindicated
- Patients with evidence of active pulmonary infection
- Patients with known allergies to Nitinol, its constituent metals, or silicone
- Patients who have not quit smoking
- Patients with large bullae encompassing greater than 30% of either lung
- Collateral ventilation of lobes (non-intact fissures)
- Concomitant interstitial lung disease
- Severe cardiovascular comorbidity or life-limiting illness

CALHN have treated 45 patients since 2014, with clinical reports provided to SAPACT in 2017 and 2020:

- There were a total of 35 patients with a response to EBV (one inconclusive). Response criteria was any one of: a ten percent increase in FEV1; a 26 metre increase in 6MWD; a four point reduction in the SGRQ; a 350mL or greater reduction in treated lobe volume; a 430mL or greater reduction in residual volume.
- For safety, 25 patients reported no complications (or not reported). Of the 20 patients with complications these included persistent cough (n=4); pneumothorax (n=3), valve coughed out (n=2) and mucous plugging (n=4).

An in-press publication shows significant improvements post-procedure for FEV1 scores, lobe volume reduction and SGRQ outcomes.[41]

NALHN provided a published abstract to SAPACT in 2020 of the results from 11 patients which concludes that "LVR with EBV demonstrated improvement of 2 and 6 months lung function (FEV1, FVC, DLCO) and exercise capacity (6MWT) in patients with severe COPD in NAHLN. There was a reduction in pulmonary hyperinflation (RV) post-procedure. However, all of these measurements are not statistically significant ($P > 0.05$). Complication rates are minimal including pneumothorax and infections".[42] In total, the team at NALHN has treated 20 patients since 2016.

<u>Local and international guidance</u>

- COPD-X guidelines recommend that "endobronchial valves may be appropriate in highly selected patients with severe COPD and hyperinflation, if collateral ventilation can be excluded (intact fissure on imaging and Chartis negative during bronchoscopy)".[35]
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD 2018) states that: "In selected patients with heterogeneous or homogeneous hyperinflation refractory to optimised medical care, surgical or bronchoscopic modes of lung volume reduction (e.g. endobronchial one-way valves, lung coils or thermal ablation, may be considered… for patients with no collateral ventilation".[43]
- HealthPACT assessed endobronchial valves in 2017. At this time six RCTs were available for both valves. HealthPACT advised that "the evidence base describing the use of endobronchial valves remains immature. Data collected under the auspices of prospective evaluation clinical trials conducted in a highly selective group of patients should be encouraged. HealthPACT does not support public investment in endobronchial valves in routine clinical practice at this time."
- In 2020, NHS England concluded that "there is enough evidence to consider making treatments with both surgery and endobronchial duckbill valves available in centres with an experienced MDT [multidisciplinary team]". This follows on from a NICE review in 2017, which recommended the use of EBV following MDT review, in patients following pulmonary rehabilitation where there is no collateral ventilation, by clinicians with specific training in doing the procedure.[14]
    - Specific referral direction provided by NHS England for lung reduction surgery was:
        - Evidence of symptomatic hyperinflation due to emphysema with impaired quality of life. Medical Research Council (MRC) Dyspnoea Scale 3 or more
        - Non-smoker at least 4 months
        - Completion of a Pulmonary Rehabilitation programme
        - Six minute walk distance >140m or Incremental Shuttle Walk Test (ISWT) >80m
        - Forced Expiratory Volume in one second (FEV_1) <50% predicted
        - Carbon Monoxide Diffusion Capacity (DLco) or Carbon Monoxide Transfer Coefficient Kco > 20% predicted
        - Residual Volume (RV): Total Lung Capacity (TLC) > 55%
        - RV> 150%
        - $PaCO_2$<7KPa (partial pressure of carbon dioxide)
        - Body Mass Index (BMI)> 18
    - The MDT assessment included: "The use of quantitative lung perfusion scans and high-resolution computer tomography (HRCT) to determine the distribution of emphysema. The greater the clarity of target areas the

	better the likely outcome from treatment. An assessment of exercise ability, either shuttle walk test (SWT) or 6 minute walking distance (6MWD) to determine the required fitness for LVR or the need for further pulmonary rehabilitation. The calculation of predicted procedural risk using published indices of body mass index, airflow obstruction, dyspnoea, exercise capacity index (BODE) and Glenfield risk scoring. Either the St George's Respiratory questionnaire or the COPD Assessment Test (CAT) score should be measured as a baseline Quality of Life assessment". ○ Referral for EBV was: "Upper or lower lobe heterogeneous emphysema without collateral ventilation; residual volume >180%, TLco (transfer capacity of the lung, for the uptake of carbon monoxide)>20; BMI >18; previous thoracic surgery" • NHS Scotland also recommended the use of EBV "for patients with severe or very severe emphysema, despite optimal medical management, following MDT review, and with no collateral ventilation. Further, that this service be consolidated within a small number of centres via a unified national referral pathway to ensure equity of access".[44] • CADTH published a Review of Clinical Effectiveness of EBV in 2019. There was no formal recommendation. • The Ludwig Boltzmann Institute reviewed EBV in 2018 and concluded that EBV "is more effective but less safe than standard therapy in selected patients with severe emphysema. Inclusion in the service catalogue is only recommended with restrictions. It should only be performed in highly specialised centres by experienced clinical experts".
FINANCIAL CONSIDERATION	
Device costs	The device is listed on the Prosthesis List with a minimum benefit of $5,686. Local costs in public hospitals are reported as $[redacted] per valve (Application). The number of valves used per patient depends on patient anatomy; an average of three valves per patient is used. For public patients there is an agreed cap of $[redacted] per patient (personal communication). The console and catheter are provided free of charge by PulmonX. Procedure costs are recovered through AR-DRG E42 (bronchoscopy, taken from IHPA cost weight round 21, 2016-17): E42B: Minor complexity $[redacted] (average length of stay 1.4 days) E42A: Major complexity $[redacted] (average length of stay 7.9 days).
Value for Money	SA Health Due to limitations of available local data, a cost-effectiveness analysis of the use of EBVs in SA was not possible. Two cost-effectiveness analyses were identified, using data from the STELVIO trial from a Dutch perspective (Hartman 2018) and the VENT EU trial from a German perspective (Pietzsch 2014). The model structure was similar in both, with QALYs derived from quality of life as measured through the EQ-5D tool. The EQ-5D score at 6 months was through the patient questionnaire (Hartman 2018), or calculated based on SGRG outcomes (Pietzsch 2014). Clinical outcomes used in the models were similar in both analyses, and included number of catheters, number of Zephyr valves, exacerbations, pneumonia, pneumothorax, bronchoscopy with and without valve replacement. The mean per-patient difference between EBV and control patients was €16,721 (Hartman 2018). The incremental cost effectiveness ratio (ICER) at 5 years was similar in both studies at approximately €39,000 and 46,000 respectively.
Funding Approvals	Australian recommendations • EBVs have not been evaluated by the Medical Services Advisory Committee. It is likely that as the service was able to be provided under existing Medicare items, a separate submission was not undertaken. • EBVs are available on the Prosthesis List with a benefit of $5,686 (Zephyr PX001, Spiration OL081). • In 2017 HealthPACT advised that 'the evidence base describing the use of endobronchial valves remains immature. Data collected under the auspices of prospective evaluation clinical trials conducted in a highly selective group of patients should be encouraged. HealthPACT does not support public investment in endobronchial valves in routine clinical practice at this time.' • SAPACT undertook an evaluation summary of EBV in 2014. SAPACT concluded that the evidence was inconclusive, with concerns regarding valve migration, pneumothorax and device removal, and gaps in the evidence concerning long-term outcomes and uncertainty regarding hospital readmission. There was a recognition that a small number of patients may benefit from the use of endobronchial valves. The SAPACT recommendation was to participate in a clinical trial, and that endobronchial valves could be used on a case-by-case basis. International recommendations As discussed under "Suitability of Patient Group/Local and international guidance", the use of EBV is approved in England, Scotland and Austria.
FEASIBILITY OF ADOPTION	
Organizational Feasibility	In SA Health, sites will use existing staff and infrastructure. A statewide approach is required for patient selection, review and reporting, to ensure quality and patient equity. This procedure may be used provided that standard arrangements are in place for clinical governance, consent and audit by the LHN(s).
Credentialing and Competency	No credentialing issues were identified. The procedure should only be provided by clinicians with specific training and accreditation. Training and proctoring will be provided by the experienced MDT at CALHN. Clinician(s) should be appropriately credentialed and approved by the SA Health Credentialing and Scope of Practice Committee (refer to paragraph 3.4.3 New Clinical Procedures, Technologies and Treatments of the SA Health Credentialing

	Policy Directive).
CONSISTENCY WITH EXPECTED SOCIETAL/ ETHICAL/ LEGAL VALUES	
Values	The service is consistent with expected societal, ethical and legal values at this time. EBVs provide an option for certain patients where current therapies have become ineffective, and provide a less invasive alternative to surgical lung volume reduction.
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