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# Endobronchial Valves for the Management of Severe Emphysema

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Rapid Review

# Key Messages

## What Is the Issue?

- People with severe emphysema who do not experience relief with non-invasive therapies such as medication, physical activity, and smoking cessation may need advanced treatments.
- Endobronchial valves are an alternative therapy that may improve exercise capacity and quality of life, and are less invasive compared to lung reduction surgery or transplants.

## What Did We Do?

- A 2019 CADTH report summarized clinical effectiveness evidence for valves compared to standard care. CADTH sought to update this evidence with new clinical research and include information on cost-effectiveness, which was not part of the previous report.
- A research information specialist conducted a literature search of the peer-reviewed and grey literature with a search strategy focused on emphysema and endobronchial valves. The search was limited to English-language documents published since 2018. One reviewer screened articles for inclusion based on predefined criteria, critically appraised the included studies, and narratively summarized the findings.

## What Did We Find?

- We did not find systematic reviews or health technology assessments published since 2018 that contained clinical evidence not already captured in the 2019 CADTH report. Two RCTs provide updated clinical evidence for endobronchial valves compared to standard care, and 1 RCT contains evidence on valves compared to lung surgery.
- The evidence suggests that valves may improve lung function, breathing ability, and physical activity in middle-aged and older adults with emphysema compared to standard care; the effect on quality of life and safety is unclear. The previous CADTH report showed lung function, breathing ability, physical activity, and quality of life were favourable for valve treatment compared to standard care.
- The previous CADTH report showed that valves resulted in harmful outcomes compared to standard care; however, in the current review, safety was difficult to assess due to poor reporting.
- When comparing valves to lung surgery, lung surgery may improve quality of life compared to valves; other outcomes did not favour one therapy over another.

# Key Messages

- For cost-effectiveness, valves may be favourable compared to standard medical care, while their cost-effectiveness compared to lung volume reduction surgery is unclear.
- One study was conducted in Canada, and no studies were conducted in children and younger adults.

## What Does it Mean?

- Endobronchial valves are a potential therapy for people with severe emphysema with some favourable clinical and cost outcomes, but the evidence for their safety is unclear.
- Decision-makers may wish to consider the balance of favourable and harmful effects in existing evidence before more high-quality evidence in Canada, especially for safety, is available.

# Table of Contents

## List of Tables



## List of Figures

# Abbreviations

| | |
|---|---|
| **6MWD** | 6-minute walking distance |
| **CAT** | COPD assessment test |
| **COPD** | chronic obstructive pulmonary disease |
| **EQ5D** | EuroQol5-Dimensions |
| **$FEV_1$** | forced expiratory volume in 1 second |
| **ICER** | incremental cost-effectiveness ratio |
| **LVRS** | lung volume reduction surgery |
| **QALY** | quality-adjusted life-year |
| **RCT** | randomized controlled trial |
| **SGRQ** | St. George's Respiratory Questionnaire |

## Research Questions

1. What is the clinical effectiveness of endobronchial valves for people living with severe emphysema?
2. What is the cost-effectiveness of endobronchial valves for people living with severe emphysema?

## Context and Policy Issues

### What Is Emphysema?

Emphysema is one of a group of lung conditions collectively called chronic obstructive pulmonary disease (COPD)[1], which is a disease that worsens over time and causes breathing difficulties, a reduction in quality of life, and potentially serious complications if untreated.[1,2] In emphysema specifically, airspaces enlarge, destroying the lungs' alveoli, affecting air exchange, reducing lung function and resulting in shortness of breath.[1,3,4]

Globally, COPD is the third leading cause of death and the seventh leading cause of poor health.[5] In Canada, 10% of adults and close to 20% of older adults experience the effects of COPD.[6] In Canada, trends over time show that both the prevalence of COPD and hospital admissions for COPD have been rising each year.[6] Across Canadian provinces, COPD increased from 7.2% to 7.6% between 2019 and 2020 for adults aged 65 years and above.[7] COPD hospitalizations in large Canadian cities for people under 75 years increased over time from 83 per 100,000 between 2006 to 2010 to 86 per 100,000 people between 2011 to 2015.[8] In Ontario specifically, COPD prevalence increased from 2006 to 2016 in younger and middle-aged adults.[9] In Canada, the population level direct annual costs of COPD range from CA$182 to CA$254 million for managing moderate exacerbation and CA$469 to CA$642 million for managing severe exacerbations.[10]

The social determinants of health affect how COPD manifests[6] and may disproportionately affect equity-deserving groups who face barriers to health care access. According to the Canadian Institute for Health Information, between 2011 and 2015, people with COPD in the lowest income quintile had 5.7 times higher hospital admissions compared to those in the highest income quintile;[6] this value was 4.5 between 2006 and 2010.[8] A study in Toronto, Ontario showed that people with COPD and limited English proficiency were more likely to be readmitted to the hospital.[6]

### What Is Endobronchial Valve Treatment?

Although there is no cure for COPD, medication, procedures, vaccinations, physical activity, and reducing smoke exposure can help people manage it.[5] People with more serious emphysema who have tried these methods without success may need lung volume reduction surgery (LVRS), bronchoscopic lung volume reduction (using valves, coils, sealants or vapour ablation), or lung transplant.[11]

Endobronchial valve treatment is a technique where one-way valves are placed in the lung to reduce trapped air and hyperinflation, to improve a patient's exercise capacity and quality of life.[3] Endobronchial valves may be preferred because they are less invasive than LVRS or transplants, involve no stitches or incisions, which reduces the chance of infections, have shorter recovery times, may be less painful, and are removable;[12]

however there can also be complications such as pneumothorax, hypoxemia, central airway distortion, pneumonia, or COPD exacerbation.[3]

In the US, 2 endobronchial valves are US FDA-approved; in Canada, 1 of these has a Health Canada medical device licence.[13]

### Why Is it Important to Do This Review?

Respirologists in Canada are increasingly interested in the applicability of endobronchial valves as an alternative therapy for people with severe emphysema who have tried medication. In 2019, CADTH published a Rapid Review summarizing the clinical effectiveness of endobronchial valves from literature published between 2014 and 2019.[14] The current report aims to update this information to include any new information on clinical effectiveness published since then. In addition, the current report includes a second research question to determine the cost-effectiveness of endobronchial valves. This will provide decision-makers with updated information on clinical effectiveness to review together with the previous CADTH report [14] and refer to more recent summarized information on cost-effectiveness.

### Objectives

To support decision-makers on the clinical effectiveness and the cost-effectiveness of endobronchial valves for people living with severe emphysema.

## Methods

### Literature Search Methods

The literature search strategy used in this report is built upon one developed for a previous CADTH report.[14] For the current report, an information specialist conducted a literature search on key resources, including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were emphysema and endobronchial valves. The search was completed on November 25, 2023 and limited to English-language documents published since January 1, 2018.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first screening level, we reviewed titles and abstracts and then retrieved and assessed potentially relevant full-text articles for inclusion. Since this report updates evidence from a previous CADTH report,[14] we only included articles if they were made available since the previous search date and were not included in the 2019 CADTH report.[14] We selected the final set of full-text articles based on the inclusion criteria in Table 1.

### Table 1: Selection Criteria

| Criteria | Description |
|---|---|
| **Population** | People living with severe emphysema who have not responded to medication |
| **Intervention** | Bronchoscopic lung volume reduction treatment with endobronchial valves |
| **Comparator** | Standard of care (e.g., lung volume reduction surgery, lung transplant, drug therapy, pulmonary rehabilitation, nutrition therapy, oxygen, palliative care) |
| **Outcomes** | Q1: Clinical effectiveness (e.g., change in lung function [$FEV_1$], change in exercise capacity [e.g., six-minute walk test], physical activity, dyspnea, disease progression, patient hospitalization, quality of life, patient satisfaction) and safety (e.g., adverse events, mortality)<br>Q2: Cost-effectiveness (e.g., cost per QALY gained, ICER, cost per adverse events avoided) |
| **Study designs** | Health technology assessments, systematic reviews, randomized controlled trials, economic evaluations |

$FEV_1$ = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

### Exclusion Criteria

We excluded articles if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were about interventions applied after endobronchial valve failure. We excluded systematic reviews or randomized controlled trials (RCTs) if the evidence was already captured in the previous CADTH report.[14]

### Critical Appraisal of Individual Studies

One reviewer critically appraised RCTs using the Downs and Black checklist[15] and economic evaluations using the Drummond checklist.[16] We did not calculate summary scores for the included studies; rather, we narratively describe the strengths and limitations of each included publication in this report.

### Equity Considerations

CADTH recognizes the need for and importance of equity considerations in health technology reviews. In this Rapid Review, we used PROGRESS-Plus[17] to guide data extraction and report writing. We did not explicitly search for information related to inequity or equity-deserving groups and their access to endobronchial valves.

## Summary of Evidence

### Quantity of Research Available

This report includes evidence from 3 RCTs[18-20] for clinical effectiveness and 2 economic evaluations[21,22] for cost-effectiveness. We did not identify any systematic reviews or health technology assessments that met the inclusion criteria and whose evidence was not already summarized in the 2019 CADTH report.[14]

Appendix 1 presents the PRISMA[23] flow chart of the study selection and Appendix 5 includes additional references of potential interest.

## Summary of Study Characteristics

Appendix 2 contains detailed characteristics of included publications.

### Included Studies for Clinical Effectiveness

Of the 3 included RCTs,[18-20] 1[18] is from the single-blind CELEB trial, which compared endobronchial valves to LVRS and was not reported in the previous CADTH report.[14] Two RCTs[19,20] reported longer term follow-up from the open-label trials EMPROVE and IMPACT reported in the previous CADTH report[14] and each used different valve types compared to standard care. The 3 RCTs[18-20] were all conducted in North American or European centres and the mean population age was between 64.0 and 66.7 years.

The RCTs included 3 different clinical populations: heterogeneous emphysema and no collateral ventilation,[18] severe heterogeneous emphysema with little-to-no collateral ventilation,[19] and severe homogeneous emphysema with little-to-no collateral ventilation.[20] Although 1 study[18] did not explicitly describe emphysema as severe, the study population had "significant hyperinflation" and was therefore included in this report.

Two articles reported gender,[18,19,] which were 41.2% to 53.7% females and 46.3% to 58.8% males across study groups. These 2 articles[18,19] did not report how sex and gender were defined or measured and did not report on other genders. The third included article[20] did not report sex or gender at all. One study[18] included self-reported ethnicity of 100% white, 0% Middle Eastern in the intervention group and 97.6% white, 2.4% Middle Eastern in the comparator group; the other studies did not report on race or ethnicity. No studies reported on other PROGRESS-Plus criteria,[1,7] such as place of residence, occupation, religion, education, socioeconomic status, social capital, or disability status.

Outcomes across studies included:

- Effectiveness: 6 minute walk distance (6MWD),[20] body mass index,[18] BODE scores (composite measure of body composition, airway obstruction, dyspnea, and exercise capacity),[18,20] COPD assessment test (CAT) scores,[18-20] clinical PROactive physical activity in COPD scores,[18] dyspnea scores,[18-20] forced expiratory volume in 1 second ($FEV_1$),[18-20] $FEV_1$ responders,[19,20] incremental shuttle walk test,[18] quality of well-being scores,[19] residual volume (RV) in lungs,[18,20] 36-Item Short Form Health Survey physical component summary,[19] and St. George's Respiratory Questionnaire (SGRQ) scores[19,20]
- Safety: adverse events,[18,20] COPD exacerbations,[19,20] death,[18-20] hospitalization,[18,20] pneumothorax,[18-20] serious adverse events,[19,20] and subcutaneous emphysema.[18]

### Included Studies for Cost-Effectiveness

Both cost-effectiveness studies[21,22] evaluated the same endobronchial valve type in people with severe emphysema. One study[22] compared the cost-effectiveness of endobronchial valves to standard care while the other study[21] compared endobronchial valves to LVRS.

The study[21] comparing valves to LVRS used a within-study time horizon (mean 81 days) and was from the payer's perspective (using health insurance and a service-providing hospital in in Switzerland). Data on effectiveness were from 1 retrospective study performed in a single centre in Switzerland, with the costs calculated based on the SwissDRG system during hospital stay and the number of valves implanted.[21] The

study enrolled 67 patients with pulmonary emphysema and hyperinflation; the intervention group had a mean age of 70 years and were 51% female, while the surgical group had a mean age of 66 years and were 37% male.[21] Cost-effectiveness was evaluated based on 3 clinical outcomes: either $FEV_1$, residual volume, or 6MWD.[21] The authors reported the incremental cost-effectiveness ratios (ICERs) for endobronchial valves compared to LVRS for each clinical outcome, however, the main assumptions of the cost-effectiveness models were not clearly reported.[21]

The study[22] comparing valves to standard care used 2 time horizons (6 months and 10 years) and was from the Dutch hospital and health insurance perspective. The study enrolled 68 people with severe emphysema from the STELVIO trial. The STELVIO trial results were included in a systematic review captured in the previous CADTH report.[14] The mean age was 59 years and 68% were female.[22] The effectiveness of the intervention was measured using data from the STELVIO trial, which used the EuroQol5-Dimensions (EQ5D) and the SGRQ to measure health-related quality of life, and the 6MWD to measure exercise capacity.[22] Dutch tariffs were used to determine the utility values corresponding to EQ5D scores.[22] Additionally, an established algorithm was used to predict EQ5D utility scores using the SGRQ score.[22] The economic evaluation only included direct medical costs and was calculated from the perspective of Dutch health insurance at the 2016 price level.[22] ICERs per quality-adjusted life-year (QALY) gained were calculated at 6 months and 10 years after the intervention.[22] The cost-effectiveness analysis assumed that there would be no transitions on disease progression after 6 months from the intervention until death.[22] The Markov model for the long-term time horizon (10-years) was initialized with 100 patients in each group, and the average age of patients at the start of the simulation was 50 years.[22]

## Summary of Critical Appraisal

Appendix 3 contains detailed about strengths and limitations of included publications.

### Clinical Effectiveness Studies

The 3 RCTs'[18-20] strengths included clear reporting and descriptions of objectives, participant eligibility criteria, trial registration, interventions, comparators, outcomes, loss to follow-up information, and adverse events. The trials[18-20] were also randomized and authors reported that study groups were comparable. The primary outcome in 2 trials[19,20] was $FEV_1$, a measure of lung function using a spirometer machine[24] and in 1 trial was BODE.[18]

In 1 RCT,[18], the primary outcome assessor was blinded to study assignment; however, a limitation was that the participants and trial coordinator were not blinded. The other 2 RCTs[19,20] had no blinding. It may have been difficult to blind participants or researchers since the intervention involved a specific procedure; however, knowledge of study assignment may have introduced performance bias (e.g., participants being treated differently if researchers knew what treatment they received, participants self-reporting outcomes differently if they knew what study group they were in) or detection bias in the 2 RCTs[19,20] where outcomes assessors were not blinded.

Although the 3 RCTs[18-20] took place across multiple centres, which may have the potential to include more variable populations, results from each specific study may not be generalizable to people who do not

match the specific population in each trial based on age, emphysema type, comorbidity exclusion criteria, or collateral ventilation in lung alveoli, which is a limitation. For example, the 3 RCTs[18-20] were conducted in middle-aged and older adults, so the results are not generalizable to children or younger adults.

Other limitations were inadequate power for safety outcomes in the IMPACT trial results,[20] a nonvalidated primary outcome in the CELEB trial (as indicated by study authors),[18] missing outcome data due to delays in study visits because of the COVID-19 pandemic in the CELEB trial,[18] variability in post-intervention care for participants in the CELEB trial,[18] and patient-reported outcomes such as CAT score and dyspnea in all included trials,[18-20] which may have biased outcomes since participants were not blinded. The CELEB trial[18] addressed missing data by imputation and sensitivity analyses, showing similar results for BODE and a smaller difference between groups for CAT score.

There may have been potential conflicts of interest because multiple study authors from 2 RCTs[18,20] received funding or resources from PulmonX, a manufacturer of endobronchial valves, and in the third RCT,[19] the funder, Olympus Corporation, was involved in study aspects such as trial design, review, and clarification of study methods. It is unclear whether this affects results for the trials[19,20] that showed favourable effects for valves.

### Cost-Effectiveness Studies

The economic evaluation studies[21,22] outlined their research questions, the form of economic evaluation, and the analysis perspectives. The study design, data collection, and outcome measures were also well-defined.[21,22] The authors of the 2 studies[21,22] presented their conclusions with appropriate caveats. The directions of the intervention effectiveness measures were consistent with the previous CADTH report[14] and the current report. However, the magnitudes of the effectiveness were based on single studies with small sample sizes (n = 67 for the retrospective study and n = 68 for the RCT) rather than systematic reviews or meta-analyses of estimates from multiple sources.[21,22] Additionally, the 2 studies[21,22] lacked details on currency price adjustments for inflation or conversion. Economic evaluation studies were based on the payer's perspectives in Switzerland[21] or the Netherlands[22] and may not apply to the health care system in Canada.

The study[21] comparing vales to LVRS lacks details on the cost-effectiveness models and model assumptions. The statistical analysis for effectiveness did not account for possible confounding variables, and the follow-up for effectiveness data differed between the intervention and control groups (mean 63 versus 103 days, P = 0.0001).[21] Additionally, the quantities of resources were not reported separately from costs, and sensitivity analyses were not performed.[21] The disaggregated form of the reported ICERs for $FEV_1$, residual volume, and 6MWD were not provided.[21] The time horizon or observation period for cost-effectiveness may be considered relatively short (mean 81 days) when considering pulmonary emphysema as a chronic condition.[21]

In the other study,[22] cost-effectiveness models only considered direct medical costs and assumed no transitions between disease progression 6 months after treatment.[22] The methods for estimating quantities and unit costs were not provided.[22] The effectiveness estimates were taken from the STELVIO trial, which

was an RCT, however the baseline measures for EQ5D score were not well-balanced between the intervention and comparator groups; the comparator group had a higher score than the intervention group meaning the ICERs (which were based on the EQ5D scores) were not reliable, particularly at 6 months.[22]

## Summary of Findings

Appendix 4 presents the main study findings.

### Clinical Effectiveness of Endobronchial Valves Compared to LVRS

No outcomes showed effectiveness for valves compared to LVRS.

The following outcome showed effectiveness for LVRS compared to valves:

- CAT (1 RCT)[18]

The following outcomes showed little-to-no difference between valves and LVRS:

- $FEV_1$ (1 RCT)[18]
- residual volume (1 RCT)[18]
- BODE (1 RCT)[18]
- body mass index (1 RCT)[18]
- dyspnea (1 RCT)[18]
- clinical PROactive physical activity in COPD score (1 RCT)[18]
- incremental shuttle walk test (1 RCT).[18]

### Clinical Effectiveness of Endobronchial Valves Compared to Standard Care

The following outcomes showed effectiveness for valves compared to standard care:

- $FEV_1$ (2 RCTs, each using different valve types)[19,20]
- $FEV_1$ responders who show greater than 12% improvement (1 RCT)[20]
- residual volume (1 RCT)[20]
- BODE (1 RCT)[20]
- dyspnea (2 RCTs each using different valve types)[19,20]
- 6MWD (1 RCT)[20]
- SGRQ score (2 RCTs each using different valve types).[19,20]

The following outcomes showed little-to-no difference between valves and standard care:

- $FEV_1$ responders who show greater than 15% improvement (1 RCT)[19]
- quality of well-being score (1 RCT)[19]
- the 36-Item Short Form Health Survey physical component summary (1 RCT)[19]

The following outcomes showed mixed results for valves and standard care:

- CAT: In 1 RCT,[19] CAT scores favoured 1 type of valve over standard care. In a third RCT,[20] there was little-to-no difference between another type of valve and standard care.

### Clinical Safety of Endobronchial Valves

Where statistical significance was reported in studies, safety outcomes showed little-to-no difference between endobronchial vales and standard care or LVRS for adverse events,[18] COPD exacerbations,[20] death,[19] pneumothorax,[19,20] or serious adverse events.[19,20] None of these safety outcomes were reported with uncertainty in the estimates or in individual groups, so the precision of these findings is unknown, and no treatment effects comparing intervention and comparator groups were provided, only the P values.

### Cost-Effectiveness of Endobronchial Valves Compared to LVRS

One study[21] reported the ICERs for endobronchial valves compared to LVRS, but these numbers are difficult to interpret. We noted that the cost per unit of $FEV_1$ improvement was higher in the endobronchial valves group compared to LVRS, while the cost per residual volume (mL) and 6MWD (metres) was lower in the endobronchial valves group compared to LVRS.[21] The results indicate that the endobronchial intervention may not be cost-effective according to $FEV_1$.It could be a cost-effective alternative to LVRS based on residual volume and 6MWD; however, the willingness-to-pay threshold was not reported.[21]

### Cost-Effectiveness of Endobronchial Valves Compared to Standard Care

Endobronchial valves have a favourable cost-effectiveness profile compared to standard care, particularly for the long-time horizon of 10 years.[22] The assumption of a discount increased the ICER-Cost, which indicates the endobronchial valves were less cost-effective after the discount because the discount assumption had a greater effect on life-years than on costs.[22] The details of the cost-effectiveness profile after considering the discount (annual discount rate of 4%) are:

- ICER-Cost per QALY gained (discounted for 5 or 10 years) for endobronchial valves compared to standard care:[22]
  - The ICER was not considered reliable at 6 months (due to unbalanced baseline), was €41,870 at 5 years and was €24,255 at 10 years using EQ5D
  - €205,129 at 1 year, €42,775 at 5 years and € 25,827 at 10 years using SGRQ
- Cost per life-years (discounted)[22]
  - €79 100 at 5 years and €34 883 at 10 years.

## Limitations

The clinical and cost-effectiveness studies were conducted in adults and older adults, so the applicability to younger adults and children, given that more younger adults have been developing COPD over time, is unclear.[9] One clinical study was conducted in Canada,[19] while the rest were conducted in the US and European countries; similarly, the cost-effectiveness studies were based on payers' perspectives in Switzerland[21] and the Netherlands.[22] As a whole, the generalizability of these findings to settings in Canada is unknown because of where the research was conducted and because Canada does not currently offer multiple valve types for treatment.

The clinical studies all had sample sizes of less than 115 total, and no intervention or comparator groups had more than 80 participants; the magnitude of the treatment effects reported may not be as precise as they would be if the studies had larger sample sizes. Another limitation of the clinical studies was the variety of ways that effectiveness or safety were measured in the included studies. The evidence included 13 measurements or scales for effectiveness and 7 measures for safety. Given the variability in measurement tools and their results, it is unclear how some evidence can be compared across studies using different outcome measurements. Clinical studies also had poor reporting of safety outcomes; study authors provided P values for the difference between groups but no treatment effects comparing groups were reported.

The quality of the economic evaluation studies was low; 1 study[21] had unclear models and assumptions in their cost-effectiveness analysis, while the other study[22] assumed that the COPD severity would remain the same 6 months after the intervention. We are unsure how these limitations affect the certainty or direction of the evidence.

No clinical or economic studies described how gender or sex were defined and did not include gender identities outside of male and female. We retained the original term that the study authors used when describing sex or gender. One clinical study reported on ethnicity for a population that was more than 97% white in both intervention and comparator groups, and no clinical or economic studies reported on other PROGRESS-Plus criteria,[17] or discussed these criteria in the context of the results. Because of this limited information, the generalizability of the evidence is unclear and potential health inequities are unknown. It is unclear whether the study populations included people from equity-deserving groups or whether these groups have access to the intervention. This Rapid Review did neither include a formal evaluation of the equity considerations for people with severe emphysema who may be eligible for receiving endobronchial valve treatment, nor did it search explicitly for information related to inequity or groups with this condition that may be underserved. PROGRESS-plus[17] was used to guide our data extraction and discussion of whether dimensions of equity were reported and where there may be gaps in the included evidence.

## Conclusions and Implications for Decision- or Policy-Making

We conducted a Rapid Review to update evidence from a 2019 CADTH report[13] and provide new information on the clinical effectiveness of endobronchial valves for people with severe emphysema; we also included economic evaluations to determine the cost-effectiveness of endobronchial valves, which was not reported on in the previous review. We found 5 studies with evidence published since 2018; 3 RCTs[18-20] on clinical effectiveness and 2 economic evaluations[21,22] on cost-effectiveness.

### Endobronchial Valve Evidence

This Rapid Review shows that different valve types are effective compared to standard care based on lung function, breathing ability, and physical activity measured through a walking test. One valve type[19] showed little-to-no difference in well-being, lung function responders, and survey-measured physical activity. The previous CADTH review[13] showed similar results; lung function, breathing ability, and physical activity were favourable for valves compared to standard care. The current review suggests that quality of life measured

through CAT scores has mixed results, with 1 valve type[19] being favoured over standard care and another valve[20] showing little-to-no difference between groups; the previous CADTH review[13] showed favourable results for quality of life outcomes for different valves compared to standard care. The previous CADTH review[13] showed increased adverse events in valve groups compared to standard care; however, in the current review, safety was difficult to assess due to poor reporting.

The current review suggests that there is no evidence for the effectiveness of 1 valve type[18] compared to LVRS; quality of life was more favourable in the LVRS group compared to the valve group, however all other outcomes (lung function, body composition, breathing difficulty, physical activity) showed little-to-no difference.[18]

Of the 2 economic evaluations identified for the same valve type, 1 study[22] showed favourable cost-effectiveness compared to standard care, particularly at a longer time horizon, and another study[21] showed valves were not cost-effective compared to LVRS based on 1 lung function outcome, but a cost-effective alternative to LVRS based on a different lung function outcome and a physical activity outcome based on a walking test.

Across the 5 included studies, only 1 RCT had participants in Canada;[19] generalizability of the evidence to the Canadian context is unclear. All studies included research conducted in middle-aged and older adults; it is unclear whether the findings apply to younger age groups. Similarly, since there was limited information on equity-deserving groups, it is unclear whether they have access to the intervention and how it might affect them. All studies had small sizes so it is unknown whether the treatment effects could have been more precise with larger sample sizes. While 1 RCT had a blinded outcome assessor,[18] participants across all studies were not blind to study assignment, and it is unclear how this may have affected outcome measurement.

## Considerations for Future Research

Further high-quality clinical research (including larger sample sizes, better safety outcome reporting, and blinding where feasible) may be needed in the following areas: different valve types compared to LVRS, inclusion of younger populations, implementation of more research in Canada, and clear inclusion of equity-deserving groups. The following factors may need to be considered in future economic evaluations: cost accounting for currency price changes for inflation or conversion, efficacy based on a high-quality systematic review(s), acceptable and unambiguous model assumptions, and inclusion of broader perspectives such as the social perspective.

## Implications for Clinical Practice

Decision-makers can use CADTH evidence from the current and 2019[13] reports to assess the clinical- and cost-effectiveness of endobronchial valves compared to standard care or LVRS, keeping in mind the safety risks reported in the previous CADTH report[13] and unclear safety outcomes in the current report. Health care providers may also wish to consider the training involved with the valve procedure, how patients are selected for treatment, the resources required to conduct the procedure (e.g., number of valves, time required, hospital stay), patient preferences, and safety risks.[13] Given Health Canada's existing licence for 1 valve

type,[13] there may be an interest in considering this treatment for people with severe emphysema who have not experienced favourable outcomes from non-invasive therapies such as medication, physical activity, or smoking reduction.

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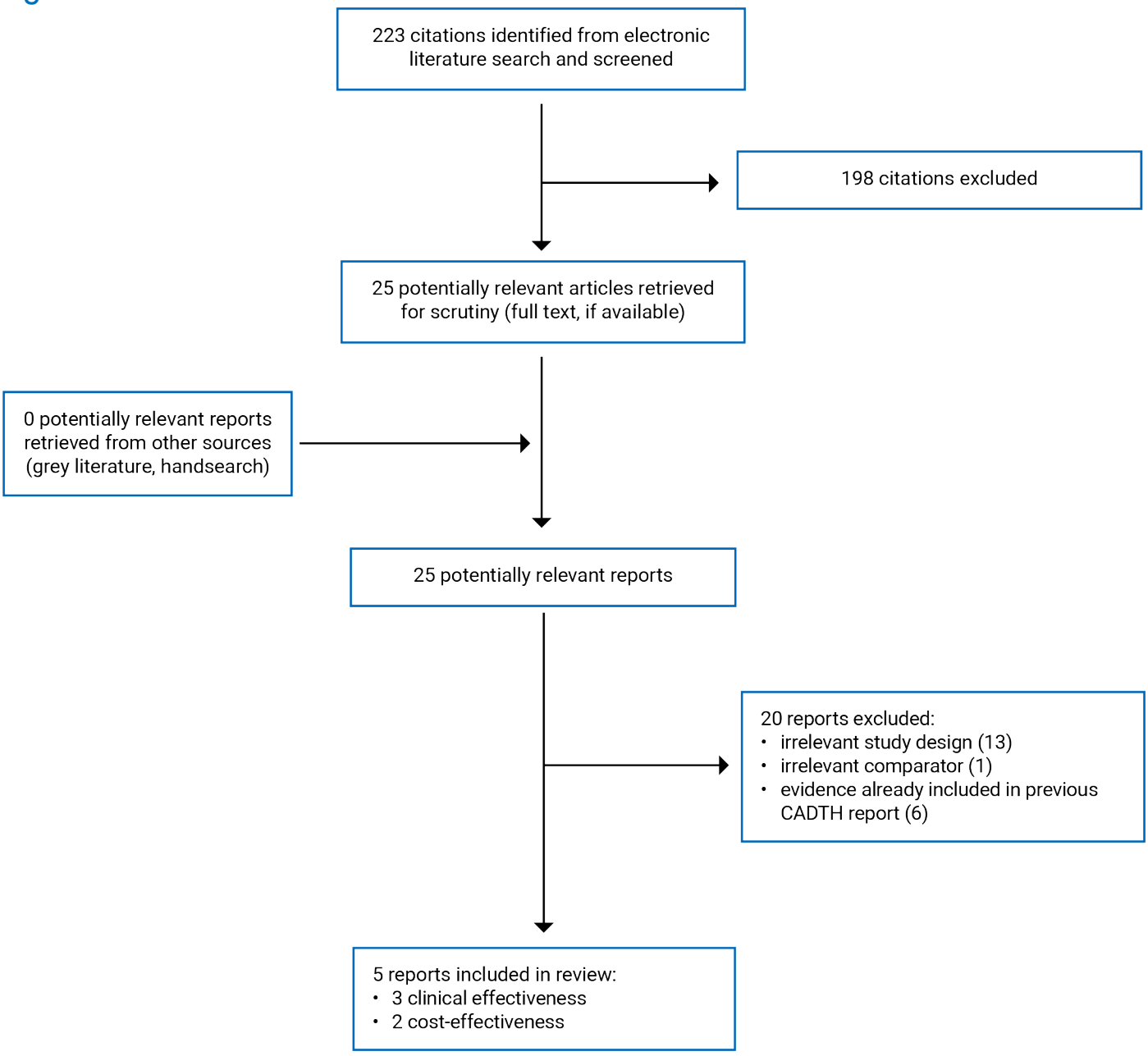
# Appendix 1: Selection of Included Studies

## Figure 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

## Table 2: Characteristics of Multicentre Randomized Controlled Trials

| Study citation, country, funding source | Study design details, trial name | Population characteristics | Intervention and comparator | Clinical outcomes, length of follow-up |
|---|---|---|---|---|
| **Buttery et al. (2023)**[18]<br>England, Scotland<br>**Funding source:** National Institute for Health Research,<br>Research for Patient Benefit Programme | Single-blind, parallel-group, superiority<br>CELEB | Adults with heterogeneous emphysema and no collateral ventilation in lung alveoli<br>**Age:**[a] mean 64 vs. 65.2 years<br>**Sex or gender:**[a] 42.6% vs. 53.7% female, 57.4% vs. 46.3% male, others NR<br>**Race or ethnicity:**[a] 100% vs. 97.6% white, 0% vs. 2.4% Middle Eastern, others NR<br>**SES:** NR | **Intervention (n = 47):**<br>Endobronchial valve<br>**Comparator (n = 41):**<br>Lung volume reduction surgery | **Primary outcome:** BODE<br>**Secondary outcomes:** AEs, body composition, death, dyspnea, $FEV_1$, hospitalization, physical activity, pneumothorax, quality of life, residual volume, subcutaneous emphysema<br>**Follow-up:** 12 months |
| **Criner et al. (2023)**[19]<br>Canada, US<br>**Funding source:** Olympus Corporation | Open-label<br>EMPROVE | Adults ≥ 40 years with severe heterogeneous emphysema and little-to-no collateral ventilation in lung alveoli<br>**Age:**[a] mean 65.1 vs. 66.7 years<br>**Sex or gender:**[a] 51.3% vs. 41.2% female, 48.8% vs. 58.8% male, others NR<br>**Race or ethnicity:** NR<br>**SES:** NR | **Intervention (n = 80):**<br>Endobronchial valve<br>**Comparator (n = 34):**<br>Standard care (COPD medication, oxygen use, pulmonary rehabilitation) | **Primary outcome:** $FEV_1$<br>**Secondary outcomes:** COPD exacerbations, death, dyspnea, quality of life, physical activity, pneumothorax, serious AEs, well-being<br>**Follow-up:** 24 months |
| **Eberhardt et al. (2021)**[20]<br>Austria, Germany, the Netherlands<br>**Funding source:** PulmonX Corporation, US | Open-label, one-way crossover<br>IMPACT | Adults ≥ 40 years with severe homogeneous emphysema and little-to-no collateral ventilation in lung alveoli<br>**Age:**[a] mean 64.3 vs. 63.2 years<br>**Sex or gender:** NR<br>**Race or ethnicity:** NR<br>**SES:** NR | **Intervention (n = 39):**<br>Endobronchial valve<br>**Comparator (n = 44):**<br>Standard care | **Primary outcome:** $FEV_1$<br>**Secondary outcomes:** AEs, BODE, COPD exacerbations, death, dyspnea, hospitalization, physical activity, pneumothorax, quality of life, residual volume, serious AEs, well-being<br>**Follow-up:** 6 months |

AE = adverse event; COPD = chronic obstructive pulmonary disease; $FEV_1$ = forced expiratory volume in 1 second; BODE = body composition, airway obstruction, dyspnea and exercise capacity; NR = not reported; SES = socioeconomic status.

[a]Intervention group vs. comparator group, respectively.

## Table 3: Characteristics of Economic Evaluations

| Study citation country, funding source | Type of analysis, time horizon, perspective | Population characteristics | Intervention and comparator | Approach | Source of clinical, cost, and utility data used in analysis | Main assumptions |
|---|---|---|---|---|---|---|
| **Franzen et al. (2022)**[21]<br>Switzerland<br>**Funding source:** Authors declared no funding related to this article | **Type:** CEA based on a retrospective study<br>**Time horizon:** within-study horizon (mean 81 days)<br>**Perspective:** the payer from basic, private or semiprivate health insurance and service-providing hospital (UHZ) | Adults with severe or very severe COPD, pulmonary emphysema, and hyperinflation<br>**Age:**[a] mean 70 vs. 66 years<br>**Sex:**[a] 51.4% vs. 36.7% female, 48.6% vs. 63.3% male, others NR<br>**Race or ethnicity:** NR<br>**SES:** NR | **Intervention (n = 37):**<br>Endobronchial valves<br>**Comparator (n = 67):**<br>Lung volume reduction surgery | Economic evaluations were conducted according to CHEERS and was not clearly reported.<br>Outcome measures: cost-per-effectiveness level, ICERs.<br>A modified cost-effectiveness diagram using a 4-field matric was provided. | Total revenues or cost unit accounting derived from SwissDRG during the hospital stay in the context of lung volume reduction. The cost of valves implanted was considered.<br>Effectiveness was collected from the retrospective parallel cohort study on $FEV_1$, residual volume, and 6MWD.<br>The cost-per-effectiveness levels were calculated. | The models and the assumptions made for the cost-effectiveness analyses are unclear. |
| **Hartman et al. (2018)**[22]<br>the Netherlands<br>**Funding source:** the Netherlands Organization for Health Research and Development | **Type:** CEA based on the STELVIO RCT<br>**Time horizon**: short-term: 6 months; long-term: 10 years<br>**Perspective**: Dutch hospital and health insurance | Patients with severe emphysema<br>N = 68<br>**Age:**[b] 59 (9) years<br>**Sex:** 68% female, others NR<br>**Race or ethnicity:** NR<br>**SES:** NR | **Intervention:**<br>Endobronchial valves<br>**Comparator**: Standard care | CEA for short-term and long-term using a Markov simulation model up to 10 years comparing valves to standard care in patients with severe emphysema in the Dutch health care system.<br>Outcome measures: costs per additional QALY; ICERs. | The analysis only included direct medical costs. Prices were calculated from the perspective of Dutch health insurance at the 2016 price level.<br>Treatment effectiveness on quality of life was measured using EQ5D and SGRQ, exercise capacity using 6MWD, utility values were based on Dutch tariffs. | Patients were distributed across GOLD stages in line with the RCT population.<br>There were no transitions between the GOLD stages 6 months after the intervention until death.<br>Markov model was initialized with 100 patients in each group. |

| Study citation country, funding source | Type of analysis, time horizon, perspective | Population characteristics | Intervention and comparator | Approach | Source of clinical, cost, and utility data used in analysis | Main assumptions |
|---|---|---|---|---|---|---|
| | | | | | Bootstrapping analyses were conducted to evaluate uncertainty. | Average patient age at simulation start was 50 years. |

6MWD = 6 minute walk distance; CEA = cost-effective analysis; CHEERS = Consolidated Health Economic Evaluation Reporting Standards; COPD = chronic obstructive pulmonary disease; EQ5D = EuroQol 5 Dimension; $FEV_1$ = forced expiratory volume in 1 second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICER = incremental cost-effectiveness ratio; NR = not reported; QALY = quality-adjusted life-year; RCT = randomized controlled trials; SGRQ = St. George's Respiratory Questionnaire; UHZ = University Hospital Zurich.

[a]Intervention group vs. comparator group, respectively.

[b]Mean (SD).

# Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

## Table 4: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[15]

| Strengths | Limitations |
|---|---|
| **Buttery et al. (2023)[18]** | |
| Authors described the objectives, main outcomes, participant criteria, interventions, baseline characteristics, and main findings.<br>Authors provided random variability of the data, number and reasons for loss to follow-up, and data on adverse events.<br>Authors reported actual P values for outcomes.<br>The person who collected primary outcome data was blind to participants' study assignment.<br>Authors conducted appropriate statistical analyses using an intention-to-treat approach and accounted for loss to follow-up using sensitivity analyses.<br>Participants were randomized to intervention and comparator groups and authors reported that the groups were well-matched.<br>Authors indicated that the study was adequately powered to detect a clinically important effect. | Authors indicated that participants were not representative of all people considered for lung volume reduction, only those eligible for both endobronchial valves and lung reduction surgery.<br>Participants and the trial coordinator were unblinded.<br>Some participants dropped out after being told to which intervention group they were randomized. Other participants crossed over from the intervention to the comparator group and vice versa.<br>Authors indicated that the primary outcome, the BODE score, has not been validated for lung reduction and that the CAT score measurement could have been biased because participants knew which intervention they received.<br>Some outcome data were missing; data collection visits were delayed because of the COVID-19 pandemic.<br>Authors noted that postdischarge care varied across participants since post-intervention rehabilitation was not recorded and this may have affected outcomes.<br>Several authors received funds or resources from pharmaceutical or health care companies including PulmonX, manufacturer of endobronchial valves; the publication reported that the funder had no role in study design, data collection, analysis, interpretation, or writing. |
| **Criner et al. (2023)[19]** | |
| Authors described the objectives, main outcomes, participant criteria, interventions, baseline characteristics, and main findings.<br>Authors provided random variability of the data, number and reasons for loss to follow-up, and data on adverse events.<br>Authors reported actual P values for outcomes.<br>Authors conducted appropriate statistical analyses and performed subgroup analyses to investigate survivorship bias.<br>Participants were randomized to intervention and comparator groups and authors reported that the groups were comparable. | The study was unblinded.<br>The primary outcome was $FEV_1$, which is an objective measure.<br>It is unclear whether the study had sufficient power to detect a clinically important effect.<br>Results may not be generalizable to people under 40 years old who do not have severe heterogeneous emphysema and little-to-no collateral ventilation.<br>The study funder, Olympus Corporation, was involved in the trial design, review, and clarification of study methods. |
| **Eberhardt et al. (2021)[20]** | |
| Authors described the objectives, main outcomes, participant criteria, interventions, baseline characteristics, and main findings. | The study was unblinded.<br>The primary outcome was $FEV_1$, which is an objective measure.<br>Results may not be generalizable to people under 40 years old |

| Strengths | Limitations |
|---|---|
| Authors provided random variability of the data, number and reasons for loss to follow-up, and data on adverse events.<br>Authors reported actual P values for outcomes.<br>Authors conducted appropriate statistical analyses using an intention-to-treat approach and accounted for missing data.<br>Participants were randomized to intervention and comparator groups and authors reported that the groups were matched for demographics and clinical characteristics. | who do not have homogeneous emphysema and little-to-no collateral ventilation.<br>It is unclear whether the study had sufficient power to detect a clinically important effect. Authors indicated that the study had a small sample size and could not show statistical significance for safety outcomes.<br>Authors noted that a longer follow-up of 12 months was not conducted since participants were crossed over to the intervention group for ethical reasons.<br>Several authors received funds or resources from pharmaceutical or health care companies including PulmonX, manufacturer of endobronchial valves. |

BODE = body composition, airway obstruction, dyspnea and exercise capacity; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease.

## Table 5: Strengths and Limitations of Economic Evaluations Using the Drummond Checklist[16]

| Strengths | Limitations |
|---|---|
| **Franzen et al. (2022)[21]** | |
| **Study design**<br>• The research question and the form of economic evaluation were stated.<br>• The target population, alternatives being compared, and outcome measures were clearly described.<br>• The perspective of the analysis was clearly stated.<br>**Data collection**<br>• The sources of effectiveness estimates and treatment costs were described.<br>• The design and results of the effectiveness were given.<br>• The outcome measures for the economic evaluation were clearly described.<br>• Characteristics of the participants included in the cost-effectiveness analysis were described.<br>• Currency and cost were reported.<br>**Analysis and interpretation of results**<br>• Methods for estimation of cost were described.<br>• Incremental analyses were reported.<br>Conclusions follow from the data reported and were accompanied by the appropriate caveats. | The economic importance of the research question, and rationale for choosing alternative interventions compared were unclear.<br>The time horizon of costs and benefits was short (mean: 81 days); no discount rate was applied due to the short time horizon.<br>Measures of intervention effectiveness were taken from a single retrospective study with a small sample size (n = 67) rather than a high-quality RCT or meta-analysis of estimates from multiple sources.<br>The statistical analysis for effectiveness did not adjust possible confounder variables such as age and smoking pack years.<br>The time points for effectiveness data differed between endobronchial valves (102.5 ± 22.8 days) and LVRS (63.2 ± 26.8 days).<br>Quantities of resources were not reported separately from costs.<br>Details of the cost-effectiveness models used were unclear.<br>Sensitivity analyses were not performed.<br>The answer to the study question remains unclear.<br>The disaggregated form of the reported ICERs for $FEV_1$, residual volume, and 6MWD was not reported.<br>The findings of this study, based on the payer and the service-providing hospital in Switzerland, may not be generalizable to the Canadian health system. |
| **Hartman et al. (2018)[22]** | |
| **Study design**<br>• The research question and the form of economic evaluation were stated.<br>• The economic importance of the research question was stated. | The rationale for choosing alternative treatment was unclear.<br>The details of for standard care were not clearly described.<br>Measures of intervention effectiveness were taken from a single RCT rather than from multiple sources or meta-analysis.<br>Details of currency price adjustments for inflation or currency |

| Strengths | Limitations |
|---|---|
| • The target population, alternatives being compared, and outcome measures were clearly described.<br>• The viewpoints of the analysis were clearly stated.<br>**Data collection**<br>• The sources of effectiveness estimates and treatment costs were described.<br>• The design and results of the effectiveness were given.<br>• The outcome measures for the economic evaluation were clearly described.<br>• Methods to value benefits were provided.<br>• Characteristics of the participants included in the cost-effectiveness analysis were described.<br>• Quantities of resources were reported separately from unit costs.<br>• The costs of 5 days hospital admission were used in this evaluation.<br>• Currency and cost were reported.<br>• The key parameters in the models were provided.<br>**Analysis and interpretation of results**<br>• The time horizon of costs and benefits were given.<br>• Methods for estimation of cost were described.<br>• ICERs were reported.<br>• The annual discount rate (4%) used in the long-term economic evaluation was provided.<br>• For stochastic data, the details of statistical tests and confidence intervals were given.<br>• Major outcomes were presented in a disaggregated as well as aggregated form.<br>Conclusions follow from the data reported and were accompanied by the appropriate caveats. | conversion were not given.<br>Only direct medical costs were considered in the model.<br>The model assumed that there were no transitions between the GOLD stages after 6 months from the treatment.<br>Methods for estimation of quantities and unit costs were not provided.<br>The findings of this study, based on Dutch health insurance perspective, may not be generalizable to the Canadian health system. |

6MWD = 6 minute walk distance; $FEV_1$ = forced expiratory volume in 1 second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICER = incremental cost-effectiveness ratio; LVRS = lung volume reduction surgery; RCT = randomized controlled trials.

# Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

## Table 6: Summary of Findings by Outcome — Effectiveness

| Study | Intervention[a] | | | Comparator[a] | | | Treatment effect intervention vs. comparator[a] |
|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | Difference | Baseline | Follow-up | Difference | |
| **6MWD[b] (metres)** | | | | | | | |
| **Eberhardt et al. (2021)**[20] | — | — | 21.3 (57.5) | — | — | −7.1 (53.4) | 28.3 (55.3)<br>P = 0.016 |
| **BMI (kg/m$^2$)** | | | | | | | |
| **Buttery et al. (2023)**[18] | — | — | 0.74 (1.57) | — | — | 0.10 (1.83) | 0.64<br>95% CI −0.27 to 1.56<br>P = 0.16 |
| **BODE score[c]** | | | | | | | |
| **Buttery et al. (2023)**[18] | — | — | −0.82 (1.61) | — | — | −1.10 (1.44) | 0.27<br>95%CI −0.62 to 1.17<br>P = 0.54 |
| **Eberhardt et al. (2021)**[20] | — | — | −0.50 (1.62) | — | 0.35 (1.16) | — | −0.85 (1.39)<br>P = 0.006 |
| **CAT score[d]** | | | | | | | |
| **Buttery et al. (2023)**[18] | — | — | Median −1<br>IQR −3 to 3 | — | — | Median −7<br>IQR −11 to −1 | −6<br>95% CI −9 to−2<br>P = 0.005 |
| **Criner et al. (2023)**[19] | 21.7 (7.0) | 21.2 (7.5) | −0.355 (7.825) | 20.7 (5.9) | 23.3 (6.3) | 2.346 (4.694) | P = 0.03 |
| **Eberhardt et al. (2021)**[20] | — | — | −1.57 (5.05) | — | — | −0.87(3.93) | −0.70 (4.51)<br>P = 0.468 |
| **c-PPAC score[e]** | | | | | | | |
| **Buttery et al. (2023)**[18] | — | — | 16.1 (16.9) | — | — | 18.3 (17.3) | −2.2<br>95% CI −15.8 to 11.4<br>P = 0.74 |

| Study | Intervention[a] | | | Comparator[a] | | | Treatment effect intervention vs. comparator[a] |
|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | Difference | Baseline | Follow-up | Difference | |
| **Dyspnea score[f]** | | | | | | | |
| Buttery et al. (2023)[18] | — | — | −0.33 (0.97) | — | — | −0.65 (0.89) | −0.32<br>95% CI −0.80 to 0.16<br>P = 0.19 |
| Criner et al. (2023)[19] | 2.6 (0.7) | 2.2 (1.0) | −0.378 (1.069) | 2.6 (0.6) | 2.9 (0.7) | 0.226 (0.617) | P = 0.001 |
| Eberhardt et al. (2021)[20] | — | — | −0.24 (0.89) | — | — | 0.17 (0.74) | −0.42 (0.81)<br>P = 0.019 |
| **$FEV_1$[g]** | | | | | | | |
| Buttery et al. (2023)[18] | — | — | 4.5% pred. (6.8) | — | — | 1.1% pred. (9.1) | 3.4<br>95% CI −0.8 to 7.6<br>P = 0.11 |
| Criner et al. (2023)[19] | 0.9 (0.3) | 0.9 L (0.3) | 0.005 L (0.163) | 0.8 L (0.2) | 0.7 L (0.3) | −0.082 L (0.156) | P = 0.01 |
| Eberhardt et al. (2021)[20] | — | — | 80 mL (180) | — | — | −40 mL (120) | 120 mL (150)<br>P < 0.001 |
| **$FEV_1$ responders[h]** | | | | | | | |
| Criner et al. (2023)[19] | — | 19.7% | — | — | 13.3% | — | P = 0.57 |
| Eberhardt et al. (2021)[20] | — | 30.2% | — | — | 8% | — | 22.2%<br>P = 0.006 |
| **ISWT[i] (metres)** | | | | | | | |
| Buttery et al. (2023)[18] | — | — | −4.8 (73.8) | — | — | 27.9 (60.7) | −32.7<br>95% CI −71.0 to 5.5<br>P = 0.09 |
| **QWB score[j]** | | | | | | | |
| Criner et al. (2023)[19] | 1.8 (0.4) | 1.6 (0.5) | — | 1.7 (0.3) | 1.6 (0.5) | — | P = 0.48 |

| Study | Intervention[a] | | | Comparator[a] | | | Treatment effect intervention vs. comparator[a] |
|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | Difference | Baseline | Follow-up | Difference | |
| **RV[k]** | | | | | | | |
| **Buttery et al. (2023)**[18] | — | — | Median −30.1% pred. IQR −53.7 to −9 | — | — | Median −36.1% pred. IQR −54.6 to −10 | −2.7 95% CI −25.4 to 19.1 P = 0.81 |
| **Eberhardt et al. (2021)**[20] | — | — | −480 mL (890) | — | — | −60mL (770) | −430 mL (830) P = 0.015 |
| **SF-36 PCS score[l]** | | | | | | | |
| **Criner et al. (2023)**[19] | 32.6 (8.0) | 35.8 (7.8) | 0.760 (7.860) | 31.6 (6.6) | 31.6 (6.2) | −2.492 (7.006) | P = 0.06 |
| **SGRQ score[m]** | | | | | | | |
| **Criner et al. (2023)**[19] | 54.8 (15.2) | 52.0 (16.9) | −2.802 (14.781) | 54.9 (14.0) | 58.5 (16.4) | 4.187 (14.339) | P = 0.03 |
| **Eberhardt et al. (2021)**[20] | — | — | −6.84 (9.76) | — | 0.63 (9.42) | — | −7.51 (9.56) P < 0.001 |

% pred. = percentage of the predicted value; 6MWD = 6 minute walk distance; BMI = body mass index, BODE = body composition, airway obstruction, dyspnea, and exercise capacity; CAT = COPD Assessment Test; c-PPAC = clinical PROactive physical activity in COPD; $FEV_1$ = forced expiratory volume in 1 second; IQR = interquartile range; ISWT = incremental shuttle walk test; L = litre; mL millilitre; QWB = Quality of Well-being Scale; RV = residual volume; SF-36 PCS = 36-Item Short Form Health Survey physical component summary; SGRQ = St. George's Respiratory Questionnaire.

[a]Mean (SD) unless otherwise indicated.

[b]An indication of an individual's exercise capacity, measured as the final distance walked in the 6-minute walk test. Higher values indicate better capacity.[25]

[c]BODE is a composite measure of disease severity including BMI, airflow obstruction based on $FEV_{1\%}$ pred, MRC dyspnea score, and exercise capacity measured by the ISWT. Higher scores are associated with higher mortality.[18]

[d]CAT is the COPD assessment test that includes patient-reported and measures the impact of COPD on health status. Higher values indicate more severe impact.[26]

[f]Dyspnea is shortness of breath and is patient-reported and can be measured using the Medical Research Council Dyspnea Scale (MRC) or the modified Medical Research Council Dyspnea Scale (mMRC). Higher values indicate more breathlessness.[27,28]

[g]$FEV_1$ is a measure of lung function using a spirometer machine.[24]

[h]Responders who showed 12% or 15% improvement in response.

[i]An indication of an individual's exercise capacity.

[j]A score based on patient reports of functioning where higher values indicate more functioning.[29]

[k]RV is a calculation of air in lungs after maximum exhalation.

[l]The Short Form-36 is a 36-item questionnaire assessing a person's quality of life. Higher values indicate better health.[30]

[m]The SGRQ is a self-reported measure of health impairment. Lower values indicate better health.[31]

## Table 7: Summary of Findings by Outcome — Safety

| Study | Intervention | | | Comparator | | | Treatment Effect |
|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | Difference | Baseline | Follow-up | Difference | |
| **Adverse events** | | | | | | | |
| **Buttery et al. (2023)**[18] | — | 39.1% | — | — | 50% | — | P = 0.262 |
| **Eberhardt et al. (2021)**[20] | — | 111 events | — | — | 54 events | — | — |
| **COPD exacerbations** | | | | | | | |
| **Criner et al. (2023)**[19] | — | 13.7% | — | — | 15.6% | — | — |
| **Eberhardt et al. (2021)**[20] | — | 18.6% | — | — | 20% | — | P = 1.000 |
| **Death** | | | | | | | |
| **Buttery et al. (2023)**[18] | 0 events | 0 events | — | 0 events | 1 events | — | — |
| **Criner et al. (2023)**[19] | — | 18% | — | — | 15% | — | P = 0.81 |
| **Eberhardt et al. (2021)**[20] | — | 0 events | — | — | 2 events | — | — |
| **Hospitalization** | | | | | | | |
| **Buttery et al. (2023)**[18] | — | 9 events | — | — | 3 events | — | — |
| **Eberhardt et al. (2021)**[20] | — | 19% | — | — | 20% | — | — |
| **Pneumothorax** | | | | | | | |
| **Buttery et al. (2023)**[18] | — | 30.4% | — | — | — | — | — |
| **Criner et al. (2023)**[19] | — | 1% | — | — | 0% | — | P = 1.00 |
| **Eberhardt et al. (2021)**[20] | — | 4.7% | — | — | 0% | — | P = 0.211 |
| **Serious adverse events** | | | | | | | |
| **Criner et al. (2023)**[19] | — | 27.5% | — | — | 15.6% | — | P = 0.41 |
| **Eberhardt et al. (2021)**[20] | — | 34.9% | — | — | 26% | — | P = 0.269 |
| **Subcutaneous emphysema** | | | | | | | |
| **Buttery et al. (2023)**[18] | — | — | — | — | 29.3% | — | — |

COPD = chronic obstructive pulmonary disease.

## Table 8: Summary of Findings of Included Economic Evaluations

| Main study findings | Authors' conclusion |
|---|---|
| **Franzen et al. (2022)**[21] | |
| Median cost unit accounting (CHF, Swiss Franc)<br>• LVRS: 28,048<br>• Endobronchial valves: 30,049<br>Cost per mL $FEV_1$ (CHF/mL)<br>• LVRS: 140.2<br>• Endobronchial valves: 166.9<br>Cost per % $FEV_1$ (CHF/%) | "A robust statement on the superiority of one of the 2 procedures in terms of cost-effectiveness cannot be made from the present study (abstract conclusion, p. 1)."[21] |

| Main study findings | Authors' conclusion |
|---|---|
| • LVRS: 1,263.4<br>• Endobronchial valves: 1,353.6<br>Cost per mL residual volume (CHF/mL)<br>• LVRS: 70.1<br>• Endobronchial valves: 33.4<br>Cost per metre (6MWD), (CHF/m)<br>• LVRS: 28,048.0<br>• Endobronchial valves: 1197.2<br>ICERs of endobronchial valves compared with LVRS for different outcome measures.<br>• $FEV_1$: −101<br>• Residual volume: 4<br>• 6MWD: 58 | |
| **Hartman et al. (2018)[22]** | |
| **Short-term evaluation (6 months)**<br>Mean cost difference between endobronchial valves and standard care:<br>• € 16721, 95% CI, 16,675 to 16,766 (after bootstrapping)<br>Mean change in EQ5D utility score<br>• 0.12, 95% CI, 0.01 to 0.24, P = 0.04<br>Mean change in SGRQ utility score<br>• 0.16, 95% CI, 0.07 to 0.24, P < 0.01<br>ICER per QALY using EQ5D (baseline EQ5D in endobronchial valve group: 0.63; in standard care group: 0.66)<br>• -€ 1,941,250 (not reliable as noted by the study authors)<br>ICER per QALY using SGRQ<br>• € 205,129, 95% CI, 203,547 to 206709 (after bootstrapping and adjusting for 1-year time period)<br>ICER for per 6MWD<br>• € 164.6, 95% CI, 159.66 to 161.27<br>ICER for per SGRQ<br>• € 1,240.71, 95% CI, 1,253.99 to 1,227.42<br>**Long-term evaluation (5 years)**<br>Cost<br>• Endobronchial valves: undiscounted: € 2,020,968; discounted: € 2,001,520<br>• Standard care: undiscounted: € 49,416; discounted: € 49,416<br>Life-years<br>• Endobronchial valve: undiscounted: 358; discounted: 334<br>• Standard care: undiscounted: 330; discounted: 309<br>EQ5D-QALY<br>• Endobronchial valve: undiscounted: 272; discounted: 253<br>• Standard care: undiscounted:220; discounted: 206<br>SGRQ-QALY<br>• Endobronchial valve: undiscounted: 240; discounted: 223<br>• Standard care: undiscounted: 190; discounted: 178<br>ICERs | "In conclusion, our results suggest that the [endobronchial valve] treatment has a favourable cost-effectiveness profile, also when compared with other treatment modalities for this patient group (p. 840)."[22] |

| Main study findings | Authors' conclusion |
|---|---|
| • Cost per life-years: undiscounted: € 71,512; discounted: € 79,100<br>• Cost per EQ5D-QALY: undiscounted: € 38,525; discounted: € 41,870<br>• ICER-Cost per SGRQ-QALY: undiscounted: € 39,638; discounted: € 42,775<br>**Long-term evaluation (10 years)**<br>Cost<br>• Endobronchial valve: undiscounted: € 2,171,464; discounted: € 2,116,914<br>• Standard care: undiscounted: € 49,416; discounted: € 49,416<br>Life-years<br>• Endobronchial valve: undiscounted: 545; discounted: 477<br>• Standard care: undiscounted:472; discounted: 418<br>EQ5D-QALY<br>• Endobronchial valve: undiscounted: 416; discounted: 363<br>• Standard care: undiscounted: 314; discounted: 278<br>SGRQ-QALY<br>• Endobronchial valve: undiscounted: 367; discounted: 321<br>• Standard care: undiscounted: 272; discounted: 241<br>ICERs<br>• Cost per life-years: undiscounted: € 29,046; discounted: € 34,883<br>• Cost per EQ5D-QALY: undiscounted: € 20,848; discounted: € 24,255<br>• ICER-Cost per SGRQ-QALY: undiscounted: € 22,375; discounted: € 25,827 | |

6MWD = 6 minute walk distance; CHF = Swiss Franc; EQ5D = EuroQol 5 Dimension; $FEV_1$ = forced expiratory volume in 1 second; ICERs = incremental cost-effectiveness ratio; LVRS = lung volume reduction surgery; mL = millilitre; QALY = quality-adjusted life-year; SGRQ = St. George's Respiratory Questionnaire.

# Appendix 5: References of Potential Interest

## Previous CADTH Rapid Review

Endobronchial Valves for the Management of Emphysema: A Review of Clinical Effectiveness. Ottawa (ON): CADTH. 2019. https://www.cadth.ca/endobronchial-valves-management-emphysema-review-clinical-effectiveness

## Posthoc Analysis of Trial Outcomes in Previous CADTH Report

Dransfield MT, Garner JL, Bhatt SP, et al. Effect of Zephyr Endobronchial Valves on Dyspnea, Activity Levels, and Quality of Life at One Year. Results from a Randomized Clinical Trial. *Ann Am Thorac Soc*. 2020;17(7):829-838. PubMed

## Systematic Reviews with Evidence in Previous CADTH Report

Patel M, Chowdhury J, Zhao H, et al. Meta-analysis and Systematic Review of Bronchoscopic Lung Volume Reduction Through Endobronchial Valves in Severe Emphysema. *J Bronchology Interv Pulmonol*. 2022;29(3):224-237. PubMed

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;17(11):1468-1475. PubMed

Xu W, Wang J, He X, Wang J, Wu D, Li G. Bronchoscopic lung volume reduction procedures for emphysema: A network meta-analysis. *Medicine (Baltimore)*. 2020;99(5):e18936. PubMed

Majid A, Labarca G, Uribe Juan P, et al. Efficacy of the Spiration Valve System in Patients with Severe Heterogeneous Emphysema: A Systematic Review and Meta-Analysis. *Respiration*. 2019;99(1):62-72. PubMed

## ECRI Clinical Evidence Assessments

Spiration Valve System (Olympus America) for treating emphysema symptoms. Clinical Evidence Assessment. Plymouth Meeting (PA): ECRI. 2023.

Zephyr Endobronchial Valve System (Pulmonx Corp.) for treating emphysema symptoms. Clinical Evidence Assessment. Plymouth Meeting (PA): ECRI. 2023.

## Reviews of Economic Studies

Vigneswaran J, Krantz S, Howington J. Economic Considerations of Lung Volume Reduction Surgery and Bronchoscopic Valves. *Thorac Surg Clin*. 2021;31(2):211-219. PubMed

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## Guidelines and Recommendations

Koegelenberg CFN, van Zyl-Smit RN, Dheda K, et al. Position statement on endoscopic lung volume reduction in South Africa: 2022 update. *Afr J Thorac Crit Care Med*. 2022;28(2). PubMed

NICE Evidence Reviews Collection. Referral criteria for lung volume reduction procedures, bullectomy or lung transplantation: Chronic obstructive pulmonary disease in over 16s: diagnosis and management: Evidence review G. London (UK): National Institute for Health and Care Excellence (NICE). 2018.

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