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SINGLE TECHNOLOGY ASSESSMENT:
Zephyr® valves system in the treatment of emphysema

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Innhold

Key messages

Chronic obstructive pulmonary disease (COPD) is a collective term for a group of chronic lung diseases that leads to obstructed airflow through an individual's airways and gives permanent impaired lung function. One of these diseases is emphysema which leads the alveoli in the lungs to lose surface area and elasticity. The uptake of oxygen will decrease, and the reduced elasticity makes it more difficult for the patient to get the air out from affected areas that can become hyperinflated. The Zephyr® valve treatment is indicated for some patients suffering from severe or very severe emphysema. The Zephyr® valve is implanted in a target lobe during a bronchoscopy procedure. The aim is to block inspiratory airflow into a hyperinflated targeted lobe of the lung and allow trapped air to escape during exhalation. The affected lung area will then become smaller, allowing healthier parts of the lung to expand.

Effect and safety: Zephyr® valve treatment probably improves FEV1 (lung function), BODE index and St. George Respiratory Questionnaire and may improve six-minute walking distance. No conclusions could be reached regarding Zephyr® valve treatment and the risk of death. The procedure may increase the risk of pneumothorax but may make little or no difference to the risk of COPD exacerbations.

Severity: Absolute shortfall for patients suffering from emhysema is 13.4 QALYs which places it in disease severity group four.

Cost-effectiveness: Based on the submitter's economic model, the ICER of Zephyr® valve treatment, when compared to standard care, is NOK [redacted] QALY in a three-year perspective and NOK [redacted] QALY in a ten-year perspective. However, 10- year estimates are considerably more uncertain than those in a 3-year perspective due to a lack of longer term efficacy and safety data. If the willingness to pay for Zephyr® is above the predicted ICER, only then Zephyr® can be cost-effective, but there remains important uncertainty.

Budget impact: The budget impact was calculated as the incremental cumulative costs for the total number of patients treated with Zephyr®. Based on manufacturer's estimate of an annual 5% increase in the use of Zephyr® and a current target population on 25 patients per year, 203 patients would receive Zephyr® treatment during a 5-year time span. In this scenario the cumulative budget consequence during a 5-year period is estimated at NOK [redacted].

Title:
Zephyr® valves system in the treatment of emphysema: A single technology assessment

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Executive summary (English)

Background

Chronic obstructive pulmonary disease (COPD) is a collective term for a group of chronic lung diseases that leads to obstructed airflow through an individual's airways and causes permanent impaired lung function. One of these diseases is emphysema, which causes the alveoli in the lungs to lose surface area and elasticity. Reduced surface area reduced the gas exchange, and reduced elasticity prevents the lung from fully emptying the air, leading to hyperinflation. There is no curative treatment for COPD, however, smoke cessation, symptomatic medication, training, and lung rehabilitation can slow down further exacerbations and loss of lung function. In specific cases, the use of endobronchial valves may be considered as a surgical alternative in some patients with severe or very severe emphysema.

The Zephyr® Valve system is a type of endobronchial valve that is implanted during bronchoscopy. The valve is intended to selectively shut off air supply to an affected area while trapped air can escape. The affected area of the lung will then collapse fully or partially, freeing up space so that healthier parts of the lung have more room to expand. The Division for Health Services at the Norwegian Institute of Public Health (NIPH) was commissioned by the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway to conduct a single health technology assessment of Zephyr® valve system for patients with severe or very severe emphysema.

Objective

The manufacturer, PULMONX submitted a single-technology assessment (STA) of Zephyr® valve system to the Norwegian Institute of Public Health for evaluation of effect, safety, and health economics. The present report is an appraisal of this STA.

Method

We used the documentation provided by the manufacturer. The literature search was checked by two librarians at NIPH. The manufacturer did not report whether they used independent screening and data extraction. We used the risk of bias assessments provided by the manufacturer. The manufacturer did not use GRADE, but we have graded the evidence. One researcher did the GRADE assessments, and another researcher checked the assessments. We categorized the certainty of evidence as high (⊕⊕⊕⊕), moderate (⊕⊕⊕○), low (⊕⊕○○) or very low (⊕○○○) according to GRADE.

According to information in the submission file , the following databases were searched in April 2020: MEDLINE, EMBASE, Cochrane (CENTRAL) and ClinicalTrials.gov. The search was meant to update a search from a NICE guideline from 2017 using the following PICO:

P	People with emphysema (heterogeneous or homogeneous)
I	Endobronchial valves (EBV), Zephyr® valves, PulmonX Inc after assessment of collateral ventilation with Chartis® flow sensor and catheter
C	Sham procedure or standard care
O	FEV_1, SGRQ, 6MWD test, BODE Index, pneumothorax episodes, COPD exacerbations episodes and death (for all causes, for respiratory complications, for IHD)

Results

The manufacturer's literature search identified four randomized trials (IMPACT, STELVIO, LIBERATE, TRANSFORM) comparing Zephyr® valves with standard medical care and one trial (BeLieVeR-HIFI) that compared Zephyr® valves with a sham procedure. The five studies included a total of 498 patients: 295 got Zephyr®, 178 received standard treatment, and 25 received sham valve procedure.

Effect and safety

There was no clear difference in **mortality** between the Zephyr®-group and the control group (risk ratio: 1.61, 95% CI from 0.44 to 5.93; ⊕○○○). These results depend on a risk ratio estimated using only seven deaths (7/270) in the Zephyr®-group and two (2/178) in the standard treatment group, implying that no clear conclusions could be reached regarding Zephyr® valve treatment and the risk of all-cause mortality. Moreover, there was no clear association between the Zephyr® procedure and the risk of **COPD exacerbations**. None of the studies found a statistically significant difference, and the pooled effect is estimated to OR 1.15 (95% CI 0.70 to 1.88; ⊕⊕○○), but the meta-analysis is based on a limited number of events (n=91) and the certainty of evidence is low.

All studies showed an important improvement in **FEV1** for the Zephyr® group compared to standard care. Studies included in the meta-analyses had different follow-up periods ranging from three to twelve months, but there was no serious heterogeneity in the results. The mean difference between the groups were 0.14 litres (95% CI 0.13 to 0.16; (⊕⊕⊕○), which is higher than the suggested minimal clinically important difference (MCID) at 0.12 litres. The use of Zephyr® valves probably result in more favorable scores on the **St. Georges's Respiratory Questionnaire (SGRQ)** after three to twelve months than standard care. A suggsted MCID for this outcome is four points, and the estimated difference was almost eight points (95% CI 5 to 11; ⊕⊕⊕○) in favour of Zephyr®. Zephyr® may improve **6-minute walking distance (6MWD)** as compared to standard care three to six months after the procedure. The available studies showed heterogenous results, but random-effect meta-analyses still showed results in favour of Zephyr® (MD 57 metres, 95% CI 36 to 78; ⊕⊕○○). MCID for 6MWD in severe COPD is estimated to approximately 30 metres. Measurements of the **BODE index** were in favour of the Zephyr®-valve in all studies. Pooled estimate across the four studies showed that the BODE index was 1.3 points lower (95% CI -1.6 to -1.0; ⊕⊕⊕○) after

Zephyr® than after standard care (MCID = -1 point). The Zephyr®-valve procedure may increase the risk of **pneumothorax** (OR 34, 95% CI 8 to 142; ⊕⊕○○).

Health economy
Based on the submitter's economic model, the ICER of Zephyr® valve treatment, when compared to standard care, is NOK [redacted] per QALY in a three-year perspective and NOK [redacted] per QALY in a ten-year perspective. However, 10- year estimates are considerably more uncertain than those in a 3-year perspective due to a lack of longer term efficay and safety data. Clinical experts also consider a ten-year time horizon to be too long compared to the life expectancy og the relevant patient group. Hence, Zephyr® valve treatment may be cost- effective in the Norwegian setting, but there remain important uncertainties.

The manufacturer anticipates a gradual increase in the number of patients undergoing a Zephyr® valve procedure with five percent each year, and the clinical expert anticipate a target population around 25 patients per year in Norway. In this scenario the cumulative budget consequences during a five-year period are estimated to NOK [redacted].

Discussion

The evidence base primarily consists of four randomized controlled trials comparing the Zephyr® valve system versus standard care, and one trial comparing Zephyr with sham treatment. The follow-up period ranged from three to twelve months. The evidence for Zephyr versus standard care did not allow drawing firm conclusions regarding mortality (RR 1.61, 95% CI 0.44 to 5.93) and the number of exacerbation episodes (OR 1.15, 95%CI 0.70 to 1.88). However, the Zephyr® valve system probably improves FEV1, SGRQ, and BODE index. It also may improve 6MWD. The improvements in functional outcomes come at the cost of increased risk of pneumothorax after the intervention (OR 33.9, 95% CI 8.1 to 141.7, low certainty of evidence).

Conclusion

Depending on perspective and willingness to pay, the Zephyr® valve system may be a cost-effective alternative to standard care for the treatment of severe emphysema in patients without collateral ventilation. However, there are still important uncertainties surrounding the long-term effect of Zephyr®, its overall impact on health outcomes and costs more than one year after treatment.

Hovedbudskap

Kronisk obstruktiv lungesykdom (KOLS) er samlebetegnelse for en gruppe kroniske lungesykdommer som hindrer fri luftstrøm gjennom luftveiene og gir varig svekket lungefunksjon. Én av disse sykdommene er emfysem som fører til at alveolene i lungene taper elastisitet og overflateareal. Oksygenopptaket vil da gå ned, og den reduserte elastisiteten gjør at det blir vanskeligere å få luft ut av affiserte lungeområder som da kan bli oppblåste (hyperinflaterte). Innsetting av en ventil, som Zephyr®, er ment å selektivt stenge av lufttilførsel til affisert lungeområde samtidig som gammel luft får slippe ut. Det affiserte lungeområdet vil da blir mindre og frigjøre plass slik at friskere deler av lungen får mer plass til å ekspandere.

Effekt og sikkerhet: Bruk av Zephyr®-ventil forbedrer sannsynligvis FEV1 (lungefunksjon), BODE-indeks og SGRQ og kan muligens forbedre resultater på 6-minutters gangtest. Vi kan ikke trekke sikre konklusjoner om effekten av Zephyr® på dødelighet. Behandlingen kan muligens gi økt risiko for pneumothorax og har muligens liten eller ingen effekt på risiko for episoder med akutte forverringer.

Alvorlighet: Absolutt prognosetap for pasienter med emfysem beregnes til 13.4 kvalitetsjusterte leveår, tilsvarende alvorlighetskategori 4.

Kostnadseffektivitet: Innsenderens økonomiske modell tilsier at ICER for behandling med Zephyr®-ventil er NOK [redacted] per kvalitetsjusterte leveår i et treårsperspektiv og NOK [redacted] per kvalitetsjusterte leveår i tiårsperspektiv. Tiårsestimatene er betydelig mer usikre enn ved tre år fordi vi mangler langtidsdata om effekt- og sikkerhet. Hvis betalingsvilligheten er høyere enn estimert ICER kan Zephyr® være kostnadseffektiv i en norsk setting, men estimatene er beheftet med betydelig usikkerhet.

Budsjettpåvirkning ble beregnet som inkrementelle kumulative kostnader for totalt antall behandlede pasienter. Basert på produsentens anslag om 5% årlig økning i bruken av Zephyr® og en nåværende målpopulasjon på 25 pasienter per år, vil 203 pasienter få Zephyr®-behandling i løpet av en 5-års periode. I dette scenariet er akkumulert budsjettkonsekvens over en 5-årsperiode beregnet til [redacted] kroner.

Tittel:
Zephyr® ventilsystem i behandlingen av emfysem: en hurtig metodevurdering

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Publikasjonstype:
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Basert på innsendt dokumentasjonspakke

Svarer ikke på alt:
Ingen vurdering av organisatoriske, juridiske eller etiske forhold

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Hvem står bak denne publikasjonen?
Folkehelseinstituttet har levert rapporten på oppdrag fra Bestillerforum for nye metoder

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Når ble litteratursøket utført?
Søk etter studier ble avsluttet i april 2020

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Sammendrag

Innledning

Kronisk obstruktiv lungesykdom (KOLS) er en samlebetegnelse for en gruppe kroniske lungesykdommer som hindrer fri luftstrøm i luftveiene og gir varig svekket lungefunksjon. En av disse sykdommene er emfysem som fører til at alveolene i lungene taper elastisitet og overflateareal. I lungevev som er preget av emfysem vil evnen til gassutveksling være redusert. Den reduserte elastisiteten vil gjøre det vanskeligere for pasienten å få luften ut av affiserte lungeområder, og det kan dannes oppblåste (hyperinflaterte) områder. Det finnes ingen kurativ behandling, men røykslutt, symptomatisk medisinering, trening og lungerehabilitering kan bremse ytterligere forverring og tap av lungefunksjon. I spesifikke tilfeller kan det være aktuelt å vurdere innsetting av endobronkialklaffer til pasienter med alvorlig eller svært alvorlig emfysem.

Zephyr® ventilsystem er en type endobronkialklaff som implanteres under bronkoskopi. Ventilen er ment å selektivt stenge av lufttilførsel til et affisert lungeområde samtidig som gammel luft får slippe ut. Det affiserte lungeområdet vil da helt eller delvis falle sammen og frigjøre plass slik at friskere deler av lungen får mer plass til å ekspandere. Område for helsetjenester i Folkehelseinstituttet (FHI) fikk i oppdrag fra Bestillerforum for nye metoder å gjennomføre en hurtig metodevurdering av Zephyr® ventilsystem for pasienter med alvorlig eller svært alvorlig emfysem.

Mål

Produsenten PULMONX sendte inn en dokumentasjonspakke for Zephyr®-ventilsystemet til FHI. Denne rapporten er en vurdering av den innsendte dokumentasjonspakken og en oppsummering av resultater om effekt, sikkerhet og helseøkonomi.

Metode

Vi vurderte dokumentasjonen som ble levert av produsenten. Litteratursøket ble vurdert av to bibliotekarer ved Folkehelseinstituttet. Produsenten rapporterte ikke om de brukte uavhengig screening og dataekstraksjon. Risiko for skjevheter ble vurdert på bakgrunn av informasjon i dokumentasjonspakken. Dokumentasjonspakken inneholdt ingen GRADE-vurderinger, men FHI har på selvstendig grunnlag benyttet GRADE til å vurdere kvaliteten til dokumentasjonen. Én forsker gjorde GRADE-vurderingene, og en annen sjekket vurderingene. Kvaliteten til dokumentasjonen ble da vurdert til høy (⊕⊕⊕⊕), moderat (⊕⊕⊕◯), lav (⊕⊕◯◯) eller svært lav (⊕◯◯◯).

Ifølge informasjonen i dokumentasjonspakken ble følgende databaser søkt i april 2020: MEDLINE, EMBASE, Cochrane (CENTRAL) og ClinicalTrials.gov. Søket var ment å oppdatere et søk fra en NICE-retningslinje fra 2017 ved å bruke følgende PICO:

P	Pasienter med emfysem
I	Endobronkial ventil (EBV), Zephyr® ventil, PulmonX Inc etter vurdering av kollateral ventilering med Chartis® sensor og kateter
C	Sham prosedyre eller standard behandling
O	FEV_1, SGRQ, 6MWD test, BODE Index, pneumothorax, KOLS-forverring og død (totalt, død etter respiratoriske komplikasjoner og død etter hjerte- og karrelaterte hendelser)

Resultat

Produsentens litteratursøk identifiserte fire randomiserte studier (IMPACT, STELVIO, LIBERATE, TRANSFORM) som hadde sammenlignet Zephyr®-ventiler med standard medisinsk behandling og en studie (BeLieVeR-HIFI) som sammenlignet Zephyr®-ventiler med en falsk (blindet) prosedyre. De fem studiene inkluderte 498 pasienter: 295 som fikk Zephyr®, 178 som fikk standardbehandling og 25 som fikk falsk ventiloperasjon.

Effekt og sikkerhet
Det var ingen klar forskjell i **dødelighet** mellom Zephyr®- og kontrollgruppen (RR 1,61; 95 % KI fra 0,44 til 5,93; ⊕○○○). Beregningen av RR er basert på kun sju dødsfall (7/270) i Zephyr®-gruppen og to (2/178) i kontrollgruppen, noe som betyr at det ikke er mulig å trekke klare konklusjoner om bruken av Zephyr®-ventiler og risiko for død. Vi fant ingen dokumentert forskjell i antall **KOLS-forverringer** mellom Zephyr® og standardbehandling. Den samlede effekten ble estimert til OR 1,15 (95% CI 0,70 til 1,8), men metaanalysen er basert på et begrenset antall hendelser (n=91) og kvaliteten til dokumentasjonen er lav.

Alle studiene viste en viktig bedring i **FEV1** for Zephyr®-gruppen sammenlignet med standardbehandling. Studiene som var inkludert i metaanalysen hadde oppfølgingstid mellom tre og tolv måneder, men det var ingen alvorlig heterogenitet i resultatene. Den gjennomsnittlige forskjellen mellom gruppene var 0,14 liter (95% KI 0,13 til 0,16; ⊕⊕⊕○). Det er mer enn den anslåtte grensen for en klinisk viktig forskjell (MCID) på 0,12 liter. Zephyr®-gruppen rapporterte bedre resultater på **St. Georges's Respiratory Questionnaire (SGRQ)** enn kontrollgruppen etter tre til tolv måneder. En endring på mer enn fire poeng anses ofte for å være en klinisk viktig forskjell for denne pasientgruppen, og den estimerte forskjellen var nesten åtte poeng (95% KI 5 til 11; ⊕⊕⊕○) i favør av Zephyr®. Måling av **BODE-indeks** viste også resultater i favør av Zephyr® i alle studier. Samlet estimat på tvers av alle fire studier viste at BODE-indeksen var 1,30 poeng lavere (95 % KI -1,62 til -0,99; ⊕⊕⊕○) der lavere score er bedre. Zephyr® kan muligens forbedre **6 minutters gangavstand (6MWD)** sammenlignet med standardbehandling tre til seks måneder etter prosedyren. De tilgjengelige studiene viste varierende resultater, men metaanalyser (random effect model) viste likevel resultater i favør av Zephyr® med MD 57 meter (95 % KI 36 til 78; ⊕⊕○○). MCID for 6MWD ved

alvorlig KOLS er estimert til ca 30 meter. Zepyhr® kan øke risiko for **pneumothorax** (OR 34; 95% KI 8 til 142; ⊕⊕○○).

Helseøkonomi
Innsenderens helseøkonomiske modell tilsier at ICER for behandling med Zephyr® sammenlignet med standardbehandling er NOK [redacted] per QALY i et treårsperspektiv og NOK [redacted] per QALY i et tiårsperspektiv. Tiårsestimatene er beheftet med betydelig større usikkerhet enn treårsperspektivet da vi mangler dokumentasjon om langtidseffekter av behandling. Kliniske eksperter vurderer også at en tiårs-horisont er svært lenge sammenlignet med forventet levealder for den aktuelle pasientgruppen. Behandling med Zephyr® kan være kostnadseffektiv i norsk setting avhengig av hvilket perspektiv og hvilken betalingsvillighet man legger til grunn, men det er stor usikkerhet om tallene.

I dokumentasjonspakken forutsetter produsenten en gradvis økning i antall pasienter som gjennomgår en Zephyr®-ventilprosedyre med fem prosent per år. Kliniske fageksperter anslår at den nåværende målpopulasjonen er ca 25 pasienter per år. Gitt et slikt scenario er de kumulative budsjettkonsekvensene over en femårsperiode beregnet til [redacted] kroner.

Diskusjon

Kunnskapsgrunnlaget som er vurdert i denne hurtige metodevurderingen består primært av fire randomiserte kontrollerte studier som sammenligner Zephyr®-ventilsystemet mot standardbehandling, og én studie som sammenligner Zephyr med falsk behandling. Oppfølgingsperioden varierte fra tre til tolv måneder. Kunnskapsgrunnlaget er for svakt til å tillate sikre konklusjoner angående dødelighet (RR 1,61, 95 % KI 0,44 til 5,93) og antall episoder med forverring (OR 1,15, 95 % CI 0,70 til 1,88). Imidlertid forbedrer Zephyr®-ventilsystemet sannsynligvis FEV1, SGRQ og BODE-indeksen. Det kan også forbedre 6MWD. Forbedringene i funksjonelle utfall kommer på bekostning av økt risiko for pneumothorax etter operasjon (OR 33,9, 95 % KI 8,1 til 141,7).

Konklusjon

Avhengig av perspektiv og betalingsvilje, kan Zephyr®-ventilsystemet være et kostnadseffektivt alternativ til standardbehandling for behandling av alvorlig emfysem. Det er imidlertid fortsatt viktige usikkerhetsmomenter knyttet til den langsiktige effekten av Zephyr® og metodens samlede effekt på helseutfall og kostnader mer enn ett år etter behandling.

Preface

The Division for Health Services at the Norwegian Institute of Public Health was commissioned by the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway to conduct a single health technology assessment of Zephyr® valve system for patients with severe or very severe emphysema. In a single-technology assessment, the technology (a pharmaceutical or a device) is assessed based on documentation submitted by the company owning the technology, or their representatives. The submission used in this single technology assessment of the Zephyr® valve system was submitted by PulmonX International, Rue de la Treille, 4 -2000 Neuchâtel (Switzerland).

The HTA unit of the Norwegian Institute of Public Health (NIPH) receives and evaluates the submitted documentation with regard to effect and safety (important clinical outcomes), resource use and assumptions made in the analysis and models submitted by the manufacturer. NIPH does not develop separate health economic models within the scope of a single technology assessment. If applicable, NIPH can obtain additional information from the manufacturer or independently retrieve updated information to make own calculations of relative effect, costs, cost-effectiveness, severity and budgetary consequences.

Project group: Beate Fagerlund (health economist), Fawaz Chaudhry (health economist), Gunhild Hagen (health economist), Geir Smedslund (senior researcher), Gunn Eva Næss (librarian), Mónica Gómez Castañeda (health economist) and Kjetil G. Brurberg (department director).

Clinical experts: Arve Sundset, Consultant pulmonologist at Oslo University Hospital, Gunnar R. Husebø, Chief physician at Haukeland University Hospital, and Peter Majak, Chief physician at Oslo University Hospital.

Patients' representatives: Jan I. Andersen has contributed on behalf of LHL (Landsforeningen for hjerte- og lungesyke).

Conflict of interest: Other authors and experts involved in this report state they have no conflict of interest to declare

Kjetil G. Brurberg *Department director*	Kåre Birger Hagen *Director systematic reviews and HTAs*	Geir Smedslund *Project coordinator*

Background

Chronic obstructive pulmonary disease (COPD) is a collective term for a group of chronic lung diseases that leads to obstructed airflow through an individual's airways and gives permanent impaired lung function. Smoking is the most common cause of COPD. Around 80% of those who have COPD smoke or have smoked. About 150,000 Norwegians have COPD[1], and the incidence of COPD in Norway is estimated to be about 20,000 per year [1].

COPD includes narrowing of the airways, loss of elasticity in the alveoli (air sacs), gradually fewer alveoli (emphysema) and increased amount of mucus (bronchitis). In emphysema, the airway obstruction is caused by loss of lung tissue. The walls in the alveoli are damaged leading several alveoli to fuse together. Consequently, the surface area of the alveoli is reduced, impairing the ability to absorb oxygen. The reduced elasticity of the affected area also prevents the lung from effectively emptying the air, leading to hyperinflated areas that occupy space and prevent more healthy parts of the lung to function properly. The individual experiences this as wheezing in the early stages of disease development when physically active, and sometimes also when resting. More symptoms include shortness of breath with mild exertion, chronic cough and recurrent respiratory infections [2, 3].

Currently, there are no curative treatment options for individuals with emphysema. However, patients with emphysema that have asthma-like symptoms can be relieved with medication. Some patients also need oxygen therapy. Severe emphysema is sometimes treated with surgical lung volume reduction, and few patients with very severe emphysema are offered lung transplantation [2, 3].

The technology: the description and use

This section is copied directly from submitter's documentation package

The Zephyr® Valve treatment is indicated for patients suffering from severe or very severe heterogeneous or homogenous emphysema of the upper and/or lower lobe, identified by Forced Expiratory Volume in 1 second (FEV_1) <45% and >15% predicted and

[1] https://www.fhi.no/nyheter/2018/150-000-har-kols/

a diagnosis of hyperinflation determined by body plethysmography (Residual Volume (RV) >175%), who are symptomatic despite optimal medical care. In addition, candidates should have little to no collateral ventilation between the target and ipsilateral lobes.

Zephyr® is a Class III implantable medical device according to Council Directive 93/42/EEC. The valve is a silicone, duckbill valve mounted in a nitinol, self-expanding retainer that is covered with a thin silicone membrane.

The device system consists of an implantable Zephyr® valve, a single use, disposable Endobronchial Loader System (ELS), and a single-patient use, disposable Zephyr® Endobronchial Delivery Catheter (EDC). The suitability of a patient for Zephyr® valve treatment is assessed by measuring the extent of the collateral ventilation (CV) in the targeted lobe. The assessment of collateral ventilation is usually performed by the quantitative lung computed tomography (QCY) analyzing using fissure integrity as a surrogate and physiologically with use of the CHARTIS Pulmonary Assessment System. CHARTIS system using the CHARTIS catheter airflow probe inserted endoscopically to measure airflow.

The technology: How does it work

This section is copied directly from submitter's documentation package
The Zephyr valve is implanted in the target lobe during a bronchoscopy procedure using a flexible delivery catheter that is guided to the targeted bronchus by inserting it through the working channel of a flexible bronchoscope. The aim is to block inspiratory airflow into a hyperinflated targeted lobe of the lung and allow trapped air to escape during exhalation. When reduction of trapped air is indicated, the Zephyr® Valve allows distal air to vent from the isolated lung segment during exhalation but does not allow refilling of this region during inhalation. With each respiratory cycle, the amount of air in the target lung segment is reduced (pneumoreduction).

The aim of implanting Zephyr® endobronchial valves is to achieve a reduction in lung volume by atelectasis (atelectasis is the collapse of the alveoli or part of the lung due to a lack of ventilation as a result of total or partial obstruction of a bronchus), allowing the other lobes of the lung to expand and thus improving lung function in the other less affected lung regions. The remaining lobes are able to expand more fully and the overall lung works more efficiently, with resultant improvement in overall lung function in patients with hyperinflation associated with severe emphysema.

When the Zephyr® endobronchial valve is deployed in the target area, the retainer expands and is anchored in place against the bronchial wall utilizing radial force, similar to a stent. The valve protector portion of the retainer surrounds the valve to prevent distortion of the valve when in contact with the bronchial wall. Because the valve is protected and isolated within the retainer and away from the bronchial wall, the one-way valve is not hindered by variation in the airway such as mucus or

inflammation. The edges of the valve are attached to the inside of the retainer to prevent the valve from collapsing during high pressure changes, such as coughing. The silicone membrane covering the retainer creates a peripheral seal between the implant and the bronchial wall. The retainer keeps the silicone membrane in contact with the bronchial wall during inhalation, exhalation, and coughing.

The valve is closed during inspiration, preventing the entry of the inhaled air into the diseased, distended area. During exhalation, the one-way valve opens, and releases air trapped in the distended area, also allowing secretions to pass through. Once the air is evacuated, the volume of the target lobe decreases, inducing atelectasis. As a result, other healthy lobes can expand in volume and, in general, the lungs can function more efficiently. The inhaled air is redistributed to less diseased areas.

For the Zephyr Valve® treatment to be effective, the targeted lobe must be isolated from airflow, both from airflow through the airways and from possible collateral ventilation between lobes (i.e. ventilation of alveolar structures through passages or channels that bypass the normal airways). This is more common in emphysema patients than in healthy subjects. When the lobe is properly occluded and isolated from airflow, trapped air in the diseased lobe is able to escape only through the valves, resulting in reduced lung volume in the targeted lobe.

Regulatory status (CE-marking) and market access of the technology

Table 1 presents the international registrations of the Zephyr® Valve. The table is based on information from the submitter.

Description of the context of use

This section is copied directly from submitter's documentation package

Patient selection is performed using the following diagnostic tools to assess the presence/absence of collateral ventilation:

1. The Stratx® Quantitative Lung CT Analysis provides, based on the CT scan of the patient, a non-invasive means to rule out patients with insufficient emphysema destruction and/or fissure completeness as this suggests too much collateral ventilation between lobes for the Zephyr® Valve procedure to be effective. In some cases, Stratx® can rule in a patient if the analysis shows 100% fissure completeness.
2. The Chartis® Pulmonary Assessment System: to confirm little or no collateral ventilation and appropriateness for the Zephyr® Valve procedure for otherwise eligible patients, a final physiological assessment with the Chartis® System is performed prior to the Zephyr® endobronchial valves placement.

Table 1: Regulatory status and international registration

Region/ country	Approval	Date	Indication
Europe*	CE mark	September 26th, 2003**	The Zephyr® Valve is an implantable bronchial valve intended to control airflow to improve lung function in patients with hyperinflation associated with severe emphysema and/or to reduce air leaks.
USA	PMA approval	June 29th, 2018	The Pulmonx Zephyr® Endobronchial Valves are implantable bronchial valves indicated for the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little to no collateral ventilation.
Australia	Therapeutic Good Certificate from TGA	October 12th, 2009	The Zephyr® Valve is an implantable bronchial valve intended to control airflow to improve lung function in patients with hyperinflation associated with severe emphysema and/or to reduce air leaks.
South Korea	Certificate from KFDA	June 12th, 2012	The Zephyr® Valve is an implantable bronchial valve intended to control airflow to improve lung function in patients with hyperinflation associated with severe emphysema and/or to reduce air leaks.
Brazil	ANVISA approval	August 16th, 2010	The Zephyr® Valve is an implantable bronchial valve intended to control airflow to improve lung function in patients with hyperinflation associated with severe emphysema and/or to reduce air leaks.
China	Certificate from SFDA and CFDA	February 17th, 2015 December 17th, 2013	

Abbreviations: *CE: Conformité Européenne; PMA: Premarket Approval; TGA: Therapeutic Goods Administration; KFDA: Korean Food and Drug Administration; ANVISA: Agência Nacional de Vigilância Sanitária; SFDA: State Food and Drug Administration; CFDA: China Food and Drug Administration*

** European CE mark: Under the European Economic Area (EEA) Agreement, Norway has the same rights and obligations as other EU Member States with regard to requirements for medical devices.*

*** Despite earlier approvals (such as the CE mark in 2003), the Zephyr Valve was introduced commercially in these countries only after rigorous clinical trials had been conducted to demonstrate clinical benefit and safety and define proper patient selection criteria.*

Literature search

Information about the search

According to information in the submission, the following databases were searched in April 2020: MEDLINE, EMBASE, Cochrane (CENTRAL) and ClinicalTrials.gov. The search was meant to update a search from a NICE guideline from 2017 [4] using the following PICO:

P	People with emphysema (heterogeneous or homogeneous)
I	Endobronchial valves (EBV), Zephyr® valves, PulmonX Inc after assessment of collateral ventilation with Chartis® flow sensor and catheter
C	Sham procedure or standard care
O	FEV_1, SGRQ, 6MWD test, BODE Index, pneumothorax episodes, COPD exacerbations episodes and death (for all causes, for respiratory complications, for IHD)

Results from the search

According to information in the submission, the submitter identified one record from the NICE guideline whereas 50 additional records were retrieved from the updated search. 44 records were excluded after screening (n=41) or because studies await assessment (n=3). Seven records from five RCTs were included.

Ongoing studies

The submitter searched for ongoing studies. The LIBERATE study has estimated completion in February 2023, and TRANSFORM is completed with no additional results. An ongoing study, called Zephyr Valve Registry (ZEVR) was still recruiting on August 4, 2021. There is a post-market clinical evaluation of the Zephyr Valve 5.5-LP EBV that was enrolling by invitation in September 2021, but no results were found. Finally, there is the Video Assisted Thoracic Surgery (VATS) Fissure Completion Prior to Zephyr® Endobronchial Valve Insertion (COVE) study which has estimated completion in December 2022.

Comments from NIPH on the search

The literature search included in the submission file was assessed by librarian Gunn Eva Næss and peer reviewed by librarian Elisabet Hafstad in October 2020. In brief, the search was too poorly documented to decide whether the search was of satisfactory quality, and hence Beate Kvist contacted the submitter for additional information regarding four main topics:

- The databases listed in Chapter 5.1.1 were not in accordance with the documented search strategy as shown in the appendix. In Chapter 5.1.1 it says that the search was conducted in Medline, in the appendix it says PubMed instead.
- The number of records (hits) found in each database was not reported, neither per search line nor per database. This is vital information when the librarian is going to test the database syntax and check for improvements.
- The search words mentioned in the PICO may differ from the words used in the search strategy in the appendix. What are the reason for this discrepancy?
- Chapter 5.1.1 in the submission refer to a NICE guideline from 2017, and it is stated that the search was based upon the PICO in the NICE guideline. It remains unclear to what extent the search performed in the submission is based on the search performed in the guideline.

The submitter responded to some of our questions, but not all issues were resolved:

- The syntax used in the searches in PubMed and Embase seems to contain errors. The submitter state they have searched in the interface of PubMed, but when we test the two first lines in a basic or advanced search we receive zero hits.
- We were able to replicate the search in Cochrane Library. Searching the same period as the one used in PubMed (01.01.2016 to 01.04.2020), we retrieved 258 hits from Cochrane alone. This is far more the 50 hits reported across all databases in the submission.

Taken together, the search in the submission file was poorly reported at best, presumably with important limitations. NIPH could not be confident that all relevant studies were identified and included in this STA, and we considered requiring more detailed documentation to proceed the STA submission. To help the process forward, however, NIPH decided to perform an independent scoping search for other systematic reviews. The search was performed in September 2021 and identified three relevant reviews [5-7]. We read the full texts, but these systematic reviews did not include any relevant primary studies apart from the five that we already had included. The scoping search was not exhaustive, and NIPH can still not guarantee that all relevant studies are identified and included. Based on information from the scoping search, however, NIPH found it reasonable to proceed with the STA submission.

Clinical effectiveness

Zephyr® valves system is produced by PulmonX. The treatment is indicated for patients with emphysema, which is a severe form of COPD (chronic obstructive pulmonary disease). The condition can either be heterogenous or homogenous with hyperinflation and must be symptomatic despite optimal medical treatment. In this section we present evidence on the clinical effectiveness of Zephyr® valves system in the treatment of emphysema.

Method

We used the documentation provided by the manufacturer. The manufacturer did not report whether they used independent screening and data extraction. We also used the risk of bias assessments provided by the manufacturer. The manufacturer did not use GRADE, but we have graded the evidence. One researcher did the GRADE assessments, and another person checked the assessments.

Outcomes and their importance

In line with the GRADE methodology, NIPH ranked outcomes by importance in collaboration with clinical experts:

- Critical outcomes:
    - Deaths and serious exacerbations (hospitalization and/or emergency room visits)
- Important but not critical
    - Moderate exacerbations, often defined as cures with systemic corticoids and/or antibiotics
    - Reduced pulmonary function: spirometry
    - Reduced health-related quality of life
    - Outcomes measuring activity or function
- Low importance for decision making
    - Mild exacerbations (increased use of bronchodilators and inhaled corticosteroids)

Some outcomes that were commonly reported in available studies were FEV_1 (forced expiratory volume in 1 second), SGRQ (St. George's Respiratory Questionnaire), 6MWD (6-minute walking distance test), and the BODE index (Body mass index, airflow Obstruction, Dyspnea and Exercise capacity). These outcomes were defined as important.

Included randomized controlled trials (RCTs)

Five RCTs were identified by the manufacturer. The five studies included a total of 498 patients. There were 295 who received Zephyr®, 178 received standard treatment, and 25 received sham valve placement.

Four studies (STELVIO, IMPACT, TRANSFORM, LIBERATE) used the Chartis®- system for detecting collateral ventilation and selecting suitable patients. The studies compared patients using Zephyr® plus standard treatment with patients who received standard treatment only. The fifth study (BeLieVeR-HIFI) employed fissure integrity on CT (surrogate for collateral ventilation) for patient selection and compared Zephyr® valve plus standard treatment with standard treatment plus a sham bronchoscopy procedure. Two comparisons were examined:

- Comparisons 1: Zephyr® valve compared with standard treatment
- Comparisons 2: Zephyr® valve compared with a sham procedure

There were seven outcomes reported for the comparison Zephyr versus standard treatment, four continuous (FEV1, SGRQ, 6MWD test, BODE Index) and three dichotomous (pneumothorax episodes, COPD exacerbation episodes and death). For the comparison Zephyr versus sham valve placement, there were no reports for death, 6MWD or BODE-index.

Table 2. Overview of available randomized controlled trials

Study (acronym, ref.), design	**Population**	**Intervention**	**Comparison**
STELVIO [8], Single center	Severe emphysema (homogenous and heterogenous) and absence of collateral ventilation confirmed by Chartis®. 34 patients received Zephyr® valves and 34 received std. treatment.	Chartis® assessment of CV and Zephyr® valves	Standard treatment
LIBERATE [9] , International multicenter	Severe heterogenous emphysema and with little or no collateral ventilation in the target lung confirmed by Chartis®. 128 patients received Zephyr® and 62 patients received std. treatment.	Chartis® assessment of CV and Zephyr® valves	Standard treatment
IMPACT [10] , International multicenter	Homogenous emphysema and absence of collateral ventilation confirmed by Chartis®. 43 patients received Zephyr® valves and 50 patients received standard treatment.	Chartis® assessment of CV and Zephyr® valves	Standard treatment
TRANSFORM [11], International multicenter	Severe heterogenous emphysema and absence of collateral ventilation confirmed by Chartis®. 65 patients received Zephyr® valves and 32 patients received standard treatment.	Chartis® assessment of CV and Zephyr® valves	Standard treatment
BeLieVeR-HIFI [12], Single specialist center	Heterogenous emphysema and intact interlobar fissures confirmed by CT scan. 25 patients received Zephyr® valves and 25 patients received sham valve placement.	CT scan assessment of complete fissures and Zephyr® valves	Sham procedure

Risk of bias for included studies

The submitter assessed the risk of bias using the Cochrane's risk of bias tool (Figure 1). The tool consists of seven domains that may be associated with systematic bias in the studies' and impair the internal validity of the study. Each domain is rated as low risk of bias (green +), unclear risk of bias (yellow ?), or high risk of bias (red -).

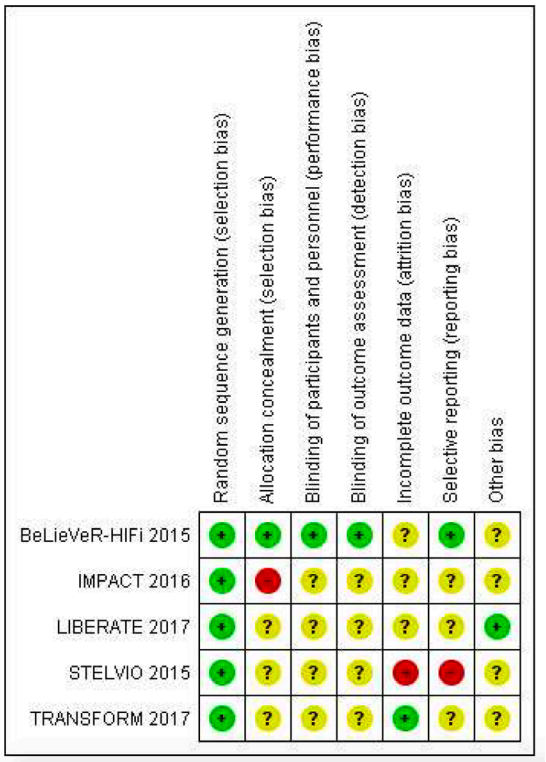


Figure 1. Risk of bias as assessed in the submitter's documentation package

NIPH's comments to risk of bias assessment

The risk of bias assessment graph is characterized by a high proportion of unclear ratings. This is unfortunate, as the risk of bias assessment is therefore inconclusive. Risk of bias assessments should ideally be performed at the outcome level, as the risk of bias can affect outcomes differently. For example, lack of blinding will inevitably be a more serious problem for outcomes based on subjective assessments than for objective outcomes such as mortality.

The high proportion of unclear ratings indicate that the assessors lack information to perform a complete assessment. This might have been different if the submitter had contacted the authors of the included trials, but the submitter did not report any contact with authors.

Effect of Zephyr versus standard care

Mortality

Four studies contibuted data to the metaanalysis, but the analysis is based on only seven deaths (7/270 – 2.59%) in the Zephyr®-group and two (2/178 – 1.12%) in the standard treatment group. Pooled risk ratio was 1.61 (95% CI 0.44 to 5.93, Figure 2), but the quality of the evidence was rated as very low implying that no clear conclusions could be reached about Zephyr® valve treatment and the risk of all-cause death mortality.

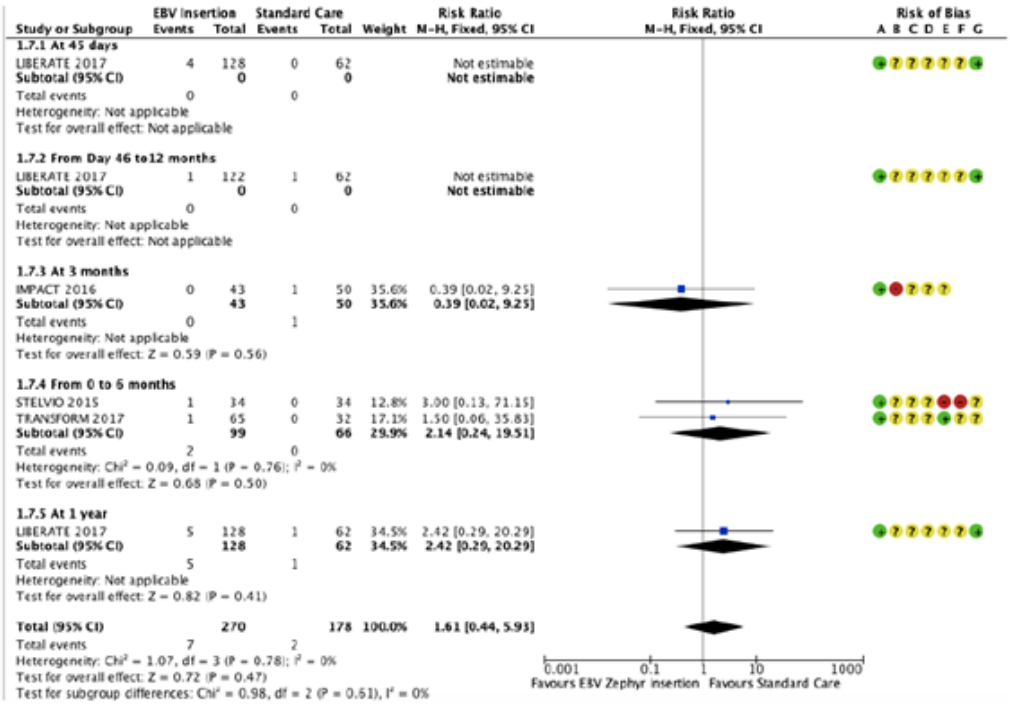


Figure 2. Meta-analysis of mortality. Figure from the submitter's documentation package.

Exacerbations

There may be little or no difference in the number of COPD exacerbations between Zephyr® and standard care (Figure 3). None of the studies found a significant difference, but the results of the meta-analysis are based on only 59 events in patients treated with Zephyr®. Hence, the results are uncertain with OR 1.15 a confidence interval ranging from 0.70 to 1.88.

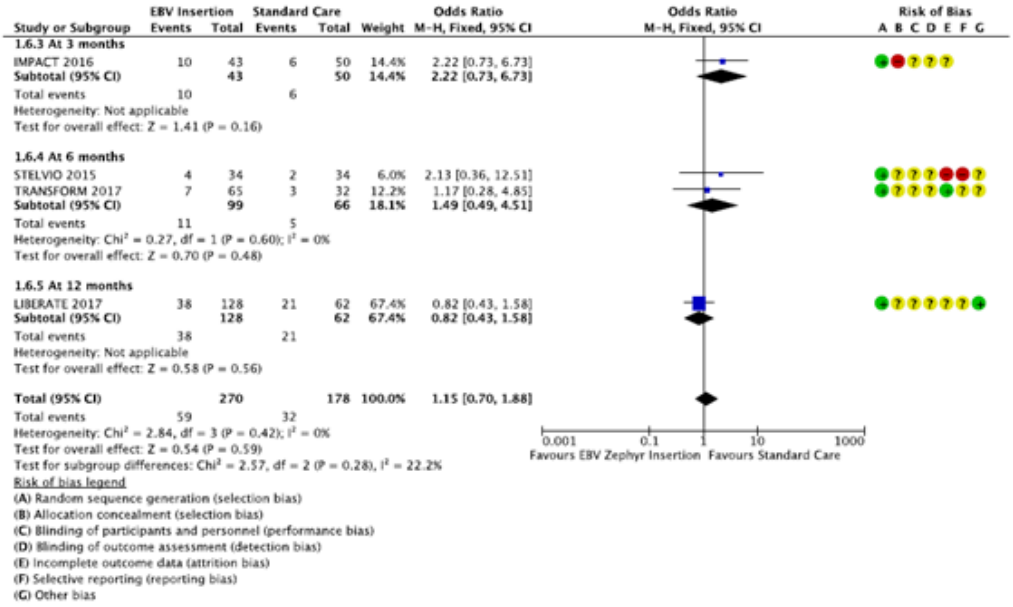


Figure 3. Meta-analysis of effect on exacerbation episodes of COPD. Illustration from the submitter's documentation package

FEV1

Figure 4 shows percent improvement in FEV_1 compared with baseline in the five RCTs. The minimal clinically important difference [MCID] was set to appoximately 12% [13, 14]. All available studies showed improvements larger than the MCID.

A meta-analysis (Figure 5) showed that the Zephyr®-group had larger improvements in FEV_1 than the control group in all available trials. Studies included in the meta-analyses had different follow-up periods ranging from three to twelve months, but there was no serious heterogeneity in the results. The difference between the groups were 0.14 liters, with a 95 percent confidence interval ranging from 0.13 to 0.16 liters.

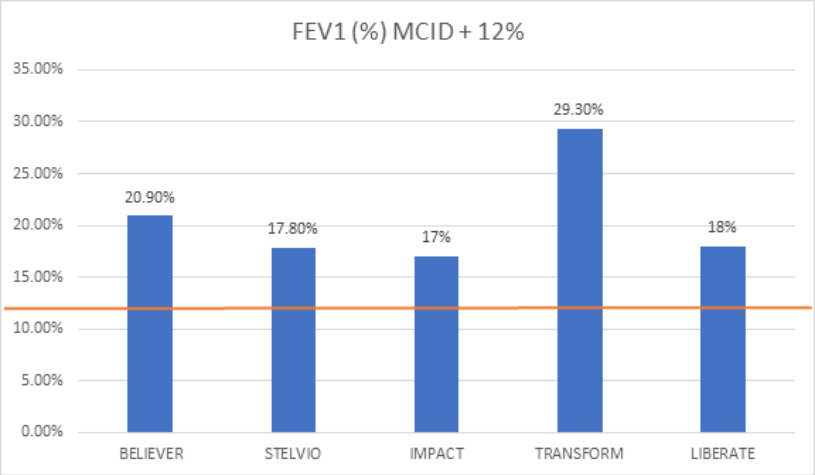


Figure 4. Percent improvement on FEV_1 compared with baseline in the five RCTs. Figure from the submitter's documentation package

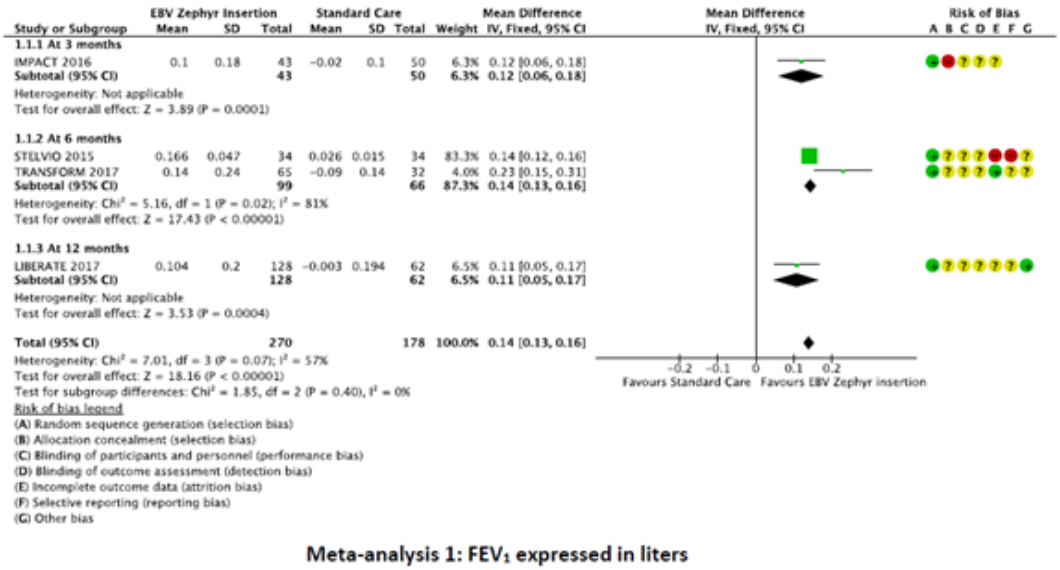


Figure 5. Meta-analysis of FEV_1. Illustration from the submitter's documentation package

St. Georges's Respiratory Questionnaire (SGRQ)

The Zephyr®-group showed more favorable scores on the St. Georges's Respiratory Questionnaire (SGRQ) than standard care. Follow-up ranged from three to twelve months, but the heterogeneity was small. The difference was almost 8 points in favour of Zephyr®, with a 95 percent confidence interval ranging from 5 to 11 points. In comparison, the minimal clinical important difference (MCID) is estimated to 4 points [13].

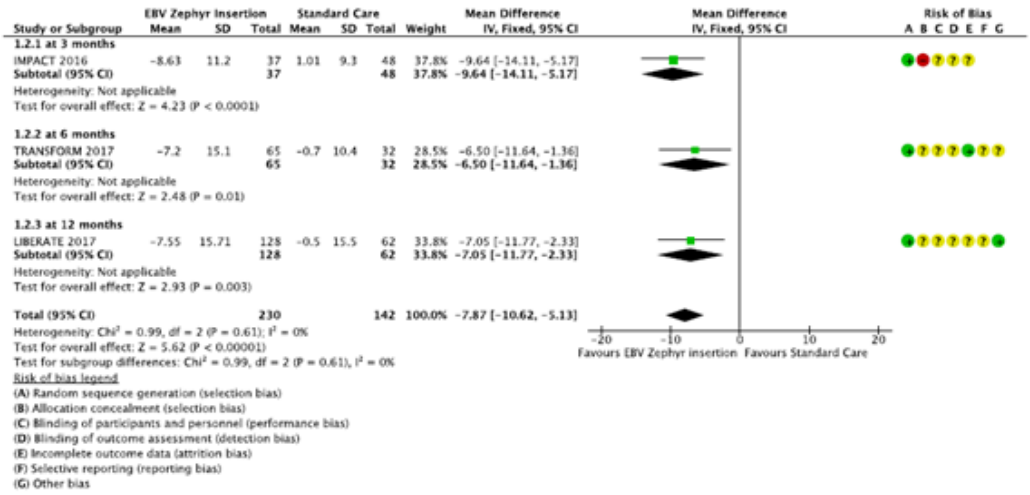


Figure 6. Meta-analysis of the effect on SGRQ-score. Illustration from the submitter's documentation package

Six minute walking distance (6MWD)

The meta-analysis in Figure 7 showed better 6-minute walking distance (6MWD) results in the Zephyr®-group than in control. Only the IMPACT study had 3 months follow-up. STELVIO and TRANSFORM had 6 months follow-up. The results were heterogenous across the studies, but the meta-analyses showed favourable outcomes following Zephyr®. Fixed-effect meta-analyses resulted in an MD of 55.75 metres (95% CI 42.56 to 68.94). Due to the heterogeneity, the random-effects model resulted in a somewhat broader confidence interval i.e. MD 57.00 metres (95% CI 36.33 to 77.67). For comparison, the minimal clinical imprtant diffence for 6MWD in people with severe COPD is estimated to be in the around 30 metres [15].

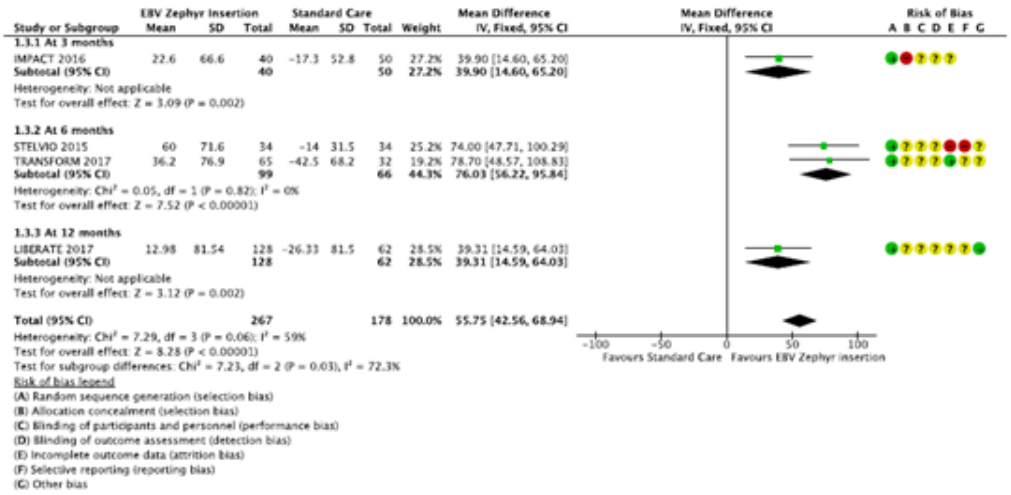


Figure 7. Meta-analysis of effect on 6MWD. Illustration from the submitter's documentation package

BODE index

Measurements of the BODE index (Body mass index, airflow Obstruction, Dyspnea and Exercise capacity) were in favour of the Zephyr®-valve in all studies (Figure 8). The BODE-index generally ranges from zero to ten, and lower scores are better. Pooled estimate across all four studies showed that the BODE index was 1.30 point lower (95% CI -1.62 to -0.99) after Zephyr® than in the control group. For comparison, a change above one point has been taken as a clinicial important difference in BODE for patients with severe emphysema [16].

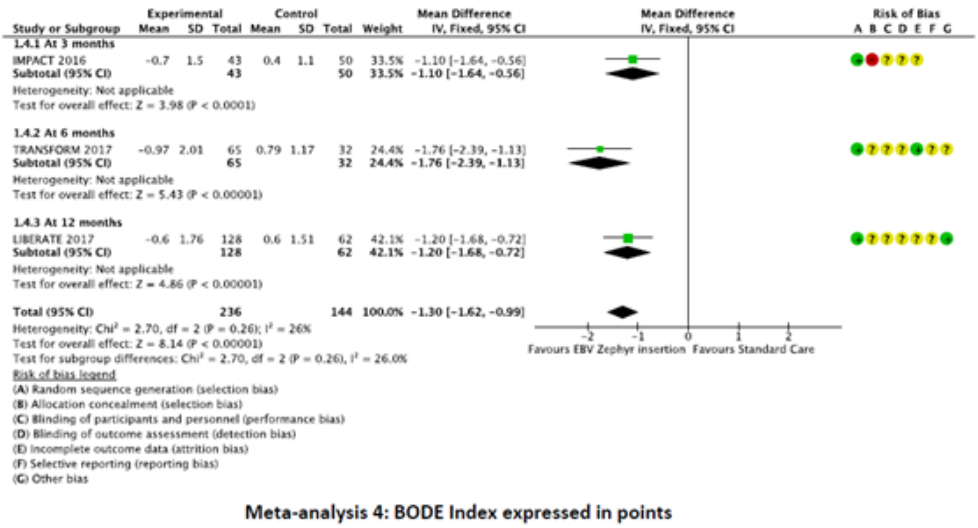


Figure 8. Meta-analysis of effect on the BODE-index. Illustration from the submitter's documentation package

Pneumothorax

Figure 8 is a meta-analysis of pneumothorax and shows best results for standard treatment in all four studies with this outcome. Odds ratio for pneumothorax is 34, but the 95 percent confidence interval ranges from 8 to 142. Hence, the risk for pneumothorax is uncertain because the meta-analysis is based on only 75 events.

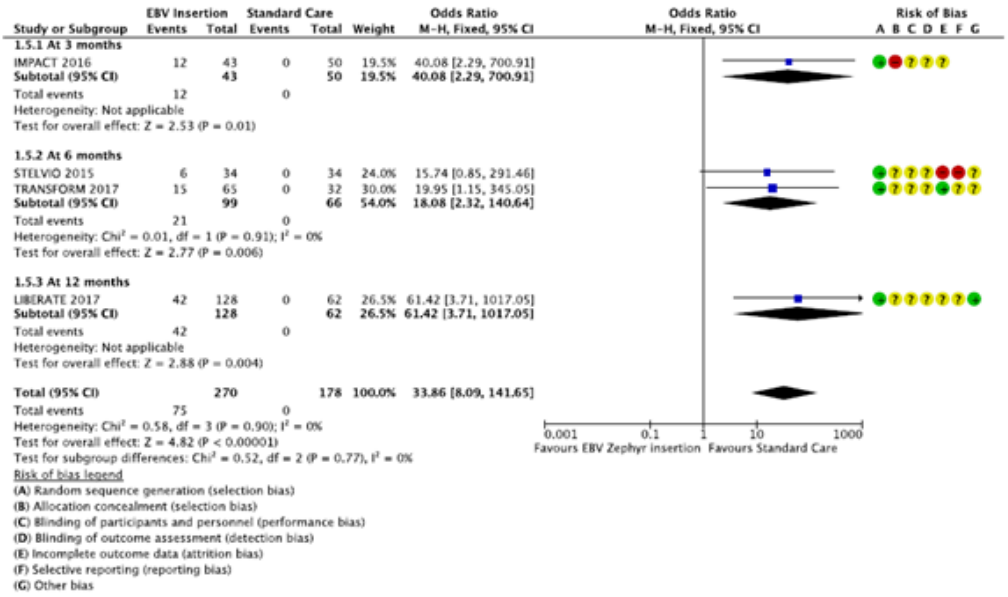


Figure 9. Meta-analysis of effect on incidence of pneumothorax. Illustration from the submitter's documentation package

Effect of Zephyr versus sham

Results for this comparison are based on one small RCT (BeLieVeR-HIFI) with 50 participants. According to the GRADE assessments, we have very low confidence in all effect estimates reported in this study, mainly because of concerns regarding risk of bias and very serious imprecision (few participants and very wide confidence intervals).

Assessment of certainty of the evidence

The GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) is a system to evaluate the overall quality of the body of evidence from a systematic review and to produce Summary of Findings tables to present the evidence to decision makers. Systematic reviewers can use GRADE to move from the results of the systematic review to make conclusions and to present the evidence. As a prolongation of the GRADE assessments, we have adhered to standardized statements for reporting effects as suggested by Cochrane [17].

NIPH used GRADE for assessing the quality of the documentation on the most important outcomes (Tables 3-4). Table 3 is a summary of findings table (SoF-table) for the comparison Zephyr versus standard treatment, and Table 4 is a SoF-table for the comparison Zephyr versus sham treatment.

The four studies included in Table 3 compare Zephyr® versus standard care. An additional trial with 50 patients (**BeLieVeR-HIFI**) compared Zephyr versus a sham procedure (Table 4). Response to treatment was assessed at 3 months. Our confidence in the results ranged from moderate to very low for Zephyr versus standard care. All results were graded as very low for Zephyr versus sham.

Zephyr valve versus standard treatment

Table 3 Summary of findings for Zephyr® compared to standard treatment. Certainty of evidence assessed by NIPH.

Patient or population: COPD
Setting: Hospital
Intervention: Zephyr® valve
Comparison: standard treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard treatment	**Risk with Zephyr® valve**				
Death follow up: range 45 days to 12 months	11 per 1 000	**18 per 1 000** (5 to 67)	**RR 1.61** (0.44 to 5.93)	448 (4 RCTs)	⨁◯◯◯ VERY LOW [a,c]	
COPD Exacerbations follow up: range 3 months to 12 months	180 per 1 000	**201 per 1 000** (133 to 292)	**OR 1.15** (0.70 to 1.88)	448 (4 RCTs)	⨁⨁◯◯ LOW [a,e]	
Pneumothorax follow up: range 3 months to 12 months	0 per 1 000 (0 to 20)	**253 per 1 000** (202 to 309)	**OR 33.86** (8.09 to 141.65)	448 (4 RCTs)	⨁⨁◯◯ LOW [a,d]	Risk with Zephyr (95% CI) computed from meta-analyses in Figure 9
FEV1 follow up: range 3 months to 12 months		MD **0.14 higher** (0.13 higher to 0.16 higher)	-	448 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	
Change in 6MWD follow up: range 3 months to 12 months		MD **55.75 higher** (42.56 higher to 68.94 higher)	-	445 (4 RCTs)	⨁⨁◯◯ LOW [a,b]	
SGRQ follow up: range 3 months to 12 months		MD **7.87 lower** (10.62 lower to 5.13 lower)	-	372 (3 RCTs)	⨁⨁⨁◯ MODERATE [a]	
BODE Index follow up: range 3 months to 12 months		MD **1.3 lower** (1.62 lower to 0.99 lower)	-	380 (3 RCTs)	⨁⨁⨁◯ MODERATE [a]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Many unclear risk of bias assessments. **b**. I-square is high.**c.** Downgraded two for wide CI. **d**. Few events. **e**. Downgraded one for wide CI.

Zephyr® valve versus sham

Table 4 Summary of findings for Zephyr® compared to sham treatment. Certainty of evidence assessed by NIPH.

Zephyr® valve compared to sham for COPD

Patient or population: COPD
Setting: Hospital
Intervention: Zephyr® valve
Comparison: sham valve placement

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with sham	Risk with Zephyr® valve			
Death - not reported				-	-
No with **exacerbation** follow-up: mean 3 months	800 per 1 000	**448 per 1 000** (448 to 912)	**RR 0.56** (0.56 to 1.14)	50 (1 RCT)	⨁◯◯◯ Very low [a,b,c]
No with **Pneumothorax** follow-up: mean 3 months	40 per 1 000	**80 per 1 000** (8 to 827)	**RR 2.00** (0.19 to 20.67)	50 (1 RCT)	⨁◯◯◯ Very low [a,b,c]
6MWD - not reported	-	-	-	-	-
No with >15% improvement in **FEV1** (FEV1) follow-up: mean 3 months	42 per 1 000	**391 per 1 000** (54 to 1 000)	**RR 9.39** (1.29 to 68.38)	47 (1 RCT)	⨁◯◯◯ Very low [a,b]
No with 4-point reduction in **SGRQ** follow-up: mean 3 months	458 per 1 000	**477 per 1 000** (261 to 880)	**RR 1.04** (0.57 to 1.92)	47 (1 RCT)	⨁◯◯◯ Very low [a,b,c]
BODE index - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Incomplete outcome data and other bias.
b. Wide CIs and low n
c. Effect size ranges from positive to negative.

Health economic evaluation

METHOD

Methods for evaluating submitted cost-effectiveness models

The primary objectives of health economic modelling are to provide a mechanism to determine the relative cost-effectiveness of the specified health intervention(s) compared to standard treatment using the best available evidence, and to assess the most important sources of uncertainty surrounding the results. To make comparisons across different treatment modalities and multiple health outcomes, economic models typically measure health outcomes in terms of quality-adjusted life years (QALYs), a variable designed to capture both life extension and health improvement. QALYs, by definition, take on a value of 1 for perfect health and 0 at death. The output of a cost-effectiveness model is expressed as an incremental cost-effectiveness ratio (ICER), which can be thought of as the extra cost of obtaining an extra life-year in perfect health. The ICER is defined as:

$$Cost_{Intervention} - Cost_{Comparator} \Big/ QALY_{Intervention} - QALY_{Comparator}$$

There is no single correct way to build economic models estimating the cost-effectiveness of a specific health intervention. Modelling requires consulting with clinical experts to gain understanding of expected disease progression, and to determine relevant treatment population, comparators, health outcomes and adverse events connected to treatment. This information informs the basic model structure and determines which clinical effect data is most important to retrieve in the systematic literature search. Once the model structure is in place, systematic searches and evidence grading are used to provide the most reliable risk information for the model, but also to collect relevant cost and quality of life data that is needed for cost-effectiveness calculations.

A model is rarely meant to capture every potential detail of the treatment landscape; rather the goal is to include sufficient details to provide a realistic view of the most significant pathways in disease progression, given the research question(s) one is trying to answer. Evaluation of health economic model is primarily about determining whether the choices made by the submitter regarding model structure and treatment comparator are reasonable; whether baseline epidemiological data reflect the population in which the analysis is being performed; whether the clinical effect data used in

the model have adequate quality; whether resource use and costs reflect the conditions of the healthcare system in question; whether there has been sufficient sensitivity and scenario analyses to determine the degree and sources of uncertainty in the model results; and whether the model displays external and internal validity. Checklists are available to help researchers systematically examine these issues.

We proceed by first describing the health economic model used in the manufacture's submission and the results generated by the model. We then provide our evaluation of the model, focusing on the following issues: model structure, choice of model parameters, use of appropriate sensitivity and/or scenario analyses to examine the extent of uncertainty in model results, and relevance of the model for the Norwegian context.

Previously published cost-effectiveness analyses

The submitter described two previously published cost-effectiveness analyses of Zephyr® valve compared to standard care, Pietzsch et al. [18] and Hartman et al [19]. The latter presented somewhat more cost-effective results than the former (Table 5).

***Table 5**: Submitted published cost-effectiveness analyses*

Publication	Population	Comparison	ICER
Cost-effectiveness of endobronchial valve therapy for severe emphysema: A model-based projection based on the VENT study, Germany [18]	58% Male, Mean age 62	Zephyr® valve vs. Standard care	5-year time horizon, discounted ICER: €46,322 per QALY gained 10-year time horizon, discounted ICER: €25,142 per QALY gained
Cost-effectiveness of endobronchial valve treatments in patients with severe emphysema compared to standard medical care, Netherlands [19]	N: 40 (Female/ men: 26/14) Mean age 59	EBV vs. Standard Care	6-month time horizon, discounted ICER: €205,129 per QALY gained 5-year time horizon, discounted ICER: €39,000 per QALY gained 10-year time horizon, discounted ICER: €21,500 per QALY gained

ICER: Incremental Cost Effectiveness Ratio; QALY: Quality Adjusted Life Years; EBV: Endobronchial Valve

Population, intervention, and comparator in the cost-effectiveness model

The submitted population, intervention, and comparator

The submitter used the same patient characteristics as found in the Liberate trial , which was a multicenter randomized controlled trial in the United States to evaluate the effectiveness and safety of Zephyr® in patients with heterogenous emphysema and little to no collateral ventilation. Patients were followed for twelve months, and their age ranged from 40 to 75 years. The primary outcome was percentage of patients with post-bronchodilator FEV_1 improvement from baseline of greater than or equal to 15%.

The intervention and comparator were taken from the cost-effectiveness analysis compiled by Hartman et al. [19]. Hartman et al. incorporated the same intervention and comparator as found in the STELVIO trial [8] which was supported by a grant from the Netherlands Organization for Health Research and Development and the economic evaluation was part of the original trial.

In the submitted model, the starting age of the hypothetical cohort was assumed to be 65-years old. A total of 1000 patients were included in each treatment arm. A thousand patients of the treatment arm were screened with the Chartis System, and patients likely to benefit from the treatment (i.e., no collateral ventilation) received Zephyr® valve insertion. The other 1000 patients were not screened and received standard care.

Norwegian Institute of Public Health assessment of the submitted population, intervention, and comparator

The population used in the cost-effectiveness model was based on a U.S. population and the age ranged from 40–75 years old. Based on feedback from our clinical experts, this range includes the start age of severe emphysema in Norway which is around 65 years. The submitted intervention and comparator are in line with our predicted PICO.

Model structure

The submitted model structure

The submitter adapted a model from a published cost-effectiveness analysis [19]. The submitted model was based on a Markov model with weekly cycles built in Microsoft Excel and assessed lifetime health outcomes and economic consequences of Zephyr® valve (EBV: Endobronchial valve) compared with standard care in patients with severe emphysema. A 10-year time horizon was used, and a 3-year scenario analysis was reported. The discount rate in the submitted model was 4% for both costs and QALYs.

The submitted model included two arms: A Zephyr® valve arm and a standard care arm. In the first step the submitted model assigned patients with severe emphysema to either Zephyr® valve or standard care. In the second step the individuals enter the Markov part of the model. The model determines changes in GOLD stages of the

individuals in every cycle by assigning probabilities to maintaining the current health status, becoming worse and progressing to the next GOLD stage based on the treatment arm (control or EBV). At each cycle of the GOLD stage, patients would follow the adjusted mortality for the relevant GOLD stage [21] and an age adjusted background mortality for the remaining survivors in Norway (for decision life-time of 10-years) [22] (Figure 10). The incidence of pneumothorax events was not reflected in the model's structure, but rather included as a cost added to total cost calculations.

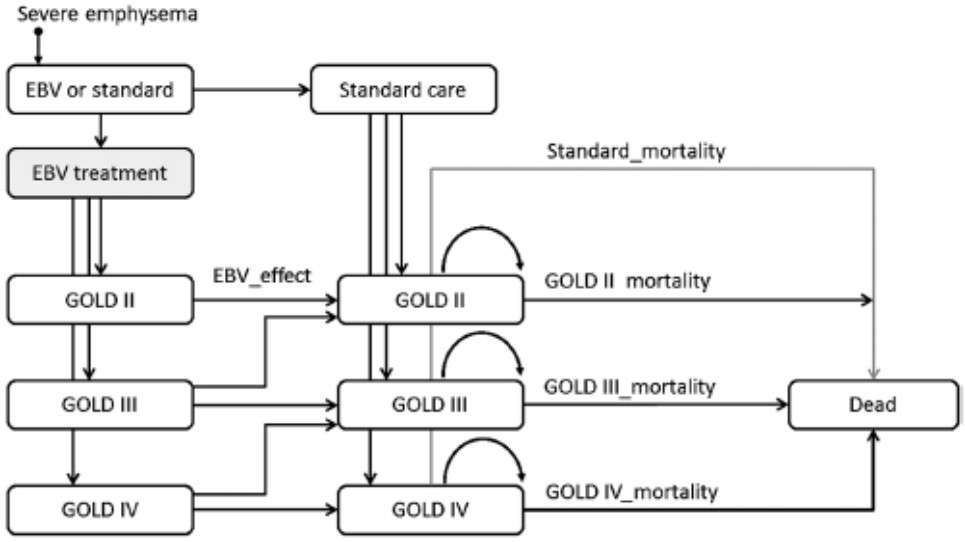


Figure 10: Submitted Markov model structure under long-term evaluation. Taken from Hartman et al. [19]

Markov Health States

Health states in the Markov model were defined by the GOLD classification system. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) introduced a classification system of COPD based on exacerbation history, symptom burden and airflow limitation. It is used to guide treatment and assess individual risk of hospitalisation

GOLD I: - Mild, FEV-1 ≥80%. Patients may have no symptoms but may experience shortness of breath while walking fast at the ground level or during a slight incline.

GOLD II: Moderate, FEV-1 50-79%. Patients may need to stop after a few minutes of walking at the ground level to catch breath.

GOLD III: Severe, FEV-1 30-49%. Patients may be too short of breath while performing simple tasks such as dressing and may find it difficult to leave the house.

GOLD IV: Very Severe, FEV-1 ≤30%. Patients may have heart or lung failure; this can make it difficult for patients to catch breath while resting. This can be categorized as End stage COPD. Exacerbations are also reported to happen in Stages II to IV.

NIPH assessment of the submitted model structure

Other cost-effectiveness analyses of treatment strategies related to COPD have looked at different health status, such as “Mild COPD”, “Moderate COPD”, “Severe COPD”, “Very severe COPD” and “Dead” as an alternative to different GOLD stages [18]. These models were based on GOLD restaging at 12 months and then followed natural history of COPD. Our clinical expert recommended using FEV1 in combination with quality of life, exacerbation, mortality, and cardiovascular comorbidity as indicators for categorization, instead of different GOLD stages. However, for this single technology assessment, we accept the structure of the submitted model.

NIPH find that some structural assumptions are worth highlighting. First, transition probabilities and treatment effect are assumed to be constant after 12 months. This might over-estimate the treatment effect given that the longest follow-up period in all studies included in the review was 12 months. There is a lack of published evidence on the treatment effect being constant over time in contrast with the outcomes in the control group. We believe, the lack of evidence should be taken into consideration when considering the impact of treatment over long time periods.

The intervention is applied to a starting cohort of patients aged 65, whereas a subgroup analysis of older patients treated with EBV could have provided meaningful insights on the cost-effectiveness. Studies have reported a higher rate of pneumothorax for EBV procedures and leading to rapid loss of volume in the targeted lobe [25]. Furthermore, EBV therapy has been demonstrated to show more benefits in patients with heterogeneous disease [25]. Finally, the impact of complications and comorbidities on EBV’s treatment effect cannot be yet reflected in the form of a QALY which adds to the overall uncertainty of the true effect of Zephyr® valves and impacts on cost- effectiveness estimates over extended time horizon.

Model parameters

Submitted clinical efficacy data

The submitted Markov model was populated with a hypothetical cohort of 1000 patients with severe emphysema (40% females) in each treatment arm across GOLD stages starting at 65-year-old. Forty percent of the patients were assumed to be in GOLD stage 3 and 60% in GOLD stage 4. The assumption may be based on the allocation criterion in the STELVIO trial [8] (32% patients in GOLD stage 3 and 68% patients in GOLD stage 4).

The transitions between the GOLD stages were modelled according to the short-term data from the LIBERATE trial [9] from 1.5- 6 months and 6 months to one year. The transition probabilities were converted from months to weeks using the rates to probability method. After one year the transition probabilities were assumed to be constant for a period of ten years, based on six months to one-year weekly probabilities. However, as the data from LIBERATE provided no information on transition probabilities

for GOLD stage 2 to 3 or 4 (for baseline to 45 days), the submitter assumed these to be the same as 1.5 – 6 months. The weekly probabilities were adjusted according to the mortality per GOLD stage (see Table 6) and age-based background mortality in Norway. Figure 11 and Figure 12 present the Markov trace for standard care and EVB, respectively for a 10-year time horizon.

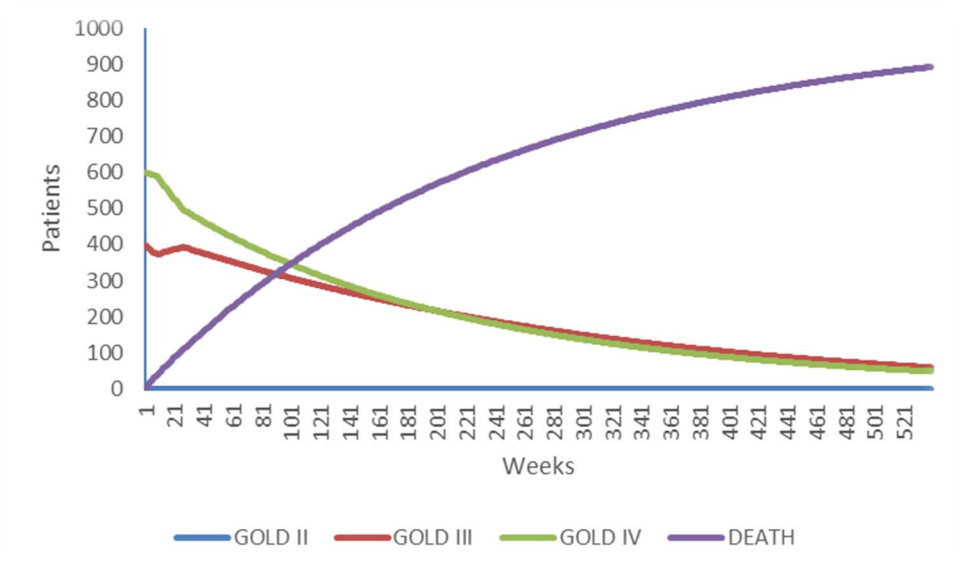


***Figure 11**: Markov Trace: Standard care*

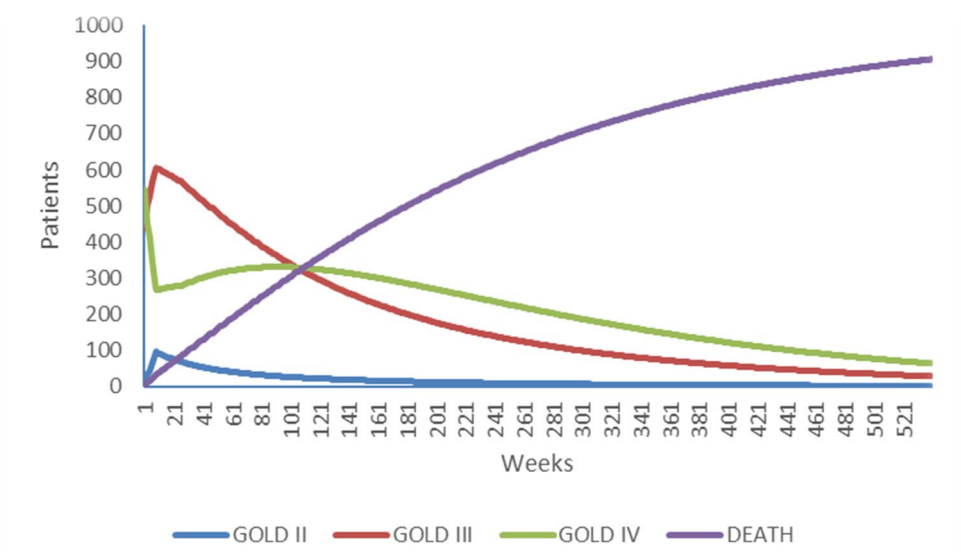


Figure 12. Markov Trace for Endobronchial Valve

Table 6: Expected mortality rates for different GOLD stages

Mortality	Standard care	EBV	Source
GOLD II	0.001/week	0.001/week	Afonso et al.
GOLD III	0.002/week	0.002/week	Afonso et al.
GOLD IV	0.006/week	0.006/week	Afonso et al.

The submitted model only included pneumothorax as a complication or adverse event. The submitter considered 28 pneumothorax episodes per 100 patients occuring in the intervention arm, and 0 in the standard care arm. This was based on the occurrence of the pneumothorax episodes in the included RCTs, hence, assumed 20 episodes to have taken place in the first three days after Zephyr® valve insertion. The remaining eight episodes of pneumothorax in the intervention arm were assumed to have occurred between day four and the end of the 12-month follow-up period. The included complication was charged as a weekly cost to the model based on the number of patients surviving between 0-12 months. Other complications were excluded in the submitted model, because the meta-analysis did not show any significant difference in their occurrence after Zephyr® valve insertion or during standard care.

Submitted cost data

The presented costs are procedure costs as well as adverse events costs for the compared alternatives. There was no association between health states (GOLD stages) and costs, rather these were associated with the time from treatment with Zephyr® as 0-6 months, 7-12 months and 12 months onwards after Zephyr®.

All costs in EURO were converted to NOK at an exchange rate of €10.6932/ NOK as on October 8th, 2020 (1NOK = €0.0935171). Weekly costs were calculated from baseline to 6 months, 7- 12 months, and 12 months onwards. In-addition the submitted cost data included the choice of appropriate NCRP codes for chest X-rays based on the submitter's evaluation.

Table 7: Cost Data

Activity	Unit costs	Quantity	Total
Cost of Standard care			
Screening			
Polyclinical consultation for COPD	€ 261.31	1.00	€ 261.31
CT scan (NCRP code SSC0AD tariff CT2 represents 40% of costs; multiplied by 2,5)	€ 63.36	1.00	€ 63.36
Polyclinical consultation for COPD	€ 261.31	4.00	€ 1 045.24
Total cost of standard care before any intervention			**€ 1 369.91**
Cost of EBV			
Hospitalization (days)	€ 865.46	3.00	€ 2 596.38
Chartis assessment	[redacted]	1.00	[redacted]
CT scan	€ 63.36	1.00	€ 63.36
Zephyr valves	[redacted]	4.00	[redacted]
Anaesthetist (hours)	€ 77.90	1.00	€ 77.90
Pneumologist (hours)	€ 62.28	1.00	€ 62.28
Nurse (hours)	€ 30.86	1.00	€ 30.86
ELS Charger and EDC catheter	[redacted]	1.00	[redacted]
Surgery room (hour)	€ 1 340.79	1.00	€ 1 340.79
Chest x-ray (NCRP code SSC0AA RG Thorax tariff RG1 represents 40% of costs; multiplied by 2,5)	€ 3.79	2.00	€ 7.58
Complications during index hospitalization- per patient			
Pneumothorax episodes during post procedure (5 hospital days + 30 min. pneumologist)	€ 4 377.72	0.20	€ 875.54
Re bronchoscopy with valve removal (DRG 88)	€ 3 739.75	0.12	€ 448.77
Re bronchoscopy with valve repositioning: cost of valve placement with the cost for 1 valve.	[redacted]	0.10	[redacted]
Complications during 1- year fu			
Polyclinical consultation for COPD 1-year follow up	€ 261.31	4.00	€ 1 045.24
Pneumothorax during follow up (DRG 95)	€ 5 264.83	0.08	€ 421.19
Total cost EBV insertion			[redacted]

Table 8. EBV 6-month period and weekly costs

Activity	Unit costs	Quantity	Total
Cost of EBV – costs 0-6 months			
Pneumothorax episodes during post procedure (5 hospital days + 30 min. pneumologist)	€ 4 377.72	0.20	€ 875.54
Re bronchoscopy with valve removal (DRG 88)	€ 3 739.75	0.06	€ 224.39
Re bronchoscopy with valve repositioning: cost of valve placement with the cost for 1 valve.	[redacted]	0.05	[redacted]
Polyclinical consultation for COPD 1-year fu	€ 261.31	2.00	€ 522.62
Pneumothorax during fu (DRG 95)	€ 5 264.83	0.04	€ 210.59
Total 0-6 months			€ 2 164.45
Weekly costs 0-6 months			[redacted]
Cost of EBV – costs 7-12 months			
Re bronchoscopy with valve removal (DRG 88)	€ 3 739.75	0.06	€ 224.39
Re bronchoscopy with valve repositioning: cost of valve placement with the cost for 1 valve.	[redacted]	0.05	[redacted]
Polyclinical consultation for COPD 1-year fu	€ 261.31	2.00	€ 522.62
Pneumothorax during fu (DRG 95)	€ 5 264.83	0.04	€ 210.59
Total 7- 12 months			[redacted]
Weekly costs 7- 12 months			[redacted]
Cost of EBV –12 months and onwards			
Polyclinical consultation for COPD	€ 261,31	4.00	€ 1 045.24
Weekly cost 12 months and onwards			**€ 20.10**

Table 9. Standard care 6-month period and weekly costs

Activity	Unit costs	Quantity	Total
Cost of Standard care: 0-6 months			
Polyclinical consultation for COPD	€ 261.31	1.00	€ 261.31
CT scan	€ 63.36	1.00	€ 63.36
Polyclinical consultation for COPD	€ 261.31	2.00	€ 522.62
Total 0-6 months			€ 847.29
Weekly costs 0-6 months			**€ 32.59**
Cost of standard care: 7-12 months			
Polyclinical consultation for COPD	€ 261.31	2.00	€ 522.62
Weekly cost 7-12 months			**€ 20.10**
Cost of standard care: 12 months and onwards			
Polyclinical consultation for COPD	€ 261.31	4.00	€ 1 045.24
Weekly cost 12 months and onwards			**€ 20.10**

A detailed overview of costs was provided in the submitter's report. We only present a summary of the most imperative assumptions below.

Zephyr valve insertion and medical costs

Zephyr valve insertion procedure took an average of 60 minutes and the resource use costs of (anesthetist, pneumologist, nurse, surgery room) were estimated from the Salary Expert Compensation Data in Oslo [26]. The average hourly costs of health personel were calculated from Salary expert Comission, 2020 and also adjusted for Covid-19 impact. Furthermore, the cost of the EBV was based on four valves per patient based on STELVIO trial [8] and included cost of follow-up and pneumothorax episodes.

The submitter was not able to find the cost for an operation room in Norway and instead used UK estimates [27]. However, the cost of hospital stay in Norway was derived from WHO choice estimates of cost for inpatient and outpatient health service delivery [28] and estimated to be three days (Table 7).

Further medical costs such as chest X rays were calculated based on the NCRP code SSC0AA (these were taken at 4 and 24 hours after the intervention). The reimbursement tariff for category RG1 represents about 40% of the resource costs and has therefore been multiplied by 2.5 to obtain the total costs. Valve removal costs were based on the DRG88 tariff (Kroniske obstruktive lungesykdommer (KOLS))[29]. In the case of a valve repositioning or replacement (involving the use of a new valve), the calculated cost for valve placement (with only 1 Zephyr® valve, no Chartis assessment and no CT scan) was used. For the frequencies of valve removal or replacement a weighted average method was used to compute the average frequency per 100 patients across LIBERATE [9], STELVIO [8], IMPACT [10] AND TRANSFORM [11] (Table 10).

Table 10. Ocurrence of Zephyr valves removal, repositioning and replacement

Study	LIBERATE	STELVIO	IMPACT	TRANSFORM	Total	Weighted average per 100 patients
No. patients receiving EBV in trial	**128**	**34**	**43**	**54**	**270**	/
Event						
Valve removal	17	5	5	5	32	12
Valve repositioning/ replacement	19	4	3	1	27	10

Adverse events and complications

As mentioned above, the submitter only included the cost of pneumotorax treatment since meta-analyses did not show a significant difference in the occurance of other complications such as COPD exacerbations. In addition, death-related costs were also excluded on the basis of not significant difference between both treatment arms.

Submitted Health Related Quality of Life (HRQoL) data

The submitter presented utility data derived from St. George's Respiratory Questionnaire (SQRQ), the 6-minute walking test (6MWD test) and Quality Adjusted Life Years (QALY) based on the Preference-based measure EuroQol5-Dimension's questionnaire (EQ5D). HRQoL data was taken from the STELVIO trial [8]. Utility estimates were time dependent and not estimated according to the relevant GOLD stage.

***Table 11**. Utility data found in submission based on the STELVIO trial*

Utility scores	Standard Care	Zephyr®	Source
EQ5D 0 month	0.66	0.63	STELVIO trial
EQ5D 1 month	0.72	0.75	STELVIO trial
EQ5D 6 months	0.67	0.75	STELVIO trial
EQ5D 12 months	0.66	0.77	STELVIO trial + extrapolated

EBV: Endobronchial Valve; EQ5D: EuroQol5-Dimensions; GOLD: Global Initiativ for Chronic Obstructive Lung Disease

NIPH assessment of the submitted model parameters

Efficacy data

In the submitted model the transitions between three GOLD stages (2, 3 and 4) were based on short term data from the Liberate study. Baseline transition probabilities in the Liberate trial were reported for 1.5- 6 months and 6-12 months for control and intervention group [9]. These were then converted to weekly transitions by the submitter. Moreover, the model assumed the treatment benefits to accrue over the remaining 9.5 years by applying transition probabilities for 6 months onwards. In contrast, no transition between GOLD stages were assumed in earlier models and patients could only leave their GOLD stage based on the disease mortality for the subsequent 9.5 years.

Based on feedback from our Norwegian clinical experts, this seemed realistic for the Norwegian setting, as patients are "getting worse" after six months (excluding mortality). As clinical experts considered the ten-year time horizon to be too long for patients with severe emphysema, the submitter provided a 3-year and 10-year comparative analysis.

The submitted economic model, adjusted for mortality between the control and intervention group. Therefore, the mortality was not significantly different in both arms compared to earlier submissions from the submitter. Of note, the meta-analyses included by the submitter did not show significant differences in mortality rates between EBV and standard care.

Cost data

The submitter presented only direct costs from a hospital perspective. We believe the approach to be appropriate overall, and cost estimates were in accordance with existing projections in the Norwegian setting. However, an extended health care perspective may have been useful to consider the relevant patient cost and social cost for the medical staff between the standard of care and intervention. We considered the use of Norwegian DRGs being a good strategy to improve the model's transferability. However, as DRGs specific to COPD are available, these should preferably have been used to a larger extent to keep cost estimates consistent across the model. Similarly, the choice regarding the appropriate NCRP codes for chest X rays to capture the actual cost across the Norwegian healthcare providers. Furthermore, we found potential limitations in terms of excluding exacerbation costs at each GOLD stage. This was argued as being less relevant based on data, however, other relevant models for EBV [18] have demonstrated impact of clinical events like exacerbation for patients in different GOLD stages.

An estimation of costs according to GOLD stages would have better reflected the impact of severity of disease on overall resource use. Moreover, we consider various costs to be underestimated. On one hand, the intervention's specialist hourly salaries (i.e., anaesthesiologist, pneumologist, nursing) seem not to include their societal component which represents approximately 1.25 of the nominal salary [30] . On the other hand, the use of the RG1 tariff to estimate the X-ray service cost might be too low as the cost

of this service in the private sector is around 850 NOK [31]. The use of the RG5 tariff might have been more accurate for the estimation of this cost [32]. Finally, operation room costs were taken from the UK which might pose some limitations in terms of transferability to the Norwegian setting. The cost assumptions were therefore tested in the sensitivity analysis to assess the extent of variation and effects on the cost effectiveness.

Utility data

The submitter presented health-related quality of life (HRQoL) utility values derived from SQRQ, 6MWD test and EQ5D. The latter is considered appropriate for cost-utility analyses. However, utility values were time dependent, and they did not reflect the actual health state of individuals according to GOLD stages. This creates uncertainty around the degree to which the utility values accurately capture the effect of the compared interventions. We believe that the estimation of utility values based on disease severity (i.e., GOLD stage) would have been more informative about the true effect of both treatment alternatives.

Adverse events:

Adverse events such as exacerbations were excluded from the model since the meta-analysis did not show any significant difference in rates of exacerbations between the treatment groups. This assumption influences estimated costs and EBV's effect on quality of life. The presence of exacerbations would not only impact costs, but also patients' quality of life as these adverse events require hospitalisation. We consider exacerbations to be an important input for the model, and its inclusion should be considered for future decision making.

Mortality

Based on the network meta-analyses submitted as part of the documentation, the model does not show significant difference in mortality between the intervention and standard care. Mortality was reduced by 1% and 2% points in the EBV arm when compared to standard care over 1 and 10 years, respectively. Comparing these results with the mortality estimates of a German study, it was found that mortality for year 1 was reported to be 2.7% and 2.8% for EBV and control, respectively [18]. The cumulative mortality in the model over 10 years had a relative risk of 0.99, slightly favouring the intervention. Therefore, in a longer time horizon the change in mortality was not significantly different from the comparator. However, the results of mortality should be considered prudently due to the limitation of the model in adjusting EBV's mortality for these to be consistent with the evidence of the meta-analysis. This variation in mortality can be explained by a methodological constraint of the model in which only GOLD stage mortality rates were applied to the correspondent GOLD stage transition probability. Thus, the use of a relative risk ratio (CI, 95%) for mortality in the EBV arm that reflected the treatment effect when applied to a given GOLD stage, in accordance with the meta-analysis, would have been useful to avoid favouring the intervention to some degree and capture the uncertainty found in the meta-analysis. Nevertheless, the mortality in the intervention arm increased over time and was not found to affect the outcomes.

Prevalence

We tested the GOLD stage wise prevalence of the Zephyr model against the 12-month GOLD staging from the VENT subgroup data [18]. The comparison was performed to test the predictive validity of the current model with an earlier model using the VENT trial. The current model had assumed a hypothetical cohort at stage 2, whereas subgroup VENT was based on actual clinical data observed during the 1-year. Hence, the current model applied the therapy effectiveness beyond 1-year, the comparison in Table 12 provides the estimated differences between group-wise staging for 12-months.

Table 12. VENT subgroup data vs Zephyr model

Gold Stage	EBV subgroup-VENT	EBV Zephyr	Control subgroup-VENT	Control Zephyr
Stage 2	13.5%*	7%	0%*	0%
Stage 3	51.4%*	58%	44.4%*	37%
Stage 4	35.1%*	33.6%	55.6%*	56.2%

*These estimates are mentioned in Pietzsch et al. [18]

The difference in prevalence might be the result of using the study population of the LIBERATE trial [9] in the submitted model to elicit weekly transition probabilities. However, there might be some overestimation of the treatment effect of Zephyr compared to the VENT study given the higher prevalence of patients in GOLD stage 3 than in GOLD stage 4 in the submitted model. We suggest that clinical experts provide some input for the estimated effect of EBV treatment in decreasing disease progression (GOLD stage 3 to 4) after 6 months. Moreover, we predict these transition probabilities to impact the ICER significantly for 3-years and 10-years onwards.

In addition, the difference in GOLD stage prevalence may also be the result of assuming there were no transitions between GOLD stages after 6 months in Hartman et al. [19], but the model accrues therapy benefits over time. This assumption might be replaced by following the natural history of COPD for long term outcomes after 12 months as presented in Pietzsch et al. [18]. This approach could provide better disease staging from actual clinical data considering disease progression in EBV to emphysematous tissue in neighbouring lobes [18]. Whether the loss is accelerated, or diminishing is unknown due to lack of long-term data.

Revised assumptions

Efficacy data

After our feedback, the submitter replaced the original population in the model for that in the LIBERATE trial which includes patients from 40-75 years [9]. This adjustment improves the transferability of the model to the Norwegian setting and aligns with the starting age of 65 years for severe emphysema, according to our clinical experts.

The treatment effect was assumed to be constant after 12 months despite data on long-term effect not being available in the literature yet. This assumption must be

considered carefully and accounted for when using the submitter's model in decision making. We consider that shortening the perspective into a 3-year period may be a good solution. Otherwise, the uncertainty could have been explored by developing alternative scenarios to the 10-year perspective. For instance, an optimistic scenario (with constant effect over time), a realistic scenario (with effect reducing over time), and a pessimistic scenario (with "0" or rapidly diminishing effect over time).

Mortality estimates in the submitter's model were assumed the same for both EBV and standard care. This assumption was justified by the meta-analyses submitted as part of the documentation. However, the interpretation of these should be made with caution since there might be implications for EBV real effect as a relative risk for mortality was not included in the model.

Cost

According to the submitted model, we consider that assumptions made around cost calculations might have resulted in conservative cost estimates. For instance, including only follow-up costs from year 2 to 10, might underestimate overall costs in the model. Additional costs could be assumed in a 10-year scenario such as costs related to complications, valve replacement, repositioning or removal of the valves due to granulation tissue with a likelihood of a lung volume reduction as a surgical alternative for a proportion of patients [33].

HRQoL

We consider that presenting QALYs per GOLD stage instead of per time period (i.e. weekly QALYs) would have improved the model's predictability of the true effect of EBV on disease progression or management of severe emphysema.

Moreover, the inclusion of QALYs decrement related to pneumothorax or other complications would have been useful to reflect the impact of this adverse event in patients' health and in elucidating the real benefit of EBV treatment. This would not be possible for the current version of the model as the authors have argued that QALYs are already adjusted for the effect of pneumothorax and an addition of a "pneumothorax QALY" may lead to double counting. We could not identify whether all patients have given data for HRQoL values which makes it more difficult to elicit a specific QALY for pneumothorax events.

Budget impact analysis

Budget impact analysis can be defined as an assessment of the financial consequences of adopting a new intervention at a population level. In other words, budget impact is the total incremental cost (additional costs) of introduction of an intervention versus non-introduction (i.e., the total expenditure of inserting the new method minus the total costs of not doing so).

According to the submitted documentation, there are about 350 patients per year estimated to be candidates for endoscopic lung volume reduction with Zephyr® valves in

Norway, and they assume a percentage increase in the annual uptake of Zephyr® from 5% to 25% over 5 years. The clinical experts we have consulted consider this number of possible candidates to be inflated and estimate that only 25 Norwegian patients will be candidates for treatment with Zephyr® each year.

We estimated the budgetary consequences of Zephyr® valve treatment in a 5- year time horizon using the annual uptake increase assumed by the submitter and the initial cohort of 25 patients who may be candidates to Zephyr® treatment according to clinical experts' opinion.

Severity considerations - Absolute shortfall (AS)

We calculated absolute shortfall (AS) based on projections about life expectancies from the health economic model. Calculation of AS has been described in more detail in the submission guideline for pharmaceutical reimbursements of the Norwegian Medicines Agency, which is based on the white paper on priority setting, and a Norwegian life table and age adjusted health related quality of life information from a general Swedish population [35]. Absolute shortfall is defined as the difference in quality adjusted life expectancies at age (A) without the disease (QALYsA), and prognosis with the disease with current standard care (PA):

AS = QALYsA – PA

In the calculations, undiscounted numbers for QALYsA and PA are used.

Expected value of perfect information (EVPI)

We estimated the EVPI for a range of thresholds. The EVPI can be defined as the maximum amount decision makers are willing to pay for having perfect information about all factors that influence which treatment choice is preferred. Thus, EVPI is the value of removing all uncertainty from a cost- effectiveness analysis [36]. EVPI is calculated as the difference in the monetary value of health gains associated with a decision based on available information and the health gains associated with a decision based on perfect information. The EVPI formula is defined as the average of the maximum net benefits (i.e. the expected net benefit using perfect information), minus the maximum of the average expected net benefits across all treatment strategies (i.e. the expected net benefit using current information) [36].

$$EVPI = Mean_{\theta}[Max_{T}(NB)] - Max_{T}[Mean_{\theta}(NB)]$$

Where NB is the net benefit for parameters θ for all treatment strategies *T.*

RESULTS

Cost-effectiveness

Submitted base-case cost-effectiveness

The submitter calculated that total costs in a 10-year perspective, including intervention costs, complication costs and further consultation costs, were [redacted] for Zephyr® valve treatment and €4,031,120 for standard care. The submitter estimated that the total QALY gain for patients treated with Zephyr® valve was 2,727 QALYs and 2,354 QALYs for patients treated by standard care. The total life years (LYs) gained with Zephyr® valve treatment were 3,638 and 3,567 with standard care. Considering these numbers, the incremental cost-effectiveness ratio (ICER) was [redacted] per QALY/ patient and [redacted] per life year gained/patient based on the submitted base-case model (Table 13). In addition, costs and effects in a 3-year perspective were calculated and results are presented in Table 14.

Table 13: Cost- effectiveness results -10-year perspective for total population.

Parameter	Zephyr®	Standard Care	Δ
Costs (€)	[redacted]	4,031,120	[redacted]
LYs	3,638	3,567	71
QALYs	2,727	2,354	373
ICER LYs	[redacted]		
ICER QALYs	[redacted]		

Note: Δ= incremental

Table 14: Cost- effectiveness results -3-year perspective for total population.

Parameter	Zephyr®	Standard Care	Δ
Costs (€)	[redacted]	2,467,846	[redacted]
LYs	2,147	2,072	75
QALYs	1,579	1,367	212
ICER LYs	[redacted]		
ICER QALYs	[redacted]		

Note: Δ= incremental

Revised cost-effectiveness and scenario results

Costs and effects were calculated for a total assumed population of 1000 patients. The costs and effects correspond to the cumulative costs and effects for the overall time considering a 3-year and 10-year perspective.

The ICER in the submitted model for a 10-year period [redacted] as those presented in the Dutch and German settings where ICERs for the same time period were slightly larger than €20,000. The higher ICER in the submitted model may be the result of higher health care costs in the Norwegian setting and the use of a weekly QALY instead of a QALY defined by GOLD stage or patient's actual health state. This was the case in

Pietzsch [18] where QALYs were assigned based on disease stage and the presence of exacerbations. This improved the quality of effect measurements and was translated into higher QALY estimates which reduced the final ICER results (€25,142/ QALY). Moreover, the submitter assumed Zephyr's treatment effect to be constant over 10 years. This assumption may have had an impact on effect estimates and potentially affected the final ICER.

Furthermore, the difference in costs between Zephyr and standard care was mainly due to the cost of therapy whereas the difference in LY gained was due to slight differences in survival based on GOLD Stage (i.e., the model did not assume change in mortality due to the treatment but applied GOLD stage specific mortality to transition probabilities). As a result, at 3 years, [redacted] of patients receiving Zephyr were alive compared to 50.5% in patients receiving standard care.

Severity considerations- Absolute shortfall (AS) results

The AS was calculated based on undiscounted quality of life projections from the health economic model. The remaining QALYs for a 65-year-old individual (QALYs A =16.3) were used given that this was the starting age of the model's cohort. The prognosis with the current standard care (PA) was 2.4 QALYs based on calculations from the submitted model. The AS was 13.9 which places disease severity in group 4 according to the STA guidelines [35].

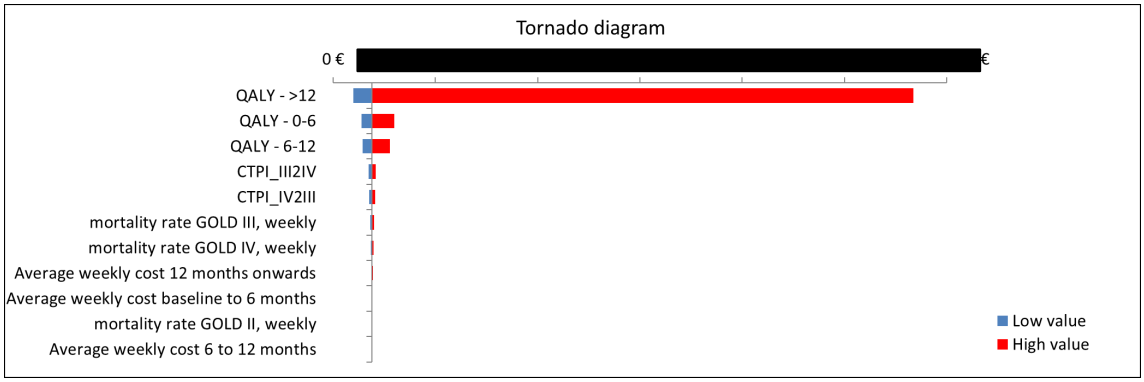
Sensitivity analyses

The submitter performed one-way and probabilistic sensitivity analyses to explore the uncertainty surrounding model parameters. As expected, the ICER was most sensitive to changes in the QALY > 12 months parameter due to the lack of clinical data to inform the model beyond a 12-month period. The results of the probabilistic sensitivity analysis showed that EBV therapy would be cost-effective for threshold values above approximately [redacted] and [redacted] for the 10- and 3- year perspective, respectively (Figure 16). We performed a two- way sensitivity analysis in addition to explore the ICER sensitivity to changes in both QALY > 12 months and transition probability of GOLD stage 3 to 4 and 4 to 3 after 6 months.

One-way sensitivity analysis

In one-way sensitivity analysis, the ICER was most sensitive to variation in the QALY >12 estimate, resulting in ICER predictions from [redacted] to [redacted] /QALY. Furthermore, both QALY estimates for 6 and 12 months showed to contribute to uncertainty surrounding the ICER. Variation of other variables did not significantly affect the ICER (Figure 13).

Figure 13: Tornado diagram



Two-way sensitivity analysis

The purpose of two-way sensitivity analysis was to explore the impact of worsening or improvement of lung function on the ICER. We tested different scenarios with pessimistic and optimistic assumptions around GOLD stage transitions and QALY values. As any decrease in lung function is associated with both the rate of change in patient's health state and the associated QALY for the specific health state. We highlighted the transition probability of GOLD stage 4 to 3 (i.e., improvement in lung function) and GOLD stage 3 to 4 (i.e., worsening of lung function) as the most imperative variables effecting lung function. Transition probabilities between GOLD stages were varied independently due to their correlation and to ensure the economic consistency of assuming other things constant. The QALY>12 months estimates for EBV were not varied for high values to avoid overestimation of a favourable treatment effect and due to the existing uncertainty around QALY values.

Results of two-way sensitivity analysis

The results of the two-way sensitivity analysis demonstrated that the ICER was more sensitive to changes in QALY >12 months (EBV) following a decrease in the probability of transitioning from GOLD stage 4 to 3 (i.e., diminishing treatment effect after 6 months with a reduction in QALYs) (Table 15a and 15c). The results were more sensitive between the 3- and 10-year period following a decrease in QALY>12 months. Moreover, the pessimistic assumption of a decrease in the treatment effect, reflected in the probability of transitioning from GOLD stage 3 to 4, proved to be more sensitive on the ICER compared to GOLD stage 4 to 3 (Table 15b and 15d). Hence, if we were to assume an optimistic scenario where there is an improvement in lung function with EBV,

the ICER ranged from [redacted] to [redacted] for the 10-year period and [redacted] to [redacted] for the 3-year period (assuming QALY>12 months are constant as base case values of 0.77). In contrast, for a pessimistic scenario with a significant reduction in the treatment effect for EBV after 12 months, the ICER ranged from [redacted] to [redacted] for the 10-year and [redacted] to [redacted] for the 3-year time horizon, assuming a constant QALY value of 0.77 (Table 15b and 15d). Lastly, the ICER was found to be highly sensitive to changes in the QALY EBV >12 months. We consider that this is the result of the uncertainty surrounding this parameter. For a 10-year period, when the QALY EBV >12 months is 0.71 and there are no patients transitioning from GOLD stage 4 to 3, the ICER was [redacted]; when the QALY EBV >12 months is 0.71 and the probability of transitioning from GOLD stage 3 to 4 is at its highest, the ICER was [redacted]

Table 15 a: Multivariate sensitivity analysis for QALY and GOLD stage 4 to 3 Transition probability greater than 6 months for Zephyr for a 10-year time horizon.

	QALY EBV>12 months				
	0.77	0.76	0.73	0.72	0.71
Gold Stage 4 to 3 (Transition Probability > 6 months)	**ICER (€)**				
0.085	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.043	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.030	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.023	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.010	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.002	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.0002	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: If the treatment effect diminished substantially after 6 months, the ICER would be more sensitive to decrement in QALY after 12 months. **Bold**: Base case values. Transition probabilities are based on weeks.

Table 15 b: Multivariate sensitivity analysis for QALY and GOLD stage 3 to 4 Transition probability greater than 6 months for Zephyr for a 10-year time horizon.

	QALY EBV>12 months				
	0.77	0.76	0.73	0.72	0.71
Gold Stage 3 to 4 (Transition Probability > 6 months)	**ICER (€)**				
0.002	[redacted]				
0.006					
0.010					
0.011					
0.012					
0.013					
0.014					
0.015					
0.016					
0.017					

Note: If the treatment effect diminished substantially after 6 months, the ICER would be more sensitive to decrement in QALY after 12 months. **Bold**: Base case values. Transition probabilities are based on weeks.

Table 15 c: Multivariate sensitivity analysis for QALY and GOLD stage 4 to 3 Transition probability greater than 6 months for Zephyr for a 3-year time horizon.

	QALY EBV>12 months				
	0.77	0.76	0.73	0.72	0.71
Gold Stage 4 to 3 (Transition Probability > 6 months)	**ICER (€)**				
0.085	[redacted]				
0.043					
0.030					
0.023					
0.017					
0.013					
0.010					
0.007					
0.004					
0.002					
0.001					
0.0002					
0					

Note: If the treatment effect diminished substantially after 6 months, the ICER would be more sensitive to decrement in QALY after 12 months. **Bold**: Base case values. Transition probabilities are based on weeks.

Table 15 d: Multivariate sensitivity analysis for QALY and GOLD stage 3 to 4 Transition probability greater than 6 months for Zephyr for a 3-year time horizon.

	QALY EBV>12 months				
	0.77	0.76	0.73	0.72	0.71
Gold Stage 3 to 4 (Transition Probability > 6 months)	**ICER (€)**				
0.002	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.006	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.01	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.011	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.012	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.016	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: If the treatment effect diminished substantially after 6 months, the ICER would be more sensitive to decrement in QALY after 12 months. **Bold**: Base case values. Transition probabilities are based on week.

Probability sensitivity analysis

The cumulative cost-effectiveness probabilities were adjusted to ensure that the number of probabilistic simulations with ICERs below a given threshold were considered relevant and that overestimations of cost-effectiveness were avoided. For instance, the model's probabilistic simulations included iterations where Zephyr intervention was dominated, and these were not included in the calculation of the cost- effectiveness acceptability curve. Thus, we found this approach to be a potential source of overestimation of Zephyr cost-effectiveness.

Once adjusted, the probability of Zephyr being cost-effective did not reach 100% at the maximum threshold of €1,300,000 in cost- effectiveness acceptability curves. This situation was the same for both 3- and 10- year time periods. In a 10-year perspective, Zephyr has a higher probability of being cost- effective at lower thresholds of €0-20,000. However, for threshold values greater than €100,000 the probability of cost-effectiveness for 3- and 10-years periods were almost similar and increased with higher threshold values (Table 16). However, at higher threshold the 3-year perspective yields greater probability of cost-effectiveness compared with the 10-year perspective. The cost-effectiveness acceptability curves and frontiers were calculated for a range of thresholds in addition to the original manuscript (see Figures 14-18)

Table 16: 3-and 10-year cost-effectiveness probability for different thresholds

Threshold	Cumulative *		Adjusted	
€	3-year	10-year	3-year	10-year
0				
20000				
50000				
100000				
150000				
200000				
250000				
300000				
350000				
400000				
1300000				

*Cumulative approach does not consider the probability of CE for standard care.

Figure 14: Cumulative cost-effectiveness acceptability curves for 3 and 10 years

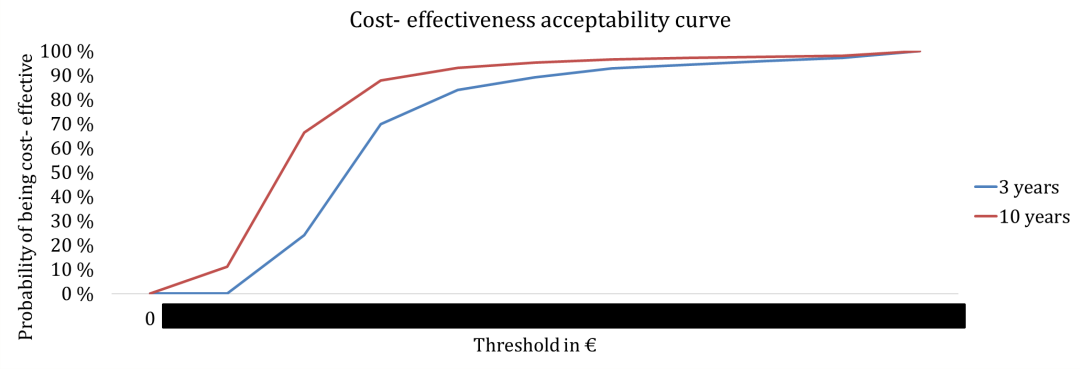


Figure 15: Adjusted cost- effectiveness acceptability curves for 3 and 10 years

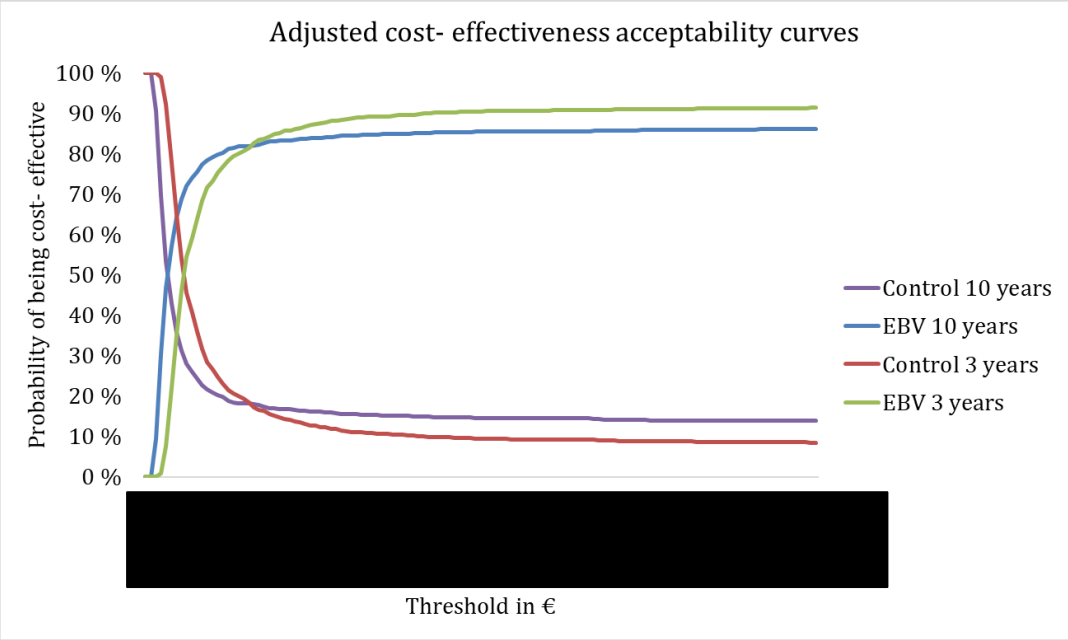


Figure 16: Adjusted cost-effectiveness acceptability frontier for 3 and 10 years

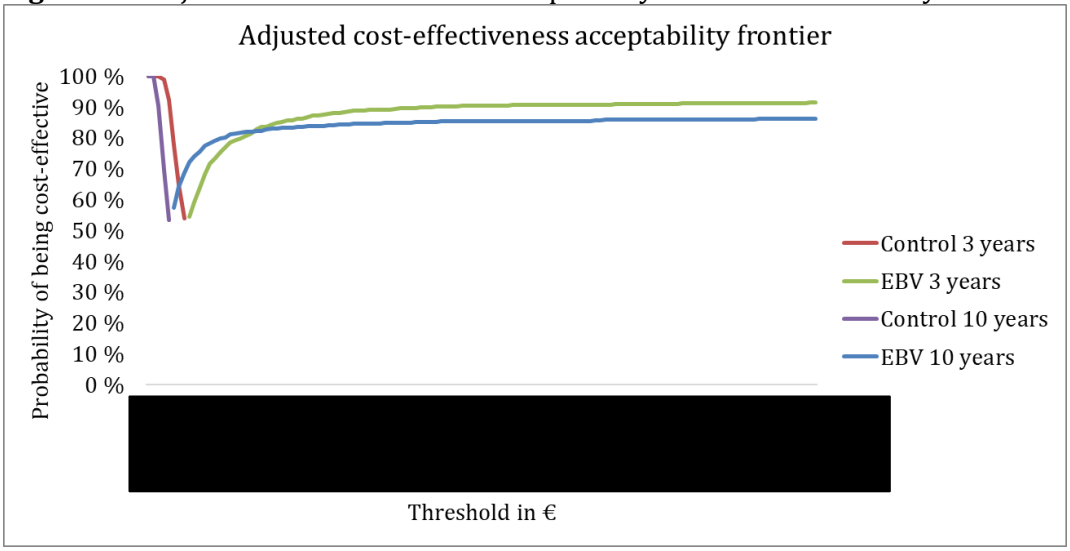


Figure 17: ICER plane for 3 years

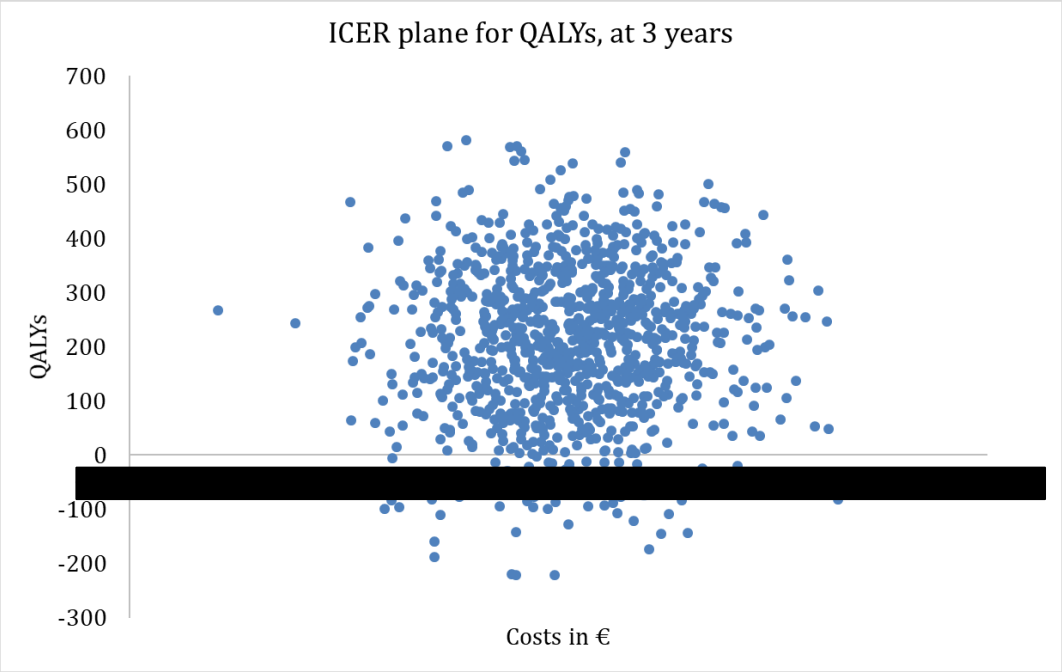
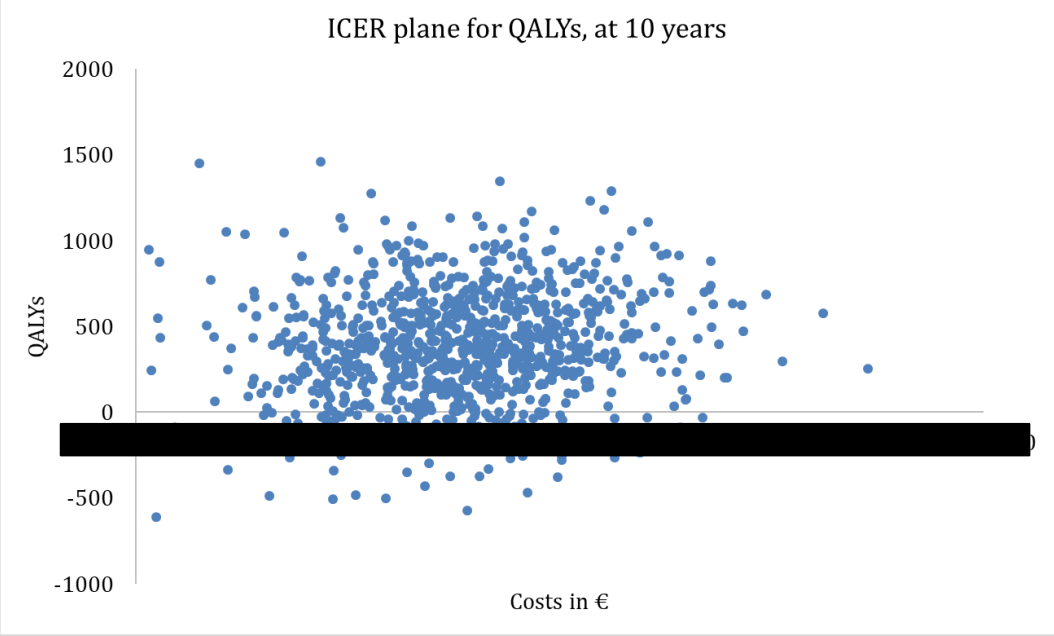


Figure 18: ICER plane for 10 years



Budget impact analysis

Submitted budget impact analysis

Budgetary consequences of the introduction of Zephyr® valve treatment were calculated as Zephyr® total costs of selection, insertion and follow up minus total costs of standard care and follow up. Calculations are based on 1-year treatment costs since the meta-analyses did not demonstrate differences in complications and health care resource use during the following years. Table 17 shows costs per patient for the first year of treatment for both Zephyr® and standard care as well as the additional or incremental costs for the introduction of Zephyr®.

Table 17: First- year costs of treatment and Zephyr® introduction per patient

Treatment	First year costs/patient (€)
Zephyr ®	[redacted]
Standard	1,463
Additional cost for the introduction of Zephyr®	[redacted]

Based on experts' opinion, we estimated a target population of 25 patients with stage III-IV COPD who are candidates for treatment per year in Norway. The submitter estimated annual percentage increases of the targeted population candidate to Zephyr® treatment. We used this annual increase to estimate the number of patients who would be candidates to Zephyr® treatment starting with 25 patients in year 0 (Table 18). The budget impact was calculated as the incremental cumulative costs for the total number of patients treated.

Table 18: The submitted budget impact

Year	% uptake increase	Population treated	Budget impact (€)
0	-	25	[redacted]
1	5%	26	
2	10%	29	
3	15%	33	[redacted]
4	20%	40	
5	25%	50	[redacted]
Cumulative budget impact over 5 years			[redacted]

Norwegian Institute of Public Health assessment of the submitted budget impact

The submitter initially overestimated the number of patients who may be potential candidates for Zephyr® treatment. However, we consider that the submitted percentage increase in uptake of Zephyr® was suitable for our recalculations. After adjusting the initial targeted population, we believe that this analysis sufficiently reflects the budgetary consequences of adopting Zephyr® in Norway. Nevertheless, we consider taking into consideration the costs of complications, such as exacerbations, in cost calculations for both Zephyr® and standard care. Although not significant in the meta-analyses submitted as part of the documentation, the incidence of COPD exacerbations demands considerably more resource use and different costs are expected to accrue over time. Therefore, we consider that budgetary consequences could include complications and not only 1-year costs to explore the real impact of adopting Zephyr® in the Norwegian setting.

Expected value of perfect information (EVPI) results

We estimated the EVPI for a range of thresholds in the current study. Figure 19 shows the population EVPI for the total number of patients considered in the model (for all relevant parameters) across a range of WTP thresholds.

At a threshold of [redacted] the population EVPI was estimated to be €5 million for a 10-year period (i.e., the cost for perfect information should not exceed €5 million to be considered worthwhile), whereas the population EVPI for a 3-year period was estimated to be €0.8 million. The EVPI was sensitive to a threshold value between [redacted] for a 10-year period and between [redacted]- [redacted] for a 3-year period. In addition, the population EVPI for the 10-year period was higher compared to that for the 3-year period at all thresholds, indicating higher value of information for the former. At higher thresholds the population EVPI increases significantly indicating a higher cost for an incorrect decision. The 10-year period has a higher cost for an incorrect decision compared to the 3-year period (Figure 19).

The results of expected value of partial perfect information (EVPPI) for the most imperative variables are presented in Figure 20. The results found that expected value of information was highest for QALY>12 months for both standard care and EBV groups. Moreover, the EVPPI for the transition probability from GOLD stage 4 to 3 (for both EBV and SC groups) also exhibited an added value for further research due to the uncertainty surrounding the mean values.

Figure 19: Population EVPI for 3 and 10 years

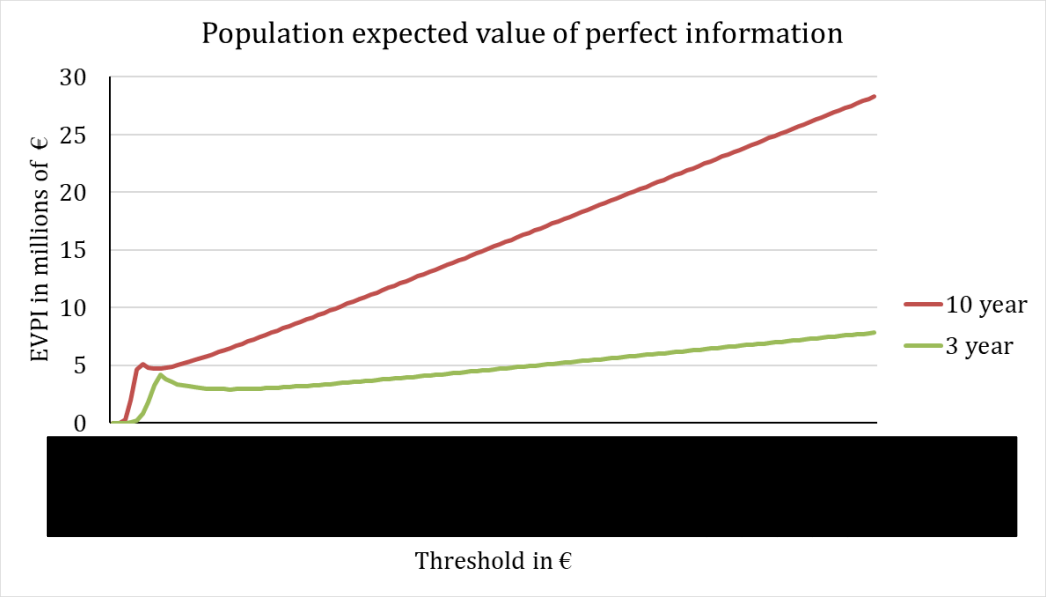
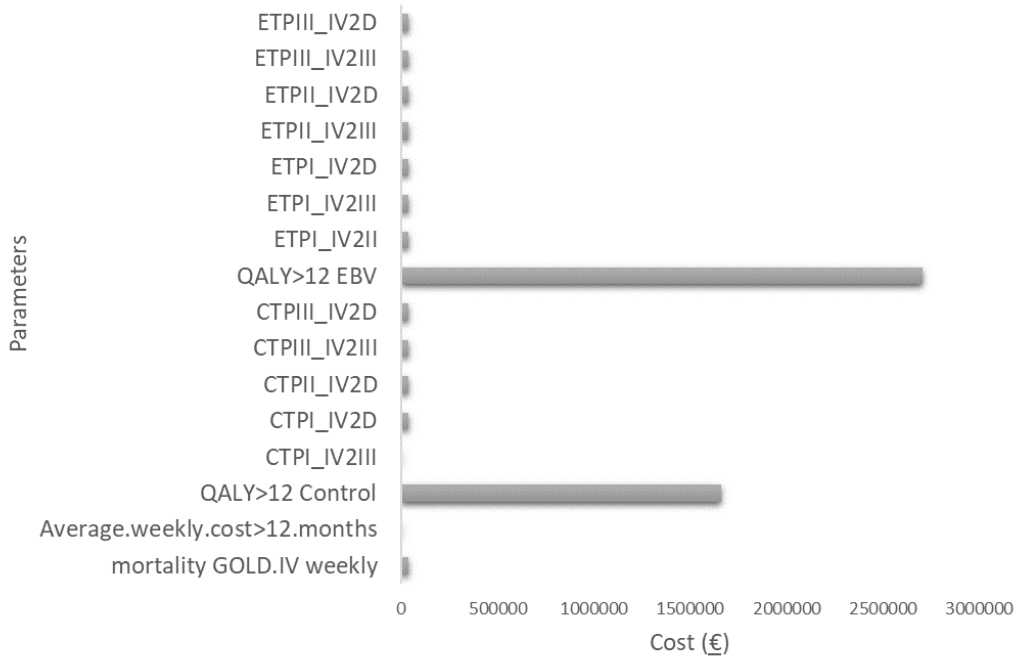


Figure 20: Expected value of partial perfect information (EVPPI)



ETP=EBV transition probability, CTP=Control transition probability, where I=baseline to 45 days, II=45 days – 6 months and III=6 months to 1 year (also applied after 6 months).

Patient- and user involvement

We contacted LHL (Landsforeningen for hjerte- og lungesyke) and explained that we wanted to involve patient representatives in the work with this STA. LHL is a member based, non-profit and comprehensive health organization with almost 54,000 members. The organization involves 250 local teams, clinics and hospitals.

LHL suggested contacting Jan I. Andersen, and hence he was invited to comment on the report and perspectives that are important to patients. His response is reproduced (in Norwegian) below. Briefly, the patient representative emphasizes the physical burden by being unable to perform more and more tasks, and the psychological burden caused by the fact that there is no cure. The existing treatment options aim at slowing down the progression and have limited long term effects. Treatments with an ability to reverse the disease progression will be very valuable.

How the condition affects patients' quality of life

«Det å miste evnen til fysisk arbeid, gå en lang tur, kanskje miste førerkortet, eller det å bli avhengig av hjelp i hverdagen. Tilstander som kryper inn på oss, påvirker vår psyke, reduserer vårt sosiale samvær og livskvalitet. Dette forverres dersom pasienten også har hjerteproblemer som ofte følger med pustebesvær. Problemene er vel ganske likt fordelt mellom alle pasientgrupper. Det vi mest ønsker oss er behandlinger som kan bedre vårt oksygenopptak og bremse sykdommens utvikling.»

How the condition affects patients' relatives

«Det vi først erfarer med pårørendes reaksjoner er angst for framtiden, og søken etter opplysninger. Pasientens psyke smitter ofte over på de nærmeste, og den fysiske tilstanden virker også på familiens muligheter for mobilitet og sosialt samvær.»

How well do patients handle the condition with existing methods (standard care)

«Det finnes mange medikamenter som fortrinnsvis skal redusere pasientens pustebesvær. Oftest for inhalasjon. Pasientene har ulike nytteerfaring med disse. Fastlegenes erfaringer med behandling av kolssyke og hvilke hjelpemidler som tilbys varierer, og noen pasienter føler usikkerhet og at det er lite hjelp å få. Ofte bytte av medisiner og doser fører også til usikkerhet.

Når veien til lege og sykehus er lang og hyppig, (som den er for mange i landet vårt) sliter det både fysisk og psykisk. Fysioterapi og fysisk trening av styrke og utholdenhet er for mange den beste medisin for å bremse utviklingen av sykdommen som det ikke er noen helbredelse for.»

Experiences and/or views on the method that are under consideration

«Da jeg er uten medisinsk kompetanse, eller erfaring med å lese kliniske studier har jeg vanskelig for å gi relevante svar på spørsmålet. Dersom behandlingen kan gis på et tidspunkt i sykdomsforløpet hvor pasienten har et rimelig resterende livsløp og håp om forbedret livskvalitet, mener jeg at pasienten vil tolerere en stor grad av ulemper.»

Discussion

Key findings

Effect and safety

The evidence base primarily consists of five randomized controlled trials. Four compared the Zephyr® valve system versus standard care, and one compared Zephyr® with sham valve replacement. The follow-up period ranged from three to twelve months. The evidence was too sparse for the comparison of Zephyr® with standard care to allow firm conclusions regarding mortality (RR 1.61, 95% CI 0.44 to 5.93), and moderate certainty evidence suggested little or no difference in the number of exacerbations (OR 1.15, 95%CI 0.70 to 1.88). However, the Zephyr® valve system was associated with improvements in FEV1, SGRQ, BODE index (moderate confidence) and 6MWD (low confidence). The improvements in functional outcomes come at the cost of increased risk of pneumothorax after surgery (OR 33.9, 95% CI 8.1 to 141.7). For the comparison between Zephyr® and sham valve replacement, we have very low confidence in the results.

Health economic evaluation

Based on the submitter's economic model, Zephyr® valve treatment generates more costs and more health in terms of QALYs compared to standard of care. However, we found that both costs and effects estimates were highly uncertain given the assumptions around long-term treatment effects.

We placed disease severity in group 4 by the AS method which also aids in the definition of a willingness to pay (WTP) threshold [35]. There is no official definition of WTP in Norway, but the Magnussen group suggested a threshold around NOK 605,000 for patients in severity group 4 [35].

Budget consequences were given in incremental cumulative costs for the total number of patients treated for a 5-year period. Only costs for the first year of treatment were included for both Zephyr® and standard care based on a lack of difference in the resource use over time showed in the submitter's documentation. The budget impact for a 5-year period was estimated around [redacted]. However, this might be an underestimation of the real budget impact of Zephyr® due to the exclusion of complications-related costs.

Evidence quality and limitations

Effect and safety

The certainty of the evidence is reasonably good for most outcomes, but the effect on mortality remains uncertain due to few and small studies with limited follow-up periods. The current effect estimate suggests increased risk of death following Zephyr® surgery, but the confidence interval shows that the true estimate can also be in favour of Zephyr®. More studies with longer follow up periods are needed to allow firm conclusions.

Health economic model

The economic model was found to be of adequate quality to reflect the cost effectiveness of EBV treatments for patients with severe emphysema in Norway. However, there are potential sources of uncertainty worth highlighting. The model was constrained to the use of weekly QALYs and costs because the primary outcomes were not observed by changes in GOLD stages but through the assessment of endpoints such as 6MWD, FEV1 and adverse events. In addition, there was no further description of GOLD stages and their association with these endpoints.

We identified uncertainty surrounding the ICER in the 10-year time horizon and conducted a two-way sensitivity analysis to explore its impact on final cost-effectiveness results. Our result suggests that the ICER is more sensitive to decrements in QALYs>12 months for EBV and, if followed by an increment in transition probability (GOLD Stage 3 to 4), the ICER increases significantly. The transition probability from GOLD Stage 4 to 3 (after 6 months) was found to be uncertain using EVPPI, however, a decrement in this probability increased the ICER but its overall responsiveness remained lower compared to the transition probability from GOLD Stage 3 to 4. This aligns with the results of the sensitivity analysis conducted in the Zephyr® model showing the ICER was most sensitive to changes in QALYs>12 months for the control arm. However, the combined effect in a multivariate analysis suggests higher sensitivity in ICER estimates. Nevertheless, it is worth noting that a decrease in therapy effectiveness may be associated with decrease in QALY in a longer time horizon.

The inclusion of adverse events such as exacerbations may slightly increase ICER estimates through adding costs (treatment costs) and reducing health effects (QALYs/LYs). A study found that 27% of patients (n=93/343) presented exacerbations in a 6-month follow up period after EBV treatment in patients with severe emphysema. Furthermore, exacerbations were found to be the most frequent serve adverse event during this period. Thus, we consider that the incidence of COPD exacerbations is significant enough to be included in the Zephyr model.

Model's assumptions for long term cost-effectiveness were based on 1-year data from the LIBERATE trial and therefore, cost-effectiveness results for a 10-year time horizon must be interpreted thoughtfully. We compared the results of the Zephyr model to other studies in Europe and found that that EBV is also a cost-effective alternative to

standard care across these settings. However, the ICER estimates for the Norwegian setting were nearly twice as high as those in other countries which suggests larger health care costs are incurred in Norway.

The submitted model's overall strengths include the estimation of an ICER that considers long term therapy effectiveness, assuming constant transition probabilities between GOLD stages 3 to 4 after 6 months. The submitter used clinical data such as the LIBERATE trial to model disease progression and health-related quality of life data from STELVIO [8] which reduces uncertainty surrounding these parameters. Furthermore, the model excluded the cost of Chartis assessment for patients receiving standard care adjusting for cost overestimations.

The limitations found in the submitted model include a constant treatment effect over a 10-year period. This may to some extent overestimate Zephyr® cost- effectiveness, as benefits accruing over time are not subject to natural decrements (e.g., related to patients' age, baseline health risks or uncertainty for therapy effectiveness). Furthermore, QALYs were based on a weekly estimate instead of patient's actual health state or GOLD stage and may not have fully captured the actual EBV treatment effect. Hence, as EVPPI found transition probabilities to be of some value for future research, the assumption regarding the long-term treatment effect determines the validity of the model to yield an appropriate ICER. Therefore, if patients have diminishing treatment effect and QALYs after 12 months than assumed in the model such an overestimation (Zephyr® effect) may lead to lower ICER predictions. Moreover, if QALYs are significantly different between GOLD stage 3 and 4 after 12 months, the impact on the ICER may be ambiguous as it would be dependent on the relative difference between these two QALY estimates. Lastly, the cost of other potential adverse events such as exacerbations were excluded from the model. Such an assumption may have underestimated total costs and yielded a lower ICER estimate. We believe the relative size of the ICER may be larger than that presented by the submitter. If these assumptions hold, a 3-year time-period may provide better ICER estimates as discrepancies regarding long term uncertainties in treatment effect and QALYs are reduced in magnitude.

Finally, we identified a network meta-analysis [7] of the effects of valves in patients with heterogenous emphysema without collateral ventilation where Zephyr® was compared to another valve treatment, Spiration. The analysis showed that both treatments had similar effect on the different endpoints (FEV1 and SGRQ scores), however, the network meta-analysis did not include mortality as an outcome. We performed a sensitivity analysis pooling Spiration and Zephyr® data on mortality, but the overall conclusions from the meta-analysis of Spiration and Zephyr versus standard care was similar as for the analysis of Zephyr® alone. Despite not finding significant evidence of Spiration effect, we consider that its inclusion would have provided a broader overview of the effect of valve treatments in general, especially when meta-analyses have shown uncertainty for mortality and pneumothorax events in patients treated with valves. In terms of cost-effectiveness, the addition of Spiration to the comparison against Zephyr or standard care could have resulted in different ICER estimates.

Consistency with other reviews

Consistency of systematic review with other reviews

Labarca et al. [6] conducted a systematic review and meta-analysis on endoscopic lung volume reduction using Zephyr® valves in patients with severe emphysema without collateral ventilation. Searches in Medline and Embase were updated in June 2018. They included the same five RCTs as presented in this STA. The risk of bias was assessed as low in more domains by Labarca than by the submitter; 21 domains were unclear in the submitter's RoB, compared to only 4 domains in Labarca et al.'s RoB. Labarca et al. had similar conclusions as in the present review: improvements in FEV1, SGRQ, BODE index and 6MWD and increased risk of pneumothorax. Mortality was not an outcome in Labarca, et al.

Iftikhar et al. [7] conducted a network comparative meta-analysis of the effects of valves in patients with heterogeneous emphysema without collateral ventilation. They also studied the effects of valves and coils in patients with mixed homogeneous and heterogeneous emphysema. PubMed and Web of Science were searched from inception until January 20, 2020. Iftikhar et al. included the same five trials. They did not report risk of bias assessments, but they concluded that there was no sign of publication bias based on funnel plots, and they came to the same conclusions regarding FEV1, SGRQ, BODE index, 6MWD and pneumothorax. They did not assess mortality.

Finally, Xu et al. [5] searched PubMed, EMBASE, Cochrane Library, and Web of Science from January 2001 to August 2017 and performed a network meta-analysis. They did a risk of bias assessment and used GRADE and included the same five trials as the other reviews. The primary outcomes were lung capacity, survival and health-related quality of life. Secondary outcomes were the SGRQ, 6MWD and mortality. Xu et al. included the same five trials and concluded similarly as the other reviews and the manufacturer except for mortality. Xu stated that endobronchial valves reduced mortality compared to medical care, but their Table 2 showed 3% deaths in both groups. And for valves versus sham control the numbers were 0/25 versus 2/25. The GRADE assessment was moderate confidence. We think that the manufacturer's conclusion is more in line with the results – namely that the numbers are small and uncertain for mortality.

In summary, we have found three systematic reviews that all included the same five trials that we report in the present review. The reviews' results are mainly in concordance with the manufacturer's conclusions, exceptions being somewhat different RoB and conclusions for mortality.

Consistency of health economic evaluation with other studies

Pietzsch et al. [18] assessed the cost-effectiveness of endobronchial valve (EBV) therapy for severe emphysema compared to the medical management of patients with high heterogeneity, complete fissures and lobar exclusion in the German health care system. Clinical data, health related quality of life, and disease staging for 12 months were taken from a subset of the VENT study . This information was used to project long-

term disease progression, mortality, and health resource utilization. Authors found that EBV treatment led to clinically meaningful disease restaging at 12 months (38% of the cohort improved staging, compared to 0% in the controls). Moreover, EBV treatment was projected to increase survival from 66-71% over 5 years. These results align with those reported in the submitted model given that the submitter used clinical data from LIBERATE. Pietzsch et al. found EBV therapy to be cost- effective at a lower ICER of €25,142 per QALY compared to [redacted] per QALY reported by the submitter. We think that the source of the difference in ICERs is the larger health care costs incurred in the Norwegian setting. Furthermore, the use of QALYs per week in the submitted model instead of QALYs based on GOLD stage and presence of exacerbations as in Pietzsch et al. may also play a role in the estimation of EBV treatment effect and final ICER predictions.

Hartman et al. [19] assessed the cost-effectiveness of EBV treatment in patients with severe emphysema compared to standard medical care from a hospital perspective in the short and long term in the Netherlands. Authors used the 6-month end point data from STELVIO trial [8] to calculated ICERs and extrapolated this to 10 years using a Markov simulation model. QALYs (based on the EQ5D Dutch tariffs), exercise capacity measured by the 6-min walk distance test (6MWT), and the St George's Respiratory Questionnaire were used as outcome measures. Furthermore, patients were assumed to not transition between GOLD stages after 6 months and could only leave their GOLD stage by dying. Hartman et al. concluded that EBV treatment has a favourable cost-effectiveness profile in the long term when compared to standard care. Similar to Pietzcsh et al., the ICER reported by Hartman et al. was around €25,000 which could confirm the overall higher costs in Norway's health care system.

In summary, we have found that other cost-effectiveness analyses report EBV as a cost-effective alternative to standard care without significant effects on disease progression and survival. Despite the ICER in the submitted model being twice as high as other analyses, Zephyr® may be cost- effective, however, may also depend on the credence given to the assumptions taken for the longer time horizon Furthermore, the assumption of a constant treatment effect over 10 years should be thoughtfully considered when making reimbursement decisions given its impact on the uncertainty surrounding effects and ICER estimates. We believe EBV therapy might be cost- effective in the Norwegian setting but there remains some uncertainty regarding the extent to which this is true. In addition, there is not a defined threshold as of now that could determine whether EBV treatment is cost-effective and to what extent.

Need for further research

The available studies have a follow-up between three and twelve months, and the long-term effects of the endobronchial valve procedure are therefore uncertain. Simultaneously, it is possible that the long-term effect may have an important impact on the cost-effectiveness of the procedure. Some of the studies included in this STA are still ongoing and may contribute long term-data in the future. The LIBERATE study has estimated completion in February 2023. Another study, the Zephyr Valve Registry (ZEVR) is also recruiting participants. There is a post-market clinical evaluation of the Zephyr Valve 5.5-LP EBV that was enrolling by invitation in September 2021. Finally, there is an ongoing pilot study of video assisted thoracic surgery (VATS) fissure completion prior to Zephyr® endobronchial valve insertion (COVE), a study with estimated completion in December 2022. Lastly, future research focusing on QALY data after 1 year for relevant GOLD stages may provide better estimates for calculating effectiveness for a long-term cost-effectiveness evaluation.

Conclusion

The Zephyr® valve system may be a cost-effective alternative to standard care for the treatment of severe emphysema in patients without collateral ventilation. However, there are still important uncertainties surrounding the long-term effect of Zephyr®, that is its overall impact on health outcomes and costs more than one year after treatment. The current health economic model assumed no difference in mortality due to uncertainty surrounding survival estimates for patients treated with Zephyr. Cost- effectiveness results were more favourable for a 10-year perspective compared to a 3-year perspective, but with significant uncertainty around QALYs greater than 12 months. Furthermore, we consider that costs related to the treatment of COPD exacerbations should be included to improve the model's transferability and validity in the Norwegian setting. We are aware that there is a lack of long- term data on Zephyr® effect and that further research is needed to fully estimate its long- term impact on patients' health, resource use and costs in the Norwegian setting. Therefore, further research focusing on the QALYs estimates may be useful to improve model's robustness.

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Appendices

Activity log

Date	Activity
21.10.2019	The Commissioning Forum commissioned a single technology assessment
23.12.2019	NIPH reached out to relevant manufacturer
13.02.2020	First meeting with manufacturer
29.05.2020	Second meeting with manufacturer
17.07.2020	NIPH received a first submission
01.09.2020 – 01.10.2020	NIPH involved three clinical experts and one patient representant from LHL
08.09.2020	NIPH contacted manufacturer with feedback on weaknesses found in the health economic model
27.10.2020	NIPH received a health economic model based with updated model structure and input data
28.10.2020	NIPH contacted manufacturer with questions and comments on the submitted literature search
30.10.2020	NIPH received feedback on the literature search
01.11.2020	NIPH in regular dialogue with clinical experts and patient representant
19.01.2021	NIPH received information from patient representant
09.03.2021	NIPH contacted manufacturer with questions about RoB
10.03.2021	NIPH received updated RoB tables
15.03.2021	NIPH contacted manufacturer with questions and comments about health economic model input, and a proposal to revise the model
28.05.2021	NIPH received the revised model
01.09.2021	NIPH conducted a scoping search to test the importance of poorly reported search in the submission file
28.09.2021	NIPH detected an important error in the calculation of ICER in the revised model
14.10.2021	Updated numbers received from the manufacturer
25.10.2021	NIPH shares draft with clinical experts.
06.12.2021	Feedback received from one clinical expert
16.12.2021	NIPH shares draft with manufacturer/submitter
17.12.2021	NIPH shares draft with patient representative
28.12.2021	NIPH receives feedback from patient representative
11.01.2022	NIPH receives feedback from manufacturer/submitter
12.01.2022	Meeting between NIPH and manufacturer/submitter discussing the feedback
23.01.2022	Report approved at FHI
25.01.2022	Report submitted to Commissioning forum

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