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Chronic obstructive pulmonary disease in over 16s: diagnosis and management

[G] Referral criteria for lung volume reduction procedures, bullectomy or lung transplantation

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Evidence review

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Referral criteria for lung volume reduction procedures, bullectomy or lung transplantation

Review questions

In people with stable COPD, what are the referral criteria for lung volume reduction procedures?

In people with stable COPD, what are the referral criteria for bullectomy?

In people with stable COPD, what are the referral criteria for lung transplantation?

Introduction

The aim of this review was to determine the effectiveness of lung volume reduction procedures, bullectomy and lung transplantation for people with stable COPD, to enable the identification of subgroups of people who show benefit from the treatment. The defining characteristics of these subgroups will inform the referral criteria for these treatments.

For the purposes of this question, five treatments were considered – lung volume reduction surgery, bronchoscopic lung volume reduction (either with valves or coils), bullectomy, and lung transplant.

Lung volume reduction surgery (LVRS) involves surgically removing the most damaged part of the lung. This allows the remaining healthier, less emphysematous lung tissue to expand. It is usually done as a “keyhole” procedure – video assisted thoracoscopic surgery (VATS) but may require an open surgery. Usually only one side at a time is operated on in modern practice. This surgery is usually done only in selected people with severe or very severe chronic obstructive pulmonary disease (COPD), significant exercise limitation and an appropriate heterogeneous pattern of emphysema.

Bronchoscopic lung volume reduction (BLVR) is a general term that refers to any of several recently developed endobronchial procedures for treating hyperinflation in advanced emphysema. This evidence review considers two procedures:

- The placement of valves to block off target areas of emphysematous lung (called endobronchial or intra-bronchial valves). This causes the target area to collapse so that it no longer traps air which obstructs the function of healthier parts of the lung. This is intended to achieve the same effect as surgically resecting the target area by LVRS.
- Placement of endobronchial coils which are intended to re-tension emphysematous lung allowing improved expiratory airflow and reducing gas-trapping.

Bullectomy is the surgical removal of a large bulla, usually defined as a dilated air space occupying more than one third of the hemithorax (the side of the chest it is on). This distinguishes it from LVRS. The most common cause of bullae is COPD. Bullae increase physiological dead space and expand at the expense of healthier more elastic adjacent lung.

This review identified studies that fulfilled the conditions specified in Table 1. For full details of the review protocol, see appendix A.

Table 1 PICO table – Lung surgery

Population	People diagnosed with COPD

Interventions	• Lung volume reduction surgery (LVRS)
	• Bronchoscopic lung volume reduction
	  ○ Endobronchial valves (and intra-bronchial valves)
	  ○ Endobronchial coils
	• Bullectomy
	• Lung transplantation

Comparator	• No intervention • Optimal medical therapy (pulmonary rehabilitation) • Each other
Outcomes	• Mortality • Hospital admissions and readmissions • Exacerbations • Gas transfer (carbon monoxide diffusion capacity (TLco, DLCO, KCO used interchangeably), PaO_2) • Change in FEV_1, rate of decline of FEV_1 • Exercise tolerance/ capacity • Symptoms (including breathlessness) • Adverse events • Quality of life, anxiety, depression • Resource use and costs

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B. In particular, the minimally important differences (MIDs) used in this review are summarised in Table 7 in appendix B. These were selected based on the literature with input from the committee.

The search strategies used in this review are detailed in appendix C.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

This review was conducted as part of a larger update of the 2010 NICE COPD guideline (CG101). A systematic literature search for randomised controlled trials (RCTs) and systematic reviews of RCTs identified 3,333 references (no date limit was used as the previous guideline recommendations were not based on a systematic literature search). Although priority screening was used for this review, all of the abstracts were screened on title and abstract. One hundred and eight papers were ordered as potentially relevant systematic reviews or RCTs based on the criteria in the review protocol. In particular, RCTs were excluded if they did not meet the criteria of enrolling people with COPD or emphysema.

Twenty-two papers were included after full text screening: all studies were RCTs, 7 systematic reviews were identified, however; none were included because the primary studies included in the reviews were already identified at full text screening. Eleven RCTs were identified for LVRS, 11 for bronchoscopic lung volume reduction (6 RCTs for endobronchial valves, 2 RCTs for intra-bronchial valves and 3 RCTs for endobronchial coils), and 0 RCTs were identified for lung transplantation or bullectomy.

One additional relevant RCT investigating endobronchial valves was identified by the committee, making a total of 23 articles.

Multiple journal papers from the same trial were identified and collated, so that trials rather than journal papers were the unit of interest. There were 16 unique trials.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. These searches returned 3,100 references in total for all the questions included in the update, and these were screened on title and abstract. No additional relevant references were found for this review question.

The process of study identification is summarised in the diagram in appendix D.

For the full evidence tables and full GRADE profiles for included studies, please see appendix E and appendix G. The references of individual included studies are given in appendix K

Excluded studies

Details of the studies excluded at full-text review are given in appendix J, along with reasons for their exclusion.

1 Summary of clinical studies included in the evidence review

2 The included RCTs and systematic reviews are summarised in the Table 2 to Table 5 below.

3 **Table 2 Lung volume reduction surgery**

Short Title	Population	Study arms	Outcomes
Clarenbach (2015)	Sample size: *30* Split between study groups *LVRS - 15 Control group - 15* Loss to follow-up *1 Incomplete follow-up in the LVRS group 1 withdrew and 1 incomplete follow up in the usual care follow up* % female: *LVRS- 43% Control group - 30%* Mean age (SD): *LVRS - 60.9 years (10.4) Control group - 65.1 years (6.1)* Mean pack years smoked (SD) *LVRS - 36.8 (11.8) Control group - 53.2 (12.7)* Mean body mass index (SD): LVRS group *23.5(5.0)* Continued medical therapy group *23.9(2.8)*	**Interventions** Lung volume reduction surgery **Controls** Continued medical therapy	**Outcome measure(s)** Percent change in FEV1 Exercise Capacity *6 minute walking distance Steps, mean per day*
Fishman (2003)	Sample size: *1218 participants* Split between study groups *LVRS - 608 participants Control group - 610 participants* % female: *LVRS - 42% Control group - 36%* Mean age (SD) *LVRS - 66.5 years (6.3) control group - 66.7 years (5.9)*	**Interventions** Lung volume reduction surgery *8 of the 17 centres will perform the operation via median sternotomy, 3 will use bilateral VATS procedures, and 6 will randomize patients to either median sternotomy or VATS. All participants completed 6-10 weeks of pulmonary rehabilitation*	**Outcome measure(s)** Mortality Change in PaO2 Change in FEV1 Exercise Capacity *6 minute walking distance* Health related quality of life *St George's respiratory questionnaire SF-36 Quality of wellbeing* Dyspnoea Borg Adverse events

Short Title	Population	Study arms	Outcomes
		Controls Ongoing medical treatment	
Goldstein (2003)	Sample size: *55 participants* Split between study groups *LVRS - 28 participants Control group - 27 participants* % female: *33.5%* Mean age (SD): *64.9 years (0.91)*	**Interventions** Lung volume reduction surgery *Surgery was performed by video-assisted thoracic surgery, or less often by median sternotomy* **Controls** Ongoing medical treatment	**Outcome measure(s)** Percent change in FEV1 Change in FEV1 *Millimetres %, predicted* Exercise Capacity *6 minute walking distance* Health related quality of life *Chronic respiratory disease questionnaire*
Hillerdal (2005)	Sample size: *106 patients* Split between study groups *LVRS - 53 participants Control group - 53 participants* % female: *58%* Mean age (SD): *62 years (no S.D)*	**Interventions** Lung volume reduction surgery *performed by median sternotomy (42 patients) and Video-assisted thoracoscopy in 3 patients* **Controls** Physical training group *small groups, a bi weekly session led by a certified physical therapist and supplemented by a programme of home exercise at least three times a week.*	**Outcome measure(s)** Percent change in FEV1 Change in PaO2 Exercise Capacity *6 minute walking distance Shuttle walk Exercise- capacity (W)* Health related quality of life *St George's respiratory questionnaire SF-36*
Miller (2005)	Sample size: *CLVR - 58 patients OBEST - 35 patients* Loss to follow-up *CLVR - 10%, 11% loss to follow up (intervention and control) OBEST - 17%, 19% loss to follow up (intervention and control)* % female: *69%*	**Interventions** Lung volume reduction surgery *Similar techniques in both studies - CLVR study used median sternotomy in all patients so did 5/6 centres of the OBEST study. One OBEST*	**Outcome measure(s)** Improvement in lung function - residual volume Improvement in lung function - total lung capacity Change in DLCO - diffusing capacity of the lung for carbon monoxide- % predicted

Short Title	Population	Study arms	Outcomes
	Mean age (SD): *63.86 years (6.65)* Mean pack years smoked (SD) *59.4 pack years (27.89)* Mean body mass index (SD) *23.79 kg/m2 (3.92)* **Split between study groups** CLVR study OBEST study	*site employed video-assisted thoracic surgery exclusively (6 patients)* **Controls** Ongoing medical treatment *optimised according to the American Thoracic Society and Canadian Thoracic Society - Included pulmonary rehabilitation, smoking cessation, yearly vaccination, oxygen therapy and therapy with bronchodilators, corticosteroids and antibiotics*	Exercise Capacity *6minute walking distance* Health related quality of life *SF-36 Chronic respiratory disease questionnaire*
Mineo (2004)	Sample size: *60 patients* Split between study groups % female: *not provided* Mean age (SD): *not provided* Split between study groups: LVRS *30 patients* Comprehensive rehabilitation programme *30 patients*	**Interventions** Lung volume reduction surgery *Unilateral surgery was performed in patients aged over 70 years with associated comorbidities, all other patients with symmetric and heterogeneous emphysema underwent bilateral surgery* **Controls** Comprehensive rehabilitation programme *3 hour supervised sessions over 5 days per week for 6 weeks*	**Outcome measure(s)** Change in DLCO - diffusing capacity of the lung for carbon monoxide- % predicted Change in FEV1 *Millimetres % predicted* Exercise Capacity *6 minute walking distance* Health related quality of life *St George's respiratory questionnaire SF-36 Nottingham health profile* mMRC dyspnoea score

Table 3: Endobronchial valves

Short Title	Population	Study arms	Outcomes
Davey (2014)	Sample size: *50 patients* Split between study groups *EBV - 25 patients Control group - 25 participants* Loss to follow-up *3 loss to follow up* % female: *38%* Mean age (SD): *62.8 years (7.4)* Mean pack years smoked (SD) *54 pack years (24)* Mean body mass index (SD) *24.1 kg/m2 (4.8)*	**Interventions** Endobronchial valves *unilateral lobar valve replacement aiming to achieve lobar atelectasis* **Controls** Bronchoscopy and Sham valves	**Outcome measure(s)** Mortality Change in FEV1 *millimetres* Exercise Capacity *6 minute walking distance* Health related quality of life *St George's respiratory questionnaire COPD assessment test* Adverse events
Kemp (2017)	Sample size: *97 subjects* Split between study groups Usual care: *32 participants* Endobronchial valves: *65 participants* % female: Usual care *33%* Endobronchial valves *43%* Mean pack years smoked (SD) Endobronchial valves *42.0 years (21.5)* Usual care *42 years (20.2)* Mean body mass index (SD) Endobronchial valves *23.7 kg/m2 (4.4)* Usual care *24.3 kg/m2 (5.3)*	**Interventions** Endobronchial valves **Controls** Usual care	**Outcome measure(s)** Percent change in FEV1 Improvement in lung function - residual volume Exercise Capacity *6 minute walking distance* Health related quality of life mMRC dyspnoea score Adverse events
Klooster (2015)	Sample size: *68 participants* Split between study groups *EBV - 34 participants Control group - 34 participants* % female: *EBV- 68% Control group -83%* Mean age (SD) *EBV - 58 years (10) Control group - 59 years*	**Interventions** Endobronchial valves **Controls** Usual care	**Outcome measure(s)** Percent change in FEV1 Mortality Change in FEV1 *Millimetres* Exercise Capacity *6 minute walking distance Steps*

Short Title	Population	Study arms	Outcomes
	(8) Mean pack years smoked (SD) *EBV - 37 pack years (18) Control group - 35 pack years (19)* Mean body mass index (SD) *EBV - 24.1kg/m2 (3.5) Control group - 24.2 kg/m2 (4.0*		*mean/day Walk intensity* Health related quality of life mMRC dyspnoea score Adverse events
Sciurba (2010)	Sample size: *321 participants* Split between study groups *EBV - 220 Control - 101* Loss to follow-up *11.8% in the intervention group 20.8% in the control group* % female: *EBV - 39.6% Control - 51.5%* Mean age (SD) *EBV - 65.34 years (6.83) Control - 64.9 years (5.84)* Mean pack years smoked (SD) Mean body mass index (SD) *EBV - 25.09 kg/m2 (3.96) Usual care - 24.82 kg/m2 (3.39)* Mean pack years smoked (SD) Continued medical therapy group *61.67 pack years (30.33)* Endobronchial valves *63.29 pack years (29.58)*	**Interventions** Endobronchial valves *A flexible bronchoscope with or without rigid bronchoscopy was used for valve implantation. Antibiotics were given intravenously before procedure, for 24 hrs after procedures and then orally for 7days.* **Controls** Continued medical therapy	**Outcome measure(s)** Mortality Change in FEV1 *Millimetres %, predicted* Health related quality of life *St George's respiratory questionnaire* mMRC dyspnoea score Adverse events
Valipour (2016)	Sample size: *93 patients* Split between study groups *EBV - 43 participants Control group - 50 participants* Loss to follow-up *7 patients (4 intervention, 3 control)* %female	**Interventions** Endobronchial valves *placement of endobronchial valves in all segments of the target lobe with the intention of lobar occlusion*	**Outcome measure(s)** Mortality Change in FEV1 *Millimetres* BODE index score (BMI, airflow obstruction, dyspnoea(breathlessness) and

Short Title	Population	Study arms	Outcomes
	EBV - 53% Control group - 68% Mean age (SD) *EBV - 63.2 years (6.0) Control group - 64.3 years (6.3)* Mean pack years smoked (SD) *EBV - 23.8 years (4.4) Control group - 42.5 years (22.0)* Mean body mass index (SD) *EBV - 23.8 years (4.4) Control group - 22.6 years (3.7)*	**Controls** Usual care	exercise capacity Exercise Capacity *6 minute walking distance* Health related quality of life *St George's respiratory questionnaire COPD assessment test* mMRC dyspnoea score Adverse events

1 **Table 4: Intra-bronchial valves**

Short Title	Population	Interventions	Outcomes
Ninane (2012)	Sample size: *73 patients* Split between study groups *IBV - 36 patients Control group - 34 patients* Loss to follow-up *3 withdrawals (2 intervention, 1 control)* % female: *IBV - 44% Control - 58%* Mean age (SD) *IBV - 61 years (7) Control - 62 years (6)*	**Interventions** IBV valve *Valves were placed in the airways by catheter delivery through a flexible bronchoscope* *Mean number of valve placed 7.3 (2)* **Controls** Bronchoscopy	**Outcome measure(s)** Change in DLCO - diffusing capacity of the lung for carbon monoxide- % predicted Change in FEV1 Exercise Capacity *6 minute walking tests* Health related quality of life *St George's respiratory questionnaire* mMRC dyspnoea score Adverse events
Wood (2014)	Sample size: *277 participants* Split between study groups *IBV - 142 patients Control - 135 patients* % female: *43%* Mean age (SD): *64.67 years (6.25)*	**Interventions** IBV valve **Controls** Bronchoscopy	**Outcome measure(s)** Change in PaO2 Change in FEV1 Exercise Capacity *6 minute walking distance* Health related quality of life *SGRQ total score* mMRC dyspnoea score Adverse events

Table 5: Endobronchial coils

Short Title	Population	Interventions	Outcomes
Deslee (2016)	Sample size: *100 participants* Split between study groups *EBC - 47 patients - received bilateral coils and 3 received unilateral coils* *Control group - 50 patients* % female: *EBC - 22% Control group - 36%* Mean age (SD) *EBC - 62.1 years (8.3) Control group - 61.9 years (7.3)* Mean pack years smoked (SD) *Coil treatment - 44years(19) Usual care - 46 years (21)* Mean body mass index (SD) *Coil treatment - 22.5kg/m2 (4.1) Usual care - 23kg/m2 (4.3)*	**Interventions** Endobronchial coils *as well as usual care. Approximately 10 coils per targeted lobe were delivered. Amoxicillin/clavulanic acid 2g immediately before procedure.* **Controls** Usual care *treated at the discretion of the physician in compliance with international guidelines – pre-randomisation rehabilitation, inhaled bronchodilators, influenza and pneumococcal vaccination with or without inhaled corticosteroids and with or without oxygen according to the degree of severity and exacerbation rate.*	**Outcome measure(s)** Percent change in FEV1 Improvement in lung function - residual volume Improvement in lung function - total lung capacity Mortality Exercise Capacity *6 minute walking distance* mMRC dyspnoea score Adverse events *Death Exacerbation Pneumothorax Pneumonia Thoracic Pain*
Sciurba (2016)	Sample size: *315 patients* Split between study groups *EBC - 158 patients Control group - 157 patients* % female: *EBC - 54.4% Control group -50.3 %* Mean age (SD): *EBC - 63.4 years (8.1) Control group - 64.3 years (7.7)* Mean pack years smoked (SD) *EBC - 50.7 pack years (27.9) Control group - 50.3 pack years (23.5)* Mean body mass index (SD) *EBC - 24.9 kg/m2 (4.6) Control - 24.5 kg.m2 (4.9)*	**Interventions** Endobronchial coils *In addition to receiving usual care - underwent implantation of 10-14 coils under fluoroscopic guidance via bronchoscopy.* **Controls** Usual care *Based on the Global Initiative for Chronic Obstructive Lung Disease guideline, whereby treatment was optimised in cooperation with the treating physician*	**Outcome measure(s)** Mortality Health related quality of life *St George's respiratory questionnaire* Adverse events
Shah (2013)	Sample size: *46 patients* Split between study groups *EBC - 23 patients Control group - 23 patients* Loss to follow-up	**Interventions** Endobronchial coils *Completed under moderate sedation, the*	**Outcome measure(s)** Change in FEV1 *%, predicted* Exercise Capacity

Short Title	Population	Interventions	Outcomes
	No loss to follow up % female: *EBC - 28% Control group -30%* Mean age (SD) *EBC - 62.0 years (7.0) Control group - 65.3 years (8.6)* Mean body mass index (SD) *EBC - 24.2 kg/m2 (4.8) Control group - 24.5 kg/m2 (4.8)*	*bronchoscope was positioned at the ostium of the target sub-segmental airway and a catheter with guide wire was advanced into the peripheral airways of the bronchial segment under fluoroscopic guidance until the tip was about 35mm from the pleural edge 10 LVRCs were planted in each lung.* **Controls** Usual care	*6 minute walking distance* Health related quality of life *St George's respiratory questionnaire* mMRC dyspnoea score

1

Quality assessment of clinical studies included in the evidence review

See evidence tables in appendix E for quality assessment of individual studies and appendix G for full GRADE tables.

Economic evidence

Included studies

A single search was conducted to cover all review question topics in this guideline update. This search returned 16,299 records, of which 16,293 were excluded on title and abstract for this review question. In addition, 1 potentially relevant article was identified by the committee. The remaining 7 papers were screened using a review of the full text and 5 were found to be relevant to the question. No UK-based analyses were identified by the review, so inclusion criteria were broadened to allow studies with a non-NHS perspective.

Excluded studies

Details of the studies excluded at full-text review are given in Appendix J, along with reasons for their exclusion.

Summary of studies included in the economic evidence review

Lung volume reduction surgery

Miller (2006) conducted a cost-utility analysis alongside an RCT (details of which are provided in the clinical evidence section) of lung volume reduction surgery (LVRS) compared with best medical care in patients with advanced emphysema from the perspective of the Canadian healthcare system, with a 2 year time horizon.

Patients' HRQoL was measured using the Health Utility Index (HUI3) at baseline, 6 weeks, 3 months, 12 months, 18 months and 24 months, with QALYs calculated via the area under the curve. Resource usage was measured directly throughout the trial, and included the initial surgical procedure, index hospital stay, medication, follow-up admissions and GP visits, rehabilitation and oxygen use. Unit costs were taken from Canadian-specific sources.

Results showed that, over 2 years, LVRS is associated with an additional cost of $28,119 CAD (~£15,700) and produces an additional 0.21 QALYs compared with best medical care, and produces and ICER of $133,900 (~£74,700).

This study was categorised as being partially applicable, as it is not conducted from the perspective of the NHS and uses the HUI3 to measure HRQoL without mapping to the EQ-5D. It was classified as having potentially serious limitations, due to a short time horizon and lack of sensitivity analysis.

National Emphysema Treatment Trial Research Group (2003) conducted a cost-utility analysis with a 3 year time horizon alongside an RCT (described in Fishman 2003) of LVRS compared with medical therapy in patients with severe emphysema. The analysis was conducted for the US, and used a societal perspective.

Patients' HRQoL was measured using the Quality of Well-Being scale at baseline, 6 months, 12 months and yearly thereafter. QALYs were calculated by weighting survival data by HRQoL. Healthcare resource usage data were taken from Medicare

claims, and included the initial surgical procedure, as well as subsequent resource use and home health services. Travel costs were calculated from data on patients' travel distance, and the federal government's reimbursement rate per mile. Costs of care provided by friends and family were calculated from estimates of the number of hours of unpaid weekly care, and the average wage for workers 20 to 64 years of age.

Results showed that, after excluding patients with a high risk of death and little chance of improved function from surgery, LVRS produces an ICER of $190,000 USD (~£133,500) per QALY compared with medical therapy at a time horizon of 3 years. The authors also reported disaggregated direct medical costs for the base-case scenario, which allowed recalculation of results solely from the perspective of the healthcare system. This produced an ICER of £195,000 per QALY, indicating that choice of perspective has little effect on results. Extrapolating to a 10 year time horizon (making the assumption that the hazard of death is equivalent between arms after 3 years) reduced the ICER to $53,000 (~£37,200) per QALY. Subgroup analyses showed that LVRS is more cost effective in patients with predominantly upper-lobe emphysema and low exercise capacity after pulmonary rehabilitation, with an ICER of $98,000 (~£68,800) per QALY at 3 years, and $21,000 (~£14,800) per QALY at 10 years. Probabilistic sensitivity analysis, conducted via non-parametric bootstrapping, indicated a high degree of uncertainty around results. The authors also reported disaggregated direct medical costs for the base-scenario, which allowed an ICER

This study was categorised as being partially applicable, as it is not conducted from the perspective of the NHS, and uses the Quality of Well-Being scale to measure HRQoL, without mapping to the EQ-5D. The study was also conducted from a societal perspective, although, as discussed, the choice of perspective does not materially affect results. It was classified as having potentially serious limitations, due to a short time horizon in the base case.

Ramsay (2007) conducted a cost-utility analysis with a 5 year time horizon alongside an RCT of LVRS compared with medical therapy in patients with severe emphysema, as an extension to the evaluation reported above (National Emphysema Treatment Trial Research Group 2003). The analysis was conducted in the US and used a societal perspective.

Methodology was similar to the National Emphysema Treatment Trial Research Group (2003) analysis. QALYs were calculated by weighting survival data by HRQoL measured using the Quality of Well-Being scale. Costs included healthcare resource usage (from Medicare data), travel costs (calculated from travel distance and federal government's reimbursement rate per mile), and unpaid care (calculated from average weekly hours care and average wage for workers 20 to 64 years of age).

Results showed that, after excluding patients with a high risk of death and little chance of improved function from surgery, LVRS produces an ICER of $140,000 USD (~£98,400) per QALY at 5 years and $54,000 (~£37,900) per QALY extrapolating to a time horizon of 10 years. A subgroup analysis showed that LVRS is more cost effective in patients with upper lobe emphysema and low exercise capacity, producing an ICER of $77,000 (~£54,100) per QALY at 5 years and $48,000 (~£33,700) per QALY at 10 years. Probabilistic sensitivity analysis, conducted via non-parametric bootstrapping, indicated a high degree of uncertainty around results.

This study was categorised as being partially applicable, as it is not conducted from the perspective of the NHS, and uses the Quality of Well-Being scale to measure

HRQoL, without mapping to the EQ-5D. The study was also conducted from a societal perspective. Insufficient detail was provided to recalculate ICERs from a healthcare system perspective in this instance. However, as with the National Emphysema Treatment Trial Research Group 2003 study, it is likely that taking a healthcare system perspective would result in only minor changes to ICERs. This study was classified as having potentially serious limitations, due to a short time horizon in the base case.

Endobronchial valve

Pietzsch (2014) conducted a cost utility analysis based on an RCT (described in Sciurba 2010) of endobronchial valve compared with medical management in patients with severe emphysema, from the perspective of the German healthcare system. The analysis used a 10 year time horizon, with outcomes from the first year derived directly from trial results, and outcomes for years 2 to 10 estimated using a decision modelling approach.

For the first year of the model, treatment effectiveness was estimated through differences in mortality and changes health-related quality of life measured at 6 and 12 months. Costs during this period included the cost of the initial surgical procedure, respiratory failure, pneumonia, and pneumothorax. Resource use data for these costs were taken directly from the trial, with unit costs taken from diagnosis-related group costs for Germany.

For years 2-10 a Markov model with states based on GOLD stages 2, 3 and 4 (defined by FEV1 % predicted) was used to predict patients' outcomes over time. The initial distribution of patients across GOLD stages in each arm was determined by trial data at 12 months. The model simulated patients' disease progression over time, and health-related quality of life, moderate and severe exacerbation frequency, and mortality were determined by disease severity, with relevant parameters taken from a previous economic analysis. Health-related quality of life was determined by patient's GOLD stage, with an additional disutility associated with mild, moderate and severe exacerbations. Similarly, patients incurred a cost per cycle of the model depending on their GOLD stage, with additional costs associated with exacerbations.

Results showed that endobronchial valve treatment is associated with an additional cost of €10,425 (~£9,100), and produced 0.41 additional QALYs (discounted at 3% per annum), resulting in an ICER of €25,142 (~£21,900) per QALY. Scenario analyses in which no discounting was applied, a higher number of valves in the initial procedure was assumed, higher rates of pneumothorax and valve migrations/expectorations/aspirations were used, and subgroup analyses for male/female populations did not substantially affect results, with the ICER remaining below €30,000 (~£26,100) per QALY in all cases.

This analysis was classified as being partially applicable, as it was not conducted from the perspective of the NHS. It was categorised as having very serious limitations, due to the lack of probabilistic sensitivity analysis. This limitation is especially pertinent, given that the ICER of endobronchial valve is close to NICE's cost-effectiveness threshold.

Endobronchial coil

Deslee (2016) conducted a cost-utility analysis alongside an RCT (details of which are provided in the clinical evidence section) of endobronchial coil treatment compared with usual care in patients with severe emphysema from the perspective of the French healthcare system with a one year time horizon.

Patients' health-related quality of life (HRQoL) was measured using the EQ-5D at baseline, 6 months and 1 year. QALYs were calculated from these values via the area under the curve method. Cost data were calculated using an individual patient microcosting approach, which accounted for duration of procedure, staff, medical devices, and type of operating room.

Results indicated that, at 1 year, endobronchial coil treatment is associated with an additional cost of $47,908 USD (~£33,700) and produces an additional 0.038 QALYs compared with usual care, and produces an ICER of $782,598 (~£549,800) per QALY. Probabilistic sensitivity analysis using bootstrapping of trial data indicated that endobronchial coil treatment has a negligible probability of being cost effective at any threshold below around $500,000 (£351,300) per QALY.

This study was categorised as being partially applicable, as it is not conducted from the perspective of the NHS. It was classified as having potentially serious limitations, due to a short time horizon.

Evidence statements

Clinical evidence statements

The format of the evidence statements is explained in the methods in appendix B.

Lung volume reduction surgery versus standard medical treatment

Very low to high quality evidence from up to 6 RCTs reporting data from up to 1,436 people with COPD and severe emphysema found improvements in FEV1, exercise capacity and health-related quality of life in people offered lung volume reduction surgery compared with people offered standard medical treatment at follow up of at least 3 months and up to 4 years, however short-term mortality was increased.

Low to moderate quality evidence from up to 2 RCTs reporting data from up to 1,272 people with COPD and severe emphysema found an increased risk of mortality at 90 days, but by 29.2 months the evidence could not differentiate mortality and by 4.3 years, the evidence showed a reduction in risk of mortality in the people offered lung volume reduction surgery compared with people offered standard medical treatment.

Very low quality evidence from 3 RCTs reporting data from 148 people with COPD and severe emphysema could not differentiate diffusion capacity for carbon monoxide in people offered lung volume reduction surgery compared with people offered standard medical treatment at 6 months follow up.

Low quality evidence from 1 RCT reporting data from 214 people with COPD and severe emphysema found no meaningful difference in breathlessness in people offered lung volume reduction surgery compared with people offered standard medical treatment.

Subgroup analyses

Moderate quality evidence showed improvements in exercise capacity in people with predominantly upper-lobe emphysema (1 RCT with 429 people), but low quality evidence could not differentiate exercise capacity in people with predominantly non upper-lobe emphysema (1 RCT with 214 people) in people offered lung volume reduction surgery compared with people offered standard medical treatment at 2 years follow up.

Low to moderate quality evidence from 1 RCT with 643 people with COPD showed improvement in health-related quality of life in both emphysema subgroups in people offered lung volume reduction surgery compared with people offered standard medical treatment at 2 years follow up, but the improvement was greater in the people with predominantly upper lobe emphysema.

Low to moderate quality evidence from 1 trial with up to 1,272 people with COPD showed that the risk of 90 day mortality was higher in both high risk and other participants[1] subgroups, but that the risk was much higher in the high risk group compared with other participants and this increased risk of mortality remained for the high risk participants at 29.2 months of follow up, but at a much lower level than before; however the evidence could not differentiate mortality in non-high risk people with the same follow up.

Low to moderate quality evidence from 1 RCT with 1,086 people with COPD showed that 90 day mortality was worse in those participants with predominantly non-upper lobe emphysema people offered lung volume reduction surgery compared with people offered standard medical treatment. In comparison, in people with predominantly upper lobe emphysema the evidence could not differentiate between people offered lung volume reduction surgery compared with people offered standard medical treatment.

Sensitivity analysis removing studies at high risk of bias

The sensitivity analyses for FEV1 and exercise capacity (6MWD) did not alter the results in a meaningful way.

Endobronchial valves versus usual care

Low to moderate quality evidence from up to 5 RCTs with up to 669 people showed an increased risk of severe adverse events and exacerbations, while low to moderate quality evidence from up to 2 RCTs with up to 186 people showed an improvement in breathlessness and FEV1 in people offered lung volume reduction using endobronchial valves compared with people offered standard medical care.

Emphysema subgroups

Low to high quality evidence from up to 4 RCTs reporting data from up to 511 people with COPD and emphysema of either heterogeneous or homogeneous distribution found an increase in the numbers of SGRQ responders and a reduction in breathlessness in people offered lung volume reduction using endobronchial valves compared with people offered standard medical care.

Very low quality evidence from 5 RCTs reporting data from up to 642 people with COPD and homogeneous emphysema found there was a meaningful improvement in FEV1 in people offered lung volume reduction using endobronchial valves compared with people offered standard medical care.

Very low quality evidence from 5 RCTs with 559 people with heterogeneous emphysema could not differentiate exercise capacity and very low quality evidence from 4 RTCs with 511 people with homogeneous emphysema could not differentiate mortality in people offered lung volume reduction using endobronchial valves compared with people offered standard medical care.

[1] Defined as those with a FEV in one second that was 20% or less predicted value and either homogeneous emphysema on CT or a carbon monoxide diffusing capacity that was 20% or less of the predicted value.

Very low quality evidence from 4 RCTs with 253 people with severe emphysema could not differentiate quality of life in people offered lung volume reduction using endobronchial valves compared with people offered standard medical care

Positive and negative collateral ventilation subgroups

Moderate quality evidence from up to 4 RCTs with up to 311 people found improvements in exercise capacity. FEV1 and the numbers of SGRQ responders in people without collateral ventilation using endobronchial valves compared with people offered standard medical care.

Low to moderate quality evidence from up to 4 RCTs with up to 43 people showed a reduction in the number of SGRQ responders, but could not differentiate exercise capacity or FEV1 in people with collateral ventilation using endobronchial valves compared with people offered standard medical care.

Complete and incomplete fissures subgroups

Low quality evidence from 39 people with complete fissures and lobar occlusion found improvements in exercise capacity and FEV1, whereas very low quality evidence from 1 RCT with 36 people with complete fissures without lobar occlusion could not differentiate exercise capacity and FEV1 between people offered lung volume reduction using endobronchial valves compared with people offered standard medical care.

Low quality evidence from 3 RCTs with 317 people with complete fissures found improvements in FEV1 in people offered lung volume reduction using endobronchial valves compared with people offered standard medical care.

Very low to low quality evidence from 1 RCT with 107 people with incomplete fissures could not differentiate FEV1, quality of life, exercise capacity, or mortality between people offered lung volume reduction using endobronchial valves compared with people offered standard medical care.

Intra-bronchial valves versus bronchoscopy and sham valve placement

Low to moderate quality evidence from 2 RCTs reporting data from up to 322 people with COPD found there was a worsening of partial pressure of carbon dioxide and an increased risk of adverse events in people offered lung volume reduction using intra-bronchial valves compared with people offered bronchoscopy and sham valve placement.

Low quality evidence from 2 RCTs reporting data from up to 320 people with COPD found there was a decrease in exercise capacity between people offered lung volume reduction using intra-bronchial valves compared with people offered bronchoscopy and sham valve placement, but the point estimate of the effect was less than the defined MID.

Moderate quality evidence from 2 RCTs reporting data from 319 people with COPD found there was no meaningful difference in FEV1 between people offered lung volume reduction using intra-bronchial valves compared with people offered bronchoscopy and sham valve placement.

Very low to low quality evidence from 2 RCTs reporting data from 322 people with COPD could not differentiate breathlessness, health-related quality of life, partial pressure of oxygen or COPD exacerbations between people offered lung volume reduction using intra-bronchial valves compared with people offered bronchoscopy and sham valve placement.

Endobronchial coils versus usual care

Very low to high quality evidence from up to 2 RCTs reporting data from up to 146 people with COPD found there were improvements in breathlessness, exercise capacity, percentage change in FEV1 and health related quality of life with an increase in SGRQ responders in people offered lung volume reduction using endobronchial coils compared with people offered standard medical treatment. However, moderate to high quality evidence showed an increased risk of pneumothorax in people offered lung volume reduction using endobronchial coils compared with people offered standard medical treatment during the 12 months after the procedure.

Moderate quality evidence from up to 1 RCT reporting data from 100 people with COPD found improvements in the % change in FEV1 between people offered lung volume reduction using endobronchial coils compared with people offered standard medical treatment, but the point estimate of effect was less than the MID.

Low to moderate quality evidence from up to 3 RTCs with up to 458 people with COPD could not differentiate adverse events or exacerbations in people offered lung volume reduction using endobronchial coils compared with people offered standard medical treatment during the 12 months after the procedure.

Sensitivity analysis

Moderate quality evidence from 1 RCT with 46 people could not differentiate breathlessness between people offered lung volume reduction using endobronchial coils compared with people offered standard medical treatment, however, the improvement in health related quality of life remained.

Economic evidence statements

Lung volume reduction surgery

One partially applicable study with potentially serious limitations (Miller 2006) found that lung volume reduction surgery (LVRS) in patients with advanced emphysema produces an ICER of $133,900 CAD (~£74,700) compared with best medical care at a time horizon of 2 years from the perspective of the Canadian healthcare system. The authors did not conduct a probabilistic sensitivity analysis.

One partially applicable study with potentially serious limitations (National Emphysema Treatment Trial Research Group 2003) found that LVRS in patients with severe emphysema produces an ICER of $190,000 USD (~£133,500) compared with medical therapy at 3 years using a societal perspective in the US. Extrapolating to a 10-year horizon reduces this ICER to $53,000 (~£37,200) per QALY. Subgroup showed that LVRS is more cost effective in patients with upper-lobe emphysema and low exercise capacity – ICERs of $98,000 (~£68,800) per QALY and $21,000 (~£14,800) per QALY at 3- and 10-year time horizons. Probabilistic sensitivity analyses showed a high degree of uncertainty around results.

One partially applicable study with potentially serious limitations (Ramsay 2007) found that LVRS in patients with severe emphysema produces an ICER of $140,000 USD (~£98,400) compared with medical therapy at 5 years using a societal perspective in the US. Extrapolating to a 10-year horizon reduces this ICER to $54,000 (~£37,900) per QALY. Subgroup showed that LVRS is more cost effective in patients with upper-lobe emphysema and low exercise capacity – ICERs of $77,000 (~£54,100) per QALY and $48,000 (£33,700) per QALY at 5- and 10-year time

horizons. Probabilistic sensitivity analysis showed a high degree of uncertainty around results.

Endobronchial valve

One partially applicable study with potentially serious limitations (Pietzsch 2014) found that endobronchial valve in patients with severe emphysema produces an ICER of €25,142 (~£21,900) compared with medical management from the perspective of the German healthcare system at a time horizon of 10 years. This result was robust to various scenario analyses. The authors did not conduct a probabilistic sensitivity analysis.

Endobronchial coil

One partially applicable study with potentially serious limitations (Deslee 2016) found that endobronchial coil treatment is unlikely to be cost effective – it produces an ICER of $782,598 (~£549,800) per QALY at a time horizon of 1 year, and is associated with a negligible probability of being cost effective below thresholds of around $500,000 (~£351,300) per QALY.

Recommendations

G1 Offer a respiratory review to assess whether a lung volume reduction procedure is suitable for people with COPD when they complete pulmonary rehabilitation and at other reviews, if all of the following apply:

- they have severe COPD, with FEV1 less than 50% and breathlessness that affects their quality of life despite optimal medical treatment (see recommendations 1.2.11 to 1.2.14 in the short guideline)
- they do not smoke
- they can complete a 6-minute walk distance of at least 140 m (if limited by breathlessness)
- they have completed pulmonary rehabilitation. **[2018]**

G2. At the respiratory review, refer the person with COPD to a lung volume reduction multidisciplinary team to assess whether lung volume reduction surgery or endobronchial valves are suitable if they have:

- hyperinflation, assessed by lung function testing with body plethysmography **and**
- emphysema on unenhanced CT chest scan **and**
- optimised treatment for other comorbidities. **[2018]**

G3. Only offer endobronchial coils as part of a clinical trial and after assessment by a lung volume reduction multidisciplinary team. **[2018]**

G4. For more guidance on lung volume reduction procedures, see the NICE interventional procedures guidance on lung volume reduction surgery, endobronchial valves, and endobronchial coils. **[2018]**

G5. Refer people with COPD for an assessment for bullectomy if they are breathless and a CT scan shows a bulla occupying at least one third of the hemithorax. **[2018]**

G6. Consider referral to a specialist multidisciplinary team to assess for lung transplantation for people who:

- have severe COPD, with FEV1 less than 50% and breathlessness that affects their quality of life despite optimal medical treatment (see recommendations 1.2.11 to 1.2.114 in the short guideline) **and**

- do not smoke **and**
- have completed pulmonary rehabilitation **and**
- do not have contraindications for transplantation (for example, comorbidities or frailty). **[2018]**

G7. Do not use previous lung volume reduction procedures as a reason not to refer a person for assessment for lung transplantation. **[2018]**

Rationale and impact

Why the committee made the recommendations

The evidence showed that people with severe COPD show improvements in lung function, exercise capacity, quality of life and long-term mortality as a result of lung volume reduction surgery. The criteria for who should be referred for this procedure are based on the criteria used in the trials reviewed by the committee and the committee's clinical expertise, taking into account current practice in the NHS.

It was not clear from the evidence whether endobronchial coils work better than standard lung volume reduction surgery. In addition, the procedure is relatively new. For these reasons, the committee recommended that it is only offered as part of a clinical trial.

The recommendations on referral for bullectomy and lung transplantation are based on the committee's knowledge and experience. The lung transplantation referral criteria were adapted from the criteria used for the respiratory review for lung volume reduction surgery. The committee noted that some people are refused lung transplantation because they have had previous lung volume reduction procedures. These people could still benefit from transplantation, so the committee made a recommendation to reflect this.

Impact of the recommendations on practice

It is current clinical practice to assess for future treatment plans after pulmonary rehabilitation. However, the criteria for referring people to a multidisciplinary team (MDT) to assess for lung volume reduction assessment have been broadened as recommended treatment options now include endobronchial valves. The broadening of criteria will lead to more referrals and improved access to these treatments. This will have an impact on resource use, in particular, as a new group of people for whom lung volume reduction surgery was unsuitable may now be treated with endobronchial valves.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the critical outcomes were long term (measured in years) overall survival and quality of life. The committee noted that although short term survival (for example at 90 days in the NETT trial) was expected to be worse in those having lung volume reduction procedures, especially lung volume reduction surgery, in the long term, those undergoing surgery may experience prolonged survival compared with those on standard medical treatment. Although quality of life was an important outcome, the committee acknowledged that as a subjective outcome it is

susceptible to bias especially in open label studies. As a result the committee considered objective outcomes on lung function such as FEV1 and residual volume as important when assessing the efficacy of any of the lung volume reduction procedures.

The quality of the evidence

The evidence was reviewed in six categories (LVRS, endobronchial valves, intra-bronchial valves, endobronchial coils, bullectomy and lung transplant) reflecting the lung volume reduction procedures available. There were no identified studies on bullectomy and lung transplantation.

Six randomised controlled studies on LVRS were identified for this review. The studies varied in follow up duration ranging from 3 months (Clarenbach (2015)) to 5 years (NETT study (2003)). The committee acknowledged that the NETT study (2003) was the largest ever randomised controlled study investigating LVRS and most follow on studies were based on its protocol. In general the studies were at either low or moderate risk of bias; apart from studies by Miller (2005) and Mineo (2004), whose bias was rated as high owing to uncertainties surrounding randomisation and blinding of participants.

Overall, when the evidence on LVRS was assessed using GRADE, the evidence was of very low to high quality, and most of the studies reporting evidence on the majority of the included outcomes. The committee also noted that there was a large variation of sample sizes ranging from 30 (Clarenbach (2015)) to 1,218 (NETT study (2003)) participants.

Six randomised controlled studies on endobronchial valves were identified for this review. The studies had short study duration periods ranging from 3 to 6 months. Two of the studies were at high risk of bias owing to lack of random sequence generation and blinding of participants and/or investigators. The committee was interested in the population characteristics of the study participants. The majority of the studies included participants with heterogeneous emphysema with complete fissures and negative collateral ventilation apart from the IMPACT study (Valipour, 2016) whose population had homogeneous emphysema and the VENT EU study (Herth, 2012) whose population also included participants with incomplete fissures. The committee agreed that because the VENT EU study had not selected participants to exclude those with collateral ventilation it was not a representative population of people with COPD who would be currently be considered for treatment with endobronchial valves and therefore had limited relevance to current practice.

Overall, when the evidence on endobronchial valves was assessed using GRADE, the evidence was of very low to moderate quality. The committee also noted that the majority of the studies had relatively small sample sizes ranging from 50 to 321 participants.

Two randomised controlled studies on intra-bronchial valves (Wood (2014) and Ninane (2012)) were identified for this review, both studies had very short duration of follow-up at 3 and 6 months. Both studies were double blinded, however the committee agreed that because the intra-bronchial valve procedures had not blocked all the airways to the target lobe (non-lobar occlusion), they did not represent effective treatment and a good result was unlikely. Though the studies remained part of the review, the committee dismissed the results from their consideration of the evidence.

Three randomised controlled studies on endobronchial coils were identified for this review. All three studies (RENEW Deslee (2016), REVELONS Sciurba (2016), and

RESET Shah (2013)) were open label and therefore at high risk of bias especially when considering subjective outcomes such as exercise capacity and quality of life. When the evidence was assessed using GRADE, the evidence was of very low to high quality. The majority of the evidence came from 2 studies (REVELONS Sciurba (2016), and RESET Shah (2013)) because the third study (RENEW Deslee (2016)) reported outcomes in a format that was not extractable.

Benefits and harms

The committee discussed the evidence and made recommendations for several stages in the referral process. The committee envisaged that the first assessment would be carried out by health professionals such as a general practitioner, physiotherapist, occupational health therapist or respiratory nurse, either at the completion of pulmonary rehabilitation or at routine monitoring appointments. If the person is viewed as being potentially eligible for lung volume reduction at this first assessment, a second assessment would be carried out by a respiratory physician during a respiratory review. A referral to the lung volume reduction multi-disciplinary team (MDT) would then be made if the person meets all of the stated criteria. The final decision of suitability would be made by the MDT, but issues around these discussions were not in the scope of this update, which focused only on criteria for referral.

Based on the evidence from this review, the committee agreed that lung volume reduction procedures should only be carried out in people who have completed pulmonary rehabilitation. Most of the studies (NETT Study (2003), Clarenbach (2015), Goldstein (2003), Miller (2005) and Hillerdal (2005) on lung volume reduction surgery, only considered the procedure in participants who had completed 6-8 weeks of pulmonary rehabilitation. The committee acknowledged that the definition of pulmonary rehabilitation was slightly different across the studies. This reflects the nature of current practice in the UK and the committee were not concerned by the different definitions as long as the programme included exercise training.

The evidence showed that lung volume reduction procedures (LVRS and endobronchial valves) improved FEV1, exercise capacity, health-related quality of life and survival in people offered lung volume reduction procedures compared with people offered standard medical treatment. As a result the committee made a “strong” recommendation for health professionals to assess people for suitability of lung volume reduction procedures at completion of pulmonary rehabilitation. The committee agreed that assessment at the completion of pulmonary rehabilitation would reflect good practice in the treatment plan of those people with severe COPD. However, the committee did not want to prevent people with COPD from accessing the respiratory review if they met the conditions listed at other times and so the recommendation included a reference to making an assessment for a respiratory review at other reviews as well as following pulmonary rehabilitation.

In addition to completion of pulmonary rehabilitation, the committee added three more requirements that people should meet to be offered a respiratory review for suitability of lung volume reduction procedure. These requirements were based on the inclusion criteria from the studies that were investigating efficacy of LVRS and endobronchial valves. The committee agreed that assessment of smoking status and exercise capacity is current routine practice upon completion of pulmonary rehabilitation, the recommendations will prompt a referral for a respiratory review if they meet all of the specified criteria. The majority of the studies on LVRS and endobronchial valves specified that participants should have stopped smoking and be able to walk a distance of greater than or equal to 140m within 6 minutes.

The committee agreed that the definition of severe COPD should be consistent across this guideline and Global Initiative for Chronic Obstructive Lung Disease (GOLD) and therefore adopted the GOLD definition of FEV1 of less than 50%. The evidence across the studies also showed that lung volume reduction procedures were considered in people with FEV1 of less than 50%, although some used a stricter threshold of 45% instead.

It was noted that many MDTs will only accept referrals for lung volume reduction procedures if the individual has confirmed emphysema on CT, and hyperinflation assessed by lung function testing, and it was therefore agreed these tests (if they have not already been carried out) should form part of the respiratory review before referral.

The committee agreed that endobronchial coils were a relatively new technology. They noted that although people who used endobronchial coils showed improvements in a number of outcomes including breathlessness and health related quality of life, the evidence was based on only 2 small RCTs, and was also associated with an increased risk of pneumothorax. In comparison, the lung volume reduction surgery results were based on data from 6 RCTs containing 1,436 people. As a result, the committee agreed more research was needed before endobronchial coils could be listed as an equivalent option to endobronchial valves or LVRS, and therefore made a recommendation to offer endobronchial coils only as part of a clinical trial.

The committee noted the lack of evidence identified on bullectomy, and agreed this was likely to be because there is a well-established indication for this procedure, and a lack of clinical equipoise to justify further research. They noted that in people with a large bulla (one occupying at least one third of the hemithorax), there was broad clinical consensus that bullectomy was a suitable treatment, and therefore agreed it appropriate to make a recommendation to this effect.

There was also a lack of evidence for the referral criteria for lung transplantation in people with COPD. As a result, the committee made an informal consensus recommendation by extrapolating and adapting the requirements for a LVR respiratory review to include an additional requirement that people are only referred if they do not have contraindications for transplant. These contraindications may include factors such as comorbidities and frailty. The committee noted that some people are refused lung transplantation because they have had a LVR procedure previously, although LVR procedures do not prevent a person from benefiting from lung transplantation. The committee made a recommendation to reflect this.

The committee also included a reference to the NICE interventional procedures guidance on the procedures covered by the recommendations in this section to provide additional information for healthcare professionals.

Cost effectiveness and resource use

The committee were presented with evidence from the literature regarding the cost effectiveness of lung volume reduction surgery (LVRS), and noted that, in all 3 studies, the ICER produced from surgery is substantially higher than the NICE threshold of £20,000 per QALY (when converted directly into GBP). It was observed that, in all 3 studies, LVRS produces a substantial QALY gain, but the ICER remains high due to very large incremental costs – primarily because of a high number of hospital days and, to a lesser degree, the cost of the surgical procedure itself.

The committee agreed that the ICER from the perspective of the NHS is likely to be considerably lower than the estimates provided in the literature for a number of

reasons. First, the number of days' hospital stay following surgery is, on average, substantially lower in the UK than those reported in the economic literature. Miller (2006) reported a mean stay of 31.1 days (of which 11.3 were spent in an ICU), while the analyses based on NETT (National Emphysema Treatment Group 2003 and Ramsay 2007) reported a mean stay of 23.3 days. By comparison, in the committee's experience LVRS is typically associated with an index stay of around 10 days for patients in the NHS. This is supported by an observational study conducted at the Royal Brompton Hospital which reports a mean length of stay of 10.5 days for patients undergoing unilateral LVRS (Clark et al. 2014).

Second, it was noted that unit costs are typically substantially higher in the US health care system, meaning that the cost of an equivalent procedure is likely to be higher in the studies based on NETT, even assuming equivalent healthcare resource use. By way of comparison, the average cost of a bed day in a state hospital in the US is around $1,880 (Kaiser State Health Facts), and around £222 for the NHS (National Tariff 2015/16). As hospital stay comprises the bulk of incremental costs associated with LVRS, the overall incremental cost of the procedure to the NHS is likely to be considerably lower than the estimates reported in the literature. The committee indicated that NHS Tariff cost of LVRS is around £8,500. This figure is largely consistent with the mean value of £7,824 for complex thoracic procedures from NHS Reference Costs 2015/16.

Third, the economic analyses in the literature use relatively short time horizons, which are likely to underestimate the QALY gain associated with LVRS. While the evaluations based on NETT do extrapolate their results to a 10 year time horizon, results show that approximately 30% of patients are still alive at the end of this period, indicating that some QALY benefit is still overlooked.

Fourth, the analyses with a 10-year time horizon based on NETT make the conservative assumption that the relative hazard of death between the 2 arms takes a value of 1.0 after the observed RCT period. The committee agreed that this was unlikely to be the case, considering study data with a longer time horizon show a continued pronounced difference in survival between arms.

Finally, the evaluations which conducted subgroup analyses found LVRS to be substantially more cost effective in people with predominantly upper-lobe emphysema and those with a low exercise capacity. This was principally due to a larger incremental QALY gain produced by LVRS in these groups. Since one of the key functions of lung volume reduction multidisciplinary teams is to assess patients' capacity to benefit from surgery, it stands to reason that LVRS would produce greater health benefits (and therefore be more cost effective) in patients identified through this process, compared with the average patient in the economic analyses included in the evidence review.

Considering these factors, the committee determined that, from the perspective of the NHS and over a lifetime time horizon, it is likely that LVRS is associated with an ICER that is cost effective at NICE's cost per QALY threshold. Assuming a cost of £8,500 for LVRS (noting that this does not account for any differences in costs beyond the initial procedure), the intervention would need to produce 0.425 additional QALYs compared with medical therapy in order to be cost effective at a threshold of £20,000 per QALY. Given that Ramsay (2007) estimates that LVRS produces 0.26 additional QALYs for the overall study population, and 0.69 additional QALYs for patients with predominantly upper lobe-emphysema and low exercise capacity at a 5 year time horizon, achieving this level of health benefit over a patients' lifetime seems highly plausible. Therefore, the committee felt justified in their recommendations referring appropriate patients to an MDT for consideration of LVRS.

The committee discussed the economic evidence for endobronchial valve therapy, and concluded that the ICER of €25,142 per QALY estimated by Pietzsch (2014) seems a reasonable reflection of cost effectiveness from the perspective of the NHS, as the cost of the procedure to the German healthcare system is more in-line with UK costs, and the analysis uses a reasonably long time horizon. The committee also raised the point that endobronchial valve therapy is associated with a relatively short hospital stay (approximately 1 day), so overall index stay costs are expected to be lower than those of LVRS. For these reasons the committee felt that endobronchial valve is likely to be cost effective compared with medical management. However, as with LVRS, the cost effectiveness of endobronchial valve therapy is likely to rest on the selection of patients with an appropriate capacity to benefit.

The committee were presented with the economic evidence for endobronchial coil therapy and concluded that, given the very high ICER and inconclusive clinical evidence, recommending its routine use would not be prudent based on current evidence.

There was no cost-effectiveness evidence for intra-bronchial valves, and the committee felt that evidence was not sufficient to recommend their use in patients with non-lobar occlusion on either clinical or economic grounds.

The committee discussed the potential resource impact of their recommendations. It was determined that, as a result, it is likely that more patients will undergo lung volume reduction procedures. This is principally because of the positive recommendation for endobronchial valves, which will increase the total number of people eligible for surgery, since the population eligible for this procedure differs somewhat from the population eligible for LVRS. Furthermore, it is possible that the recommendations will increase the number of people being considered for surgery by multi-disciplinary teams (MDTs), and therefore the total number of people actually undergoing procedures.

Assuming a cost per lung volume reduction procedure of around £8,500, in order to produce a resource impact of over £1 million, an extra 118 procedures would need to be carried out per year. Considering that, by the committee's estimation, between approximately 600 and 1400 lung volume reduction procedures are currently carried out per year, an increase of this magnitude seems plausible. This is also without accounting for the increase in costs due to more patients being assessed by MDTs which, given a current baseline of around 9,500 patients being considered for procedures per year, can also be expected to contribute substantially to resource impact if a higher proportion of patients are referred following completion of pulmonary rehabilitation. Therefore, it is likely that these recommendations will produce a significant resource impact.

Other factors the committee took into account

The committee discussed potential equalities issues around smoking and in particular, those raised by making recommendations that excluded current smokers from referral for lung volume reduction procedures and transplantation. They noted that smoking status is correlated with low socioeconomic status, and is a factor that is both amenable to change and of particular importance for COPD disease management and progression. They also noted that it was inappropriate to make different recommendations for people with COPD treatment based on their smoking status, unless the treatment was less effective for smokers or posed an increased risk to them that outweighed the potential benefits. The committee agreed that in the cases of lung volume reduction procedures and transplantation it was appropriate to restrict referral to non-smokers for these procedures based on the exclusion of

current smokers from the majority of the studies on LVRS and endobronchial valves and the resulting lack of evidence for effectiveness in this group of people, and the known risks associated with the procedures that mean they cannot be justified in people where there is no evidence of benefit.

1 Appendices

2 Appendix A – Review protocols

3 Review protocol for lung surgery

Field (based on PRISMA-P)	Content
Review question	In people with stable COPD, what are the referral criteria (for example intact fissures) for lung surgery?
Type of review question	Intervention
Objective of the review	To determine the effectiveness of lung surgery for people with stable COPD, and to identify which subgroups of people benefit from treatment
Eligibility criteria – population	People diagnosed with COPD (by any means including Global Strategy for the Diagnosis, Management and Prevention of COPD, GOLD, guideline; American Thoracic Society criteria for COPD; European Respiratory Society criteria)

Eligibility criteria – interventions	• Lung volume reduction (LVR) surgery
	• Bronchoscopic LVR
	  ○ Endobronchial valves
	  ○ Endobronchial coils
	• Bullectomy
	• Lung transplantation

Eligibility criteria – comparators	• No intervention • Optimal medical therapy (pulmonary rehabilitation) • Each other
Outcomes	• Mortality (30/90 day) • Survival • Hospital admissions, re-admissions and bed days • Exacerbations • Symptoms including breathlessness (e.g. Borg dyspnoea score, Modified MRC scale for dyspnoea) and orthopnoea • Gas transfer (carbon monoxide diffusion capacity (Transfer Factor of the Lung for Carbon Monoxide, TLco; Diffusing capacity of the lungs for carbon monoxide, DLCO, KCO

	used interchangeably), arterial oxygen pressure, PaO2) • Exercise capacity/ exercise tolerance (e.g. 6 minute walking distance, 6MWD, treadmill test and the shuttle walk test) • Change in FEV1, rate of change of FEV1 • Adverse events: all, severe, treatment discontinuation • Quality of life (e.g. St. George's respiratory questionnaire, SGRQ, overall score) • Resource use and costs
Eligibility criteria – study design	• RCTs • Systematic reviews of RCTs
Other exclusion criteria	• Trials with a follow-up of less than 12 weeks • Publications not in English
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups: • Re-intervention rates • Multimorbidities (including COPD with asthma, bronchopulmonary dysplasia, bronchiectasis, anxiety or depression) • Smoking status (smokers versus non-smokers or, data permitting, never smoked, ex-smokers and current smokers). • Intact fissures on lung imaging (+/- Chartis bronchoscopy) • FEV1 > 20% predicted • PaCO2 < 7.3 kPa • TLco > 20% predicted • Upper lobe predominant emphysema • Exercise capacity (for example 6MWD) • Elevated Pulmonary artery pressures • Tissue destruction (densitometry) Subgroup analyses will only be conducted if the majority of trials report data for the listed categories in an accessible format.
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this

	process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B
Information sources – databases and dates	See Appendix C Main Searches: • Cochrane Database of Systematic Reviews – CDSR (Wiley) • Cochrane Central Register of Controlled Trials – CENTRAL (Wiley) • Database of Abstracts of Reviews of Effects – DARE (Wiley) • Health Technology Assessment Database – HTA (Wiley) • EMBASE (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) The search will not be date limited as the previous guideline recommendations were not based on a systematic literature search. Economics: • NHS Economic Evaluation Database – NHS EED (Wiley) • Health Economic Evaluations Database – HEED (Wiley) • EconLit (Ovid) • Embase (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) The economics search will cover all questions and will be date limited from the previous search January 2009-May 2017.
Identify if an update	Update of 2004 COPD guideline question:

	What is the role of oxygen therapy in patients with stable COPD?
Author contacts	Guideline update
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables).
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B
Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Confidence in cumulative evidence	See Appendix B
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Damien Longson (until September 2017) and Andrew Molyneux (from September 2017) in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised

	the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

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Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination), and was always a minimum of 250.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared with that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared with that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline.
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process, they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 6. When systematic reviews were used as a source of primary data, any unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE/CERQual tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 6 Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. All studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences in important confounding variables at baseline these studies were not included in any meta-analysis and were reported separately.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Cohort studies were quality assessed using the CASP cohort study checklist. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was

calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence as identified, only pooled results are presented.

Meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 3.3.4.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 7. For other mean differences where no MID is given below the line of no effect is used. Where the authors have defined MIDs for a specific outcome this is reported as a dichotomous outcome and the line of no effect is used.

Table 7 Identified MIDs

Outcome	MID	Source
Borg dyspnoea score	2 units (-2, +2)	Ries AL. Minimally clinically important difference for the UCSD shortness of breath questionnaire, Borg Scale, and Visual Analog Scale. J COPD 2005; 2: 105–110.
6 minute walk distance	26m (-26, +26)	Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J (2011); 37: 784–790.
Total score in St. George's respiratory questionnaire	4 points (-4,+4)	Schünemann HJ, Griffith L, Jaeschke R, et al. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. J Clin Epidemiol (2003); 56: 1170–1176.
Change in FEV_1	100ml (-100ml, +100ml)	Cazzola M, MacNee W, Martinez M et al., Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008; 31: 416–468.

For standardised mean differences where no other MID was available, a MID of 0.2 was used, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988). The committee specified that any difference in mortality would be clinically meaningful, and therefore the line of no effect was used as an MID. For other relative risks, where no MID was specified, the GRADE default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. Where incidence rate ratios have been used, the GRADE rules for relative risks were applied.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated as either moderate quality (quasi-randomised studies) or low quality (cohort studies) and the quality of the evidence for each outcome was further downgraded or not from this point, based on the criteria given in Table 8.

Table 8 Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If MIDs (one corresponding to meaningful benefit; one corresponding to meaningful harm) were defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one MID, and twice if it crossed both the upper and lower MIDs. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following five conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

For outcomes with a defined MID, evidence statements were divided into 4 groups as follows:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

The number of trials and participants per outcome are detailed in the evidence statements, but in cases where there are several outcomes being summarised in a single evidence statement and the numbers of participants and trials differ between outcomes, then the number of trials and participants stated are taken from the outcome with the largest number of trials. This is denoted using the terminology ‘up to’ in front of the numbers of trials and participants.

The evidence statements also cover the quality of the outcome based on the GRADE table entry. These can be included as single ratings of quality or go from one quality level to another if multiple outcomes with different quality ratings are summarised by a single evidence statement.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 9.

Table 9 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 10.

Table 10 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable

UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions were made on this basis, this is noted in the relevant section.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

Main searches

Sources searched for this review question:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Identification of evidence

The population terms have been updated from the original guideline to include potential co-morbidities such as asthma, bronchopulmonary dysplasia and bronchiectasis. These were excluded in the original strategy.

In this update, several lines of the strategy have been focused with the use of the term 'chronic' to reduce retrieval of articles focusing on acute signs or symptoms.

Additional acronyms for COPD have been included and on recommendation from the guideline committee, terms around 'breathlessness' have been added.

Searches were re-run in February 2018 and also included searching Medline epub ahead of print.

Review question search strategy

- In people with stable COPD, what are the referral criteria (for example intact fissures) for lung surgery?

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases.

Search strategy

Medline Strategy, searched 14th June 2017 **Database: Ovid MEDLINE(R) 1946 to June Week 1 2017** **Search Strategy:**
1 lung diseases, obstructive/
2 exp pulmonary disease, chronic obstructive/
3 (copd or coad or cobd or aecb).tw.
4 emphysema*.tw.
5 (chronic* adj4 bronch*).tw.
6 (chronic* adj3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) adj3 obstruct*).tw.

Medline Strategy, searched 14th June 2017 Database: Ovid MEDLINE(R) 1946 to June Week 1 2017 Search Strategy:
7 (pulmonum adj4 (volumen or pneumatosis)).tw.
8 pneumonectasia.tw.
9 *Dyspnea/
10 (chronic* adj3 (breath* or respirat*) adj3 (difficult* or labor* or labour* or problem* or short*)).tw.
11 (chronic* adj3 (dyspnea* or dyspnoea* or dyspneic or breathless*)).tw.
12 or/1-11
13 Lung/su (Surgery)
14 Pulmonary Surgical Procedures/
15 ((lung* or alveolar or pulmonary) adj2 (surg* or operat* or procedure*)).tw.
16 Pneumonectomy/
17 ((lung* or pneumoplasty or volume) adj2 reduction*).tw.
18 ((lung* or pneumonic or pulmonary) adj2 resect*).tw.
19 (pneumonectom* or pneumoresection* or pulmonectom*).tw.
20 Bronchoscopy/
21 bronchoscop*.tw.
22 bullectom*.tw.
23 Lung Transplantation/
24 ((lung* or pulmonary) adj4 (transplant* or grafting* or allotransplant*)).tw.
25 ((endobronchial or intrabronchial or intra bronchial) adj4 (nitinol or coil* or valve* or spring* or spiral*)).tw.
26 (LVR or LVRS or LVRC).tw.
27 or/13-26
28 12 and 27
29 animals/ not humans/
30 28 not 29
31 limit 30 to english language
32 limit 31 to (letter or historical article or comment or editorial or news or case reports)
33 31 not 32

Note: In-house RCT and systematic review filters were appended

Study design filters and limits

The MEDLINE systematic review (SR) and Randomized Controlled Trial (RCT) filters were appended to the review question above and are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Study design filters

The MEDLINE SR and RCT filters are presented below.
Systematic Review
1. Meta-Analysis.pt.
2. Meta-Analysis as Topic/
3. Review.pt.

The MEDLINE SR and RCT filters are presented below.
4. exp Review Literature as Topic/ 5. (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. 6. (review$ or overview$).ti. 7. (systematic$ adj5 (review$ or overview$)).tw. 8. ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. 9. ((studies or trial$) adj2 (review$ or overview$)).tw. 10. (integrat$ adj3 (research or review$ or literature)).tw. 11. (pool$ adj2 (analy$ or data)).tw. 12. (handsearch$ or (hand adj3 search$)).tw. 13. (manual$ adj3 search$).tw. 14. or/1-13 15. animals/ not humans/ 16. 14 not 15
RCT 1 Randomized Controlled Trial.pt. 2 Controlled Clinical Trial.pt. 3 Clinical Trial.pt. 4 exp Clinical Trials as Topic/ 5 Placebos/ 6 Random Allocation/ 7 Double-Blind Method/ 8 Single-Blind Method/ 9 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. 10 (random$ adj3 allocat$).tw. 11 placebo$.tw. 12 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. 13 or/1-12 14 animals/ not humans/ 15 13 not 14 *Note: analysts requested cross-over studies to be removed.*

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

No date limit was used as the previous guideline recommendations were not based on a systematic literature search.

Health Economics search strategy

Economic evaluations and quality of life data

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)
- EconLit (Ovid)

- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to population search terms in MEDLINE, MEDLINE In-Process and EMBASE to identify relevant evidence and can be seen below. Searches were carried out on 5th May 2017 with a date limit from the previous search of January 2009 – May 2017. Searches were re-run in February 2018.

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

Health economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations
1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25
Quality of life
1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations

5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
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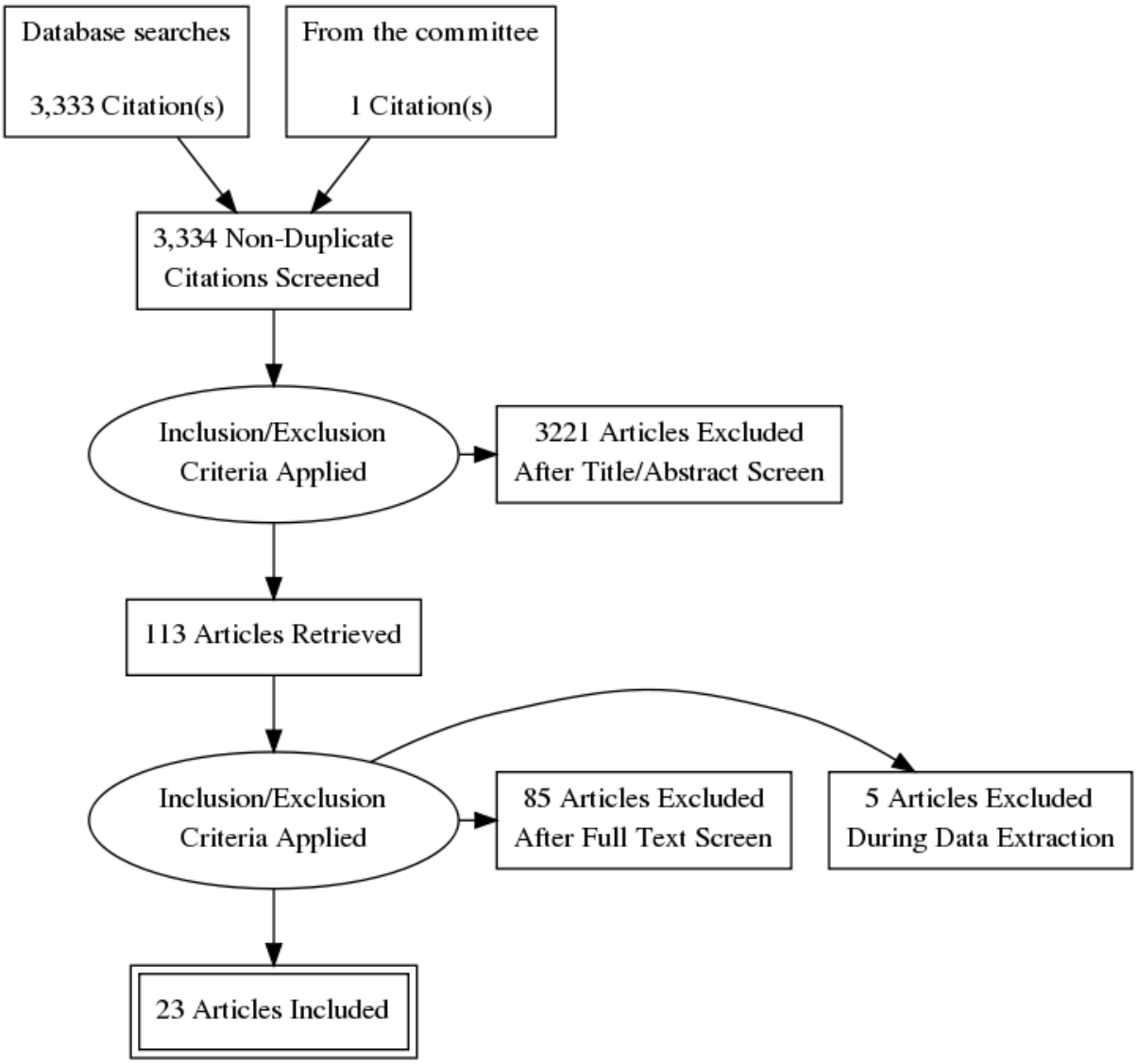
Appendix D – Clinical evidence study selection



1 Appendix E – Clinical evidence tables

2 Lung volume reduction surgery

Short Title	Title	Study Characteristics	Risk of Bias and directness
Clarenbach (2015)	LVRS improves endothelial function and blood pressure in patients with COPD: A randomized-controlled trial	**Study type** Randomised controlled trial **Study details** Study location Switzerland Study setting University Hospital Study dates No details provided Duration of follow-up 3 months Sources of funding Lunge Zurich **Inclusion criteria** Between 40 and 75 years old Severe COPD Based on the NETT study **Exclusion criteria** COPD exacerbation in the previous 6 weeks Mental or physical disability precluding informed consent or compliance with the protocol **Sample characteristics** Sample size	**Random sequence generation** Low risk of bias "Eligible patients were randomised 1:1 to one of the two groups" **Allocation concealment** Low risk of bias "Allocation concealment was performed by the use of sealed envelopes" **Blinding of participants and personnel** Unclear risk of bias Not defined - unclear if the participants were blinded to the intervention- most unlikely as the intervention required consent and was surgery **Blinding of outcome assessment** Low risk of bias "All measurements were analysed by one examiner, who was blinded to the randomization protocol (M.K.)" **Incomplete outcome data** Low risk of bias No issues identified

Short Title	Title	Study Characteristics	Risk of Bias and directness
		30 Split between study groups LVRS - 15 Control group - 15 Loss to follow-up 1 Incomplete follow-up in the LVRS group 1 withdrew and 1 incomplete follow up in the usual care follow up %female LVRS- 43% Control group - 30% Mean age (SD) LVRS - 60.9 years (10.4) Control group - 65.1 years (6.1) Mean pack years smoked (SD) LVRS - 36.8 (11.8) Control group - 53.2 (12.7) Mean body mass index (SD) LVRS group 23.5(5.0) Continued medical therapy group 23.9(2.8) **Interventions** Lung volume reduction surgery **Controls** Continued medical therapy **Outcome measure(s)** Percent change in FEV1 Exercise Capacity 6 minute walking distance Steps, mean per day	**Selective reporting** Low risk of bias No issues identified **Other sources of bias** Low risk of bias None identified **Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
Fishman (2003) **NETT STUDY**	A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema	**Study type** Randomised controlled trial **Study details** Associated study Criner Gerard J, and Sternberg Alice L. (2008). National Emphysema Treatment Trial: the major outcomes of lung volume reduction surgery in severe emphysema. Proceedings of the American Thoracic Society, 5, pp.393-405. Krachman Samuel L, Chatila Wissam, Martin Ubaldo J, Nugent Thomas, Crocetti Joseph, Gaughan John, Criner Gerard J, National Emphysema Treatment Trial Research, and Group . (2005). Effects of lung volume reduction surgery on sleep quality and nocturnal gas exchange in patients with severe emphysema. Chest, 128, pp.3221-8. Kaplan Robert M, Sun Qiankun, Naunheim Keith S, and Ries Andrew L. (2014). Long-term follow-up of high-risk patients in the National Emphysema Treatment Trial. The Annals of thoracic surgery, 98, pp.1782-9. Naunheim Keith S, Wood Douglas E, Mohsenifar Zab, Sternberg Alice L, Criner Gerard J, DeCamp Malcolm M, Deschamps Claude C, Martinez Fernando J, Sciurba Frank C, Tonascia James, Fishman Alfred P, National Emphysema Treatment Trial Research, and Group (2006) Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. The Annals of	**Random sequence generation** Unclear risk of bias the study was a randomised study however the details were not provided **Allocation concealment** Unclear risk of bias as above **Blinding of participants and personnel** Unclear risk of bias no details provided **Blinding of outcome assessment** Unclear risk of bias no details provided **Incomplete outcome data** Low risk of bias none identified **Selective reporting** Low risk of bias none identified **Other sources of bias** Unclear risk of bias none identified **Overall risk of bias** Moderate limited details were provided on randomisation and

Short Title	Title	Study Characteristics	Risk of Bias and directness
		thoracic surgery 82, 431-43 NETT study **Study location** USA - 17 clinical centres Study setting 17 clinics Study dates Study started October 1997 Duration of follow-up 6 months, 12 months and yearly after that Sources of funding supported by contracts with the National Heart, Lung and Blood Institute **Inclusion criteria** Emphysema Heterogeneous or homogeneous emphysema A post-bronchodilator FEV1 <45% predicted Radiographic evidence of bilateral emphysema Severe airflow obstruction and hyperinflation Participation in pulmonary rehabilitation with the attainment of preset performance goals Post bronchodilator TLC>100% and RV>150% PO2 >45mmHg on room air Approval of surgery by pulmonary physician, thoracic surgeon, and anaesthesiologist post rehabilitation and prior to randomization post rehabilitation 6-miute walk of greater than 140m signed consents for screening rehabilitation and randomisation	blinding of participants and during outcome assessments **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Non-smoking for 4 months to initial interview and throughout screening Must complete pre-randomisation assessments, rehabilitation program and all post-rehabilitation and randomisation assessments **Exclusion criteria** Severe comorbidities A history of recurrent clinically significant respiratory infection Previous LVR, lung transplant or bullectomy Characteristics that place them at high risk for perioperative morbidity or mortality disease believed to be unsuitable for LVRS **Sample characteristics** Sample size 1218 participants Split between study groups LVRS - 608 participants Control group - 610 participants %female LVRS - 42% Control group - 36% Mean age (SD) LVRS - 66.5 years (6.3) control group - 66.7 years (5.9) **Interventions** Lung volume reduction surgery 8 of the 17 centres will perform the operation via median sternotomy, 3 will use bilateral VATS procedures, and 6 will randomize patients to either	

Short Title	Title	Study Characteristics	Risk of Bias and directness
		median sternotomy or VATS. All participants completed 6-10 weeks of pulmonary rehabilitation **Controls** Ongoing medical treatment **Outcome measure(s)** Mortality Change in PaO2 Change in FEV1 Exercise Capacity 6 minute walking distance Health related quality of life St George's respiratory questionnaire SF-36 Quality of wellbeing Dyspnoea Borg Adverse events	
Goldstein (2003)	Influence of lung volume reduction surgery (LVRS) on health related quality of life in patients with chronic obstructive pulmonary disease	**Study type** Randomised controlled trial **Study details** Associated study Dolmage T E, Waddell T K, Maltais F, Guyatt G H, Todd T R. J, Keshavjee S, van Rooy , S , Krip B, LeBlanc P, and Goldstein R S (2004) The influence of lung volume reduction surgery on exercise in patients with COPD. The European respiratory journal 23, 269-74 Study location Canada Study setting	**Random sequence generation** Low risk of bias "The patient was then allocated to surgery or ongoing treatment according to the randomisation code (random numbers table, block randomisation in groups of four)" **Allocation concealment** Low risk of bias "The physician and surgeon remained unaware of the arm to which the patient would be allocated. They advised the coordinator of the patient's eligibility"

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Hospital Study dates Not stated Duration of follow-up 3, 6, 12 months Sources of funding Physicians services incorporated foundation, West Park health centre **Inclusion criteria** Severe COPD <75 years FEV1 <40% Forced vital capacity <0.7 hyperinflation at total lung capacity by plethysmograph >120% Quit smoking for >6 months Receiving optimal pharmacological management **Exclusion criteria** Mental or physical disability precluding informed consent or compliance with the protocol Asthma Previous lung surgery Pleural disease General contradictions to surgery Inability to attend for rehabilitation or follow up Pulmonary hypertension (systolic PAP >42mmHg or mean PAP >35mmHg) Hypercapnia (PaCO2 >6.6kPa) Homogeneous disease	**Blinding of participants and personnel** Low risk of bias As above **Blinding of outcome assessment** Low risk of bias "Research assistants who were blind to the patient's group allocation conducted all outcome assessments at 3,6,9,12 months after randomisation" **Incomplete outcome data** Low risk of bias no concerns **Selective reporting** Low risk of bias Non identified **Other sources of bias** High risk of bias Small sample size **Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Sample characteristics Sample size 55 participants Split between study groups LVRS - 28 participants Control group - 27 participants %female 33.5% Mean age (SD) 64.9 years (0.91) **Interventions** Lung volume reduction surgery surgery was performed by video-assisted thoracic surgery, or less often by median sternotomy **Controls** Ongoing medical treatment **Outcome measure(s)** Percent change in FEV1 Change in FEV1 Millimetres %, predicted Exercise Capacity 6 minute walking distance Health related quality of life Chronic respiratory disease questionnaire	
Hillerdal (2005)	Comparison of lung volume reduction surgery and physical training on health status and	**Study type** Randomised controlled trial **Study details** Study location	**Random sequence generation** Low risk of bias "randomisation was done according to separate lists, randomised for each centre in blocks of four patients"

Short Title	Title	Study Characteristics	Risk of Bias and directness
	physiologic outcomes: a randomized controlled clinical trial	Sweden Study setting 7 thoracic surgery in Sweden Study dates March 1997 and March 2000 Duration of follow-up 1 year Sources of funding Swedish Heart Lung foundation **Inclusion criteria** Severe emphysema CT scan showing diffuse emphysema and areas of more severe local involvement on CT and/or scintigraphy FEV1 of greater than 35% of predicted normal value after bronchodilation Well motivated patients, with low health related quality of life, willing to accept surgery **Exclusion criteria** Pleural disease Hypercapnia with PaCo2 55mmHg Continued smoking Prior radiation treatment, scars or fibrosis of the lungs Asthma or chronic bronchitis with large amounts of sputum and/or repeated infections Severe heart disease DLCO <20% predicted Long term treatment with oral steroids and/or Cushingoid habitus Other factors that make surgery, rehabilitation or follow up impossible or difficult: gross overweight, untreated	**Allocation concealment** Low risk of bias "all randomisation was strictly consecutive and the randomisation procedure was concealed from the participants" **Blinding of participants and personnel** High risk of bias there was no sham surgery therefore participants or personnel were not blinded **Blinding of outcome assessment** Unclear risk of bias no details provided **Incomplete outcome data** Low risk of bias non identified **Selective reporting** Low risk of bias non identified **Other sources of bias** High risk of bias Protocol changed by the safety committee - A DLCO of < or equal to 20% was added to the exclusion after they reviewed the data of the first 5 patients who died after surgery, prior to this 8 patients in the LVRS group and 2 in the training group with levels at or below this were included in the study

Short Title	Title	Study Characteristics	Risk of Bias and directness
		malignancy, psychiatric disease or drug abuse **Sample characteristics** Sample size 106 patients Split between study groups LVRS - 53 participants Control group - 53 participants %female 58% Mean age (SD) 62 years (no S.D) **Interventions** Lung volume reduction surgery performed by median sternotomy (42patients) and Video-assisted thoracoscopy in 3 patients **Controls** Physical training group small groups, a bi weekly session led by a certified physical therapist and supplemented by a programme of home exercise at least three times a week. **Outcome measure(s)** Percent change in FEV1 Change in PaO2 Exercise Capacity 6 minute walking distance Shuttle walk Exercise capacity (W) Health related quality of life St George's respiratory questionnaire SF-36	**Overall risk of bias** Moderate due to the change of protocol, those deaths at a different threshold were still included in the overall analysis, making it unclear on the referral criteria for LVRS intervention, as well as uncertainties surrounding blinding of outcome assessment **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
Miller (2005)	Lung volume reduction surgery vs medical treatment: for patients with advanced emphysema	**Study type** Randomised controlled trial **Study details** Canadian Lung Volume Reduction Overholt-Blue Cross Emphysema Surgery Trial (OBEST) **Canadian Lung Volume Reduction** Study location Canada Study setting Canada-wide, four centres Study dates July 1997 to September 2001 Duration of follow-up 6 months Sources of funding Canadian Institute of Health Research and Tyco **Overholt-Blue Cross Emphysema Surgery Trial** (OBEST) Study location USA, Massachusetts Study setting 11 participating hospitals located in the Commonwealth of Massachusetts Study dates October 1998 to January 2002 Duration of follow-up 6 months Sources of funding	**Random sequence generation** Unclear risk of bias *Authors refer to randomisation but the process was not detailed* **Allocation concealment** Unclear risk of bias *no details provided* **Blinding of participants and personnel** Unclear risk of bias *No details provided* **Blinding of outcome assessment** Unclear risk of bias *No details provided* **Incomplete outcome data** Low risk of bias *Non identified* **Selective reporting** Low risk of bias *Non identified* **Other sources of bias** High risk of bias *Small sample sizes* **Overall risk of bias** High *Due to uncertainties surrounding randomisation and*

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Thoracic foundation, the Biovascular Corp Inc, Blue Cross Shield of Massachusetts and the United States Surgical Corporation **Inclusion criteria** Canadian Lung Volume Reduction OBEST study **Canadian Lung Volume Reduction** Emphysema Breathlessness - CRQ of 4 or greater Age - 80 years or greater FEV1, % predicted of 15-40% FEV1 response to bronchodilator, 30% predicted or 300ml PCO2, mmHg <55 Evidence of Emphysema via CT scan Compliance with rehabilitation BMI/ideal body weight 17-32kg/m2 **OBEST study** Emphysema Breathlessness - MRC of 1 or less Age - 75 years or greater FEV1, % predicted of <40% FEV1 response to bronchodilator, 30% predicted or 300ml Evidence of Emphysema via CT scan Compliance with rehabilitation **Exclusion criteria** Ventilator dependency	*blinding of participants* **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Presence of a lung mass Prior thoracic surgery All patients who underwent surgery for emphysema were randomised into the study unless 1. They had previously undergone an operation on the contralateral lung for emphysema at another institution, 2. A lung mass was identified 3. a large (>5 cm), discrete Presence of collateral ventilation in both target lobes Receiving mechanical ventilation Bullous disease >5cm Chest wall deformity Prior thoracotomy Obliterated pleural space Severe comorbidities Registered for lung transplant **Sample characteristics** Sample size CLVR - 58 patients OBEST - 35 patients Loss to follow-up CLVR - 10%, 11% loss to follow up (intervention and control) OBEST - 17%, 19% loss to follow up (intervention and control) %female 69% Mean age (SD) 63.86 years (6.65) Mean pack years smoked (SD) 59.4 pack years (27.89) Mean body mass index (SD) 23.79 kg/m2 (3.92)	

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Split between study groups CLVR study OBEST study **CLVR study** LVR 30 patients Ongoing medical treatment 28 patients **OBEST study** LVRS 24 patients Ongoing medical treatment 14 patients **Interventions** Lung volume reduction surgery Similar techniques in both studies - CLVR study used median sternotomy in all patients so did 5/6 centres of the OBEST study. One OBEST site employed video-assisted thoracic surgery exclusively (6 patients) **Controls** Ongoing medical treatment optimised according to the American Thoracic Society and Canadian Thoracic Society - Included pulmonary rehabilitation, smoking cessation, yearly vaccination, oxygen therapy and therapy with bronchodilators, corticosteroids and antibiotics	

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Outcome measure(s) Improvement in lung function - residual volume Improvement in lung function - total lung capacity Change in DLCO - diffusing capacity of the lung for carbon monoxide- % predicted Exercise Capacity 6minute walking distance Health related quality of life SF-36 Chronic respiratory disease questionnaire	
Mineo (2004)	Impact of lung volume reduction surgery versus rehabilitation on quality of life	**Study type** Randomised controlled trial **Study details** Study location Italy Study dates January 1996 and January 1999 Duration of follow-up 6 months Sources of funding MURST COFIN 2001 **Inclusion criteria** None reported **Exclusion criteria** Asthma or chronic bronchitis with large amounts of sputum and/or repeated infections Clinically significant bronchiectasis Presence of bullae	**Random sequence generation** Low risk of bias *"...patients were randomised by computer into 2 groups..."* **Allocation concealment** Unclear risk of bias *No details provided* **Blinding of participants and personnel** Unclear risk of bias *No details provided* **Blinding of outcome assessment** Unclear risk of bias *No details provided* **Incomplete outcome data** Low risk of bias *none identified*

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Sample characteristics Sample size 60 patients Split between study groups %female not provided Mean age (SD) not provided **Split between study groups** LVRS 30 patients Comprehensive rehabilitation programme 30 patients **Interventions** Lung volume reduction surgery Unilateral surgery was performed in patients aged over 70 years with associated comorbidities, all other patients with symmetric and heterogeneous emphysema underwent bilateral surgery **Controls** Comprehensive rehabilitation programme 3 hour supervised sessions over 5 days per week for 6 weeks **Outcome measure(s)** Change in DLCO - diffusing capacity of the lung for carbon monoxide- % predicted Change in FEV1 Millimetres % predicted	**Selective reporting** Low risk of bias *None identified* **Other sources of bias** Unclear risk of bias *Different procedures was given the over 70s* **Overall risk of bias** High *Due to uncertainties on blinding and allocation concealment* **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Exercise Capacity 6 minute walking distance Health related quality of life St George's respiratory questionnaire SF-36 Nottingham health profile mMRC dyspnoea score	

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2 **Endobronchial valves**

Short Title	Title	Study Characteristics	Risk of Bias and directness
Davey (2014) **The BeLieVer-HIfi study**	Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (BeLieVeR-HIFi)	**Study type** Randomised controlled trial **Study details** The BeLieVer-HIfi study Associated study *Zoumot Z, Davey C, Jordan S, McNulty WH, Carr DH, Hind MD, Hansell DM, Rubens MB, Banya W, Polkey MI, Shah PL, and Hopkinson NS (2015) A randomised controlled study of Bronchoscopic Lung Volume Reduction with endobronchial valves for patients with Heterogeneous emphysema and Intact interlobar Fissures: the BeLieVeR-HIFi study. Southampton (UK): NIHR Journals Library* **Inclusion criteria** Post bronchodilator FEV1<50% predicted Total lung capacity >100% predicted Substantial breathlessness (mMRC OF >3)	**Random sequence generation** Low risk of bias *..Randomly assigned patient (1:1) to either EBV or control groups using predetermined block randomisation with a block of 10, computer generated by trial statistician...* **Allocation concealment** Low risk of bias *double blinded to both study...* **Blinding of participants and personnel** Low risk of bias *Masking was maintained by having 2 separate teams, one which undertook the randomised procedures and a separate team masked to study assignment, responsible for recruitment and the assessments...*

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Heterogeneous emphysema and intact interlobar fissures a restricted exercise capacity (6mwd <450m) **Exclusion criteria** Pulmonary hypertension and associated conditions that will limit exercise An inability to tolerate bronchoscopy under heavy sedation or anaesthesia Substantial daily sputum production **Sample characteristics** Sample size 50 patients Split between study groups EBV - 25 patients Control group - 25 participants Loss to follow-up 3 loss to follow up %female 38% Mean age (SD) 62.8 years (7.4) Mean pack years smoked (SD) 54 pack years (24) Mean body mass index (SD) 24.1 kg/m2 (4.8) **Interventions** Endobronchial valves unilateral lobar valve replacement aiming to achieve lobar atelectasis	**Blinding of outcome assessment** Low risk of bias *Masking was maintained by having 2 separate teams, one which undertook the randomised procedures and a separate team masked to study assignment, responsible for recruitment and the assessments...* **Incomplete outcome data** Low risk of bias *None identified* **Selective reporting** Low risk of bias *None identified* **Other sources of bias** High risk of bias *Small sample size* **Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Controls Bronchoscopy and Sham valves **Outcome measure(s)** Mortality Change in FEV1 millimetres Exercise Capacity 6 minute walking distance Health related quality of life St George's respiratory questionnaire COPD assessment test Adverse events Adverse events Exacerbations Pneumothorax Migration of valves Pneumonia	
Kemp (2017) **TRANSFORM study**	A Multicentre RCT of Zephyr(R) Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM).	**Study type** Randomised controlled trial **Study details** TRANSFORM study Study location *17 sites across Europe* Study dates *June 2014 and June 2016* Duration of follow-up *3 months*	**Random sequence generation** Low risk of bias *"...randomised in a 2:1 fashion (blocked design and concealed envelopes).....* **Allocation concealment** Low risk of bias *as above* **Blinding of participants and personnel** High risk of bias

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Sources of funding *Pulmonx Corporation* **Inclusion criteria** Severe emphysema Total lung capacity that was more than 100% FEV1 (% predicted) of at least 15% and not more than 45% Post bronchodilator TLC>100% and RV>150% Able to perform a 6 minute walking distance of at least 140m Ex-smokers **Sample characteristics** Sample size *97 subjects* Split between study groups Usual care *32 participants* Endobronchial valves *65 participants* %female Usual care *33%* Endobronchial valves *43%*	*open label study* **Blinding of outcome assessment** Unclear risk of bias *no details provided* **Incomplete outcome data** Low risk of bias *none identified* **Selective reporting** Low risk of bias *none identified* **Other sources of bias** Low risk of bias *none identified* **Overall risk of bias** Moderate *due to open label status and uncertainties surrounding blinding of outcome assessment* **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Mean age (SD) Usual care *63.0 years (6.0)* Endobronchial valves *64.9 years (8.0)* Mean pack years smoked (SD) Endobronchial valves *42.0 years (21.5)* Usual care *42 years (20.2)* Mean body mass index (SD) Endobronchial valves *23.7 kg/m2 (4.4)* Usual care *24.3 kg/m2 (5.3)* **Interventions** Endobronchial valves **Controls** Usual care **Outcome measure(s)** Percent change in FEV1 Improvement in lung function - residual volume Exercise Capacity *6 minute walking distance* Health related quality of life mMRC dyspnoea score	

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Adverse events **Adverse events** Pneumothorax	
Klooster (2015) **The STELVIO TRIAL**	Endobronchial valve treatment versus standard medical care in patients with emphysema without interlobar collateral ventilation (the stelvio-trial)	**Study type** Randomised controlled trial **Study details** Associated study *Hartman Jorine E, Klooster Karin, Slebos Dirk-Jan, Ten Hacken, and Nick H T (2016) Improvement of physical activity after endobronchial valve treatment in emphysema patients. Respiratory medicine 117, 116-21* The STELVIO TRIAL **Inclusion criteria** Older than 35 years of age Heterogeneous emphysema and intact interlobar fissures CT scan indicates heterogeneous severe emphysema (i.e. based on visual assessment of a treatment target lobe) - CT scan indicates intact fissures as assessed on the sagittal reconstructions of a thin slice CT Post bronchodilator FEV1 <60% predicted Post bronchodilator TLC>100% and RV>150% Breathlessness score of ≥2 on the mMRC scale of 0-4 (where higher scores indicate more severe emphysema) Patient has stopped smoking for a minimum of 6 months prior to entering the study	**Random sequence generation** Low risk of bias *"...randomly assigned patients in a 1:1 ratio, using a randomisation list that was computer generated in blocks of four"* **Allocation concealment** Low risk of bias *"...The principal investigator and study personnel did not have access to the list..."* **Blinding of participants and personnel** Low risk of bias *as above* **Blinding of outcome assessment** Unclear risk of bias *No details provided* **Incomplete outcome data** Low risk of bias *No issues identified* **Selective reporting** Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Signed informed Consent Subject is willing and able to comply with all study testing and procedures according to protocol and guidelines Lobar occlusion during endobronchial valve treatment achieved with study device (bronchoscopy required to assess **Exclusion criteria** Evidence of collateral ventilation in the target lobe **Sample characteristics** Sample size 68 participants Split between study groups EBV - 34 participants Control group - 34 participants %female EBV- 68% Control group -83% Mean age (SD) EBV - 58 years (10) Control group - 59 years (8) Mean pack years smoked (SD) EBV - 37 pack years (18) Control group - 35 pack years (19) Mean body mass index (SD) EBV - 24.1kg/m2 (3.5) Control group - 24.2 kg/m2 (4.0) **Interventions** Endobronchial valves **Controls** Usual care	*No issues identified* **Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Outcome measure(s) Percent change in FEV1 Mortality Change in FEV1 Millimetres Exercise Capacity 6 minute walking distance Steps mean/day Walk intensity Health related quality of life mMRC dyspnoea score Adverse events Adverse events Exacerbations Intervention reversed Pneumothorax Migration of valves	
Sciurba (2010) **The VENT US study**	A randomized study of endobronchial valves for advanced emphysema	**Study type** Randomised controlled trial **Study details** Associated study *Herth Felix J. F, Noppen Marc, Valipour Arschang, Leroy Sylvie, Vergnon Jean-Michel, Ficker Joachim H, Egan Jim J, Gasparini Stefano, Agusti Carlos, Holmes-Higgin Debby, Ernst Armin, and International Vent Study Group (2012) Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. The European respiratory journal 39, 1334-42* *European arm of the study*	**Random sequence generation** High risk of bias *No details provided* **Allocation concealment** High risk of bias *No details provided* **Blinding of participants and personnel** High risk of bias *No details provided* **Blinding of outcome assessment** High risk of bias

Short Title	Title	Study Characteristics	Risk of Bias and directness
		The VENT US study Endobronchial Valve for Emphysema Palliation Trial Study location USA Study setting 31 centres Study dates December 2004 to April 2006 Duration of follow-up 6 months Sources of funding Emphasys Medical (Pulmonx and the National institutes of Health **Inclusion criteria** Severe emphysema Between 40 and 75 years old Total lung capacity that was more than 100% Residual volume that was more than 150% of the predicted value FEV1 (% predicted) of at least 15% and not more than 45% **Exclusion criteria** Severe comorbidities An inability to walk >140m in 6minutes Severe hypertension Presence of bullae **Sample characteristics** Sample size	*No details provided* **Incomplete outcome data** Low risk of bias *No issues identified* **Selective reporting** Low risk of bias *No issues identified* **Other sources of bias** Unclear risk of bias *No sham control, potential placebo effect in the intervention group. In general baseline characteristics were similar between the control and intervention groups, however the intervention group had a significantly higher number of participants requiring oxygen therapy compared to the control group. Sample size was lower than the a priori sample estimate.* **Overall risk of bias** High *No details were provided regarding the randomisation process and blinding for this study* **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		321 participants Split between study groups EBV - 220 Control - 101 Loss to follow-up 11.8% in the intervention group 20.8% in the control group %female EBV - 39.6% Control - 51.5% Mean age (SD) EBV - 65.34 years (6.83) Control - 64.9 years (5.84) Mean pack years smoked (SD) Mean body mass index (SD) EBV - 25.09 kg/m2 (3.96) Usual care - 24.82 kg/m2 (3.39) **Interventions** Endobronchial valves A flexible bronchoscope with or without rigid bronchoscopy was used for valve implantation. Antibiotics were given intravenously before procedure, for 24 hrs after procedures and then orally for 7days. **Controls** Continued medical therapy **Outcome measure(s)** Mortality Change in FEV1 Millimetres %, predicted Health related quality of life St George's respiratory questionnaire mMRC dyspnoea score	

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Adverse events Adverse events Exacerbations Pneumothorax Migration of valves Respiratory failure Hospital days Pneumonia	
Valipour (2016) **The IMPACT study**	Endobronchial Valve Therapy in Patients with Homogeneous Emphysema. Results from the IMPACT Study	**Study type** Randomised controlled trial **Study details** Study location Austria, Germany and Netherlands Study setting Multicentre - conducted at 8 centres across three countries Study dates August 2014 to January 2016 Duration of follow-up 3 month Sources of funding Pulmonx corporation **Inclusion criteria** Severe emphysema Total lung capacity that was more than 100% >40 years of age FEV1 (% predicted) of at least 15% and not more than	**Random sequence generation** Low risk of bias "*Randomisation used a blocked design and concealed envelopes that were opened after the CV negative status ...*" **Allocation concealment** Low risk of bias *concealed in sealed envelopes as described above* **Blinding of participants and personnel** Unclear risk of bias *No details provided* **Blinding of outcome assessment** Unclear risk of bias *No details provided* **Incomplete outcome data** Low risk of bias no issues identified

Short Title	Title	Study Characteristics	Risk of Bias and directness
		45% Residual volume (RV % predicted) of at least 200 **Exclusion criteria** Presence of collateral ventilation in both target lobes **Sample characteristics** Sample size 93 patients Split between study groups EBV - 43 participants Control group - 50 participants Loss to follow-up 7 patients (4 intervention, 3 control) %female EBV - 53% Control group - 68% Mean age (SD) EBV - 63.2 years (6.0) Control group - 64.3 years (6.3) Mean pack years smoked (SD) EBV - 23.8 years (4.4) Control group - 42.5 years (22.0) Mean body mass index (SD) EBV - 23.8 years (4.4) Control group - 22.6 years (3.7) **Interventions** Endobronchial valves placement of endobronchial valves in all segments of the target lobe with the intention of lobar occlusion **Controls** Usual care	**Selective reporting** Low risk of bias *No issues identified* **Other sources of bias** Unclear risk of bias *Short follow up period, (study still ongoing, follow up scheduled at 6 months and 12 months)* **Overall risk of bias** Moderate *due to the short follow up period, and uncertainties regarding blinding* **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Outcome measure(s) Mortality Change in FEV1 Millimetres BODE index score (BMI, airflow obstruction, dyspnoea(breathlessness) and exercise capacity Exercise Capacity 6 minute walking distance Health related quality of life St George's respiratory questionnaire COPD assessment test mMRC dyspnoea score Adverse events Adverse events Exacerbations Pneumothorax Migration of valves Pneumonia	

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2 **Intra-bronchial**

Short Title	Title	Study Characteristics	Risk of Bias and directness
Ninane (2012)	Multicentre European study for the treatment of advanced emphysema with bronchial valves	**Study type** Randomised controlled trial **Study details** Study location Six Countries -	**Random sequence generation** Low risk of bias *The authors state "...the statistician created block of randomisation sealed envelopes that were provided to each*

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Study setting 7 sites Duration of follow-up 3 months Sources of funding Spiration Inc **Inclusion criteria** Between 40 and 75 years old Predominantly upper lobe emphysema (confirmed by CT scan evaluation by investigator) and severe breathlessness satisfies the ATS/ERS guidelines for management of stable COPD FEV1</= 45% of predicted Total lung capacity >100% of predicted and residual volume >150% of predicted Able to perform a 6 minute walking distance of at least 140m Abstained from smoking for the last 4 months and for the duration of the study **Exclusion criteria** Asthma requiring >15mg prednisolone daily DLCO <20% predicted Severe comorbidities Evidence of other diseases that can compromise survival - e.g., lung cancer or renal failure Previous LVR, lung transplant or bullectomy Severe gas exchange abnormalities (PCO2 <45 mmHg on room air (Denver criterion:Pao2 <30mmHg) 2 or more hospitalisations due to COPD exacerbations or respiratory infections in the past year	*of the clinical sites..."* **Allocation concealment** Low risk of bias *"...The envelopes were opened in numerical order only after the patient was anesthetized and the bronchoscopic evaluation of the airways was completed..."* **Blinding of participants and personnel** Low risk of bias *as above* **Blinding of outcome assessment** Unclear risk of bias *no details provided* **Incomplete outcome data** Low risk of bias *No issues identified* **Selective reporting** Low risk of bias *No issues identified* **Other sources of bias** Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Bronchitis with sputum production >60cc per day Giant bulla (>1/3 volume of lung) Diffuse emphysema with alpha1-antitrypsin deficiency **Sample characteristics** Sample size 73 patients Split between study groups IBV - 36 patients Control group - 34 patients Loss to follow-up 3 withdrawals (2 intervention, 1 control) %female IBV - 44% Control - 58% Mean age (SD) IBV - 61 years (7) Control - 62 years (6) **Interventions** IBV valve Valves were placed in the airways by catheter delivery through a flexible bronchoscope Mean number of valve placed 7.3 (2) **Controls** Bronchoscopy **Outcome measure(s)** Change in DLCO - diffusing capacity of the lung for carbon monoxide- % predicted Change in FEV1 Exercise Capacity 6 minute walking tests Health related quality of life	**Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		St George's respiratory questionnaire mMRC dyspnoea score Adverse events Adverse events Exacerbations	
Wood (2014)	The IBV Valve trial: a multicentre, randomized, double-blind trial of endobronchial therapy for severe emphysema	**Study type** Randomised controlled trial **Study details** Study location USA Study setting Hospital Study dates not stated Duration of follow-up 6 months Sources of funding Spiration Inc **Inclusion criteria** Between 40 and 75 years old Predominantly upper lobe emphysema (confirmed by CT scan evaluation by investigator) and severe breathlessness satisfies the ATS/ERS guidelines for management of stable COPD FEV1</= 45% of predicted Total lung capacity >100% of predicted and residual volume >150% of predicted Able to perform a 6 minute walking distance of at least	**Random sequence generation** Unclear risk of bias *Details not provided, however authors mention that random assignment with allocation concealment took place after anaesthesia for bronchoscopy* **Allocation concealment** Unclear risk of bias As above **Blinding of participants and personnel** Low risk of bias *this was a double blind study* **Blinding of outcome assessment** Unclear risk of bias *No details provided* **Incomplete outcome data** Low risk of bias *None identified*

Short Title	Title	Study Characteristics	Risk of Bias and directness
		140m Abstained from smoking for the last 4 months and for the duration of the study **Exclusion criteria** DLCO <20% predicted Evidence of other diseases that can compromise survival - e.g., lung cancer or renal failure Pregnant or lactating Severe gas exchange abnormalities (PCO2 <45 mmHg on room air (Denver criterion:Pao2 <30mmHg) **Sample characteristics** Sample size 277 participants Split between study groups IBV - 142 patients Control - 135 patients %female 43% Mean age (SD) 64.67 years (6.25) **Interventions** IBV valve **Controls** Bronchoscopy **Outcome measure(s)** Change in PaO2 Change in FEV1 Exercise Capacity	**Selective reporting** Low risk of bias *None identified* **Other sources of bias** Low risk of bias *None identified* **Overall risk of bias** Moderate *the study was double blinded but the authors did not provide details on random sequence generation and how the allocation concealment was done.* **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		6 minute walking distance Health related quality of life SGRQ total score mMRC dyspnoea score Adverse events Adverse events Pneumothorax Respiratory failure Pneumonia	

1 Endobronchial coils

Short Title	Title	Study Characteristics	Risk of Bias and directness
Deslee (2016) **REVOLENS Randomized Clinical Trial**	Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomized Clinical Trial	**Study type** Randomised controlled trial **Study details** Study location France Study setting 10 sites Study dates March 2013 to December 2014 Duration of follow-up 12 months **Inclusion criteria** Post bronchodilator FEV1<50% predicted Patients with bilateral emphysema Residual volume of greater than 220% predicted	**Random sequence generation** Low risk of bias *Eligible patients were randomised in a 1:1 fashion to receive usual care or coils using a centralised computer-generated randomisation system with fixed blocks of 4.* **Allocation concealment** Unclear risk of bias *not defined* **Blinding of participants and personnel** Unclear risk of bias *not defined* **Blinding of outcome assessment** Unclear risk of bias

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Formal rehabilitation within the previous 12 months **Exclusion criteria** None reported **Sample characteristics** Sample size 100 participants Split between study groups EBC - 47 patients - received bilateral coils and 3 received unilateral coils Control group - 50 patients %female EBC - 22% Control group - 36% Mean age (SD) EBC - 62.1 years (8.3) Control group - 61.9 years (7.3) Mean pack years smoked (SD) Coil treatment - 44years(19) Usual care - 46 years (21) Mean body mass index (SD) Coil treatment - 22.5kg/m2 (4.1) Usual care - 23kg/m2 (4.3) **Interventions** Endobronchial coils as well as usual care. Approximately 10 coils per targeted lobe were delivered. Amoxicillin/clavulanic acid 2g immediately before procedure.	*Not defined* **Incomplete outcome data** Low risk of bias *No concerns identified* **Selective reporting** Low risk of bias *No concerns identified* **Other sources of bias** High risk of bias *no control or placebo for the coil treatment - potential intervention effect on outcomes such as the 6 minute walking test which is effort dependent* **Overall risk of bias** High *due to uncertainties regarding blinding and lack of control group* **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Controls Usual care treated at the discretion of the physician in compliance with international guidelines – pre-randomisation rehabilitation, inhaled bronchodilators, influenza and pneumococcal vaccination with or without inhaled corticosteroids and with or without oxygen according to the degree of severity and exacerbation rate. **Outcome measure(s)** Percent change in FEV1 Improvement in lung function - residual volume Improvement in lung function - total lung capacity Mortality Exercise Capacity 6 minute walking distance mMRC dyspnoea score Adverse events Death Exacerbation Pneumothorax Pneumonia Thoracic Pain	
Sciurba (2016) **The RENEW study**	Effect of Endobronchial Coils vs Usual Care on Exercise Tolerance in Patients With Severe Emphysema: The RENEW Randomized Clinical Trial	**Study type** Randomised controlled trial **Study details** The RENEW study Study location Multicentre Study setting 21 North American and 5 European sites Study dates	**Random sequence generation** Low risk of bias *"blinded block randomisation (block size of 4) stratified by type of emphysema occurred on a 1:1 basis between usual care and usual care treatment with endobronchial coils using computerised automated system directed by an independent contractor.."*

Short Title	Title	Study Characteristics	Risk of Bias and directness
		December 2012 and November 2015 Duration of follow-up 12 months Sources of funding PnemRx Inc. **Sample characteristics** Sample size 315 patients Split between study groups EBC - 158 patients Control group - 157 patients %female EBC - 54.4% Control group -50.3 % Mean age (SD) EBC - 63.4 years (8.1) Control group - 64.3 years (7.7) Mean pack years smoked (SD) EBC - 50.7 pack years (27.9) Control group - 50.3 pack years (23.5) Mean body mass index (SD) EBC - 24.9 kg/m2 (4.6) Control - 24.5 kg.m2 (4.9) Mean age (SD) Usual care Endobronchial coils **Interventions** Endobronchial coils In addition to receiving usual care - underwent implantation of 10-14 coils under fluoroscopic guidance via bronchoscopy	**Allocation concealment** Low risk of bias *see above* **Blinding of participants and personnel** Low risk of bias *the personnel was blinded* **Blinding of outcome assessment** Low risk of bias *not described but likely to be blinded as described above* **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Controls Usual care Based on the Global Initiative for Chronic Obstructive Lung Disease guideline, whereby treatment was optimised in cooperation with the treating physician **Outcome measure(s)** Mortality Health related quality of life St George's respiratory questionnaire Adverse events Adverse events Exacerbations Pneumothorax Respiratory failure Hospital days Pneumonia	
Shah (2013) **The RESET trial**	Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial	**Study type** Randomised controlled trial **Study location** UK Study setting three sites in the UK Study dates January 2010 and October 2011 Duration of follow-up	**Random sequence generation** Low risk of bias "Randomisation sequence was computer-generated in blocks of four and stratified by treatment centres..." **Allocation concealment** Low risk of bias *"...investigators were unaware of the block sizes."* **Blinding of participants and personnel** Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias and directness
		90 days **Inclusion criteria** Older than 35 years of age High resolution CT scan indicates unilateral or bilateral emphysema High solution CT scan indicates homogeneous or heterogeneous emphysema A post-bronchodilator FEV1 <45% predicted Total lung capacity >100% predicted Patient has marked breathlessness score >2 on mMRC scale 0-4 Patient has stopped smoking for a minimum of 8 weeks before enrolment Patient or legal guardian read, understood and signed the informed consent **Exclusion criteria** A change in FEV1 greater than 20% post bronchodilator A single-breath diffusing capacity for carbon monoxide <20% predicted A history of recurrent clinically significant respiratory infection An inability to walk >140m in 6minutes Evidence of other diseases that can compromise survival - e.g., lung cancer or renal failure Pregnant or lactating An inability to tolerate bronchoscopy under heavy sedation or anaesthesia Clinically significant bronchiectasis Previous LVR, lung transplant or bullectomy Participation in other pulmonary drug studies with	*As above, however "...the bronchoscopists and patients were aware of treatment allocation ..."* **Blinding of outcome assessment** Low risk of bias *"..all assessments were done by independent research nurses and physiologists who were masked to treatment allocations..."* **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Unclear risk of bias *potential response bias as the SGRQ was self-administered* **Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		30 days enrolment **Sample characteristics** Sample size 46 patients Split between study groups EBC - 23 patients Control group - 23 patients Loss to follow-up No loss to follow up %female EBC - 28% Control group -30% Mean age (SD) EBC - 62.0 years (7.0) Control group - 65.3 years (8.6) Mean body mass index (SD) EBC - 24.2 kg/m2 (4.8) Control group - 24.5 kg/m2 (4.8) **Interventions** Endobronchial coils Completed under moderate sedation, the bronchoscope was positioned at the ostium of the target sub-segmental airway and a catheter with guide wire was advanced into the peripheral airways of the bronchial segment under fluoroscopic guidance until the tip was about 35mm from the pleural edge 10 LVRCs were planted in each lung **Controls** Usual care	

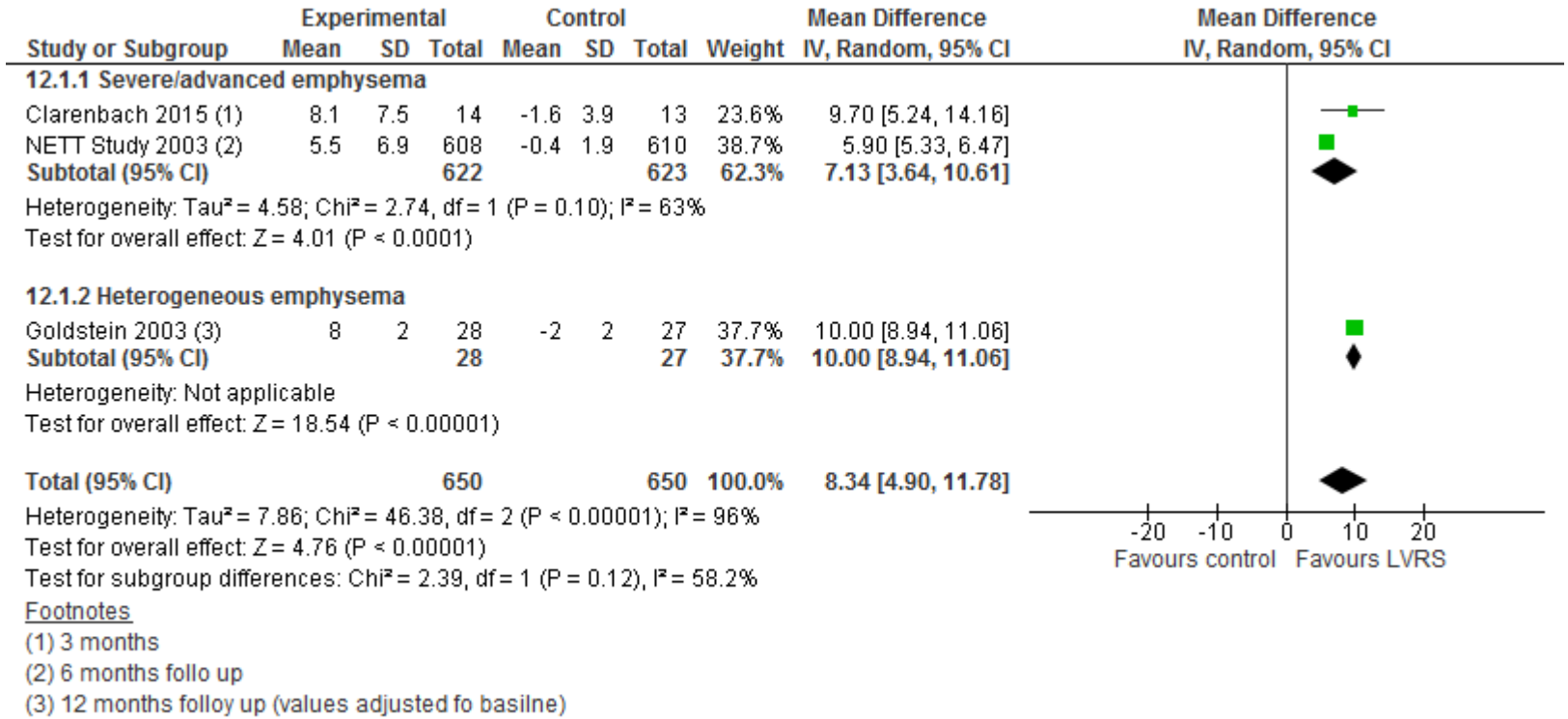
Short Title	Title	Study Characteristics	Risk of Bias and directness
		Outcome measure(s) Change in FEV1 %, predicted Exercise Capacity 6 minute walking distance Health related quality of life St George's respiratory questionnaire mMRC dyspnoea score	

1

1 Appendix F – Forest plots

2 Lung volume reduction surgery

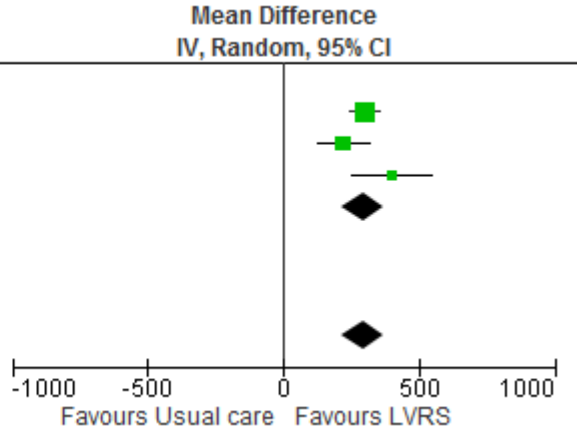
3 Lung function - FEV1 % predicted



4

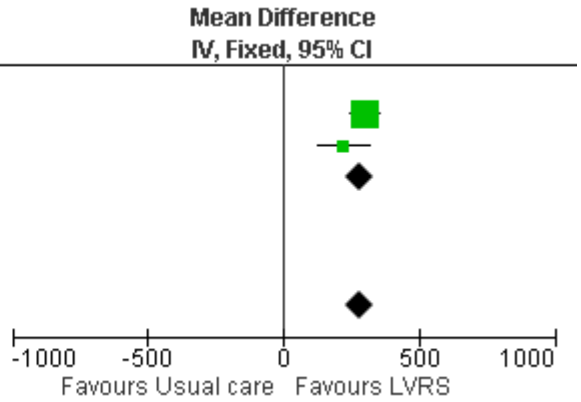
Lung function - FEV1 (ml)

Study or Subgroup	LVRS Mean	LVRS SD	LVRS Total	Usual Care Mean	Usual Care SD	Usual Care Total	Weight	Mean Difference IV, Random, 95% CI
12.2.1 12 months follow-up								
Goldstein 2003	1,000	100	24	700	100	26	48.5%	300.00 [244.52, 355.48]
Hillerdal 2005	860	250	34	640	160	39	32.1%	220.00 [122.11, 317.89]
Mineo 2004	1,200	363	27	800	156	27	19.4%	400.00 [250.97, 549.03]
Subtotal (95% CI)			**85**			**92**	**100.0%**	**293.71 [215.03, 372.39]**
Heterogeneity: Tau² = 2522.75; Chi² = 4.18, df = 2 (P = 0.12); I² = 52%								
Test for overall effect: Z = 7.32 (P < 0.00001)								
Total (95% CI)			**85**			**92**	**100.0%**	**293.71 [215.03, 372.39]**
Heterogeneity: Tau² = 2522.75; Chi² = 4.18, df = 2 (P = 0.12); I² = 52%								
Test for overall effect: Z = 7.32 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Sensitivity analysis: lung function - FEV1 (ml)

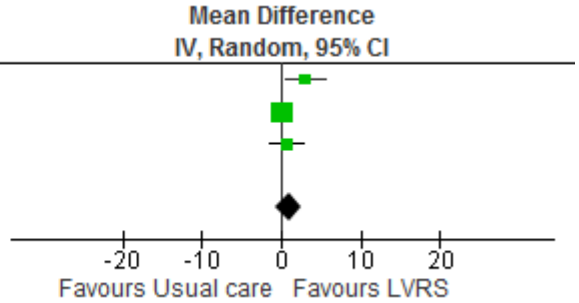
Study or Subgroup	LVRS Mean	LVRS SD	LVRS Total	Usual Care Mean	Usual Care SD	Usual Care Total	Weight	Mean Difference IV, Fixed, 95% CI
12.17.1 12 months follow-up								
Goldstein 2003	1,000	100	24	700	100	26	75.7%	300.00 [244.52, 355.48]
Hillerdal 2005	860	250	34	640	160	39	24.3%	220.00 [122.11, 317.89]
Subtotal (95% CI)			**58**			**65**	**100.0%**	**280.55 [232.28, 328.82]**
Heterogeneity: Chi² = 1.94, df = 1 (P = 0.16); I² = 49%								
Test for overall effect: Z = 11.39 (P < 0.00001)								
Total (95% CI)			**58**			**65**	**100.0%**	**280.55 [232.28, 328.82]**
Heterogeneity: Chi² = 1.94, df = 1 (P = 0.16); I² = 49%								
Test for overall effect: Z = 11.39 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Lung function – Diffusion capacity for carbon monoxide (DLCO) ml/min/mmHg

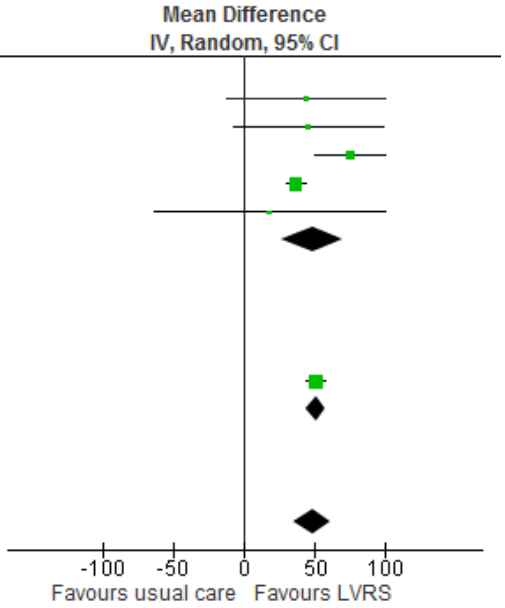
Study or Subgroup	LVRS Mean	LVRS SD	LVRS Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Random, 95% CI
CLVR Study 2005	1.55	4.45	30	-1.46	5.35	28	21.8%	3.01 [0.47, 5.55]
Mineo 2004	0	0.52	28	-0.1	0.51	27	52.1%	0.10 [-0.17, 0.37]
OBEST study 2005	0.51	2	24	-0.22	3.4	11	26.0%	0.73 [-1.43, 2.89]
Total (95% CI)			**82**			**66**	**100.0%**	**0.90 [-0.65, 2.45]**

Heterogeneity: Tau² = 1.18; Chi² = 5.26, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 1.14 (P = 0.26)

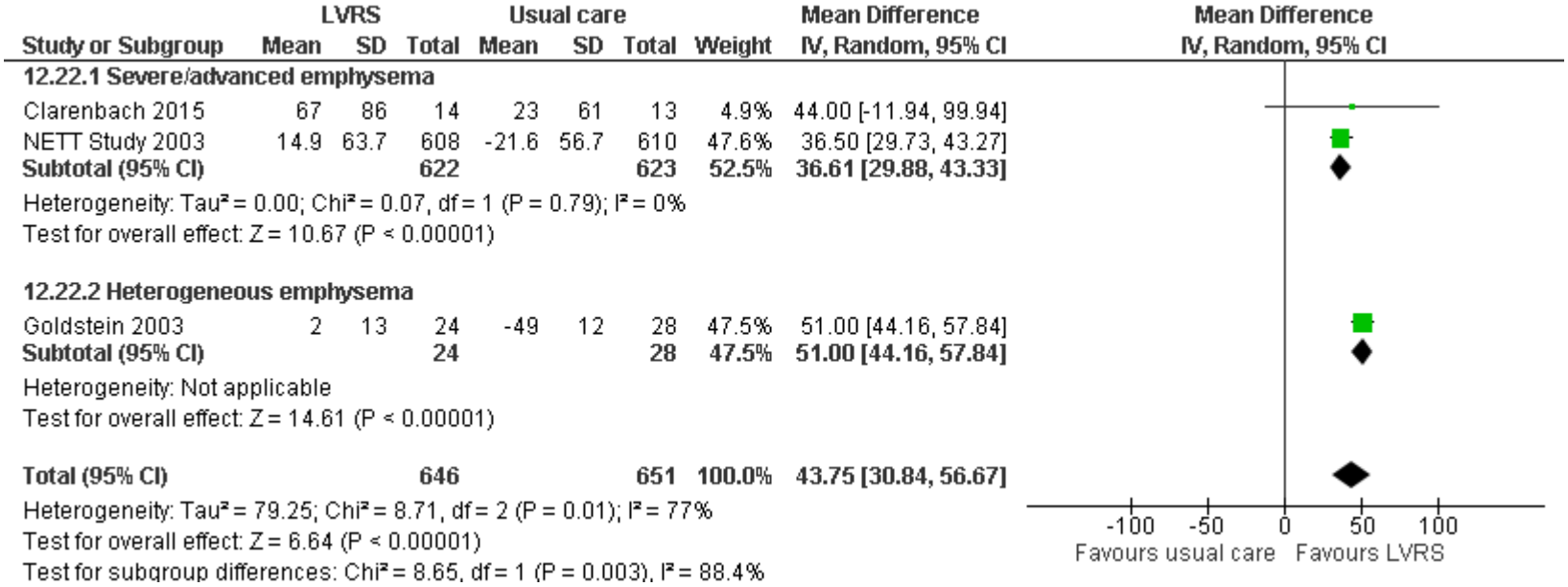


Exercise capacity – 6 minute walking distance, (m)

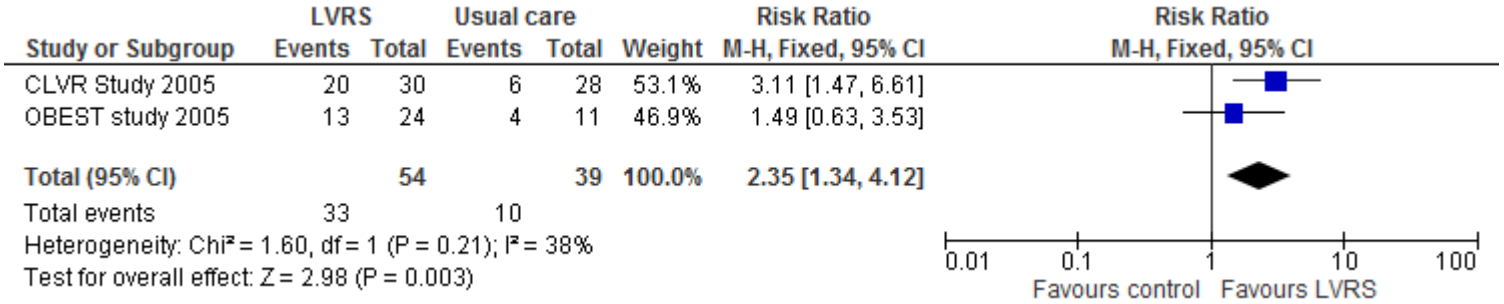
Study or Subgroup	LVRS Mean	LVRS SD	LVRS Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Random, 95% CI
12.7.1 Severe/advanced emphysema								
Clarenbach 2015	67	86	14	23	61	13	4.6%	44.00 [-11.94, 99.94]
CLVR Study 2005	46	110	30	0.6	97	28	5.0%	45.40 [-7.89, 98.69]
Mineo 2004	458	53.0008	27	383	33.1276	19	15.8%	75.00 [50.07, 99.93]
NETT Study 2003	14.9	63.7	608	-21.6	56.7	610	36.3%	36.50 [29.73, 43.27]
OBEST study 2005	43	87	24	25	126	11	2.2%	18.00 [-64.19, 100.19]
Subtotal (95% CI)			**703**			**681**	**63.8%**	**48.10 [26.24, 69.96]**
Heterogeneity: Tau² = 281.78; Chi² = 8.87, df = 4 (P = 0.06); I² = 55%								
Test for overall effect: Z = 4.31 (P < 0.0001)								
12.7.2 Heterogeneous emphysema								
Goldstein 2003	2	13	24	-49	12	28	36.2%	51.00 [44.16, 57.84]
Subtotal (95% CI)			**24**			**28**	**36.2%**	**51.00 [44.16, 57.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 14.61 (P < 0.00001)								
Total (95% CI)			**727**			**709**	**100.0%**	**48.19 [35.51, 60.87]**
Heterogeneity: Tau² = 103.40; Chi² = 14.97, df = 5 (P = 0.01); I² = 67%								
Test for overall effect: Z = 7.45 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.80), I² = 0%								



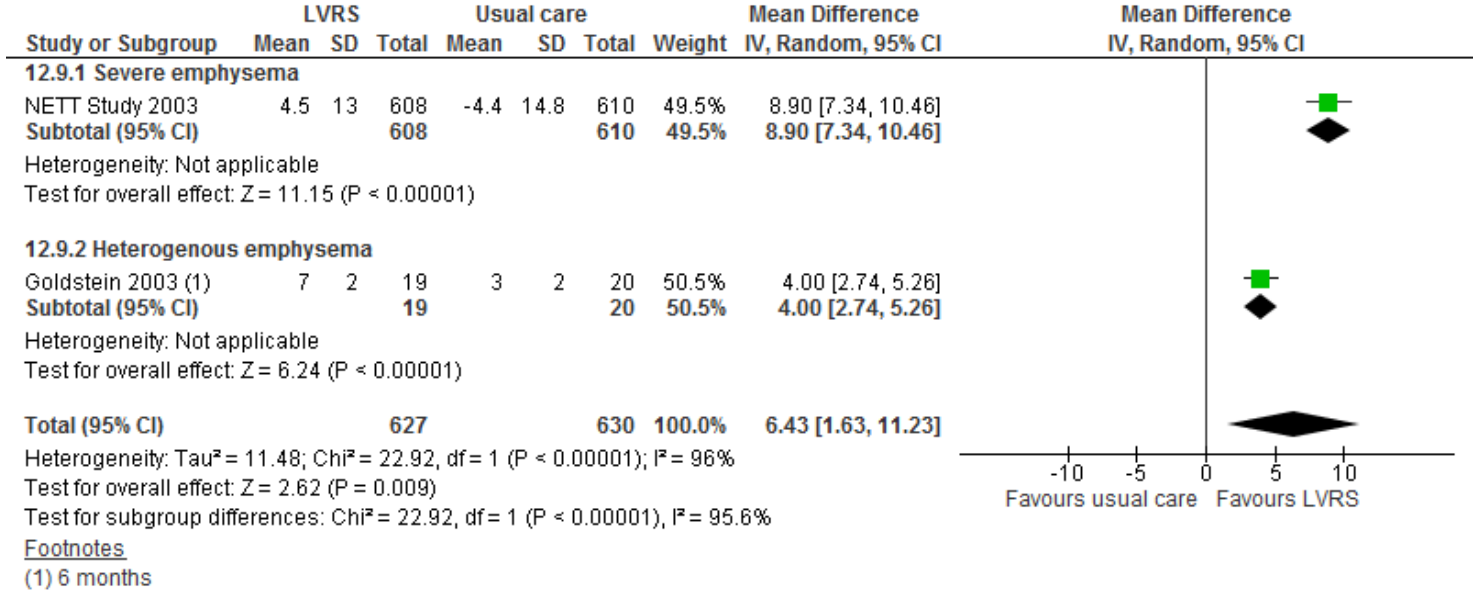
Sensitivity analysis: exercise capacity – 6 minute walking distance, (m)



Exercise capacity – 6 minute walking distance, (m) increase of more than 30m

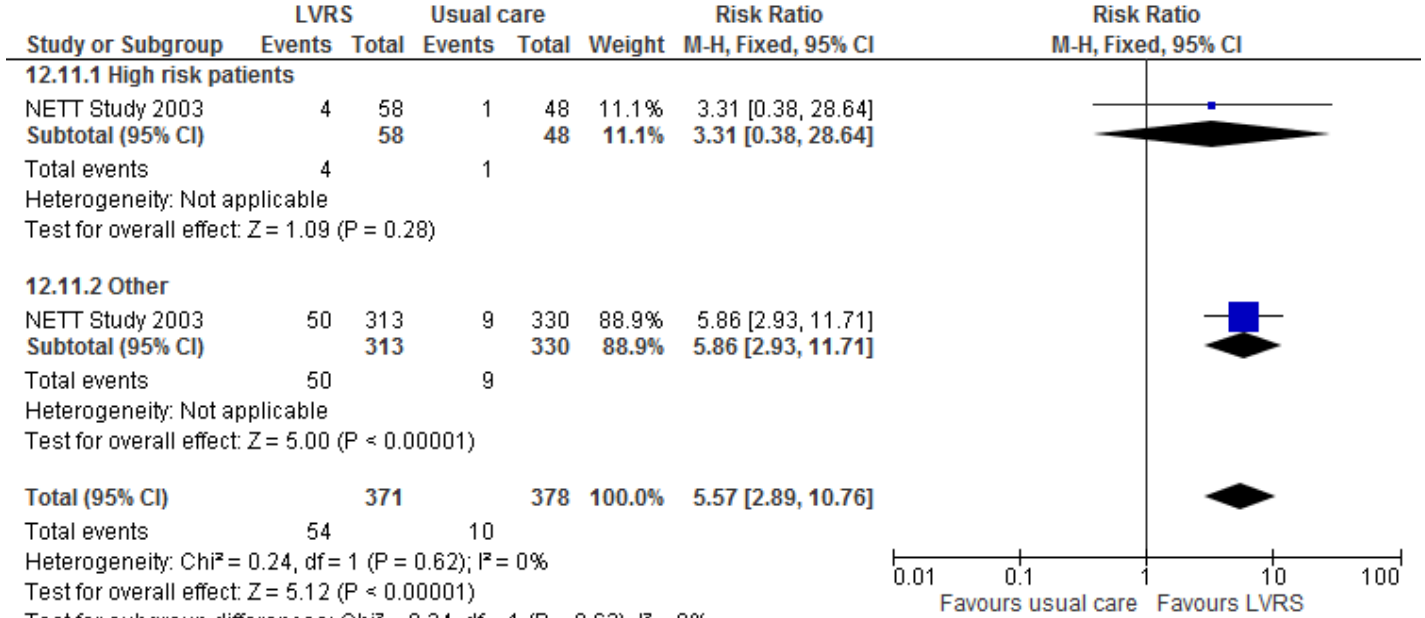


1 **Exercise capacity – Maximal capacity (Power W)**

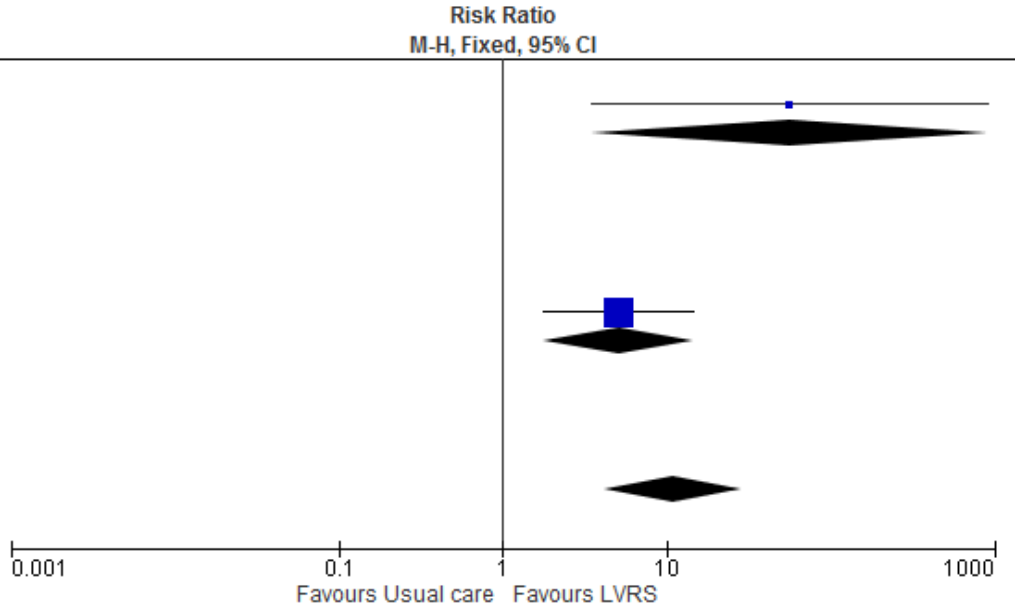


2

Exercise capacity - Improvement in exercise capacity[b]



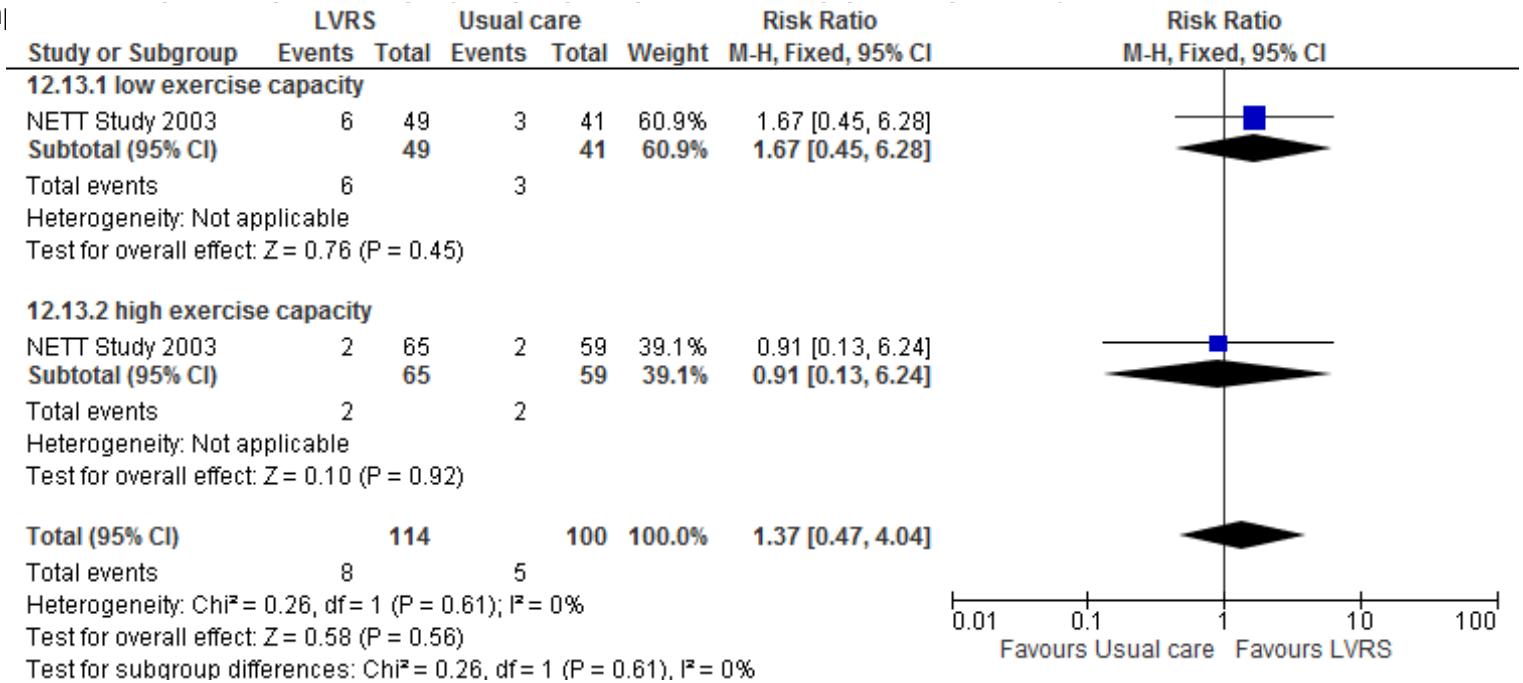
Improvement in exercise capacity (predominantly upper lobe emphysema)



Footnotes

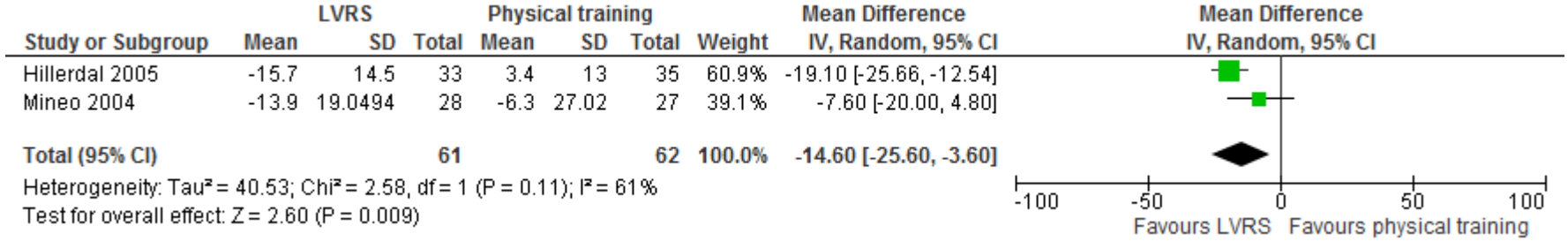
(1) Note - heterogenity is not relevant here as the figures come from the same study and the two subgouops make up the total population of those with upper lobe emphysema

1 **Im**

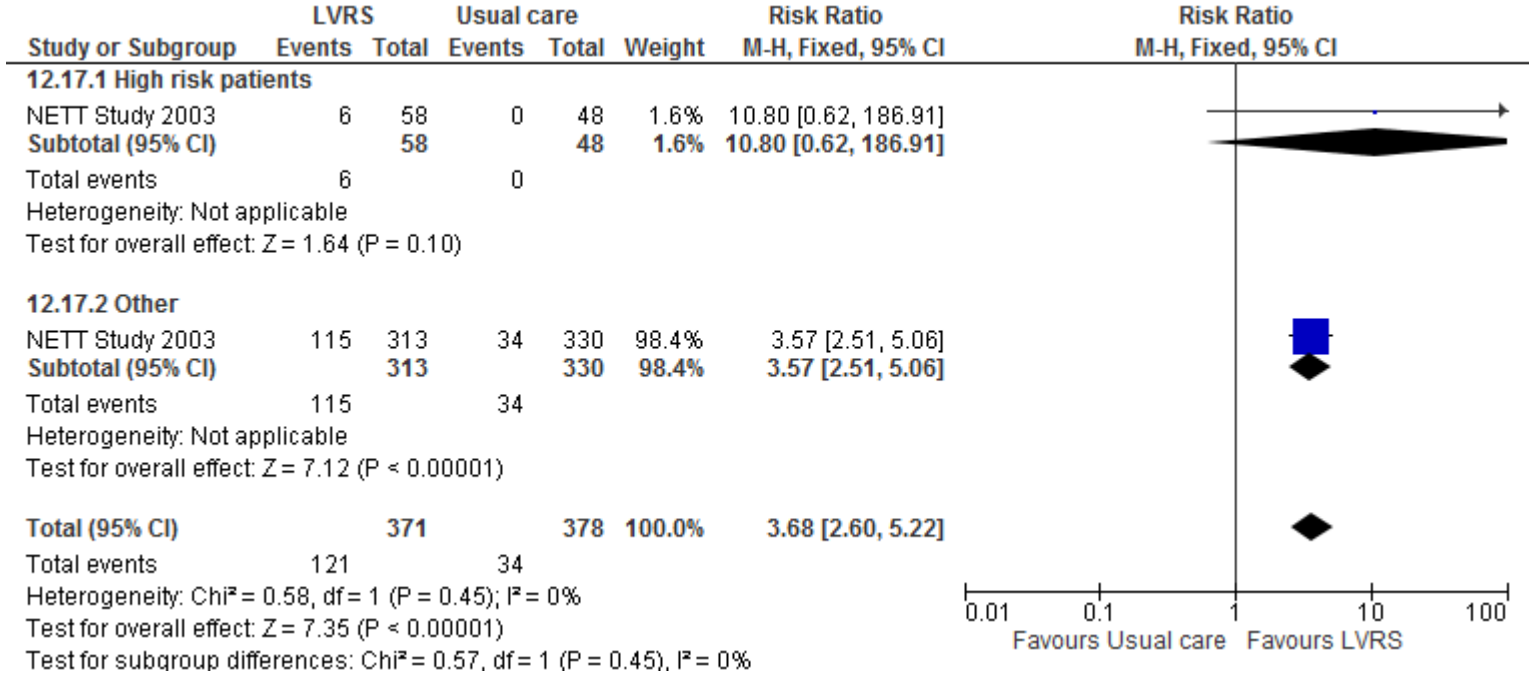

LVRS
Usual care
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
12.13.1 low exercise capacity
NETT Study 2003 6 49 3 41 60.9% 1.67 [0.45, 6.28]
Subtotal (95% CI) 49 41 60.9% 1.67 [0.45, 6.28]
Total events 6 3
Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)
12.13.2 high exercise capacity
NETT Study 2003 2 65 2 59 39.1% 0.91 [0.13, 6.24]
Subtotal (95% CI) 65 59 39.1% 0.91 [0.13, 6.24]
Total events 2 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)
Total (95% CI) 114 100 100.0% 1.37 [0.47, 4.04]
Total events 8 5
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%
0.01
0.1
1
10
100
Favours Usual care
Favours LVRS

2
3

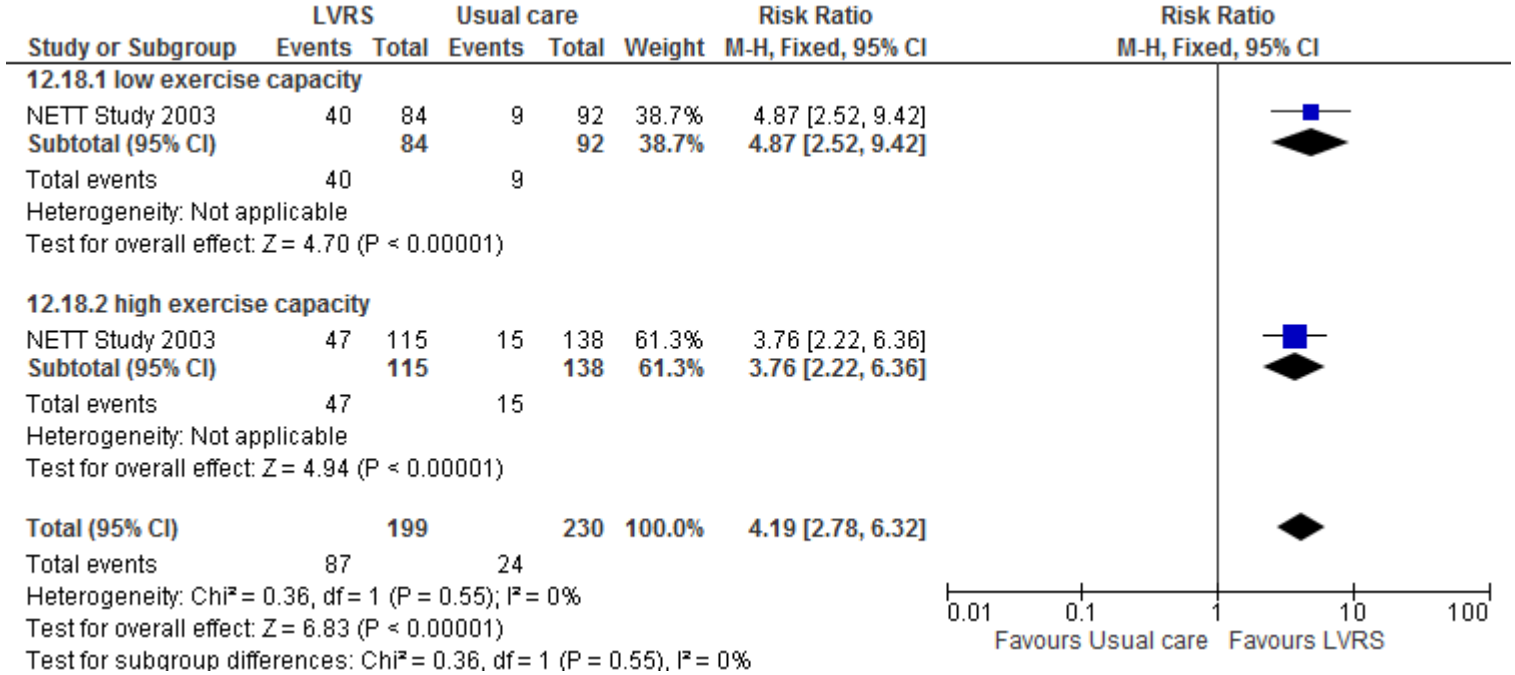
Health related quality of life - St George's respiratory questionnaire (SGRQ) at 12 months



Improvement in SGRQ (≥ 4 units) at 2 years follow up



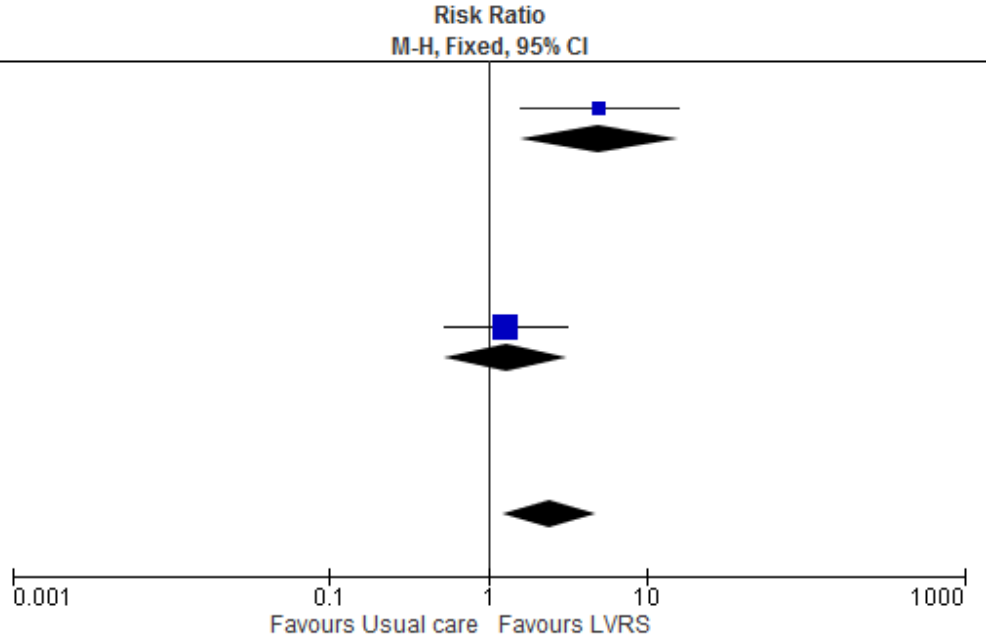
1 **Improvement in SGRQ (≥ 4 units) at 2 years follow up in patients with predominantly upper lobe emphysema**



2

All patients with predominantly non-upper lobe emphysema - health related quality of life

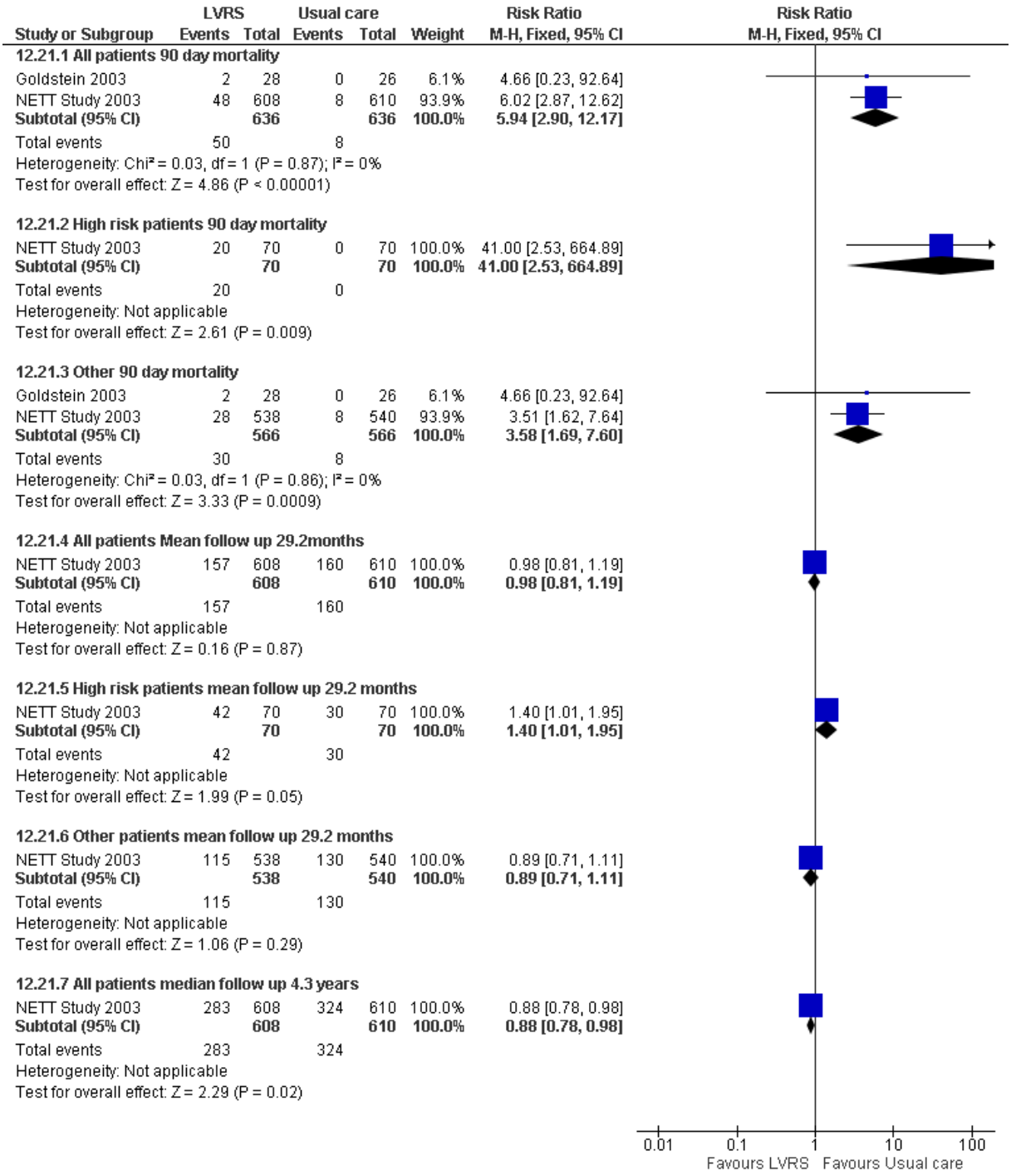
Study or Subgroup	LVRS Events	LVRS Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.20.1 low exercise capacity						
NETT Study 2003 (1)	18	49	3	41	30.8%	5.02 [1.59, 15.85]
Subtotal (95% CI)		**49**		**41**	**30.8%**	**5.02 [1.59, 15.85]**
Total events	18		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.75 (P = 0.006)						
12.20.2 high exercise capacity						
NETT Study 2003	10	65	7	59	69.2%	1.30 [0.53, 3.19]
Subtotal (95% CI)		**65**		**59**	**69.2%**	**1.30 [0.53, 3.19]**
Total events	10		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)		**114**		**100**	**100.0%**	**2.44 [1.24, 4.83]**
Total events	28		10			
Heterogeneity: Chi² = 3.41, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 2.57 (P = 0.01)						
Test for subgroup differences: Chi² = 3.30, df = 1 (P = 0.07), I² = 69.7%						



Footnotes

(1) Note - heterogenity is not relevant here as the figures come from the same study and the two subgouops make up the total population of those with upper lobe emphysema

Mortality

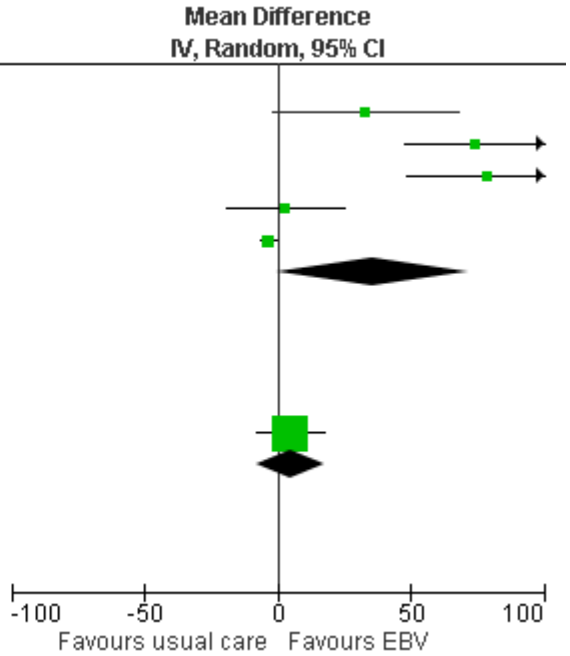

LVRS
Usual care
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
12.21.1 All patients 90 day mortality
Goldstein 2003 2 28 0 26 6.1% 4.66 [0.23, 92.64]
NETT Study 2003 48 608 8 610 93.9% 6.02 [2.87, 12.62]
Subtotal (95% CI) 636 636 100.0% 5.94 [2.90, 12.17]
Total events 50 8
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 4.86 (P < 0.00001)
12.21.2 High risk patients 90 day mortality
NETT Study 2003 20 70 0 70 100.0% 41.00 [2.53, 664.89]
Subtotal (95% CI) 70 70 100.0% 41.00 [2.53, 664.89]
Total events 20 0
Heterogeneity: Not applicable
Test for overall effect: Z = 2.61 (P = 0.009)
12.21.3 Other 90 day mortality
Goldstein 2003 2 28 0 26 6.1% 4.66 [0.23, 92.64]
NETT Study 2003 28 538 8 540 93.9% 3.51 [1.62, 7.64]
Subtotal (95% CI) 566 566 100.0% 3.58 [1.69, 7.60]
Total events 30 8
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 3.33 (P = 0.0009)
12.21.4 All patients Mean follow up 29.2months
NETT Study 2003 157 608 160 610 100.0% 0.98 [0.81, 1.19]
Subtotal (95% CI) 608 610 100.0% 0.98 [0.81, 1.19]
Total events 157 160
Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.87)
12.21.5 High risk patients mean follow up 29.2 months
NETT Study 2003 42 70 30 70 100.0% 1.40 [1.01, 1.95]
Subtotal (95% CI) 70 70 100.0% 1.40 [1.01, 1.95]
Total events 42 30
Heterogeneity: Not applicable
Test for overall effect: Z = 1.99 (P = 0.05)
12.21.6 Other patients mean follow up 29.2 months
NETT Study 2003 115 538 130 540 100.0% 0.89 [0.71, 1.11]
Subtotal (95% CI) 538 540 100.0% 0.89 [0.71, 1.11]
Total events 115 130
Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)
12.21.7 All patients median follow up 4.3 years
NETT Study 2003 283 608 324 610 100.0% 0.88 [0.78, 0.98]
Subtotal (95% CI) 608 610 100.0% 0.88 [0.78, 0.98]
Total events 283 324
Heterogeneity: Not applicable
Test for overall effect: Z = 2.29 (P = 0.02)
0.01
0.1
1
10
100
Favours LVRS
Favours Usual care

1 Endobronchial valves

2 Exercise capacity: 6 minute walking distance (metres)

3

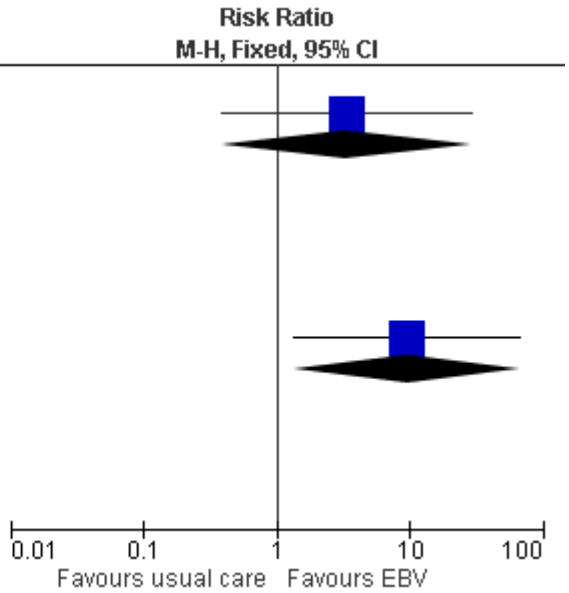
Study or Subgroup	Endobronchial valves Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 All heterogeneous emphysema								
BeLieVer-HIFi 2015	29	70.2554	25	-4	55.7198	25	18.3%	33.00 [-2.15, 68.15]
STELVIO 2015	60	71.6504	34	-14	31.5262	34	19.8%	74.00 [47.69, 100.31]
TRANSFORM 2017	36.2	76.9	65	-42.5	68.2	32	19.2%	78.70 [48.57, 108.83]
Vent EU 2012	13	35	44	10	44	19	20.5%	3.00 [-19.32, 25.32]
Vent US 2010	-2.8	14.2991	220	0.6	12.1573	101	22.2%	-3.40 [-6.43, -0.37]
Subtotal (95% CI)			**388**			**211**	**100.0%**	**35.70 [-0.15, 71.56]**
Heterogeneity: Tau² = 1506.18; Chi² = 64.18, df = 4 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 1.95 (P = 0.05)								
3.1.3 Incomplete fissure								
Vent EU 2012	5	30	67	0	34	40	100.0%	5.00 [-7.75, 17.75]
Subtotal (95% CI)			**67**			**40**	**100.0%**	**5.00 [-7.75, 17.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.77 (P = 0.44)								



4 Test for subgroup differences: Chi² = 2.50, df = 1 (P = 0.11), I² = 60.0%

Exercise capacity – improvement in 6 minute walking distance (m) – increase of more than 35m

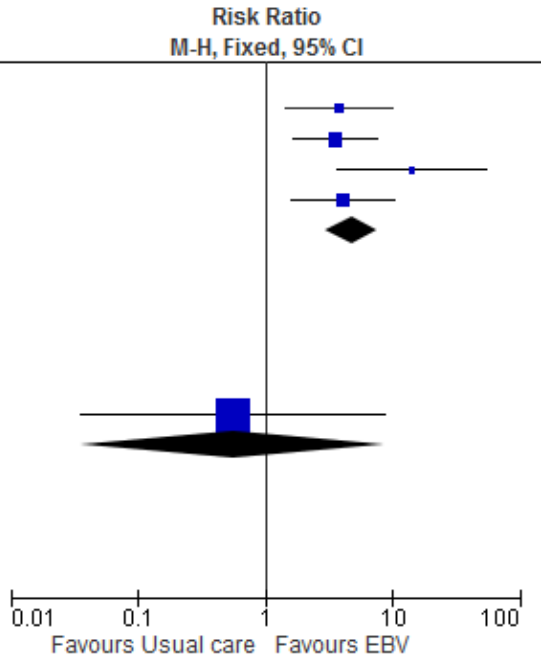
Study or Subgroup	EBV Events	EBV Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 No lobar occlusion						
Vent EU 2012	3	17	1	19	100.0%	3.35 [0.38, 29.26]
Subtotal (95% CI)		**17**		**19**	**100.0%**	**3.35 [0.38, 29.26]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.27)						
3.2.2 Lobar occlusion						
Vent EU 2012	10	20	1	19	100.0%	9.50 [1.34, 67.27]
Subtotal (95% CI)		**20**		**19**	**100.0%**	**9.50 [1.34, 67.27]**
Total events	10		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.25 (P = 0.02)						



Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.48), I² = 0%

1 **Exercise capacity – improvement in 6 minute walking distance (m) – increase of at least 26m**

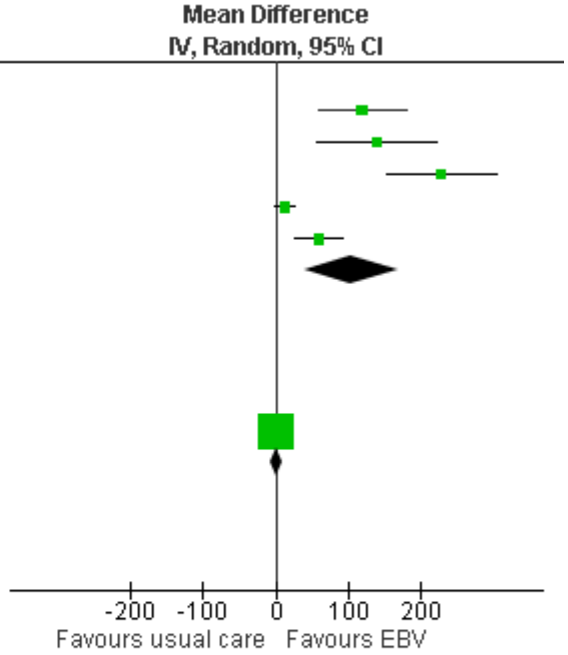
Study or Subgroup	EBV Events	EBV Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Collateral ventillation negative						
BeLieVer-HIFi 2015	12	19	4	24	21.1%	3.79 [1.45, 9.88]
IMPACT 2016	20	40	7	50	37.1%	3.57 [1.68, 7.59]
STELVIO 2015	20	23	2	33	9.8%	14.35 [3.71, 55.49]
TRANSFORM 2017	33	63	4	31	32.0%	4.06 [1.58, 10.44]
Subtotal (95% CI)		**145**		**138**	**100.0%**	**4.83 [3.03, 7.71]**
Total events	85		17			
Heterogeneity: Chi² = 3.48, df = 3 (P = 0.32); I² = 14%						
Test for overall effect: Z = 6.60 (P < 0.00001)						
3.4.2 Collateral ventilation positive						
BeLieVer-HIFi 2015	0	4	4	24	100.0%	0.56 [0.04, 8.77]
Subtotal (95% CI)		**4**		**24**	**100.0%**	**0.56 [0.04, 8.77]**
Total events	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.68)						



2

1 **Lung function – Force expiratory volume/second (millimetres)**

Study or Subgroup	Endobronchial valves Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.6.1 Heterogeneous/severe/homogeneous emphysema								
IMPACT 2016 (1)	100	180	43	-20	100	50	19.6%	120.00 [59.48, 180.52]
STELVIO 2015 (2)	161	232	34	21	86	34	17.1%	140.00 [56.83, 223.17]
TRANSFORM 2017	140	240	65	-90	140	32	17.9%	230.00 [154.12, 305.88]
Vent EU 2012	15	29	44	2	22	19	23.3%	13.00 [-0.09, 26.09]
Vent US 2010 (3)	34.5	178.3631	220	-25.4	116.0007	101	22.2%	59.90 [27.23, 92.57]
Subtotal (95% CI)			**406**			**236**	**100.0%**	**104.81 [39.26, 170.37]**
Heterogeneity: Tau² = 4759.62; Chi² = 51.60, df = 4 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 3.13 (P = 0.002)								
3.6.3 Incomplete fissure								
Vent EU 2012	0	23	67	-2	19	40	100.0%	2.00 [-6.06, 10.06]
Subtotal (95% CI)			**67**			**40**	**100.0%**	**2.00 [-6.06, 10.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.49 (P = 0.63)								



Test for subgroup differences: Chi² = 9.31, df = 1 (P = 0.002), I² = 89.3%

Footnotes

(1) Homogeneous emphysema

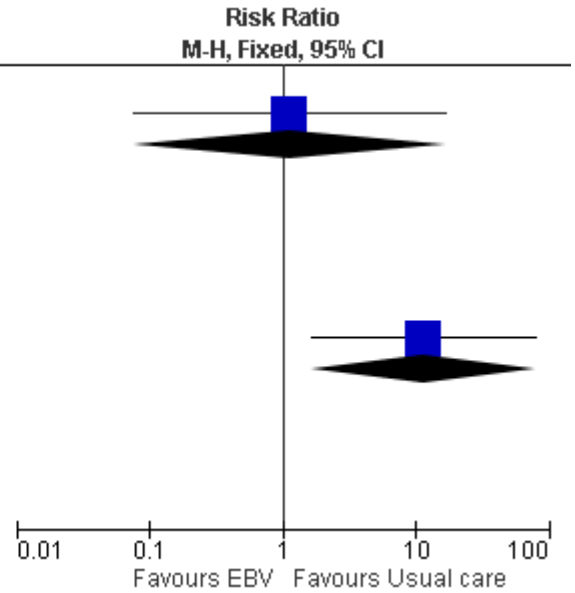
(2) Severe emphyseam without interlobar collateral ventilation

(3) Heterogeneous emphysema

2

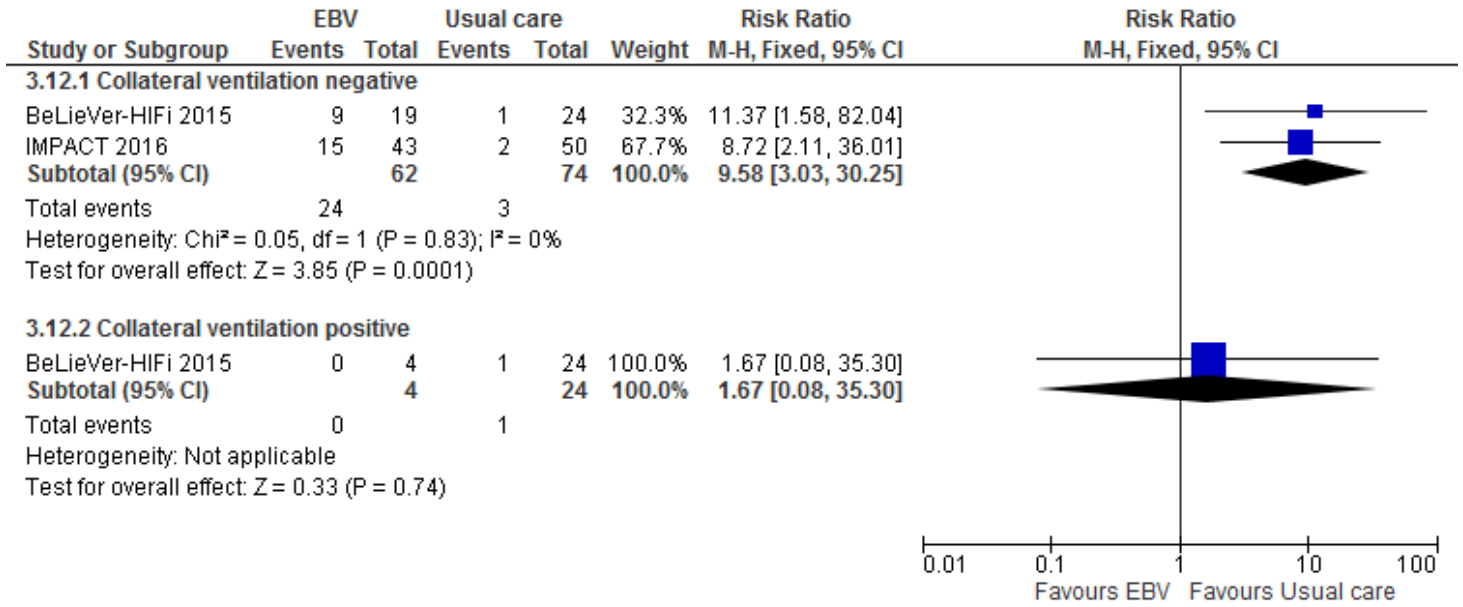
Lung function- Improvement in FEV1 (>15%) higher favours EBV

Study or Subgroup	EBV Events	EBV Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.10.1 No Lobar occlusion						
Vent EU 2012	1	17	1	19	100.0%	1.12 [0.08, 16.52]
Subtotal (95% CI)		**17**		**19**	**100.0%**	**1.12 [0.08, 16.52]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						
3.10.2 Lobar occlusion						
Vent EU 2012	12	20	1	19	100.0%	11.40 [1.64, 79.41]
Subtotal (95% CI)		**20**		**19**	**100.0%**	**11.40 [1.64, 79.41]**
Total events	12		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.46 (P = 0.01)						



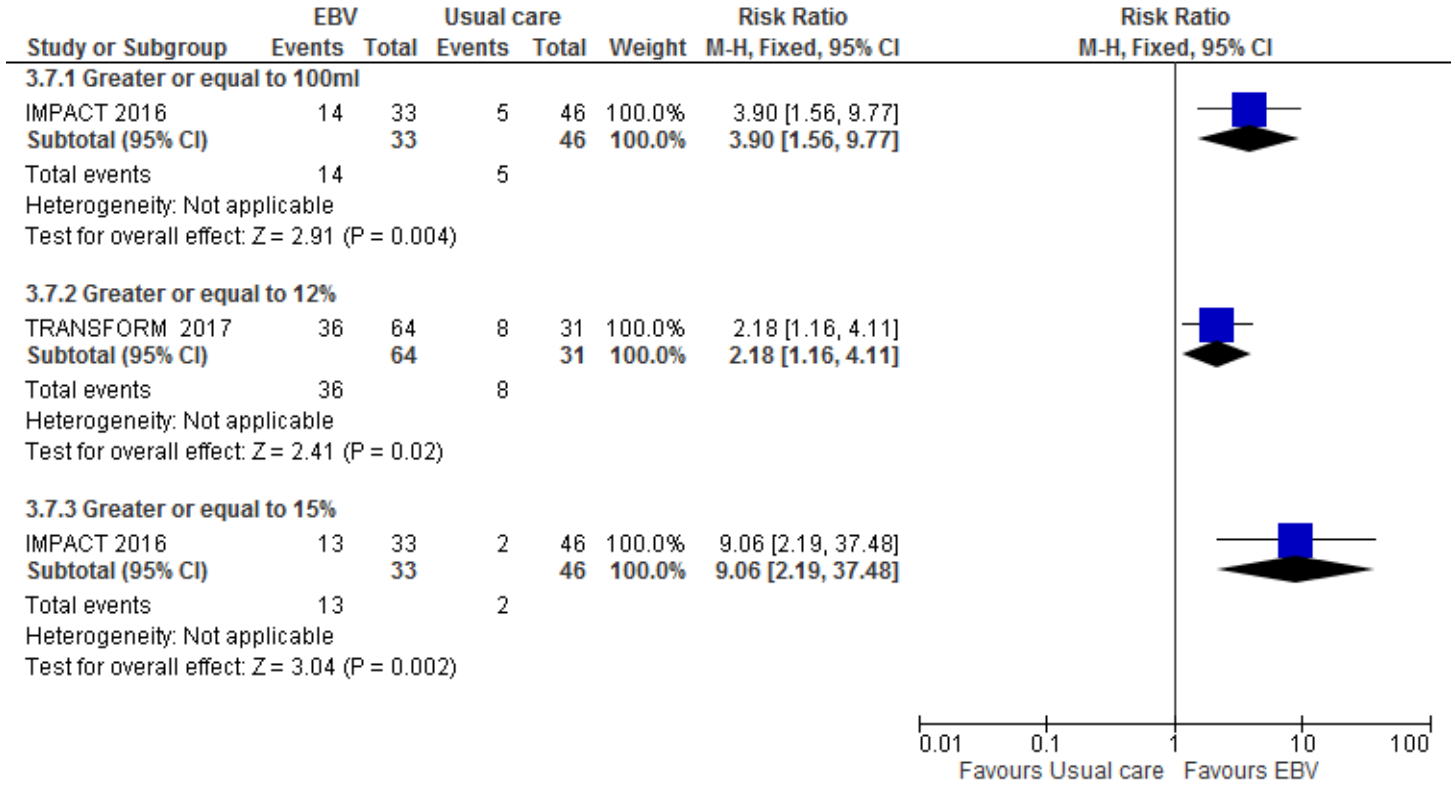
Test for subgroup differences: Chi² = 1.88, df = 1 (P = 0.17), I² = 46.8%

1 **Lung function- Collateral ventilation FEV1, >15% improvement**



2

1 **Lung function – change in FEV1**

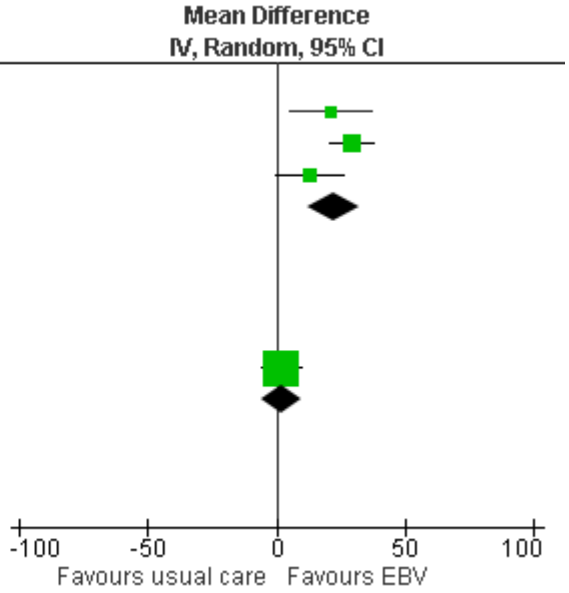


2

1 **Lung Function - FEV1 % predicted**

2

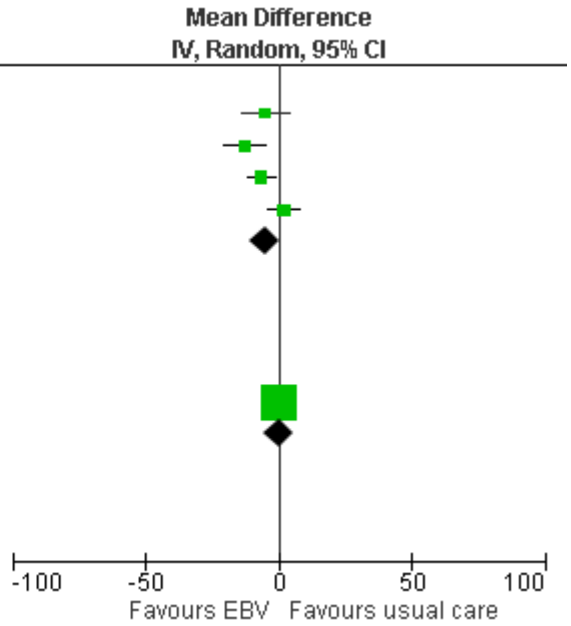
Study or Subgroup	Endobronchial valves Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.13.2 Complete Fissure								
BeLieVer-HIFi 2015	24.77	40.6028	25	3.87	7.7765	25	24.8%	20.90 [4.69, 37.11]
TRANSFORM 2017	20.7	29.6	65	-8.6	13	32	43.8%	29.30 [20.81, 37.79]
Vent EU 2012	15	29	44	2	22	19	31.3%	13.00 [-0.09, 26.09]
Subtotal (95% CI)			**134**			**76**	**100.0%**	**22.10 [11.65, 32.55]**
Heterogeneity: Tau² = 46.11; Chi² = 4.35, df = 2 (P = 0.11); I² = 54%								
Test for overall effect: Z = 4.15 (P < 0.0001)								
3.13.3 Incomplete fissure								
Vent EU 2012	0	23	67	-2	19	40	100.0%	2.00 [-6.06, 10.06]
Subtotal (95% CI)			**67**			**40**	**100.0%**	**2.00 [-6.06, 10.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.49 (P = 0.63)								



3 Test for subgroup differences: Chi² = 8.91, df = 1 (P = 0.003), I² = 88.8%

Health related quality of life – St George's respiratory questionnaire, emphysema and incomplete fissures subgroups

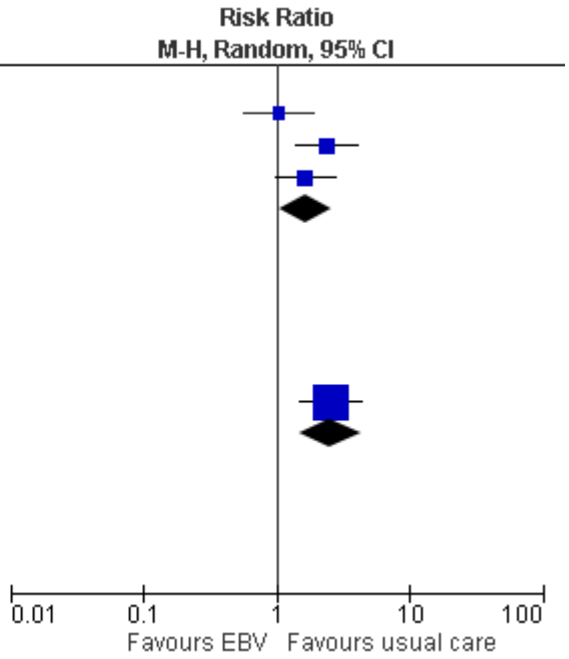
Study or Subgroup	Endobronchial valves Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.15.1 Severe emphysema								
BeLieVer-HIFi 2015	-8.72	20.5921	25	-3.66	10.8048	25	20.2%	-5.06 [-14.18, 4.06]
STELVIO 2015	-15.7	16.3	19	-3	9.1	24	22.3%	-12.70 [-20.88, -4.52]
TRANSFORM 2017	-7.2	15.1	65	-0.7	10.4	32	29.9%	-6.50 [-11.64, -1.36]
Vent EU 2012	0	15	44	-2	9	19	27.7%	2.00 [-4.00, 8.00]
Subtotal (95% CI)			**153**			**100**	**100.0%**	**-5.24 [-11.18, 0.70]**
Heterogeneity: Tau² = 23.84; Chi² = 8.93, df = 3 (P = 0.03); I² = 66%								
Test for overall effect: Z = 1.73 (P = 0.08)								
3.15.3 Incomplete fissure								
Vent EU 2012	-1	14	67	-1	14	40	100.0%	0.00 [-5.48, 5.48]
Subtotal (95% CI)			**67**			**40**	**100.0%**	**0.00 [-5.48, 5.48]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								



Test for subgroup differences: Chi² = 1.61, df = 1 (P = 0.20), I² = 38.0%

Health-related quality of life -St George's Respiratory questionnaire improvement by 4 points, emphysema subgroups

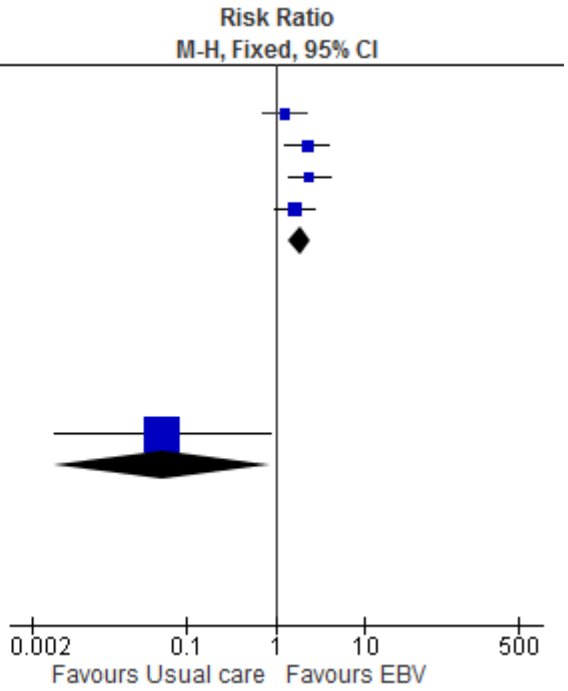
Study or Subgroup	EBV Events	EBV Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
3.16.1 heterogeneous emphysema						
BeLieVer-HIFi 2015	11	23	11	24	30.1%	1.04 [0.57, 1.92]
STELVIO 2015	19	24	11	33	35.0%	2.38 [1.41, 4.01]
TRANSFORM 2017	35	62	11	32	34.9%	1.64 [0.97, 2.78]
Subtotal (95% CI)		**109**		**89**	**100.0%**	**1.63 [1.04, 2.56]**
Total events	65		33			
Heterogeneity: Tau² = 0.08; Chi² = 4.03, df = 2 (P = 0.13); I² = 50%						
Test for overall effect: Z = 2.12 (P = 0.03)						
3.16.2 Homogeneous emphysema						
IMPACT 2016	21	31	12	45	100.0%	2.54 [1.48, 4.37]
Subtotal (95% CI)		**31**		**45**	**100.0%**	**2.54 [1.48, 4.37]**
Total events	21		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.37 (P = 0.0007)						



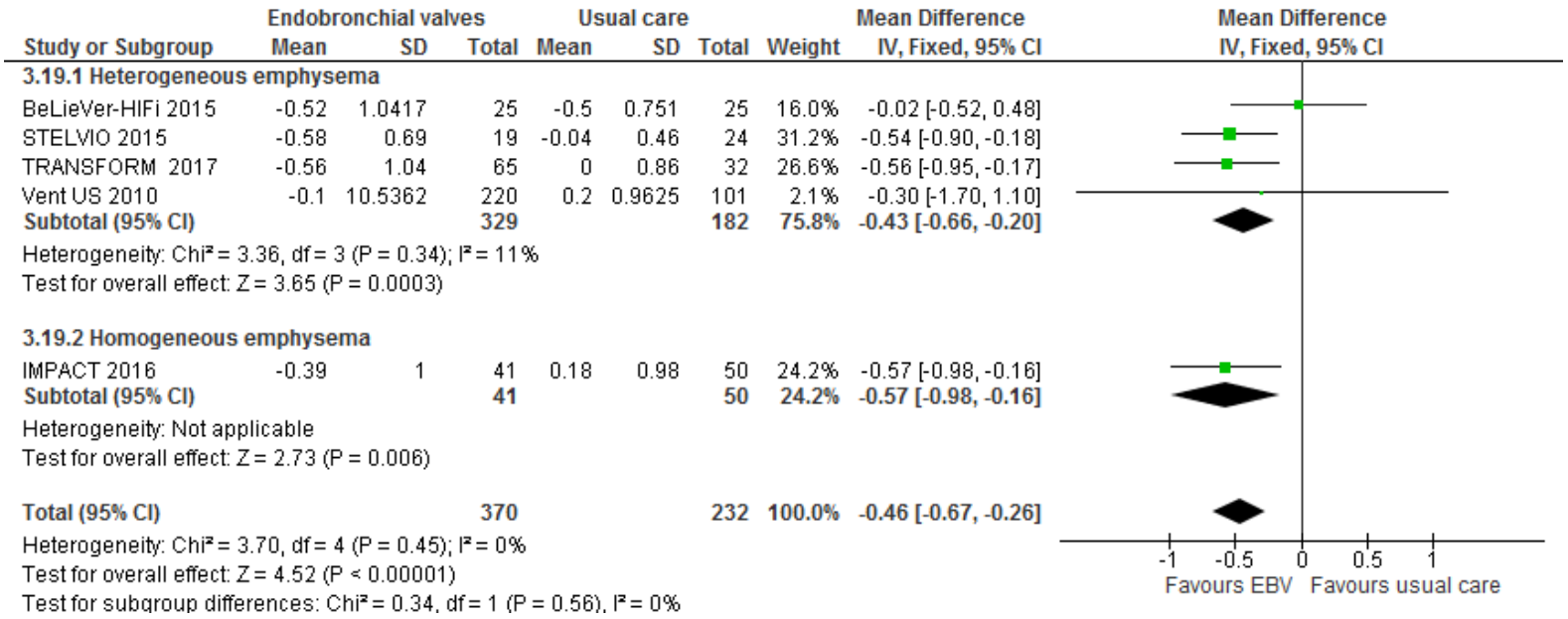
Test for subgroup differences: Chi² = 1.52, df = 1 (P = 0.22), I² = 34.0%

Health related quality of life – St George's respiratory questionnaire improvement by 4 points, collateral ventilation subgroups

Study or Subgroup	EBV Events	EBV Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.17.1 Collateral ventilation negative						
BeLieVer-HIFi 2015	11	19	11	24	22.1%	1.26 [0.71, 2.26]
IMPACT 2016	21	37	12	48	23.8%	2.27 [1.29, 3.99]
STELVIO 2015	19	24	11	33	21.1%	2.38 [1.41, 4.01]
TRANSFORM 2017	35	62	11	32	33.0%	1.64 [0.97, 2.78]
Subtotal (95% CI)		**142**		**137**	**100.0%**	**1.86 [1.42, 2.45]**
Total events	86		45			
Heterogeneity: Chi² = 3.24, df = 3 (P = 0.36); I² = 7%						
Test for overall effect: Z = 4.44 (P < 0.00001)						
3.17.2 Collateral ventilation positive						
BeLieVer-HIFi 2015	0	19	11	24	100.0%	0.05 [0.00, 0.87]
Subtotal (95% CI)		**19**		**24**	**100.0%**	**0.05 [0.00, 0.87]**
Total events	0		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.06 (P = 0.04)						



1 **Breathlessness – modified MRC dyspnoea scale**



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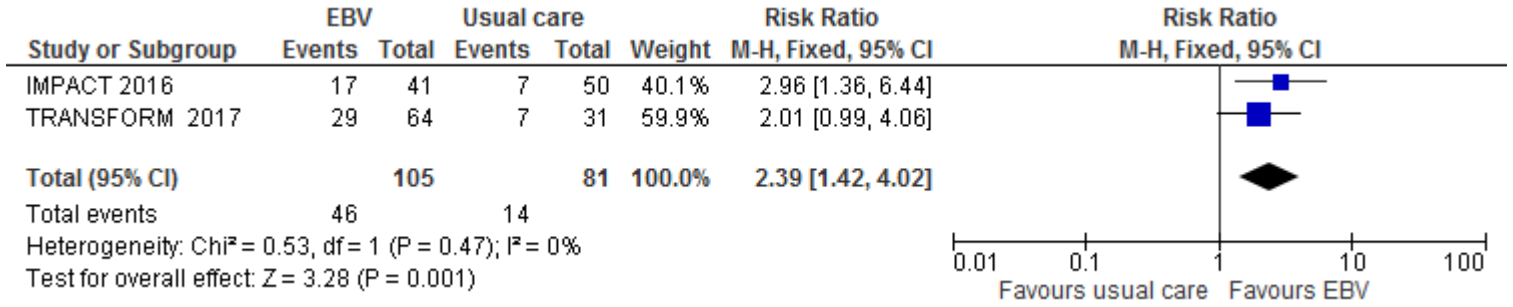
1 **Breathlessness - modified MRC dyspnoea improvement of 1 point**



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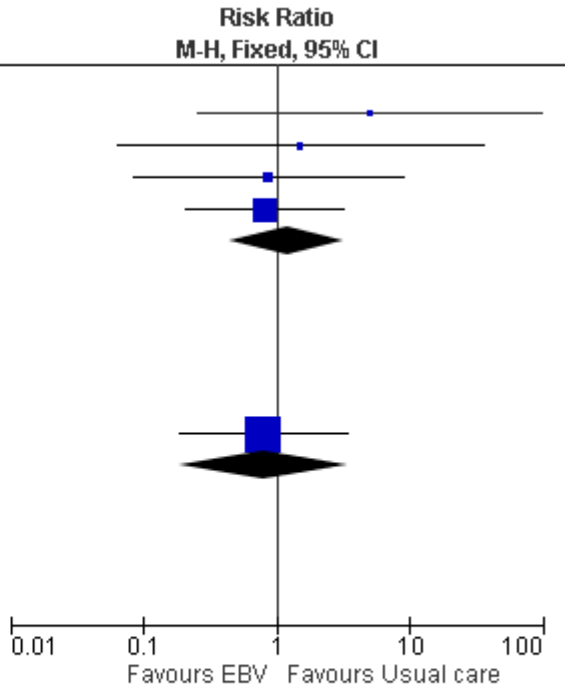
1 **Mortality**

Study or Subgroup	EBV Events	EBV Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.22.1 Heterogeneous emphysema						
BeLieVer-HIFi 2015	2	25	0	25	7.3%	5.00 [0.25, 99.16]
TRANSFORM 2017 (1)	1	65	0	32	9.8%	1.50 [0.06, 35.83]
Vent EU 2012 (2)	2	44	1	19	20.5%	0.86 [0.08, 8.96]
Vent US 2010	6	214	3	87	62.5%	0.81 [0.21, 3.18]
Subtotal (95% CI)		**348**		**163**	**100.0%**	**1.20 [0.45, 3.22]**
Total events	11		4			
Heterogeneity: Chi² = 1.28, df = 3 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
3.22.3 Incomplete fissure						
Vent EU 2012	4	67	3	40	100.0%	0.80 [0.19, 3.38]
Subtotal (95% CI)		**67**		**40**	**100.0%**	**0.80 [0.19, 3.38]**
Total events	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						



Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%

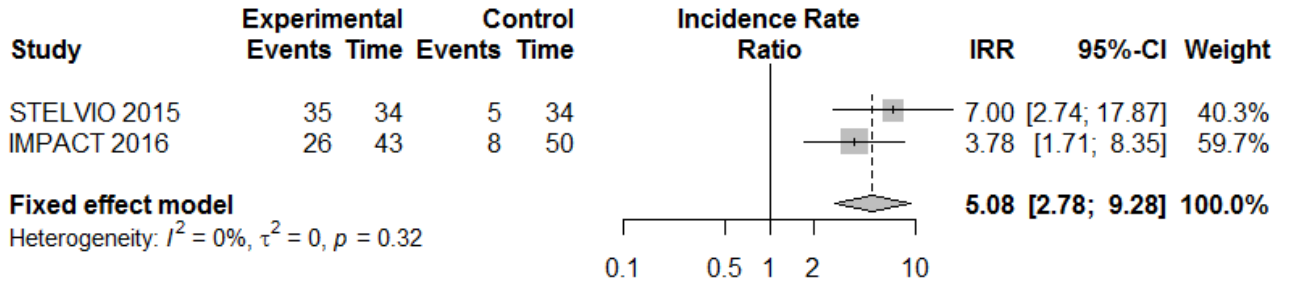
Footnotes

(1) 30 days mortality

(2) 12 months follow up

2

1 **All severe adverse events as reported by the trials**



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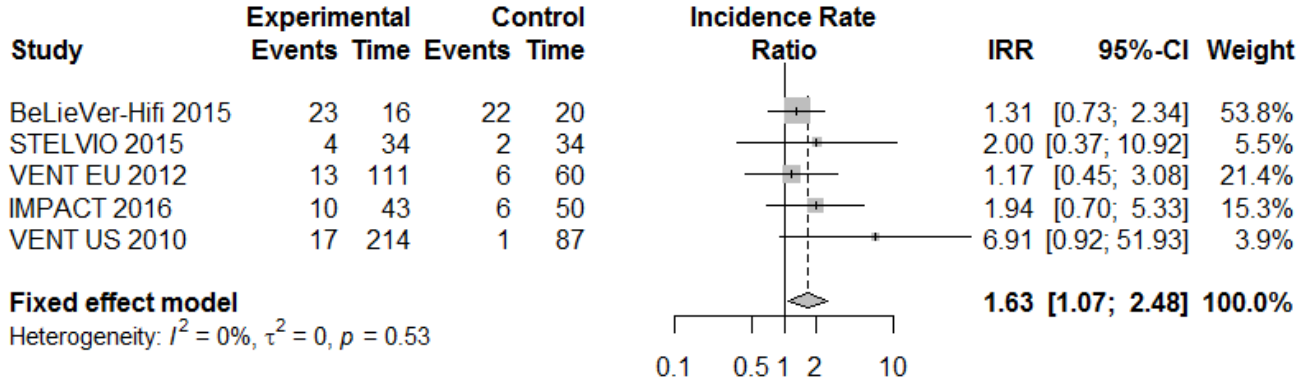
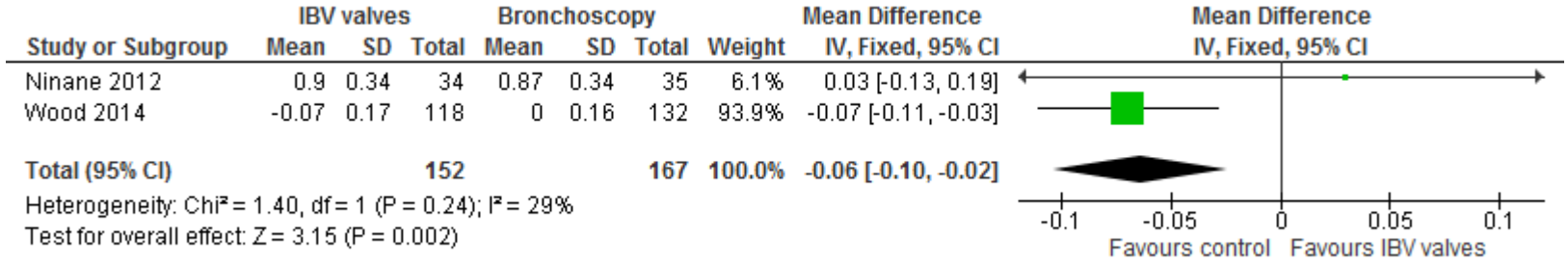
3 **COPD exacerbations (serious or requiring hospitalisations)**



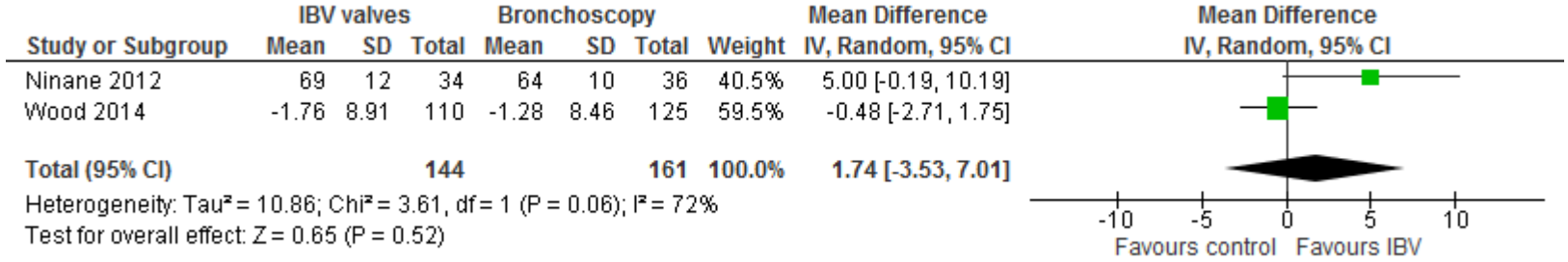
4

Intra-bronchial valves

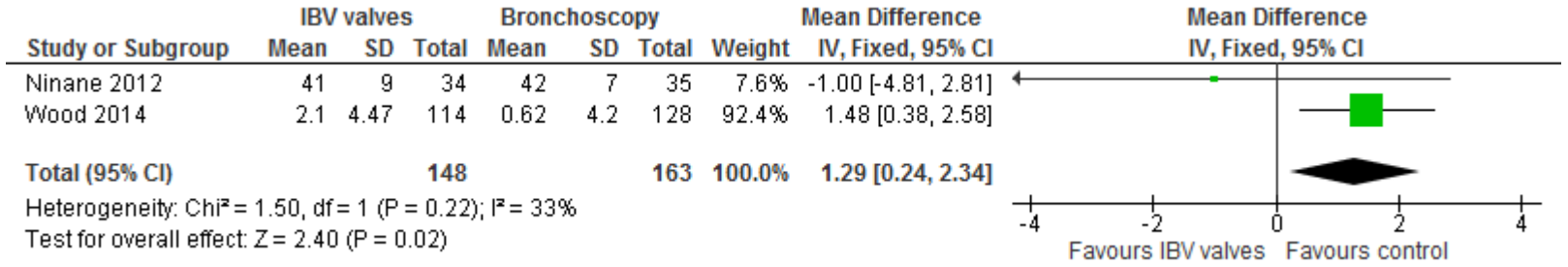
Lung function - FEV1 (litres)



Lung function – arterial blood gas (PO_2) mmHg

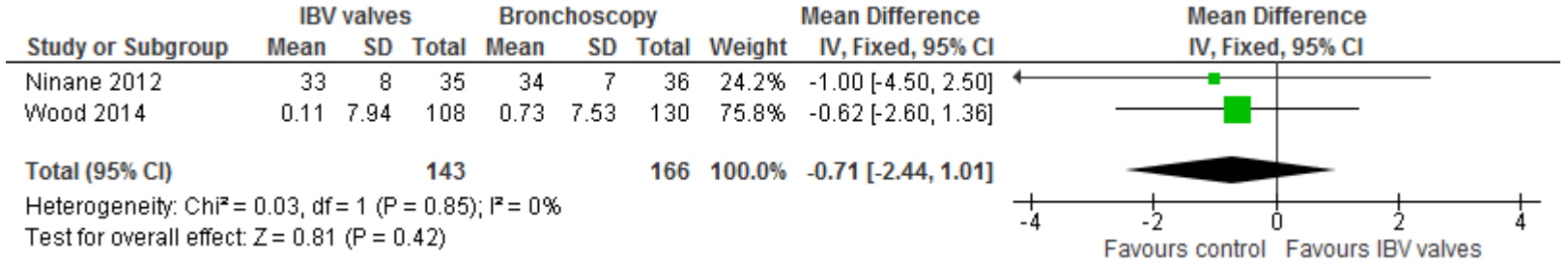


1 **Lung function – arterial blood gas (PCO_2) mmHg**



2

3 **Health related quality of life – Short health form –physical component score**

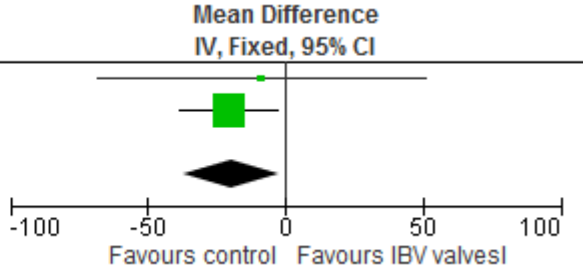


4

1 **Exercise capacity - 6 minute walking distance (metres)**

	IBV valves			Bronchoscopy				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Ninane 2012	344	118	33	353	131	34	8.4%	-9.00 [-68.66, 50.66]
Wood 2014	-24.02	69.81	120	-3.4	76.63	133	91.6%	-20.62 [-38.66, -2.58]
Total (95% CI)			**153**			**167**	**100.0%**	**-19.65 [-36.92, -2.37]**

Heterogeneity: Chi² = 0.13, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)

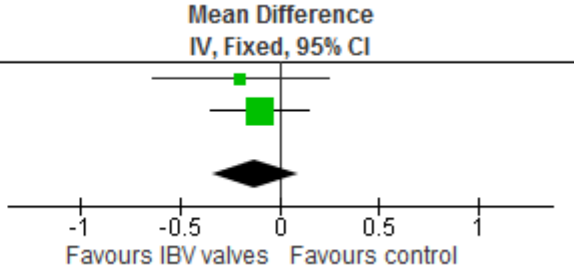


2

3 **Breathlessness – Modified MRC score**

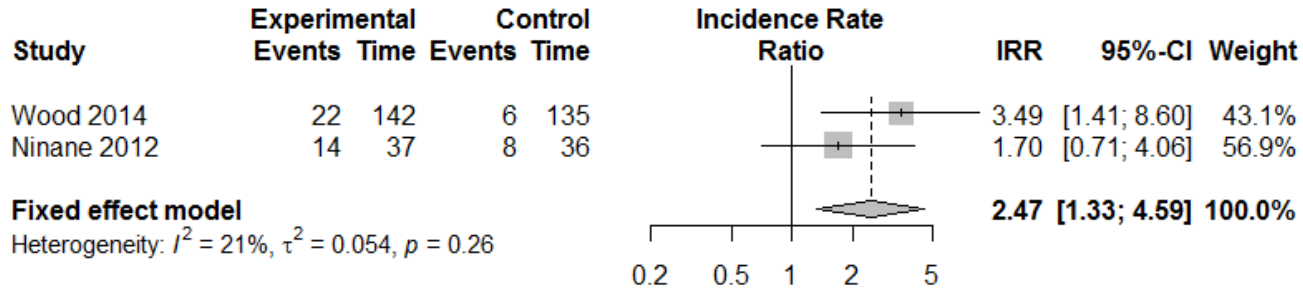
	IBV valves			Bronchoscopy				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Ninane 2012	2.5	1	35	2.7	0.9	36	24.2%	-0.20 [-0.64, 0.24]
Wood 2014	-0.24	1.02	119	-0.14	1	133	75.8%	-0.10 [-0.35, 0.15]
Total (95% CI)			**154**			**169**	**100.0%**	**-0.12 [-0.34, 0.09]**

Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.12 (P = 0.26)



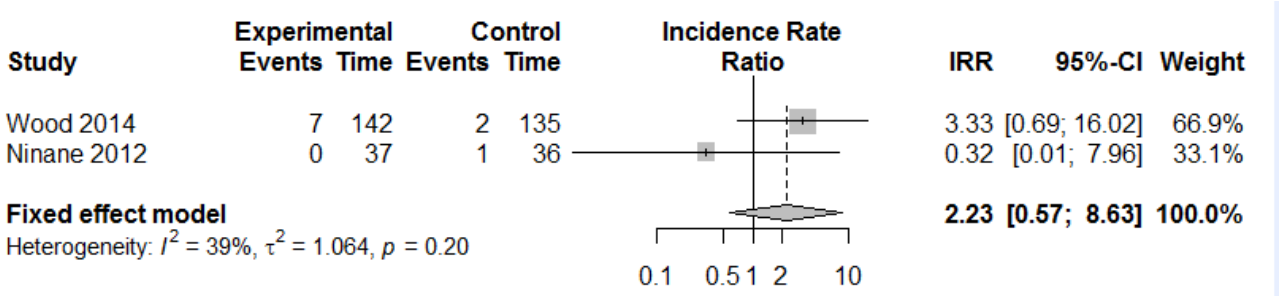
4

1 **IBV - All Adverse Events**



2

3 **IBV - COPD Exacerbations**



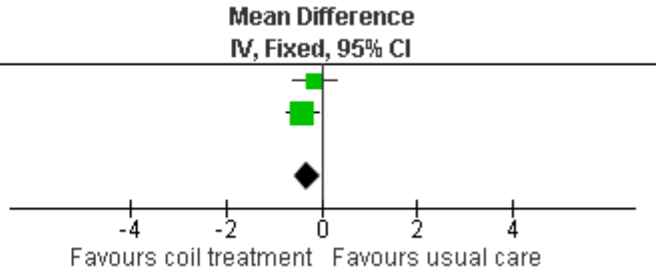
4

1 Endobronchial coils

2 Breathlessness

Study or Subgroup	Coil treatment Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
RESET 2013	-0.24	0.7631	23	-0.09	0.8094	23	37.4%	-0.15 [-0.60, 0.30]
Revolens 2016	-0.5	1.0556	50	-0.1	0.7037	50	62.6%	-0.40 [-0.75, -0.05]
Total (95% CI)			**73**			**73**	**100.0%**	**-0.31 [-0.58, -0.03]**

Heterogeneity: Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 2.16 (P = 0.03)

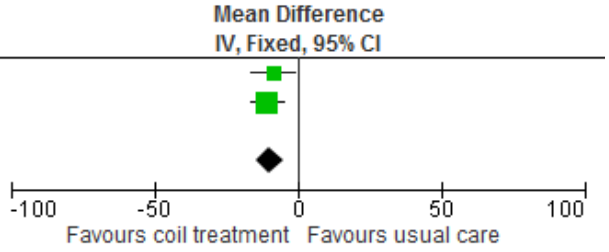


3

4 Health related quality of life – St George's respiratory questionnaire score (total)

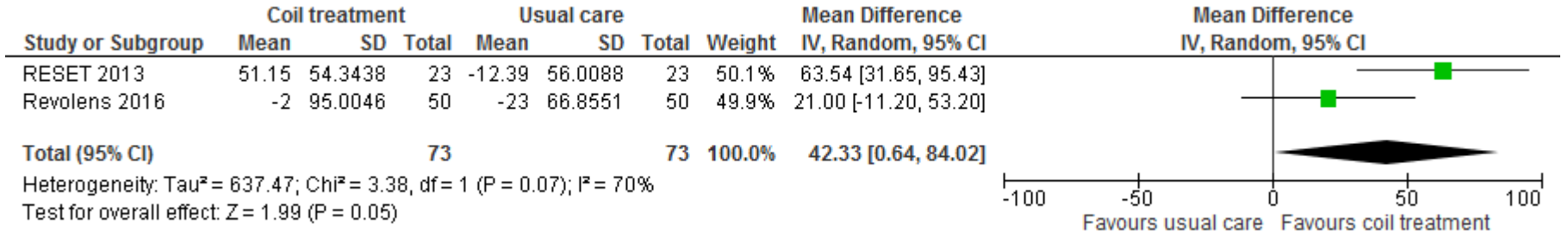
Study or Subgroup	Coil treatment Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
RESET 2013	-8.11	13.2275	23	0.25	13.4819	23	36.4%	-8.36 [-16.08, -0.64]
Revolens 2016	-9.1	17.5934	50	1.5	11.6117	50	63.6%	-10.60 [-16.44, -4.76]
Total (95% CI)			**73**			**73**	**100.0%**	**-9.78 [-14.44, -5.13]**

Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 4.12 (P < 0.0001)



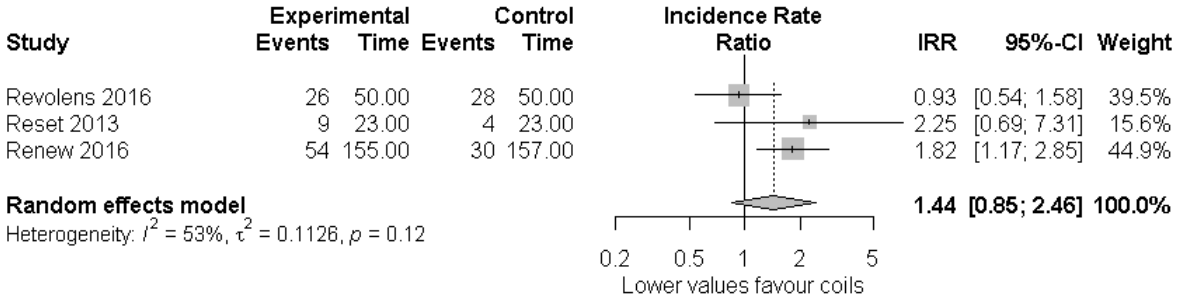
5

1 **Exercise capacity - 6 minute walking test (m)**



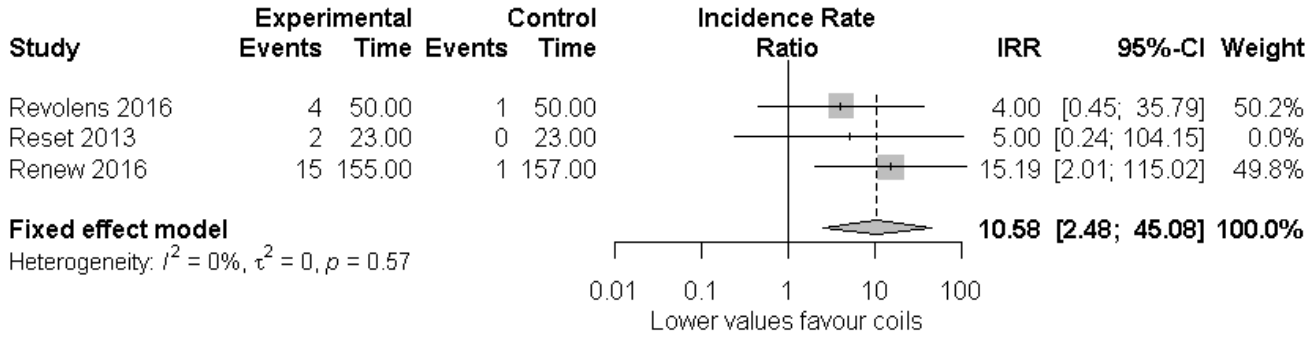
2

3 **All adverse events**



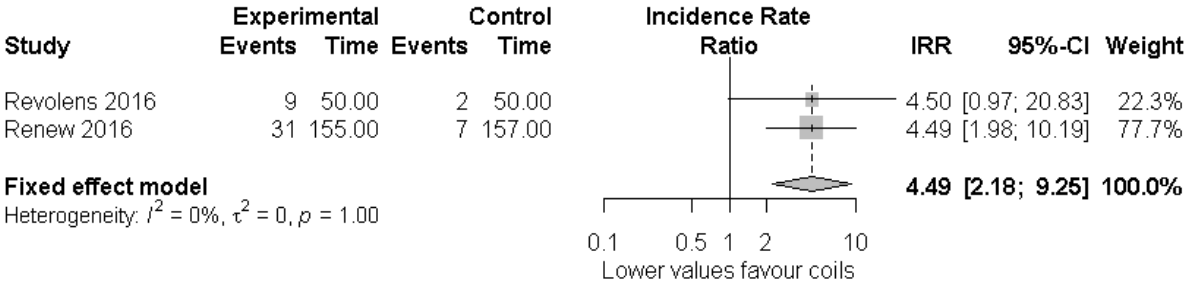
4

1 **Adverse events - Pneumothorax**



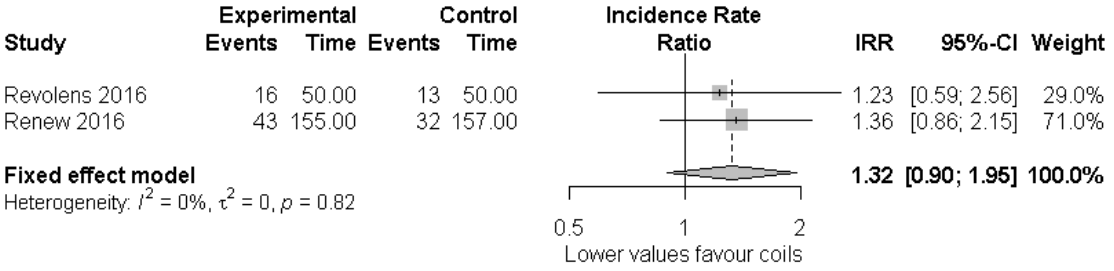
2

1 **Adverse events – Pneumonia**



2

3 **Adverse events – COPD exacerbation**



4

1 Appendix G – GRADE tables

2 Lung volume reduction surgery

3 Lung volume reduction surgery vs ongoing medical treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Lung function - FEV1 % predicted higher favours LVRS										
3	RCT	1,300	MD 8.34 (4.90, 11.78)	-	-	Serious[1]	Very serious[2]	Not serious	Not serious	Very low
Lung function - FEV1 (ml) higher favours LVRS										
3	RCT	177	MD 293.71 (215.03, 372.39)	-	-	Serious[1]	Serious[3]	Not serious	Not serious	Low
Sensitivity analysis- lung function - FEV1 (ml) higher favours LVRS, excluding study at high risk of bias										
2	RCT	123	MD 280.55 (232.28, 328.82)	-	-	Not serious	Serious[3]	Not serious	Not serious	Moderate
Lung function – Diffusion capacity for carbon monoxide (DLCO) ml/min/mmHg, higher favours LVRS										
3	RCT	148	MD 0.90 (-0.65, 2.45)	-	-	Very serious[4]	Serious[3]	Not serious	Serious[5]	Very low
Exercise capacity – 6 minute walking distance, (m), higher favours LVRS										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
6	RCT	1436	MD 48.19 (35.51, 60.87)	-	-	Serious[1]	Very Serious[2]	Not serious	Not serious	Very low
Sensitivity analysis- exercise capacity – 6 minute walking distance, (m) higher favours LVRS, excluding studies at high risk of bias										
3	RCT	1297	MD 43.75 (30.84, 56.67)	-	-	Serious[4]	Very Serious[1]	Not serious	Not serious	Very low
Exercise capacity- subgroup analyses										
Exercise capacity – 6 minute walking distance, (m) increase of more than 30m, higher favours LVRS										
2	RCT	93	RR 2.35 (1.34, 4.12)	25.64 per 100 people	60.26 per 100 (34.36, 105.64)	Very serious[4]	Serious[3]	Not serious	Not serious	Very low
Exercise capacity – Maximal capacity (Power W), higher favours LVRS										
2	RCT	1,257	MD 6.43 (1.63, 11.23)	-	-	Serious[1]	Very Serious[2]	Not serious	Not serious	Very low
Exercise capacity - Improvement in exercise capacity[b] (all patients), 2 years follow up, higher numbers favour LVRS										
1 (NETT Study 2003)	RCT	749	RR 5.57 (2.89, 10.76)	2.56 per 100 people	14.74 per 100 (7.56, 28.47)	Serious[1]	N/A	Not serious	Not serious	Moderate
Improvement in exercise capacity (patients with predominantly upper lobe emphysema at 2 years follow up, higher numbers favour LVRS										
1 (NETT Study 2003)	RCT	429	RR 10.99 (4.17, 28.94)	1.74 per 100 people	19.11 per 100 (7.25, 50.33)	Serious[1]	N/A	Not serious	Not serious	Moderate
Improvement in exercise capacity (patients with predominantly non-upper lobe emphysema, higher numbers favour LVRS										
1 (NETT Study 2003)	RCT	214	RR 1.37 (0.47, 4.04)	5.00 per 100 people	6.85 per 100 (2.35, 20.20)	Serious[1]	N/A	Not serious	Serious[6]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Breathlessness – Borg scale, lower favours LVRS										
1 (Goldstein 2003)	RCT	39	MD 1.10 (0.79, 1.41)	-	-	Not serious	N/A	Not serious	Not serious	High
Health related quality of life - St George's respiratory questionnaire at 12 months - lower numbers favours LVRS										
2	RCT	127	MD –14.60 (-25.60, -3.60)	-	-	Serious[3]	Not serious	Not serious	Serious[6]	Low
Improvement in SGRQ[c] at 2 years follow up, higher numbers favour LVRS										
1 (NETT Study 2003)	RCT	749	RR 3.68 (2.60, 5.22)	8.99 per 100 people	33.10 per 100 (23.39, 46.95)	Serious[3]	N/A	Not serious	Not serious	Moderate
Improvement in SGRQ[c] at 2 years follow up in patients with predominantly upper lobe emphysema, higher numbers favour LVRS										
1 (NETT Study 2003)	RCT	429	RR 4.19 (2.78, 6.32)	10.43 per 100 people	43.72 per 100 (29.01, 65.95)	Serious[3]	N/A	Not serious	Not serious	Moderate
Improvement in SGRQ[c] at 2 years follow up in predominantly non-upper lobe emphysema, higher numbers favour LVRS										
1 (NETT Study 2003)	RCT	214	RR 2.44 (1.24, 4.83)	10.00 per 100 people	24.40 per 100 (12.40, 48.30)	Serious[3]	N/A	Not serious	Serious[6]	Low
All patients 90 day mortality, lower numbers favour LVRS										
2	RCT	1,272	RR 5.94 (2.90, 12.17)	1.26 per 100 people	7.47 per 100 (3.65, 15.31)	Serious[1]	Not serious	Not serious	Not serious	Moderate
All patients mortality mean follow up 29.2 months, lower numbers favour LVRS										
1 (NETT Study 2003)	RCT	1218	RR 0.98 (0.81, 1.19)	26.23 per 100 people	25.70 per 100 (21.25, 31.21)	Serious[1]	N/A	Not serious	Serious[5]	Low
All patients median follow up 4.3 years[d], lower numbers favour LVRS										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (NETT Study 2003)	RCT	1218	RR 0.88 (0.78, 0.98)	53.11 per 100 people 324/610	46.74 per 100 (41.43, 52.05)	Serious[1]	N/A	Not serious	Serious[5]	Low
Mortality –subgroup analyses										
High risk patients[a], 90 day mortality, lower numbers favour LVRS										
1 (NETT Study 2003)	RCT	140	RR 41.00 (2.53, 664.89)	Unable to calculate as 0 events in the control	-	Serious[1]	N/A	Not serious	Not serious	Moderate
Non- high risk patients, 90 day mortality, lower numbers favour LVRS										
1 (NETT Study 2003)	RCT	1132	RR 3.58 (1.69, 7.60)	1.41 per 100 people	5.06 per 100 (2.39, 10.74)	Serious[1]	N/A	Not serious	Not serious	Moderate
High risk patients[a] mean follow up 29.2 months, lower numbers favour LVRS										
1 (NETT Study 2003)	RCT	140	RR 1.40 (1.01, 1.95)	42.86 per 100	60.00 per 100 (43.29, 83.57)	Serious[1]	N/A	Not serious	Not serious	Moderate
Other patients mean follow up 29.2 months, lower numbers favour LVRS										
1 (NETT Study 2003)	RCT	1,078	RR 0.89 (0.71, 1.11)	24.07 per 100 people	21.43 per 100 (17.09, 26.72)	Serious[1]	N/A	Not serious	Serious[5]	Low
90 day mortality (predominantly upper lobe emphysema) lower numbers favour LVRS										
1 (NETT Study 2003)	RCT	717	RR 1.56 (0.60, 4.09)	1.88 per 100 people	2.93 per 100 (1.13, 7.68)	Serious[1]	N/A	Not serious	Serious[5]	Low
90 day mortality (predominantly non-upper lobe emphysema), lower numbers favour LVRS										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (NETT Study 2003)	RCT	369	RR 11.36 (2.17, 59.49)	0.57 per 100 people	6.45 per 100 (1.23, 33.80)	Serious[1]	N/A	Not serious	Not serious	Moderate

a) high risk patients were defined as those with a FEV in one second that was 20% or less predicted value and either homogeneous emphysema on CT or a carbon monoxide diffusing capacity that was 20% or less of the predicted value

b) improvement was defined as an increase in the maximal workload of more than 10W from the patient's post rehabilitation base-line value (24 months FU)

c) in this study improvement was defined as a decrease in the score on the St George's Respiratory Questionnaire of more than 8 points from the patient's post rehabilitation base-line value (24 months FU)

d) The follow-up for the earliest people recruited in the study was between 7 and 8 years

1. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias
2. I^2 greater than 66.7%
3. I^2 between 33.3% and 66.7%
4. > 33.3% of the weight in a meta-analysis came from studies at high risk of bias
5. Non-significant result
6. 95% confidence interval crosses one end of a defined MID interval

1 Endobronchial valves

2 Endobronchial valves vs usual care

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Exercise capacity - 6 minute walking distance (metres) higher number favours EBV										
Subgroup analysis - heterogeneous emphysema										
5	RCT	559	MD 35.70 (-0.15, 71.56)	-	-	Very serious[1]	Very serious[2]	Not serious	Serious[5]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Subgroup analysis – incomplete fissures										
1 (Vent EU 2012)	RCT	107	MD 5.00 (-7.75, 17.75)	-	-	Very Serious[1]	N/A	Not serious	Not serious	Low
Exercise capacity – improvement in 6 minute walking distance (m) – increase >35m higher favours EBV										
Subgroup analysis – complete fissures – no lobar occlusion										
1 (Vent EU 2012)	RCT	36	RR 3.35 (0.38, 29.26)	5.26 per 100 people	17.63 per 100 (2.00, 154.00)	Very Serious[1]	N/A	Not serious	Very serious[6]	Very low
Subgroup analysis – complete fissures – lobar occlusion										
1 (Vent EU 2012)	RCT	39	RR 9.50 (1.34, 67.27)	5.26 per 100 people	50.00 per 100 (7.05, 354,05)	Very Serious[1]	N/A	Not serious	Not serious	Low
Exercise capacity – improvement in 6 minute walking distance (m) – increase of at least 26m higher favours EBV										
Subgroup analysis - negative collateral ventilation										
4	RCT	311	RR 4.83 (3.03, 7.71)	12.32 per 100 people	59.50 per 100 (37.33, 94.98)	Serious[3]	Not serious	Not serious	Not serious	Moderate
Subgroup analysis - positive collateral ventilation										
1 (BeLieVer-HiFi 2015)	RCT	28	RR 0.56 (0.04, 8.77)	16.67 per 100 people	9.33 per 100 (0.67, 146.17)	Not serious	N/A	Not serious	Very serious[6]	Low
Lung function - FEV1 (ml) higher favours EBV										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Subgroup analysis – homogeneous and heterogeneous emphysema										
5	RCT	642	MD 104.81 (39.26, 170.37)	-	-	Serious[3]	Very serious[2]	Not serious	Serious[5]	Very low
Subgroup analysis - incomplete fissure										
1 (VENT EU 2012)	RCT	107	MD 2.00 (-6.06, 10.06)	-	-	Very Serious[1]	N/A	Not serious	Not serious	Low
Lung function – improvement in FEV1 (>15%) higher favours EBV										
Sub group analysis - complete fissure and no lobar exclusion										
1 (VENT EU 2012)	RCT	36	RR 1.12 (0.08, 16.52)	5.26 per 100 people	5.89 per 100 (0.42, 86.95)	Very Serious[1]	N/A	Not serious	Very serious[6]	Very low
Subgroup analysis - complete fissures and lobar exclusion										
1 (VENT EU 2012)	RCT	39	RR 11.40 (1.64, 79.41)	5.26 per 100 people	60.00 per 100 (8.63, 417.95)	Very Serious[1]	N/A	Not serious	Not serious	Low
Lung function - FEV1, >15% improvement, collateral ventilation subgroups										
Subgroup analysis - Collateral ventilation negative										
2	RCT	136	RR 9.58 (3.03, 30.25)	4.05 per 100 people	38.84 per 100 (12.28, 122.64)	Serious[3]	Not serious	Not serious	Not serious	Moderate
Subgroup analysis - Collateral ventilation positive										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (BeLieVer-HiFi 2015)	RCT	28	RR 1.67 (0.08, 35.30)	4.17 per 100 people	6.96 per 100 (0.33, 126.04)	Not serious	N/A	Not serious	Very serious[6]	Low
Lung function – change in FEV1, higher favours EBV										
Subgroup analysis - greater or equal to 100ml										
1 (IMPACT 2016)	RCT	79	RR 3.90 (1.56, 9.77)	10.87 per 100 people	42.39 per 100 (16.96, 106.20)	Serious[3]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - greater or equal to 12%										
1 (TRANSFORM 2017)	RCT	95	RR 2.18 (1.16, 4.11)	25.81 per 100 people	56.26 per 100 (29.94, 106.06)	Serious[3]	N/A	Not serious	Serious[5]	Low
Subgroup analysis - greater or equal to 15%										
1 (IMPACT)	RCT	79	RR 9.06 (2.19, 37.48)	4.35 per 100 people	39.39 per 100 (9.52, 162.96)	Serious[3]	N/A	Not serious	Not serious	Moderate
Lung function - FEV1 % predicted higher favours EBV										
Subgroup analysis - complete fissures										
3	RCT	317	MD 22.10 (11.65, 32.55)	-	-	Serious[3]	Serious[4]	Not serious	Not serious	Low
Subgroup analysis – incomplete fissures										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Vent EU 2012)	RCT	107	MD 2.00 (-6.06, 10.06)	-	-	Very Serious[1]	N/A	Not serious	Serious[7]	Very low
Health-related quality of life St George's Respiratory questionnaire (total score) lower favours EBV										
Subgroup analysis –Severe emphysema										
4	RCT	253	MD -5.24 (-11.18, 0.70)	-	-	Serious[3]	Serious[4]	Not serious	Serious[5]	Very low
Subgroup analysis –Incomplete fissures										
1 (Vent EU 2012)	RCT	107	MD 0.00 (-5.48, 5.48)	-	-	Very serious[1]	N/A	Not serious	Very serious[6]	Very low
Health-related quality of life- improvement in St George's respiratory questionnaire – reduction by 4 points, higher favours EBV										
Subgroup analysis – heterogeneous emphysema										
3	RCT	198	RR 1.63 (1.04, 2.56)	37.08 per 100 people	60.44 per 100 (38.56, 94.92)	Serious[3]	Not serious	Not serious	Serious[5]	Low
Subgroup analysis – homogeneous emphysema										
1 (IMPACT 2016)	RCT	76	RR 2.54 (1.48, 4.37)	26.67 per 100 people	67.73 per 100 (39.47, 116.53)	Serious[3]	N/A	Not serious	Not serious	Moderate
Health related quality of life – improvement in St George's respiratory questionnaire – reduction by 4 points, higher favours EBV										
Subgroup analysis – Collateral ventilation negative										
4	RCT	279	RR 1.86 (1.42, 2.45)	32.85 per 100 people	61.09 per 100	Serious[3]	Not serious	Not serious	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					(46.64, 80.47)					
Subgroup analysis – Collateral ventilation positive										
1 (BeLieVer-HiGi 2015)	RCT	43	RR 0.50 (0.00, 0.87)	45.83 per 100 people	22.92 per 100 (0.00, 39.88)	Not serious	N/A	Not serious	Serious[5]	Moderate
Breathlessness – Modified MRC score - lower favours EBV										
Subgroup analysis – heterogeneous emphysema										
4	RCT	511	MD -0.43 (-0.66, -0.20)	-	-	Not serious	Not serious	Not serious	Not serious	High
Subgroup analysis – homogeneous emphysema										
1 (IMPACT 2016)	RCT	91	MD -0.57 (-0.98, -0.16)	-	-	Serious[3]	N/A	Not serious	Not serious	Moderate
Breathlessness modified MRC – improvement by 1 point – higher numbers favour EBV										
2	RCT	186	RR 2.39 (1.42, 4.02)	17.28 per 100 people	41.31 per 100 (24.54, 69.48)	Serious[3]	Not serious	Not serious	Not serious	Moderate
Mortality – lower numbers favours EBV										
Subgroup analysis – heterogeneous emphysema										
4	RCT	511	RR 1.20 (0.45, 3.22)	2.45 per 100 people	2.94 per 100 (1.10, 7.90)	Very Serious[1]	Not serious	Not serious	Serious[7]	Very low
Subgroup analysis- with incomplete fissures										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Vent EU 2012)	RCT	107	RR 0.80 (0.19, 3.38)	7.55 per 100 people	6.00 per 100 (1.43, 24.15)	Very Serious[1]	N/A	Not serious	Serious[7]	Very low
All severe adverse events*										
2	RCT	161	IRR 5.08 (2.78, 9.28)	-	-	Serious[3]	Not serious	Not serious	Not serious	Moderate
COPD exacerbations										
5	RCT	669	IRR 1.63 (1.07, 2.48)	-	-	Serious[3]	Not serious	Not serious	Serious[5]	Low

1. More than 33.3% of the weight in a meta-analysis came from studies at high risk of bias
2. I^2 was greater than 66.7%
3. More than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias
4. I^2 was between 33.3% and 66.7%
5. 95% confidence interval crosses one end of a defined MID interval
6. 95% confidence interval crosses both ends of a defined MID interval
7. Non-significant result

* Adverse events included bronchospasm, COPD exacerbations, death, pneumonia, and respiratory failure

1 **Intra-bronchial valves**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Lung function - FEV1 (litres), higher numbers favour intra-bronchial valves										
2	RCT	319	MD -0.06 (-0.10, -0.02)	-	-	Serious[1]	Not serious	Not serious	Not serious	Moderate
Lung function – arterial blood gas (PO_2) mmHg, higher numbers favour intra-bronchial valves										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2	RCT	305	MD 1.74 (-13.53, 7.01)	-	-	Serious[1]	Very serious[2]	Not serious	Serious[3]	Very Low
Lung function – arterial blood gas (PCO_2) mmHg, lower numbers favour intra-bronchial valves										
2	RCT	311	MD 1.29 (0.24, 2.34)	-	-	Serious[1]	Not serious	Not serious	Not serious	Low
Health related quality of life – Short health form –physical component score, higher numbers favour intra-bronchial valves										
2	RCT	309	MD -0.71 (-2.44, 1.01)	-	-	Serious[1]	Not serious	Not serious	Serious[3]	Low
Exercise capacity - 6 minute walking distance (metres), higher number favours intra-bronchial valves										
2	RCT	320	MD -19.65 (-36.92, -2.37)	-	-	Serious[1]	Not serious	Not serious	Serious[4]	Low
Breathlessness – Modified MRC score, lower numbers favour intra-bronchial valves										
2	RCT	322	MD -0.12 (-0.34, 0.09)	-	-	Serious[1]	Not serious	Not serious	Serious[3]	Low
All serious adverse event*, lower numbers favour intra-bronchial valves										
2	RCT	322	IRR 2.47 (1.33, 4.59)	-	-	Serious[1]	Not serious	Not serious	Not serious	Moderate
COPD exacerbations, lower numbers favour intra-bronchial valves										
2	RCT	322	IRR 2.23 (0.57, 8.63)	-	-	Serious[1]	Not serious	Not serious	Very serious[5]	Very low

1. Greater than 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias
2. The I^2 was greater than 66.7%
3. Non-significant result
4. 95% confidence interval crosses one end of a defined MID interval
5. 95% confidence interval crosses both ends of a defined MID interval

*Adverse events included bronchospasm, COPD exacerbations, death, pneumonia, pneumothorax and respiratory failure

1 Endobronchial coils

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in Breathlessness (mMRC dyspnoea scale), lower numbers favour endobronchial coils										
2	RCTs	146	MD* -0.31 (-0.58, -0.03)	-	-	Very serious[1]	Not serious	Not serious	Not serious	Low
Sensitivity analysis for breathlessness excluding studies at high risk of bias										
1 (RESET 2013)	RCTs	46	MD -0.15 (-0.60, 0.30)	-	-	Not serious	N/A	Not serious	Serious[5]	Moderate
Change in health related quality of life - St George's respiratory questionnaire score (total), lower number favour endobronchial coils										
2	RCTs	146	MD -9.78 (-14.44, -5.13)	-	-	Very Serious[1]	Not serious	Not serious	Not serious	Low
Sensitivity analysis for SGRQ excluding studies at high risk of bias										
1 (RESET 2013)	RCTs	46	MD -8.36 (-16.08, -0.64)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
Health related quality of life - St George's respiratory questionnaire score >4 points improvement, higher numbers favour endobronchial coils										
1 (RESET 2013)	RCT	46	RR 3.00 (1.31, 6.89)	10 people per 100	30 people per 100 (13.10, 68.90)	Serious[2]	N/A	Not serious	Not serious	Moderate
Health related quality of life St George's respiratory questionnaire score >8 points improvement, higher numbers favour endobronchial coils										
1 (RESET 2013)	RCT	46	RR 4.33 (1.42, 13.21)	7 people per 100	28 people per 100 (9.94, 92.47)	Serious[2]	N/A	Not serious	Not serious	Moderate
Exercise capacity - improvement in 6 minute walking test (m), higher numbers favour endobronchial coils										
2	RCTs	146	MD 42.33 (0.64, 84.02)	-	-	Very Serious[1]	Very serious[3]	Not serious	Serious[4]	Very Low
6 minute walk test >54m improvement, higher numbers favour endobronchial coils										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (REVOLENS 2016)	RCT	100	RR 2.00 (1.00, 4.02)	9 people per 100	18 people per 100 (9.00, 36.18)	Not serious	N/A	Not serious	Serious[4]	Moderate
6 minute walk test >54m improvement, higher numbers favour endobronchial coils										
1 (RESET 2013)	RCT	46	RR 4.25 (1.69, 10.70)	8.69 people per 100	37 people per 100 (14.69, 92.98)	Not serious	N/A	Not serious	Not serious	High
FEV1 (litres), higher numbers favour endobronchial coils										
1 (REVOLENS 2016)	RCTs	100	MD 0.08 (0.03, 0.13)	-	-	Not serious	N/A	Not serious	Serious[4]	Moderate
% change in FEV1, higher numbers favour endobronchial coils										
1 (RESET 2013)	RCT	46	MD 10.62 (0.64, 20.60)	-	-	Not serious	N/A	Not serious	Not serious	High
All Adverse events, lower numbers favour endobronchial coils**										
3	RCTs	458	IRR 1.44 (0.85, 2.46)	-	-	Serious[1]	Serious	Not serious	Serious[4]	Low
Pneumothorax through 12 months, lower numbers favour endobronchial valves										
3	RCTs	458	IRR 10.58 (2.48, 45.08)	-	-	Not serious	Not serious	Not serious	Not serious	High
Pneumonia, lower numbers favour endobronchial coils										
2	RCTs	412	IRR 4.49 (2.18, 9.25)	-	-	Not serious	Not serious	Not serious	Not serious	High
COPD exacerbation through 12 months, lower numbers favour endobronchial coils										
2	RCTs	412	IRR 1.32 (0.90, 1.65)	-	-	Not serious	Not serious	Not serious	Serious[4]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

*mean difference and not standardised because both studies used the same breathlessness tool

**adverse events included pneumonia, pneumothorax, COPD exacerbation, haemoptysis and respiratory failure.

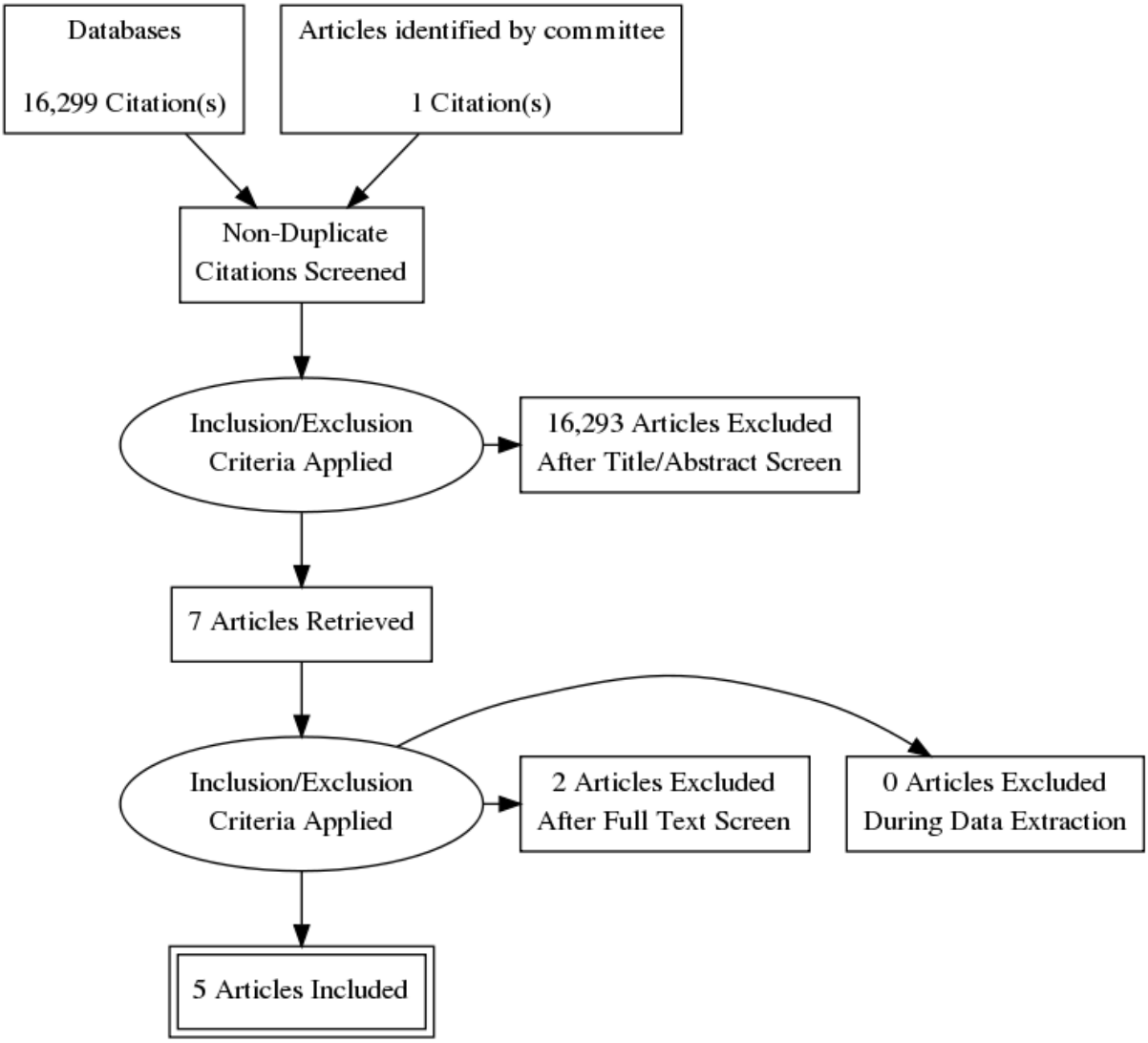
***A pneumothorax is an abnormal collection of air in the pleural space between the lung and the chest wall

1. Greater than 33% of the weight in a meta-analysis came from studies at high risk of bias
2. Moderate risk of bias, questionnaire was self-administered
3. The I^2 was greater than 66.7%
4. 95% confidence interval crosses one end of a defined MID interval
5. Non-significant result

1

1 Appendix H – Economic evidence study selection

2



3

1 Appendix I – Health economic evidence profiles

2 Lung volume reduction surgery

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Miller (2006)	1. Partially applicable [a] 2. Potentially serious limitations [b]	Lung volume reduction surgery versus best medical care	Canadian healthcare system	One year Not specified (assumed none)	ICER for LVRS versus usual care: $133,900 CAD (~£74,700) per QALY	None

(a) Not conducted from the perspective of the UK healthcare system
(b) Has a short time horizon of 2 years, no sensitivity analysis, discount rate not specified

3

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
National Emphysema Treatment Research Group (2003)	1. Partially applicable [a] 2. Potentially serious limitations [b]	Lung volume reduction surgery versus medical therapy	US – societal perspective	Three years 3%	ICER for LVRS versus medical therapy: $190,000 USD (~£133,500) per QALY	Extrapolating to a 10 year time horizon produces an ICER of $53,000 (~£37,200) per QALY. Subgroup analysis in patients with upper-lobe emphysema and low exercise capacity produces an ICER of $98,000 (~£68,800) per QALY at 3 years and $21,000 (~£14,800) per QALY at 10 years. Probabilistic sensitivity analysis shows substantial uncertainty for all subgroups.

(a) Not conducted from the perspective of the UK healthcare system, EQ-5D not used to measure HRQoL
(b) Has a short time horizon of 3 years

1

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Ramsay (2007)	1. Partially applicable [a] 2. Potentially serious limitations [b]	Lung volume reduction surgery versus medical therapy	US – societal perspective	Five years 3%	ICER for LVRS versus medical therapy: $140,000 USD (~£98,400) per QALY	Extrapolating to a 10 year time horizon produces an ICER of $54,000 (~£37,900) per QALY. Subgroup analysis in patients with upper-lobe emphysema and low exercise capacity produces an ICER of $77,000 (~£54,100) per QALY at 3 years and $48,000 (~£33,700) per QALY at 10 years. Probabilistic sensitivity analysis shows substantial uncertainty for all subgroups.

(a) Not conducted from the perspective of the UK healthcare system, EQ-5D not used to measure HRQoL
(b) Has a short time horizon of 3 years

2 **Endobronchial valve**

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Pietzsch (2014)	1. Partially applicable [a] 2. Very serious limitations [b]	Endobronchial valve versus medical management	German healthcare system	10 years 3%	ICER for endobronchial valve versus medical management: €25,142 (~£21,900) per QALY	Scenario analyses in which no discounting was applied, a higher number of valves in the initial procedure was assumed, higher rates of pneumothorax and valve

	migrations/expectorations/aspirations were used, and subgroup analyses for male/female populations did not substantially affect results.

(a) Not conducted from the perspective of the UK healthcare system
(b) Does not conduct a probabilistic sensitivity analysis, despite reporting an ICER of borderline cost effectiveness

1

Endobronchial coil

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Deslee (2016)	1. Partially applicable [a] 2. Potentially serious limitations [b]	Endobronchial coil treatment versus usual care	French healthcare system	One year N/A (time horizon is one year)	ICER for endobronchial coil treatment versus usual care: $782,598 per QALY	Probabilistic sensitivity analysis showed that endobronchial coil is associated with a negligible probability of being cost-effective at thresholds up to around $500,000 per QALY.

(c) Not conducted from the perspective of the UK healthcare system
(d) Has a short time horizon of one year

1 Appendix J – Excluded Studies

2 Clinical studies

Short Title	Title	Reason for exclusion
Abumossalam (2016)	Poor man medical pneumoplasty: Bronchoscopic lung volume reduction with hot saline versus dissolved doxycycline as a neoteric remedy of pulmonary emphysema	Not a randomised control trial
Agteren (2017)	Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease	Systematic review – all studies for include already included in this review
Benzo (2009)	Integrating health status and survival data: the palliative effect of lung volume reduction surgery	Data not reported in an extractable format
Calverley (2003)	Closing the NETT on lung volume reduction surgery	Review article but not a systematic review
Choi (2015)	Effectiveness of bronchoscopic lung volume reduction using unilateral endobronchial valve: a systematic review and meta-analysis	Systematic review including non RCTs
Come (2012)	Lung deflation and oxygen pulse in COPD: results from the NETT randomized trial	Study does not contain any of the outcomes of interest
Criner (2007)	Effect of lung volume reduction surgery on resting pulmonary hemodynamics in severe emphysema	Does not contain a population of people with COPD
Criner (2009)	Biologic lung volume reduction in advanced upper lobe emphysema: phase 2 results	Not a randomised control trial
Criner (2011)	The National Emphysema Treatment Trial (NETT)Part II: Lessons Learned about Lung Volume Reduction Surgery	Secondary publication of an included study that does not provide any additional relevant information.
Davey (2015)	Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial	Duplicate reference
de Oliveira (2017)	Combined Bone Marrow-Derived Mesenchymal Stromal Cell Therapy and One-Way Endobronchial Valve Placement in Patients with Pulmonary Emphysema: A Phase I Clinical Trial	Not a randomised control trial

Short Title	Title	Reason for exclusion
Deslee (2012)	Cost-effectiveness of lung volume reduction coil treatment in emphysema. STIC REVOLENS	Study not reported in English
Deslee (2014)	Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial	Not a randomised control trial
Deslee (2015)	Lung volume reduction coil treatment improves exercise capacity at 6 months in severe emphysema: Preliminary results of the randomized control trial revolens	Conference abstract
Eberhardt (2010)	Unilateral vs. bilateral endoscopic lung volume reduction in patients with severe heterogeneous emphysema: a comparative randomised case study	Conference abstract
Eberhardt (2012)	Complete unilateral vs partial bilateral endoscopic lung volume reduction in patients with bilateral lung emphysema	Comparator in study does not match that specified in protocol
Eberhardt (2014)	Upper versus lower lobes EBV lung reduction treatment in severe emphysema	Conference abstract
Eberhardt (2016)	A multicenter, prospective, randomized, controlled trial of endobronchial valve therapy vs standard of care in homogeneous emphysema (IMPACT)	Conference abstract
Elstad (2012)	Bronchial valve treatment of emphysema: Procedure and device safety results from a double-blind randomized trial	Conference abstract
Geddes (2000)	Effect of lung-volume-reduction surgery in patients with severe emphysema	Data not in an extractable format. All outcomes of interest reported as median
Hartman (2015)	Long-term follow-up after bronchoscopic lung volume reduction treatment with coils in patients with severe emphysema	Not a randomised control trial
Hartman (2015)	Daily physical activity significantly improves after endobronchial valve treatment in patients with emphysema	Conference abstract
Hensley (2000)	Lung volume reduction surgery for diffuse emphysema	More recent systematic review included that covers the same topic
Herth (2010)	Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study	Not a randomised control trial No control group
Herth (2010)	Implantation of the lung volume reduction coil for treatment of severe	Conference abstract

Short Title	Title	Reason for exclusion
	emphysema - Early results of a pilot clinical study	
Herth (2011)	Endobronchial valves for emphysema palliation trial - The Euro vent trial	Conference abstract
Herth (2015)	Lung volume reduction using endobronchial valves in COPD patients with low emphysema heterogeneity scores	Conference abstract
Hopkinson (2015)	Endobronchial valves for emphysema-open label treatment of control patients following completion of the believer-HIFI study	Conference abstract
Iftikhar (2014)	Predictors of efficacy for endobronchial valves in bronchoscopic lung volume reduction: A meta-analysis	Duplicate reference
Iftikhar (2014)	Predictors of efficacy for endobronchial valves in bronchoscopic lung volume reduction: A meta-analysis.	Duplicate reference
Iftikhar (2014)	Efficacy of bronchoscopic lung volume reduction: a meta-analysis	Duplicate reference
Iftikhar (2014)	Efficacy of bronchoscopic lung volume reduction: A meta-analysis	Systematic review – All studies in this review were included as primary papers
Jorgensen (2003)	Effects of lung volume reduction surgery on left ventricular diastolic filling and dimensions in patients with severe emphysema	Not a randomised control trial
Kaplan (2007)	Lung volume reduction surgery vs medical therapy for severe emphysema	Review article but not a systematic review
Kaplan (2015)	Quality of well-being outcomes in the National Emphysema Treatment Trial	Duplicate reference
Keller (1997)	Thoracoscopic lung volume reduction surgery reduces dyspnea and improves exercise capacity in patients with emphysema	Not a randomised control trial
Kemp (2012)	Randomised controlled trial of repneu endobronchial coils for the treatment of severe emphysema with hyperinflation (reset study)	Conference abstract
Kim (2012)	Chronic bronchitis is associated with worse survival in advanced emphysema	Conference abstract
Klooster (2015)	Endobronchial valve treatment versus standard medical care in patients with emphysema without interlobar collateral ventilation	Duplicate reference

Short Title	Title	Reason for exclusion
Klooster (2015)	Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation	Duplicate reference
Kozora (2005)	Improved neurobehavioral functioning in emphysema patients following lung volume reduction surgery compared with medical therapy	Secondary publication of an included study that does not provide any additional relevant information
Kretschman (2010)	Improved ventilatory efficiency (VE/VCO2) after LVRS is associated with weight gain	Conference abstract
Kumar (2015)	Efficacy of bronchoscopic lung volume reduction: Meta-analysis	Conference abstract
Kumar (2017)	Early Trends in Bronchoscopic Lung Volume Reduction: A Systematic Review and Meta-analysis of Efficacy Parameters	Systematic review – All studies in this review were included as primary papers
Liu (2015)	Efficacy and safety of endobronchial valves for advanced emphysema: a meta analysis	Systematic review – All studies in this review were included as primary papers
Maggiore (1999)	Lung volume reduction for patients with severe COPD	Conference abstract
Mercer (1999)	Comparison of functional state between bilateral lung volume reduction surgery and pulmonary rehabilitation: a six-month followup study	Full text paper not available
Miller (2006)	A randomized clinical trial of lung volume reduction surgery versus best medical care for patients with advanced emphysema: a two-year study from Canada	Data not reported in an extractable format
Mysore (2013)	Lung volume reduction surgery for diffuse emphysema: A cochrane meta-analysis	Conference abstract
Nader (2012)	Bronchial valve treatment of emphysema: Study design and methods for a double-blind randomized trial	Conference abstract
Ninane (2010)	The European multicenter, single blinded and randomized study of bronchial valves for the treatment of advanced emphysema: Procedural results	Conference abstract
Ninane (2011)	Results of BODE index in the European multi-center study for the treatment of advanced emphysema with bronchial valves	Conference abstract

Short Title	Title	Reason for exclusion
Robbins (2000)	More evidence for the short-term beneficial effects of lung volume reduction surgery	Conference abstract
Sciurba (2016)	Efficacy of Endobronchial Coil Implantation in Patients with Advanced Emphysema: results of the RENEW Trial	Conference abstract
Shah (2011)	Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial	Not a relevant intervention -Airway Stents
Strange (2007)	Design of the Endobronchial Valve for Emphysema Palliation Trial (VENT): a non-surgical method of lung volume reduction	Rationale and design paper
Tiong (2006)	Lung volume reduction surgery for diffuse emphysema	More recent systematic review included that covers the same topic
Upala (2016)	Underweight and obesity increase the risk of mortality after lung transplantation: A systematic review and meta-analysis	Systematic review including non RCTs
Valipour (2012)	Target lobar volume reduction and COPD outcome measures after endobronchial oneway valve therapy	Conference abstract
Valipour (2012)	Endobronchial valve therapy improves bode index in patients with advanced emphysema	Conference abstract
Van Agteren (2016)	Lung volume reduction surgery for diffuse emphysema: A cochrane systematic meta-analysis	Duplicate reference
Van Agteren (2016)	Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease: A cochrane systematic review and metaanalysis	Systematic review – All studies in this review were included as primary papers
van Agteren (2017)	Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease	Duplicate reference
Washko (2014)	Results of the aspire endoscopic lung volume reduction trial at study termination	Conference abstract
Weiss (2016)	A placebo-controlled, randomized trial of mesenchymal stromal cells combined with one-way endobronchial valve therapy in severe COPD	Conference abstract
Zoumot (2012)	Outcomes of the repneu endobronchial coils for the treatment of severe emphysema with hyperinflation (reset) trial	Conference abstract

Short Title	Title	Reason for exclusion
Zoumot (2012)	Randomized controlled trial of repneu endobronchial coils for the treatment of severe emphysema with hyperinflation (reset)	Conference abstract
Zoumot (2013)	6 and 12 month outcomes following RePneu bronchoscopic lung volume reduction coil treatment	Conference abstract
Zoumot (2013)	Preliminary medium-term follow-up data from a single centre experience of a randomised controlled crossover study of the lung volume reduction coils	Conference abstract
Zoumot (2015)	Endobronchial coils for severe emphysema are effective up to 12 months following treatment: medium term and cross-over results from a randomised controlled trial	Crossover results of an already data extracted study
Zoumot (2015)	Lung Volume Reduction in Emphysema Improves Chest Wall Asynchrony	Not a randomised study because analysis not carried out in the randomised groups

1 **Economic studies**

Short title	Title	Reason
Ramsay (2001)	Economic analysis of lung volume reduction surgery as part of the National Emphysema Treatment Tria	Protocol for economic analysis
Ramsey (2008)	Cost-effectiveness of lung volume reduction surgery	Review article of previous analyses

2

3

Appendix K – References

Clinical studies

Included clinical studies

Clarenbach C, Sievi N, Brock M, Schneiter D, Weder W, and Kohler M (25) LVRS improves endothelial function and blood pressure in patients with COPD: A randomized-controlled trial. European Respiratory Journal 46, no pagination

Criner Gerard J, and Sternberg Alice L (2008) National Emphysema Treatment Trial: the major outcomes of lung volume reduction surgery in severe emphysema. Proceedings of the American Thoracic Society 5, 393-405

Davey C, Zoumot Z, McNulty W, Jordan S, Carr D, Rubens M, Hansell D, Polkey M, Shah P, and Hopkinson N (2014) Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (BeLieVeR-HIFi). European Respiratory Journal 44, no pagination

Deslee Gaetan, Mal Herve, Dutau Herve, Bourdin Arnaud, Vergnon Jean Michel, Pison Christophe, Kessler Romain, Jounieaux Vincent, Thiberville Luc, Leroy Sylvie, Marceau Armelle, Laroumagne Sophie, Mallet Jean Pierre, Dukic Sylvain, Barbe Coralie, Bulsei Julie, Jolly Damien, Durand-Zaleski Isabelle, Marquette Charles Hugo, and Group Revolens Study (2016) Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomized Clinical Trial. JAMA 315, 175-84

Dolmage T E, Waddell T K, Maltais F, Guyatt G H, Todd T R. J, Keshavjee S, van Rooy , S , Krip B, LeBlanc P, and Goldstein R S (2004) The influence of lung volume reduction surgery on exercise in patients with COPD. The European respiratory journal 23, 269-74

Fishman Alfred, Martinez Fernando, Naunheim Keith, Piantadosi Steven, Wise Robert, Ries Andrew, Weinmann Gail, Wood Douglas E, National Emphysema Treatment Trial Research, and Group (2003) A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. The New England journal of medicine 348, 2059-73

Goldstein R S, Todd T R. J, Guyatt G, Keshavjee S, Dolmage T E, van Rooy , S , Krip B, Maltais F, LeBlanc P, Pakhale S, and Waddell T K (2003) Influence of lung volume reduction surgery (LVRS) on health related quality of life in patients with chronic obstructive pulmonary disease. Thorax 58, 405-10

Hartman Jorine E, Klooster Karin, Slebos Dirk-Jan, Ten Hacken, and Nick H T (2016) Improvement of physical activity after endobronchial valve treatment in emphysema patients. Respiratory medicine 117, 116-21

Herth Felix J. F, Noppen Marc, Valipour Arschang, Leroy Sylvie, Vergnon Jean-Michel, Ficker Joachim H, Egan Jim J, Gasparini Stefano, Agusti Carlos, Holmes-Higgin Debby, Ernst Armin, and International Vent Study Group (2012) Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. The European respiratory journal 39, 1334-42

Hillerdal Gunnar, Lofdahl Claes-Goran, Strom Kerstin, Skoogh Bengt-Eric, Jorfeldt Lennart, Nilsson Folke, Forslund-Stiby Dycke, Ranstam Jonas, and Gyllstedt Erik (2005) Comparison

of lung volume reduction surgery and physical training on health status and physiologic outcomes: a randomized controlled clinical trial. Chest 128, 3489-99

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