NHS England

Evidence review: Lung Volume Reduction by Endobronchial Valves for Severe Emphysema

NHS England

Evidence review: Lung Volume Reduction by Endobronchial Valves for Severe Emphysema

First published:	February 2018
Updated:	Not applicable
Prepared by:	Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

Indication and epidemiology

- Chronic obstructive pulmonary disease (COPD) is a progressive chronic lung disease that is characterised by varying degrees of chronic bronchitis (chronic inflammation of the central airways) and emphysema (van Agteren et al 2017).
- Emphysema is characterised by damaged lung parenchyma with loss of its elasticity, resulting in hyperinflation of the lung, reduced airflow, reduced capacity for efficient gas exchange between the alveoli and the blood, and breathlessness (van Agteren et al 2017).
- Patients with COPD commonly have increasing breathlessness (particularly a feature of emphysema), a persistent chesty cough with phlegm (chronic bronchitis), frequent chest infections and persistent wheezing, and may suffer from weight loss and tiredness. The symptoms usually worsen gradually over time and make daily activities increasingly difficult, although treatment can help slow the progression. For many patients there are periods when symptoms get suddenly worse (exacerbations), particularly during the winter (NHS Choices, 2016).
- In England, over one million people live with COPD, around 25,000 deaths each year are attributable to COPD, and over 113,000 emergency hospital admissions were for COPD in 2013/14 (Public Health England 2015). As patients with COPD tend to have a combination of varying degrees of chronic bronchitis and emphysema, emphysema will have contributed to a large proportion of these, although we are not able to identify the exact contribution of the emphysematous component of the disease to these statistics.
- In most cases emphysema results predominantly from cigarette smoke or other noxious particles such as air pollutants which lead to oxidative stress, chronic inflammation and gradual destruction of lung tissue (van Agteren et al 2017).
- Emphysema can be homogeneous or heterogeneous in the way it affects the lungs. Typically heterogeneity refers to variation between the lobes of the lungs (interlobar), but it can also be within a lobe (intralobar), and the amount of heterogeneity varies (van Agteren et al 2017).
- The distribution of emphysema also varies. For example centrilobular emphysema is most closely associated with smoking and affects respiratory bronchioles predominantly in the upper lung, panlobular emphysema due to alpha 1 anti-trypsin deficiency is found mainly in the lower lobes and paraseptal emphysema occurs in the subpleural region.
- Conventional treatment for COPD involves short- and long-acting bronchodilators, sometimes in combination with inhaled steroids, pulmonary rehabilitation, oxygen supplementation for some patients, and a focus on smoking cessation. Patients with severe emphysema experience frequent respiratory exacerbations triggered by a variety of factors. At more advanced stages of the disease patients respond less well to conventional medical treatment and medical treatment options are limited (van Agteren et al 2017, NICE 2017).

The intervention

- Lung volume reduction using endobronchial valves aims to reduce the hyperinflation that results from damaged and destroyed lung tissue and is not targeted at the chronic inflammation. It is therefore aimed at people whose COPD includes severe emphysema (van Agteren et al 2017).
- The aim of insertion of endobronchial valves for lung volume reduction in emphysema is to achieve atelectasis (deflation/collapse) of selected lung segments. It uses an endoscopic

approach, which is less invasive than open or thoracoscopic lung volume reduction surgery (NICE 2017).

- Valve insertion is carried out with the patient under sedation or general anaesthesia. Using a delivery catheter passed through a bronchoscope, a synthetic valve is placed in the target location and fixed to the bronchial wall. The valve is designed to prevent air inflow during inspiration but to allow air and mucus to exit during expiration. Several valves may be needed (one or more for each segment of the lung to be treated). Patients may sometimes be given antibiotics and/or steroids.
- Two devices with different designs are available for this procedure: one is duckbill shaped and tends to be referred to as an endobronchial valve (also known as EBV or Zephyr valve) and the other is umbrella shaped and tends to be referred to as an intrabronchial valve (also known as IBV or Spiration valve) (NICE 2017).
- Before the procedure, it is usual practice to assess the presence of collateral ventilation (when air enters a lobe of the lung through a passage other than the normal airway). A surrogate for this is computerised tomography (CT) scanning to assess the completeness of fissures (referred to in this document as 'complete' or 'intact' fissures). A functional approach, specially developed for use before insertion of airway valves, involves a specially designed balloon catheter with a flow sensor (NICE 2017).

Existing national policies and guidance

- The National Institute for Health and Care Excellence (NICE) published interventional procedures guidance in December 2017 on the insertion of endobronchial valves for lung volume reduction in emphysema following their review of a systematic review and meta-analysis which included eight randomised controlled trials (RCTs), five of duckbill-shaped valves and three of umbrella-shaped valves (NICE IPG600 2017). NICE's recommendations are as follows:

  "Current evidence on the safety and efficacy of endobronchial valve insertion to reduce lung volume in emphysema is adequate in quantity and quality to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit.

  Patient selection should be done by a multidisciplinary team experienced in managing emphysema, which should typically include a chest physician, a radiologist, a thoracic surgeon and a respiratory nurse.

  Patients selected for treatment should have had pulmonary rehabilitation. The procedure should only be done to occlude volumes of the lung where there is no collateral ventilation, by clinicians with specific training in doing the procedure." (NICE 2017)

2. Summary of results

- This evidence review is based on two systematic reviews with meta-analysis (SRMAs) of seven randomised controlled trials (RCTs) of endobronchial valves for patients with severe emphysema, and three further RCTs, two of which are based on patients included in the SRMAs. Two of the RCTs comparing valve treatment with maximal medical therapy included in the SRMAs relate to the umbrella type of endobronchial valve and the remainder (five RCTs) relate to the duckbill type of valve. Some of the duckbill type valve studies also assessed effectiveness in subgroups relating to heterogeneity of emphysema, collateral ventilation (CV) and occlusion of target lung lobes.
- The most commonly reported outcomes relate to mortality, lung function, exercise capacity,

quality of life (QoL) and adverse events.

- The Cochrane SRMA by van Agteren et al (2017) was the most comprehensive study and is therefore quoted most often below.
- Mortality:

  For the duckbill type valve, no significant effect on mortality was found by end of follow-up compared to patients who had maximal medical therapy alone (odds ratio (OR) 1.07, p=0.86, n=703) and there was also no significant difference when data for those with intact fissures (an indicator of lack of CV) and those not assessed for CV were analysed separately (van Agteren et al 2017).

  For the umbrella type valve, no significant effect on mortality was found (n=350, OR 4.95, p=0.08) (van Agteren et al 2017).

- Lung function:

  For the duckbill type valve, the main measure of lung function assessed was the forced expiratory volume in one second (FEV_1), which improved significantly more in valve treated patients than controls (11.44% between group mean difference (BGMD), n=703, p<0.0001) (Wang et al 2017). The improvement was significantly larger in patients with heterogeneous emphysema compared to homogenous emphysema (BGMD 16.36%, p=0.00001), in patients without CV (p=0.0002), and in those where the valves resulted in complete lobar occlusion (p=0.005 and p=0.006 in two studies) (van Agteren et al 2017). A minimal clinically important difference (MCID) (≥10% increase in FEV_1) was achieved significantly more frequently in treated patients (risk ratio (RR) 2.96, p=0.002, n=703).

  Other measures of lung function, including residual volume (RV), total lung capacity (TLC), RV/TLC, forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO), also showed statistically significant changes that favoured valve treatment over maximal medical therapy. For RV and RV/TLC there was evidence to suggest that the difference was meaningful to patients (for example in two of three RCTs that reported on this measure, significantly more treated patients achieved a MCID in RV and one study found that 63% of patients and 9% of controls achieved the MCID in RV/TLC (p<0.001, n=107) (van Agteren et al 2017).

  For umbrella type valves, no significant difference in FEV_1 was found at 3 months in one study (n=73, p=0.065) and a significant change in FEV_1 in favour of controls at 6 months in the other study (n=277, p=0.001). Changes in RV and RV/TLS also favoured controls. There was a 0.38 litres greater reduction in RV in controls (95% CI 0.12 to 0.65, n=322), a significantly greater reduction in RV/TLC in controls (p=0.01, n=73) and no significant effect of valves on TLC (n=322) (van Agteren et al 2017).

- Exercise capacity:

  For the duckbill type valve, there was a significantly greater improvement in six minute walk distance (6MWD) in valve patients than controls (BGMD 38.12 metres, 95% CI 8.68 to 67.56, n=379). No significant difference was found relating to CV in two trials comparing those with and without intact fissures, but at a trial level, the two trials that selected only patients with intact fissures found significantly more improvement in 6MWD than the three trials that did not (p=0.01) (van Agteren et al 2017). Wang et al (2017) found that a MCID of 26 metres was achieved significantly more often in valve patients (p=0.01, n=703).

  Other measures of exercise capacity also suggested significant benefits of valves at six months, including an increase in steps per day (BGMD 1340 steps, p=0.001), locomotion duration per day (p=0.001) and walk intensity (p=0.014), although no significant difference was seen at six months in sitting duration (p=0.230) or duration of inactivity (p=0.126) (n=43)

(Hartman et al 2016).

For the umbrella type valve, van Agteren et al (2017) found significantly less improvement in 6MWD in valve patients compared to controls (BGMD -19.54 metres, 95% CI -37.11 to -1.98, n=316).

- Quality of life (QoL):

  For the duckbill type valve, three validated measures of QoL developed specifically for respiratory disease patients, the St George's Respiratory Questionnaire (SGRQ), modified Medical Research Council dsypnoea scale (mMRC), and the Clinical COPD Questionnaire (CCQ) suggested significant benefits of valve treatment (SGRQ: BGMD -7.29, 95% CI -11.12 to -3.45, n=695; CCQ: BGMD -0.74, p=0.002, n=68; mMRC: BGMD -0.35, p=0.0008), although no significant effect was found with the COPD Assessment Test (CAT) (p=0.23) or on the SF-36 mental health or physical component scores. Based on proportions achieving the MCID, there was evidence that for SGRQ and mMRC the improvement was clinically important (p=0.0002 and p<0.00001). Changes in SGRQ were significantly greater in patients with heterogeneous emphysema (p=0.005) although they were significant in homogenous emphysema too (p<0.0001), and were significant compared to controls in patients with intact fissures but not those without intact fissures (with CV) (BGMD -9.03 vs 0.00) (van Agteren et al 2017 and Wang et al 2017).

  For the umbrella type valve, no significant effect was found on either the SGRQ (p=0.24, n=350) or mMRC (n=240, p=0.47) (Wang et al 2017).

- One RCT of the duckbill type valve found a significant improvement in the BODE disease severity index[1] (BGMD 1.8, p<0.001, n=97) (Kemp et al 2017).
- Adverse events (AEs) were significantly more common in patients treated with the duckbill type valve than in controls. The most frequent severe AEs were exacerbations of COPD (RR 2.01, p=0.01), pneumothorax (RR 9.65, p=0.0001) and pneumonia (RR 2.17, p=0.10), particularly distal to the valve, and 23 of 433 patients suffered valve expectoration, aspiration or migration, with valve removal in 40. With the umbrella type valve AEs were also significantly more common than in controls (p=0.004) (van Agteren et al 2017).
- Mean and median procedure times were between 18 and 33.8 minutes for duckbill type valves and 62 minutes for umbrella type valves, and the mean duration of hospital stay reported varied from one to 2.2 days.
- Cost effectiveness for the duckbill valve was calculated as EUR 46,322 (£41,227) per QALY gained at five years and EUR 25,142 (£22,376) per QALY at ten years (Pietzch et al 2014). However, this cost is likely to be a significant underestimate because the study excluded from their analysis patients with incomplete occlusion of target lobes who are likely to have incurred the same or higher costs and poorer outcomes than those for whom complete occlusion is achieved. Incomplete occlusion cannot always be avoided.
- Thus overall, despite issues such as heterogeneity, and lack of blinding in most studies of duckbill type valves, the significant and consistent results on a range of measures suggests that they provide significant meaningful benefit to patients in terms of lung function, exercise capacity and QoL. Evidence relating to some of these outcome measures suggests that there is a greater benefit in patients with heterogeneous emphysema, patients without CV to the target lobe and those where lobar occlusion is complete, although patients with homogenous emphysema may benefit too. However, this needs to be weighed against the increase in serious AEs when making individual patient decisions and the fact that cost-effectiveness is

[1] The BODE index is a multidimensional grading system for predicting the risk of death among COPD patients using body mass index, degree of airflow obstruction, dyspnoea and 6MWD.

not clear.

- Umbrella type valves appear to have a negative effect or no effect on these outcome measures. However, this may be due to the strategy tested rather than the type of valve, as the strategy in the two RCTs was partial occlusion of bronchi bilaterally, whereas in the duckbill valve trials it was complete occlusion of the most damaged areas of lung.

3. Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: PubMed, Embase, Cochrane, TRIP and NHS Evidence (see section 10 for search strategy).
- The search dates for publications were between 1st January 2007 and 23rd November 2017.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4. Results

Six papers are included in this rapid evidence review (RER). These include two systematic reviews with meta-analysis (SRMAs), by van Agteren et al (2017) (a Cochrane systematic review) and by Wang et al (2017). Both SRMAs include the same seven randomised controlled trials (RCTs) of valve treatment compared to maximal medical therapy (n=1053, range n=50 to 321). Three further RCTs were included. One RCT was published after the SRMAs (Kemp et al 2017, n=97) and the other two RCTs (Hartman et al 2016, n=43, and Brown et al 2012, n=421) use data included in the SRMAs but provide analysis of different outcome measures. The Cochrane SRMA (van Agteren et al 2017) includes analysis of a range of outcome measures, while the SRMA by Wang et al (2017) focuses on clinical effectiveness in terms of minimal clinically important differences (MCIDs) for a similar but smaller range of outcome measures. The Cochrane SRMA also includes analyses relating to whether the emphysema is heterogeneous or homogenous, whether or not there is collateral ventilation to the treated area of lung and whether or not the valves resulted in lobar occlusion. Both SRMAs reported results separately for duckbill type valves (five RCTs) and umbrella type valves (two RCTs); the three further RCTs included here all used duckbill type valves.

One study of cost-effectiveness was identified (Pietzch et al 2014), which analysed data from a subset of patients included in the above SRMAs.

Because of the number of RCTs and SRMAs of RCTs identified, covering a total of 1,150 patients, case series and reviews of case series were not included as they provide much lower quality evidence.

Although broadly matching the PICO criteria, none of the included studies specified that patients underwent pulmonary rehabilitation prior to enrolment, and two of the RCTs (Hartman et al 2016 and Brown et al 2012) did not provide detail regarding heterogeneity or separate results for patients with homogenous versus heterogeneous emphysema. The exact follow-up protocols, for example the degree of monitoring of patients and whether valves were replaced or repositioned when issues were found, was not described in the studies but there was an indication in the Cochrane review that this varied between RCTs (van Agteren et al 2017).

Question 1: In people with severe emphysema, what is the evidence for the clinical effectiveness and safety of lung volume reduction by endobronchial valves?
The outcomes measured included mortality, lung function, quality of life, exercise capacity and, adverse events, with some analyses stratified by length of follow-up, heterogeneity of emphysema, collateral ventilation and occlusion status of treated lobes. Results for the two types of valves were presented separately in the SRMAs, and are also presented separately in this review.

Mortality
Neither SRMA found a statistically significant difference in mortality by end of follow-up between treated and control groups for either type of valve. For the duckbill type valve the Cochrane SRMA also analysed mortality data where available for the post-operative period, 90 days, six and 12 months and found no statistically significant difference at any of these time points (p values not given but 95% confidence intervals (CIs) were all wide).

Duckbill type valve:
The Cochrane SRMA found the odds ratio (OR) for mortality by end of follow-up for the five RCTs (n=703) to be 1.07 (95% CI 0.47 to 2.43, p=0.86). There were 15 deaths in the treatment group (n=433) and eight in the controls (n=270) (35 per 1000 versus 30 per 1000). The SRMA by Wang et al (2017) likewise found no statistically significant difference in mortality relating to valve insertion (relative risk (RR) 1.56, 95% CI 0.47 to 5.18, p=0.47).

In the post-operative period, at 90 days, six and 12 months the OR for mortality between valve treated patients and controls were 3.12 (95% CI 0.12 to 80.39), 2.17 (95% CI 0.67 to 7.02), 2.04 (95% CI 0.32 to 13.16) and 0.85 (95% CI 0.33 to 2.22) respectively. However, apart from the 90 day time point (five RCTs), only two RCTs provided data for the other time points (van Agteren et al 2017).

The RCT by Kemp et al (2017) reported one death in the treated group (n=65) and none in controls (n=32) in six months. The death occurred post-operatively in hospital due to a pneumothorax.

Umbrella type valve:
The Cochrane SRMA found the OR for mortality by end of follow-up for the two RCTs (n=350) to be 4.95 (95% CI 0.85 to 28.94, p=0.08). There were seven deaths in the treatment group (n=179) and one in the controls (n=171) (28 per 1000 versus 6 per 1000). The SRMA by Wang et al (2017) likewise found no statistically significant difference in mortality relating to valve insertion (RR 4.78, 95% CI 0.84 to 27.31, p=0.08).

Lung function - Change in forced expiratory volume in one second (FEV_1) from baseline
Studies of duckbill type valves found a statistically significant improvement in FEV_1 from baseline in treated patients compared to controls. However for umbrella type valves, one study found no significant effect on FEV_1 and the other found a statistically significant difference in favour of the control group.

Duckbill type valve:
The Cochrane review reported a between group standardised mean difference in improvement in FEV_1 of 0.48% in the treated group compared to controls (n=703, 95% CI 0.32 to 0.64) by end of follow-up, with the between group mean difference (BGMD) being 0.77, 0.40 and 0.33 at 90 days, six and 12 months respectively (95% CI 0.43 to 1.11, 0.22 to 0.58 and 0.01 to 0.65 respectively). However, it is difficult to reconcile this figure with other figures for this outcome measure in this study and in the study by Wang et al (2017) (see discussion, section 5). These results were all statistically significant. The meta-analysis by Wang et al (2017) of the same studies found a 11.44% BGMD in the change in FEV_1 from baseline in favour of valves ($p<0.0001$) and Kemp et al (2017, n=97) found a BGMD of 0.2 litres ($p<0.001$) as well as a significant change in the FEV_1 when analysed as a percent of predicted FEV_1 (BGMD 29.3%, $p<0.001$).

Umbrella type valve:
Of the two studies, one found no significant effect on FEV_1 at three months (n=73, mean FEV_1 0.90 litres for valves and 0.87 litres for controls, $p=0.065$, only final FEV_1 values reported), whereas the other study found that the change in FEV_1 was statistically significantly in favour of controls at six months (n=277, 2.11% decrease in FEV_1 in valve patients and 0.04% increase in controls, $p=0.001$) (van Agteren et al 2017).

Lung function - Change in residual volume (RV) from baseline
Overall studies of duckbill type valves found a significant reduction in RV from baseline in treated patients compared to controls, whereas the opposite was found for umbrella type valves.

Duckbill type valve:
The Cochrane SRMA found a significant reduction in RV in treated patients and no significant change in controls (n=200; valve patients -0.58 litres, 95% CI -0.77 to -0.39; control patients range of change in RV -0.13 to +0.05) (van Agteren et al 2017).
Kemp et al (2017) likewise found a significant reduction in RV in the valve group compared to controls (BGMD -0.7 litres, 95% CI -1.1 to -0.3, $p=0.002$).

Analysis of results of an RCT by Brown et al (2012) used CT scans to estimate changes in RV following valve treatment and found a significant reduction (0.45 litres) in target lobe RV at total lung capacity (n=289, $p<0.0001$), with no significant change in controls (0.005 litres, $p=0.70$). The same was true for the group of patients who had had a greater than 50% reduction in target lobe volume (TLV) as a result of valve treatment (n=49, 1.09 litres reduction in RV of the target lobe, $p<0.0001$; and 0.555 litres reduction in whole lung RV, $p<0.0001$). This study also looked at changes in RV in the ipsilateral lobe[2] for those patients with a greater than 50% reduction in TLV, and found an average increase in RV of 0.481 litres in the ipsilateral lobe (n=49, $p<0.0001$). They found no significant change in RV in the contralateral lobe for these patients ($p=0.16$). A proxy measure of RV (change in the amount of low attenuation relative area on CT scan) also indicated significant reduction in RV for those in whom valve treatment reduced the TLV by over 50% (reduction of 4.8 percentage points, standard error (SE) 1.2).

Umbrella type valve:
The two studies together suggested that the reduction in RV was more favourable in control

[2] Ipsilateral lobe – the other lobe of the same (right or left) lung

patients than in those treated with valves (n=322, BGMD 0.38 litres, 95% CI 0.12 to 0.65) (van Agteren et al 2017).

Lung function – Change in total lung capacity (TLC) from baseline
Studies suggest that duckbill type valves, but not umbrella type valves, reduce TLC.

Duckbill type valve:
The Cochrane SRMA found a significant reduction in TLC in valve patients and not in controls (n=107, valve group mean change in TLC -0.34 litres, 95% CI -0.46 to -0.23; controls range of change in TLC -0.12 to +0.002, BGMD not stated) (van Agteren et al 2017).

Umbrella type valve:
Umbrella type valves were not found to make a significant difference to TLC compared to control patients (n=322, BGMD 0.14, 95% CI -0.12 to 0.39) (van Agteren et al 2017).

Lung function – Change in ratio of RV to TLC (RV/TLC) from baseline
Studies suggest a reduction in RV/TLC in patients treated with the duckbill type valve compared to controls, but the opposite for the umbrella type valve.

Duckbill type valve:
The Cochrane SRMA found a greater reduction in RV/TLC in valve patients compared to controls (n=118, valve group mean change in RV/TLC -5.76%, 95% CI -1.06 to -10.45; controls range of change in RV/TLC -0.4 to -0.64%, BGMD not stated) (van Agteren et al 2017).
Brown et al (2012) found that in patients who achieved over 50% reduction in target lobe volume following valve treatment, there was a significant reduction in the RV/TLC ratio (n=49, mean reduction of 4.5 percentage points, SE 1.3).

Umbrella type valve:
For umbrella type valves, the reduction in RV/TLC was significantly greater in the control group, suggesting a negative effect of the valves (n=73, p=0.01, BGMD not provided) (van Agteren et al 2017).

Lung function – Change in forced vital capacity (FVC) from baseline
Duckbill type valve:
The Cochrane SRMA found one study that showed a greater improvement in FVC in the valve treated group compared to controls (n=68, BGMD 14.4%, SD 27.8) (van Agteren et al 2017).

Lung function – Change in diffusion capacity of lung for carbon monoxide (DLCO) from baseline
Duckbill type valve:
The Cochrane SRMA found one study that showed a significantly greater improvement in DLCO in the valve treated group compared to controls (n=50, median improvement 0.30 mmol/min/kPa in valve group, 0 in control group, p=0.003) (van Agteren et al 2017).

Exercise capacity – Change in six minute walk distance (6MWD) from baseline
Overall there was a significantly greater improvement in 6MWD in patients treated with the duckbill type valve compared to controls, but the opposite was seen for the umbrella type valve.

Duckbill type valve:
The Cochrane SRMA found significantly greater improvement in 6MWD in valve treated patients compared to controls (n=379, BGMD 38.12 metres, 95% CI 8.68 to 67.56) (van Agteren et al 2017).

The SMRA by Wang et al (2017) likewise found a significant improvement in 6MWD in valve treated patients compared to controls (BGMD 33.86 metres, 95% CI 11.54 to 56.19, p=0.003), as did the RCT by Kemp et al (2017) (BGMD 78.7 metres, 95% CI 46.3 to 111.0, p<0.001).

Umbrella type valve:
For umbrella type valves there was significantly less improvement in 6MWD in valve patients compared to controls (n=316, BGMD -19.54 metres, 95% CI -37.11 to -1.98) (van Agteren et al 2017).
Wang et al (2017) likewise found a statistically significantly lower improvement in 6MWD in valve treated patients compared to controls (BGMD -18.77 metres, 95% CI -35.27 to -2.28, p=0.03).

Exercise capacity – Increase in steps per day at six months
Duckbill type valve:
In an RCT by Hartman et al (2016), patients treated with valves had a significantly higher increase in steps per day at six months than controls (n=43, BGMD 1340 steps, SD 380, p=0.001; % change from baseline 57.1%, SD 73.3). Mean steps per day had increased in the valve group and decreased in controls.

Exercise capacity – Increase in locomotion duration percent per day at six months
Duckbill type valve:
The RCT by Hartman et al (2016) found that patients treated with valves had a significantly higher increase than controls in the percent of a day spent in locomotion (n=43, BGMD 1.28%, SD 0.37, p=0.001; % change from baseline 36.4%, SD 49.7). Mean locomotion duration had increased in the valve group and decreased in controls.

Exercise capacity – Increase in walk intensity (average body acceleration) at six months
Duckbill type valve:
The RCT by Hartman et al (2016) found that patients treated with valves had a significantly higher increase than controls in the intensity of their walk (average body acceleration) at six months (n=43, BGMD 0.00948g, SD 0.0036, p=0.014; % change from baseline 4.6%, SD 8.4). Mean walk intensity had increased in the valve group and decreased in controls.

Exercise capacity – Increase in sitting duration at six months
Duckbill type valve:
The RCT by Hartman et al (2016) found no significant difference between valve and control patients in the change in the percent of each day spent sitting at six months (n=43, BGMD -1.86, SD 1.52, p=0.230).

Exercise capacity – Increase in duration of inactivity at six months
Duckbill type valve:
The RCT by Hartman et al (2016) found no significant difference between valve and control patients in the change in the percent of each day spent inactive at six months (n=43, BGMD -1.49, SD 0.95, p=0.126).

Quality of life (QoL) – St George's Respiratory Questionnaire (SGRQ)[3] changes from baseline
Studies of duckbill type valves found a statistically significant improvement from baseline in this measure of QoL whereas no significant effect was found for umbrella type valves.

Duckbill type valve:

[3] The SGRQ is a 50-item validated patient questionnaire designed to measure health-related quality of life specifically in respiratory patients.

The Cochrane review found a statistically significant BGMD for improvement in SGRQ related to valves (n=695, reduction of 7.29 points, 95% CI -11.12 to -3.45) by end of follow-up, which continued to be significant when the study showing the largest improvement was excluded from the analysis (BGMD -5.34, 95% CI -7.43 to -3.24). The BGMD was -8.75, -7.09 and -4.05 at 90 days, six and 12 months respectively (95% CI -12.76 to -4.74, -12.59 to -1.60 and -6.51 to -1.59 respectively). These results were all statistically significant.
The meta-analysis by Wang et al 2017 of the same studies found a BGMD of -7.06 (95% CI -10.71 to -3.41, p=0.0001).
The RCT by Kemp et al (2017) also found a significant improvement in SGRQ in valve patients (-7.2 points) compared to controls (-0.7 points), with a BGMD of -6.5 points (95% CI -12.4 to -0.6, p=0.031).

Umbrella type valve:
The Cochrane review found no significant effect on SGRQ by end of follow up (n=350, BGMD 2.64 units, 95% CI -0.28 to 5.56). This was also true for the SRMA by Wang et al (2017) of the same studies (BGMD 2.30, 95% CI -1.50 to +6.11, p=0.24).

Quality of life – COPD assessment test (CAT) score[4]
Duckbill type valve:
The Cochrane SRMA found no significant effect of valves on this QoL measure in two studies (n=50, p=0.23; and n=93, BGMD -0.9, 95% CI -2.9 to +1.1) (van Agteren et al 2017).

Quality of life – mMRC score[5]
Duckbill type valve:
The Cochrane SMRA found one study that saw no significant change from baseline (n=50, p=0.40) and two studies that showed significant improvement in QoL with this measure (n=93, BGMD -0.57 units, 95% CI -0.98 to -0.16; and n=321, BGMD -0.3 units, 95% CI -0.50 to -0.01) (van Agteren et al 2017).
The meta-analysis of the same studies by Wang et al (2017) found the improvement in mMRC score to be statistically significant (BGMD -0.35, 95% CI -0.56 to -0.14, p=0.0008).
Kemp et al (2017) also found a significant improvement in mMRC score in the valve group compared to controls (BGMD -0.6, 95% CI -1.0 to -0.1, p=0.010).

Umbrella type valve:
The Cochrane SRMA found no effect on QoL as measured by this score in either study of umbrella type valves (n=240, p=0.43; and n=73, p=0.64) (van Agteren et al 2017).
The meta-analysis of the same two studies by Wang et al (2017) likewise found no statistically significant effect (BGMD -0.08, 95% CI -0.29 to +0.13, p=0.47).

Quality of life – CCQ score[6]
Duckbill type valve:
One study found a significant effect in favour of valves on this QoL measure (n=68, BGMD -0.74, p=0.002) (van Agteren et al 2017).

[4] The COPD Assessment Test (CAT) is a validated questionnaire for people with COPD designed to measure the impact of COPD on a person's life, and how this changes over time.
[5] The mMRC scale ranges from 0-4 and is a validated tool used to establish levels of functional impairment or perceived impairment due to dyspnoea attributable to respiratory disease.
[6] The CCQ is an easy to complete QoL questionnaire which has been well-validated in COPD. It consists of 10 items (each scored between 0 and 6), divided into three domains (symptoms, functional, mental).

Quality of life – SF-36[7]
Umbrella type valve:
Neither of the two studies included in the Cochrane SRMA that assessed the effect of valves on patients' SF-36 scores found a significant effect. One study found no effect on the physical component score of the SF-36 at six months (n=240, BGMD -0.62, 95% CI -2.59 to +1.35, p=0.07). The other study (n=73) found no effect on either the mental component or the physical component score at three months (p=0.93 and p=0.73). (van Agteren et al 2017)

Disease severity index – BODE index[8]
Duckbill type valve:
Kemp et al (2017) found a significantly greater improvement in this measure in valve patients compared to controls at six months (BGMD -1.8, 95% CI -2.6 to -0.9, p<0.001).

Duration of hospital treatment
Duckbill type valve:
The Cochrane SRMA reported median post treatment hospital stay as 1 day (range 1-13 days) from one study (n=68), and mean or median procedure times reported in three studies were 18, 27 and 33.8 minutes (van Agteren et al 2017).

Umbrella type valve:
In one study (n=277) the median hospital stay was 1 day with no difference between valve and control groups, but the mean hospital stay was 2.2 days (SD 6.6) in the valve group and 1.0 days (SD 0) for controls. The other study (n=73) reported no difference in days hospitalised (1.1 days, SD 0.3, p=0.26). The mean procedure time was reported by one study (n=73) as 62 minutes (SD 17) (van Agteren et al 2017).

Adverse events - mortality
No statistically significant effect was found on mortality (see above).

Adverse events – serious adverse events (SAEs) (as defined by authors or each RCT)
Duckbill type valve:
The Cochrane SRMA found overall that there were significantly more SAEs in valve patients than controls (72 SAEs in 297 valve patients versus 18 in 185 controls, OR 5.85, 95% CI 2.16 to 15.84, p=0.0005). Pneumonia distal to the valve was the most common SAE. Other results reported in the SRMA from individual RCTs include one RCT (n=93) where 44% of the valve group and 12% of controls had SAEs leading to death or hospitalisation. In another RCT (n=68), there were 59 non-serious AEs in the valve group and 35 in controls, p<0.001. (van Agteren et al 2017).

The RCT by Kemp et al (2017) reported significantly more respiratory related SAEs in six months in patients treated with valves compared to controls (44 events in 31 of 65 valve patients (47.7%) vs four events in three of 32 control patients (9.4%), p<0.001).

Umbrella type valve:
The Cochrane SRMA reported significantly more AEs in patients treated with valves than controls (n=350, 26 AEs in 179 valve patients (143 per 1000) versus 8 AEs in 171 controls (47 per 1000), OR 3.41, 95% CI 1.48 to 7.84, p=0.004). The most frequent SAEs were COPD exacerbations,

[7] SF-36 is a validated tool used to measure patient reported overall health status with questions in eight areas including physical role functioning and mental health. It is not specific to respiratory diseases.
[8] The BODE index is a multidimensional grading system for predicting the risk of death among COPD patients using body mass index, degree of airflow obstruction, dyspnoea and 6MWD.

respiratory failure, pneumothorax and pneumonia. Procedural AEs were principally bronchospasms and dyspnoea (van Agteren et al 2017).

Adverse events – COPD exacerbations

Duckbill type valves:

The SRMA by Wang et al (2017) reported a significantly higher RR of COPD exacerbation with hospitalisation in patients treated with valves compared to controls (RR 2.01, 95% CI 1.19 to 3.40, p=0.01).

The Cochrane SRMA of the same studies reported details separately for four RCTs. One RCT (n=50) found no difference in COPD exacerbations between groups; a second RCT (n=93) found 76.7% of valve patients and 40% of controls had COPD exacerbations, with no significant difference in exacerbation rates requiring hospitalisation (16.3% vs 12%, p value not given); in a third RCT (n=68) four of 34 valve patients required hospitalisation for COPD exacerbation; a fourth RCT (n=321) found that exacerbations requiring hospitalisation were significantly more common in the valve group at six months but not 12 months (p=0.03 and p=0.84) (van Agteren et al 2017).

In the RCT by Kemp et al (2017) 4.6% of 65 valve patients and no controls had a COPD exacerbation in the first 30 days.

Umbrella type valves:

COPD exacerbations were one of the more common adverse events in valve patients (18 in 179 valve patients, number in controls not stated) (van Agteren et al 2017).

Adverse events – pneumothorax

Duckbill type valve:

The SRMA by Wang et al (2017) reported a significantly higher RR of pneumothorax in patients treated with valves compared to controls (RR 9.65, 95% CI 3.04 to 30.60, p=0.0001).

The Cochrane SRMA of the same studies reported details separately for four RCTs. One RCT (n=50) found no difference in pneumothorax between groups; a second RCT (n=93) found significantly more in the valve group had a pneumothorax (25.6% vs 0%, p<0.001); in a third RCT (n=68) six of 34 valve patients had a pneumothorax; a fourth RCT (n=171) found that patients with pneumothorax lasting over seven days were patients with high lung volume reduction and more positive clinical response (van Agteren et al 2017).

The RCT by Kemp et al (2017) reported significantly more pneumothoraces in six months in patients treated with valves compared to controls (20 pneumothoraces in 19 of 65 valve patients (29.2%) versus four in three of 32 control patients (9.4%), p<0.001). The median time to onset was one day, 14 of 19 patients required an intervention and/or hospitalisation (8 managed by observation only); 11 required chest drain; one operation; one died in hospital of cardiac arrest due to pneumothorax), and there was no difference in any outcome measure at three or six months in the valve group between patients who did and did not experience pneumothorax.

Umbrella type valves:

Pneumothorax was one of the more common adverse events in valve patients (number not provided) (van Agteren et al 2017).

Adverse events – pneumonia

Duckbill type valve:

The SRMA by Wang et al (2017) reported no significant difference in the rate of pneumonia in valve treated patients compared to controls (RR 2.17, 95% CI 0.86 to 5.49, p=0.10).

The Cochrane SRMA of the same studies reported details separately for three RCTs. One RCT (n=50) found no difference in pneumonia between groups; a second RCT (n=93) found no

patients with pneumonia in the valve group; in a third RCT (n=68) two of 34 valve patients had pneumonia; in a fourth RCT (n=321) the most common AE was pneumonia distal to the valve (4.2% at 12 months) (van Agteren et al 2017).
In the RCT by Kemp et al (2017) 4.6% of 65 valve patients and no controls had pneumonia in the first 30 days.

Umbrella type valves:
Pneumonia was one of the more common adverse events in valve patients (number not provided) (van Agteren et al 2017).

Adverse events – valve expectoration, migration and removal/replacement
Duckbill type valve:
The Cochrane SRMA reported this outcome separately for the five RCTs. Of 25 patients, four expectorated their valves (replaced in three) and two needed valves to be removed; of 43 patients, five had valve migration and/or replacement; of 34 patients, seven had unacceptable adverse events causing valves to be removed; of 111 patients, 14 suffered valve expectoration, migration or aspiration; of 220 patients, 31 had valves removed (van Agteren et al 2017).
The RCT by Kemp et al (2017) reported that of 65 patients treated with valves, seven required bronchoscopy for an adverse event: five to remove a valve due to pneumothorax, one to replace a valve after one day due to expectoration and one for loss of effect.

Question 2: Are there any subgroups of patients who are likely to derive greater or worse benefit from the intervention?
All the data relating to subgroups were for the duckbill type valve and were analysed in the two SRMAs.

Heterogeneous versus homogenous emphysema:
Lung function - FEV_1:
The Cochrane SMRA found a significantly larger change in FEV1 from baseline in patients with heterogeneous emphysema than with homogeneous emphysema, p=0.00001 (n=137, BGMD 16.36%, 95% CI 9.02 to 23.70) (van Agteren et al 2017).

Quality of life - SGRQ:
The Cochrane SRMA found one study that analysed this and found a statistically significant difference favouring patients with heterogeneous emphysema over homogenous emphysema (n=68, p=0.005) (heterogeneous emphysema: BGMD -19, 95% CI -31 to -6; homogeneous emphysema: BGMD -12, 95% CI -21 to -4). However, there was a significant improvement in SGRQ in patients with both types of emphysema and another RCT included in this SRMA also found a statistically significant improvement in SGRQ in patients with homogenous emphysema (n=93, BGMD -9.64, 95% CI -14.09 to -5.20, p<0.0001).

Collateral ventilation (CV):
Mortality:
Valve treatment had no statistically significant effect on mortality compared to controls in either patients with intact fissures (an indicator that they do not have CV) (n=211, three RCTs, OR 1.93, 95% CI 0.40 to 9.35) nor in those where CV was not tested (n=492, two RCTs, OR 0.85, 95% CI 0.33 to 2.22) (van Agteren et al 2017).

Lung function - FEV_1:
In three RCTs where patients were only included if they had intact fissures there was a statistically significant improvement in FEV_1 in patients treated with valves compared to controls (n=532, BGMD 18.15%, 95% CI 11.81 to 24.48) whereas for patients with collateral ventilation (n

not provided) the BGMD was not significant at only 2.48% (95% CI -2.63 to 7.59). The difference between the effects of valves on FEV_1 in patients with and without CV was significant (p=0.0002) (van Agteren et al 2017).
The SRMA by Wang et al (2017) of the same studies found a significant BGMD in absolute increase in FEV_1 compared to controls for patients with complete fissures or low CV of 17.50% (95% CI 11.86-23.13), p<0.00001).

Exercise capacity – 6MWD
The Cochrane SRMA found two studies that separated results for patients with and without intact fissures and found no significant difference (n=321 and n=171, p value not stated). When comparing results at trial level however, they found that RCTs that selected patients with intact fissures (three RCTs, n=208) showed significantly more improvement in 6MWD (BGMD 50.19, 95% CI 24.96 to 75.41) compared to the two trials that did not select patients in this way (n=171, BGMD 5.00, 95% CI -21.00 to 31.00) (p=0.01) (van Agteren et al 2017).
The SRMA by Wang et al (2017) found that patients with complete fissures or low CV had a higher BGMD (BGMD 50.17 metres, 95% CI 25.04 to 75.29, p<0.0001) than was found when all patients' data were analysed together (BGMD 33.86 metres, 95% CI 11.54 to 56.19, p=0.003).

Quality of life - SGRQ:
The Cochrane SRMA found a significant improvement in SGRQ in patients with intact fissures (n=266, BGMD -9.03, 95% CI -5.98 to -12.07), but not in those whose fissures were not intact (n not stated, BGMD 0.00, 95% CI -5.48 to 5.48).
The SRMA by Wang et al (2017) also found a significant improvement in SGRQ when analysing data for patients with complete fissures or low CV of -8.55 points (95% CI -12.83 to -4.26, p<0.0001) (van Agteren et al 2017).

Complete versus partial occlusion of lobe:
Lung function - FEV_1
Two RCTs included in the Cochrane SMRA found a significantly greater increase in FEV_1 at 12 months in patients where the valves resulted in complete lobar occlusion compared to those without complete occlusion (28% and 20.6% with complete occlusion versus 2% and 5.2% in those without complete occlusion, p=0.005 and p=0.006 for the two studies respectively, n not stated) (van Agteren et al 2017).

Quality of life - SGRQ:
The two RCTs included in the Cochrane SRMA that analysed data by lobar occlusion status did not find a significant difference in change in SGRQ between groups with and without lobar occlusion (4 point improvement versus 2 point worsening, p=0.4 in one study and 5.4 versus 0.3 point improvement, p=0.12 in the other study) (n not stated) (van Agteren et al 2017).

Question 3: The degree to which the benefits reach clinically meaningful differences
In general the positive results for duckbill type valves reached clinically meaningful levels, as assessed by both SRMAs and by Kemp et al 2017. All of the results for this question were for duckbill type valves.

Lung function - FEV_1
Wang et al's 2017 SRMA of RCTs for duckbill type valves considered the minimal difference that is clinically important (MCID) for FEV_1 as a change of at least ten percent. This was achieved significantly more frequently in treated patients than in controls by end of follow-up: in 122 of 433 valve patients and 33 of 270 controls (risk ratio (RR) 2.96, 95% CI 1.49 to 5.87, p=0.002).
The Cochrane SRMA presented the results for the same RCTs separately for each RCT using a

MCID of 15% for three studies and 10% for the fourth study. All showed a significant benefit from valves (van Agteren et al 2017). Kemp et al (2017) defined the MCID as an increase of 12% and likewise found a statistically significant benefit from valves at three and six months (n=97, 55.4% and 56.3% of valve patients achieved an increase in FEV_1 of ≥12% versus 6.5% and 3.2% of controls, p<0.001).

Lung function - RV

For duckbill valves, two of the three studies included in the Cochrane SRMA that measured this found significantly more clinically important reduction in RV (defined as 430 mls or more reduction) in valve treated patients compared to controls (n=93, 44.2% of valve patients versus 18% of controls, p=0.006; and n=68, 71% of valve patients versus 3% of controls, p<0.001), whereas a third study found no significant effect (n=50, MCID 350 mls, p=0.24) (van Agteren et al, 2017).

Kemp et al (2017) defined the minimal reduction in RV that is clinically important as 430 mls and found a significant difference in the proportion that achieved this (37 of 64 (57.8%) valve patients; 8 of 31 (25.8%) controls, p=0.003).

Lung function – RV/TLC

The Cochrane SRMA found one study that defined the MCID in RV/TLC as a 4% reduction and found that this was achieved in 63% of valve patients and 9% of controls (n=68, p<0.001) (van Agteren et al 2017).

Exercise capacity – 6MWD

The SRMA by Wang et al (2017) defined the MCID as a 26 metre improvement in 6MWD and found that this was achieved in a significantly higher proportion of duckbill valve treated patients compared to controls (n=703, 175 of 433 valve patients versus 60 of 270 controls, RR 2.90, 95% CI 1.24 to 6.79, p=0.01).

The Cochrane SRMA reviewed the same five studies as Wang et al, but reported on the studies' results individually. They found three studies which also defined the minimal improvement in 6MWD as 26 or more metres. All found a significantly greater proportion of valve treated patients achieving this level of improvement compared to controls (n=50, 12 valve patients versus 4 controls achieved MCID, p=0.01; n=93, 50% of valve patients versus 14% of controls achieved MCID, p=0.0002; n=68, 88% of valve patients vs 6% of controls, p<0.001). A fourth study defined the MCID as a 15% improvement and found no significant effect of valve treatment (n=321, p=0.28) (van Agteren et al 2017).

Kemp et al (2017) also found a significantly higher proportion of the valve treated group increasing their 6MWD by 26 metres or more (33 of 63 (52.4%) valve patients; 4 of 31 (12.9%) controls, p<0.001).

Quality of life - SGRQ

Wang et al's 2017 SRMA of RCTs for duckbill type valves defined the MCID for SGRQ as a decrease of four or more points. This was achieved significantly more frequently in treated patients than controls by end of follow-up: in 174 of 433 valve patients versus 74 of 270 controls (RR 1.53, 95% CI 1.22 to 1.92, p=0.0002).

The Cochrane SRMA presented these results separately for each study using a MCID of four points for three studies and eight points for one study. One study (n=50) found no benefit of valves on this measure (p=1.0) whereas the other two studies found a significant benefit from valves for a MCID of four points (p=0.001 and p=0.003 respectively, n=68 and n=93); and in one study for a MCID of eight points (p<0.0001, n=93) (van Agteren et al 2017).

Kemp et al (2017) defined the MCID for SGRQ as a four point reduction and likewise found a statistically significant benefit from valves (35 of 62 (61.7%) valve patients; 11 of 32 (34.4%) controls, p=0.042).

Quality of life - mMRC
Taking the MCID for mMRC as one or more points, Wang et al (2017) found a significant clinically important benefit of duckbill type valves (n=585, 113 of 374 valve patients and 26 of 211 controls reached MCID, RR 2.53, 95% CI 1.71 to 3.76, p<0.00001).
Kemp et al (2017) also found a significant clinically important benefit relating to this measure of QoL (29 of 64 (43.8%) valve patients; 7 of 31 (22.6%) controls, p=0.032).

Question 4: Evidence of cost effectiveness of these procedures compared to maximal medical support?

Only one study of cost-effectiveness was found (Pietzch et al 2014). It relates to duckbill type valves. No cost-effectiveness studies relating to umbrella type valves were found.

The study used data from two related RCTs (the "VENT" trials) that were included in the Cochrane SRMA, one from the European Union and one from the US (n=171 and n=321 respectively). The cost-effectiveness analysis was carried out retrospectively in relation to a subgroup of patients for whom complete lobar occlusion was achieved (n=37) amongst those with high heterogeneity of emphysema and intact fissures (n=76). It assumed an average use of 3.08 valves per participant and initial cost of valve placement of EUR 9,581 (£8,527[9]). Discounted costs were estimated to be EUR 20,734 (£18,453) for valve patients and EUR 10,435 (£9,287) for controls at five years; and EUR 25,857 (£23,013) for valve patients and EUR 15,432 (£13,734) for controls at ten years (discounted at 3% per year).

Considering total incremental quality adjusted life years (QALYs) gained by treatment of 0.22 at five years and 0.41 at ten years (discounted at 3% per year), the incremental cost-effectiveness ratio (ICER) was EUR 46,322 (£41,227) per QALY gained at five years and EUR 25,142 (£22,376) per QALY gained at ten years.

5. Discussion

The six studies found in this RER include two SRMAs of the same seven RCTs, one further RCT, two analyses of data from RCTs included in the SRMAs for different outcome measures and one cost-effectiveness study. Almost all the research included pertains to the duckbill type of valve, with only two of the RCTs included in the SRMAs being for the umbrella type valve.

The PICO for this RER stated that the patient population of interest is people with "symptomatic pulmonary emphysema with demonstrable hyperinflation, persisting after pulmonary rehabilitation". It was not clear in any of the papers reviewed what proportion of patients had undergone pulmonary rehabilitation prior to enrolment in the trials. Hence it is difficult to be sure whether the results would have differed for the particular population of interest (those who had undergone pulmonary rehabilitation).

Umbrella type valve:
The SRMA by van Agteren et al (2017) graded much of the evidence relating to the umbrella type valve as high quality (for example for change in SGRQ, RV and adverse events) or moderate quality (for example for changes in mortality, FEV_1, TLC and 6MWD). Both of the trials included a sham procedure for controls and were therefore less susceptible to bias in the assessment of outcomes than some of the trials of the duckbill type valve.

[9] Based on currency conversion rate of EUR 1 = £0.89 as current on 12th Jan 2018.

Although there were seven deaths among treated patients and only one in controls, the difference was not statistically significant. Other outcome measures tended to show no benefit from the valves (for example for quality of life as measured by the SGRQ and mMRC scores, and change in TLC) or, for some measures, better outcomes among control patients than valve patients (for example for the change in FEV_1 at six months in one study, change in RV, change in RV/TLC in one study, and change in 6MWD). There were also significantly more adverse events among treated patients.

Thus evidence to date does not support the use of umbrella type endobronchial valves for severe emphysema. However, the two trials of this type of valve both had a different treatment strategy from the trials of the duckbill type of valve. They used the valves to only partially occlude the lung lobes bilaterally, in order to avoid or reduce resulting atelectasis and its complications, whereas trials of the duckbill type valve all aimed for complete occlusion and atelectasis of the most diseased lobe(s) of the lung. The lack of benefit seen in these two studies may therefore relate to the treatment strategy rather than to the type of valve used. This is also suggested by a third study of umbrella type valves (Eberhardt et al 2012) that was found but was not included in this RER because the comparator was out of scope. Eberhardt et al compared 11 patients treated with unilateral umbrella type valves with the aim of total occlusion of one lobe with another group of 11 patients where the strategy was incomplete occlusion of two contralateral lobes. At 30 and 90 days, significant differences were reported for FEV_1, 6MWD, mMRC and SGRQ, in favour of unilateral treatment.

Duckbill type valve:
Overall, trials of the duckbill type of valve provided more positive results. However, a number of factors mean that they should be treated with some caution.

Firstly, there was little long term data, with most studies limited to 12 months or less. Thus longer term outcomes are not known.

Secondly, for some outcome measures (FEV_1, SGRQ, RV/TLC and 6MWD) the SRMAs found significant heterogeneity in the results which reduces the quality of the evidence, although a random effects statistical model was used in the analyses for these measures to take account of this. One trial found significantly more positive results than the others for change in SGRQ; however, when the data were reanalysed omitting the data from this trial the benefits were still found to be significant (van Agteren et al 2017). The significant improvement in FEV_1 in treated patients was described as low quality evidence (van Agteren et al 2017). This was because results were combined from trials that did and did not attempt to exclude patients with CV and there was a wide range in the mean improvement, with considerably better results in one of the studies; this may have been due to more vigorous monitoring and replacing of valves to improve fit in this study.

The BGMD in FEV_1 improvement was quoted as 0.48% in the SRMA by van Agteren et al (2017). It is difficult to reconcile this figure with that of 11.44% quoted by Wang et al (2017), especially as these studies quote the MCID for FEV_1 as an increase of at least 10% (15% for some studies) and all studies found a statistically significant BGMD in the proportion of patients who achieved this MCID in FEV_1.

For other outcome measures, the SRMA (van Agteren et al 2017) graded the quality of evidence as low quality (for change in RV/TLC, SGRQ and 6MWD) or moderate quality (change in RV and in TLC), with only evidence pertaining to adverse events being graded as high quality.

The study by Hartman et al (2016), which analysed data from previous RCTs for additional

outcome measures related to exercise capacity (additional to 6MWD), lost many patients to follow-up who did not use the accelerometer, reducing the quality of this study. Also it is not clear what patients were told about exercise in this study nor whether they had undergone pulmonary rehabilitation. The authors state, however, that the improvement was seen "without any specific encouragement on physical activity."

The study by Brown et al (2012) evaluated patients included in previous RCTs that are included in the SRMAs for changes in lung volumes seen on CT scan. They sought to evaluate whether there was an expansion in volume of other more healthy areas of lung when valves reduced the volume of the treated lobes. Although the results suggest that when the most damaged lobes are treated with valves and reduce in volume the other lobes expand, this study does not provide evidence that lung function improves as a result of this. It did not provide baseline data, such as age, to allow assessment of the generalisability of the results and there was no indication that assessors were blinded to the treatment group of the patient, which could have resulted in bias (assessment of lung volumes was semi-automated but included some manual editing).

Apart from one of the five RCTs included in the SRMAs by Agteren et al (2017) and Wang et al (2017), there was no sham procedure for control patients in the other RCTs and in one RCT the outcome assessments were also not blinded. This lack of blinding could lead to bias and a placebo effect with more favourable assessments of outcomes in the valve treated group, thus exaggerating the apparent effectiveness of the intervention.

Despite this, the relatively large number of positive results for a wide range of outcome measures, from a relatively large number of independent RCTs suggests a true benefit of treatment with the duckbill type of valve in patients with severe emphysema when the strategy is to occlude the bronchus and thus exclude the most affected lobe(s) of the lung. This was particularly seen for patients without CV, for those with heterogeneous emphysema (although benefit was also seen in homogenous emphysema), and where complete lobar exclusion was achieved. However, the significantly higher number of adverse events in the treated group compared to controls needs to be considered when making decisions with patients.

Cost effectiveness:
The cost-effectiveness study suggests that use of the duckbill type valve to occlude bronchi in order to exclude more severely damaged lobes of lung in severe emphysema is close to the NICE threshold for cost-effectiveness at ten years at £22,376 per QALY gained. However, there is a major potential flaw with this analysis as it only included the subgroup of patients for whom the valves had been effective in occluding air flow to the target lobe (37 of 76 patients with complete fissures and high heterogeneity of emphysema). The objective of the RCTs from which the patients were drawn had been to occlude the most severely affected portions of lung, but this was not successful in many patients (Brown et al 2012). While fissure completeness and heterogeneity of emphysema can be assessed pre-operatively, "successful lobar exclusion" cannot, and hence the true cost of valve treatment should be based on all patients who had valve treatment that was aimed at excluding the target lobe, including those where it failed to completely occlude air flow to the target lobe. As the latter patients are likely to have had poorer outcomes while still incurring the costs of treatment and its complications, the true cost effectiveness of valve treatment is likely to be lower than that calculated by this study (and true ICERs higher).
NB: It is not clear from the report how patients were selected for inclusion, in particular how occlusion status was known, though use of the word "successful" implies that it was post valve insertion.

Furthermore, the lack of blinding in the RCTs that this study is based on means that a placebo effect associated with valve implantation may have biased the outcomes, making the intervention

appear more effective than it is. Also, extrapolation to five and ten years was based on observations in the 12 months post treatment. Although this took account of different stages of disease in different patients at the time of treatment and the disease progression rates seen, it is possible that the longer term effects of valves are different. Late pneumothorax, infection requiring valve removal and loss of atelectasis were not considered because of the paucity of evidence available regarding these possible later complications.

Thus, although only direct medical costs were included in the analysis, and not effects on indirect costs such as wages, travel and caregivers, which if lower in treated patients might increase the apparent cost effectiveness of valve treatment (lower ICER), the cost effectiveness calculations in this study should be treated with extreme caution given the issues described above.

6. Conclusion

Emphysema is a relatively common chronic progressive respiratory disease, usually caused by cigarette smoking. It results in hyperinflated damaged lung with reduced capacity for gas exchange and hence breathlessness and eventually respiratory failure. Patients with severe emphysema respond less well to conventional treatment and medical treatment options are limited. The insertion of endobronchial valves in these patients aims to reduce the volume of the most damaged areas of the lung, thus allowing less affected areas to expand and function more effectively. NICE has recently published guidance supporting their use in patients who have had pulmonary rehabilitation, to occlude volumes of lung where there is no CV (NICE 2017).

This RER similarly finds that there is adequate quantity and quality of evidence regarding the effectiveness of this procedure (in terms of improvements in lung function, exercise capacity and QoL) to support the use of the duckbill type of endobronchial valve for patients with heterogeneous emphysema to occlude more severely affected lobes of lung which have no CV. However, decision makers should bear in mind the incidence of serious adverse events related to the procedure (such as COPD exacerbations and pneumothorax), and the fact that there is not sufficient evidence available to support a conclusion that the procedure is cost effective at the £20,000 per QALY or £30,000 per QALY thresholds used by NICE.

Current evidence does not support the use of umbrella type endobronchial valves, although further RCTs of this type of valve in patients with severe emphysema using a treatment strategy that involves complete occlusion of more severely affected areas of lung which do not have a CV may be beneficial.

7. Evidence Summary Tables

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Systematic reviews with meta-analysis (SRMAs)									
van Agteren et al 2017 (Cochrane)	S1 SRMA (search date 7th Dec 2016) of 14 RCTs, of which 7 were for valves: Valipour et al 2016 (IMPACT) Klooster et al 2015 (STELVIO) Davey et al 2015 (BeLieVeR HIFi) Wood et al 2014	n=1053 (7 RCTs), of which n=703 (range 50 to 321) for duckbill valve (5 RCTs) and n=350 (range 93 to 277) for umbrella valve (2 RCTs) Valipour et al 2016 (IMPACT): valve group n=43, controls n=50; mean age 64 years for valve group and 63 years for controls; 39% male; homogenous emphysema	6 RCTs used the "duckbill" or "endobronchial" valve. 2 RCTs used the "umbrella" or "intrabronchial" valve (Wood et al and Ninane et al). Valipour et al 2016 (IMPACT): duckbill type valves (optimal medical care for controls). Klooster et al 2015 (STELVIO): duckbill type valves (standard medical care in concordance with GOLD guidelines for controls) Davey et al 2015	Primary Clinical effectiveness Mortality	Mortality by end of follow-up	**Duckbill type valve** (5 RCTs): 15 deaths (n=433) in treatment group (35 per 1000), 8 deaths (n=270) in controls (30 per 1000), Odds ratio (OR) 1.07 (95% confidence interval (CI) 0.47-2.43), p=0.86 **Umbrella type valve** (2 RCTs): 7 deaths (n=179) in treatment group (28 per 1000), 1 death (n=171) in controls (6 per 1000), OR 4.95 (95% CI 0.85 to 28.94), p=0.08	9	Direct Patient populations generally match the PICO specification except that it is not clear that patients had received pulmonary rehabilitation and for some studies it is not clear whether collateral ventilation was assessed pre-operatively	A third study of umbrella type valves (Eberhardt et al 2012) was included in the systematic review. However, this study compared unilateral and bilateral valves and is therefore outside the scope of this rapid evidence review (RER). Long term data were scarce with most studies limited to 12 months. Thus longer term outcomes are not known. Fixed effects modelling methods were used, with a sensitivity analysis performed using a random effects model. For most of the analyses the results of the fixed effects modelling are presented, except for SGRQ, RV/TLC and 6MWD, where random effects modelling results were reported due to the heterogeneity in the results, which reduces the quality of the evidence. The meta-analysis did not find a significant effect of valves on mortality rates for either type of valve. This result was graded as moderate quality[10] evidence. Note that of the 7 deaths with umbrella type valves, 6 were in the study by Wood et al (2014). The results for FEV_1 were graded as low quality for the duckbill type valve and moderate quality for the umbrella type valve. The significant improvement in FEV_1 found with the duckbill type valve should be interpreted with caution and was described as low quality evidence because some trials assessed fissure intactness and attempted to excluded
				Secondary Clinical effectiveness Mortality	Mortality stratified by follow-up (duckbill type valve)	**Duckbill type valve** Postoperative: n=118 (2 RCTs), OR 3.12 (95% CI 0.12 to 80.39) 90-day: n=703 (5 RCTs), OR 2.17 (95% CI 0.67 to 7.02) 6 months: n=239 (2 RCTs), OR 2.04 (95% CI 0.32 to 13.16) 12 months: n=492 (2			

[10] Cochrane SRMAs use a GRADE system to assess the quality of evidence taking account of risk of bias due to limitations in the design and execution of studies, imprecision, indirectness, inconsistency and publication bias. The different levels of quality are described as follows: High quality - very confident that the true effect lies close to that of the estimate of the effect; Moderate quality - moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low quality - confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect; Very low quality - very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect (van Agteren et al 2017).

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	(IBV) Herth et al 2012 (VENT EU) Ninane et al 2012 Sciurba et al 2012 (VENT US)	; mean FEV_1 28.4% of predicted in valve group, 29.9% for controls. 3 months follow-up to date. Klooster et al 2015 (STELVIO): n=34 for both groups; mean age 58 years for valve group, 59 years for controls; 32% male; homogenous and heterogeneous emphysema ; mean FEV_1 29% of predicted in both groups. 6 months follow-up. Davey et al 2015 (BeLieVeR HIFi): n=25 in each group; mean age 62 years in treatment	(BeLieVeR HIFi): unilateral valve placement (duckbill type valve) (sham valve placement for controls) Wood et al 2014 (IBV): partial bilateral placement of umbrella type valve (sham procedure for controls) Herth et al 2012 (VENT EU): unilateral duckbill type valve placement (controls on standard medical care). Optimal care for all as per GOLD guidelines. Ninane et al 2012: partial bilateral placement of umbrella type valves (sham procedure for controls) Sciurba et al 2010 (VENT US): unilateral duckbill type			RCTs), OR 0.85 (95% CI 0.33 to 2.22).			patients with collateral ventilation whereas others did not, there was a wide range in mean change in FEV_1 in all studies, and one of the studies (Klooster et al 2015) had considerably better results than the other studies, resulting in heterogeneity. This may have been due to more vigorous monitoring and replacing of valves to improve fit in this study. Evidence relating to change in SGRQ from baseline was graded as low quality for the duckbill type valve and high quality for the umbrella type valve. Evidence relating to changes in RV was graded as moderate quality for the duckbill type valve and high quality for the umbrella type valve. Evidence relating to changes in TLC was graded as moderate quality for both types of valve. Evidence relating to changes in 6MWD was graded as low quality for the duckbill type valve and moderate quality for the umbrella type valve. Evidence relating to adverse events by end of follow-up was graded as high quality for both types of valve. Both umbrella type valve studies (Wood et al 2014 and Ninane et al 2012) aimed to achieve partial lobar occlusion (bilaterally) in order to prevent lobar atelectasis from occurring, rather than total occlusion (and hence atelectasis) which was usually the aim in the duckbill valve studies. Apart from Davey et al 2015, Wood et al 2014 and Ninane et al 2012, which used sham procedures for control patients, the other studies were at high risk of bias from lack of blinding of participants and personnel. The lack of blinding in these studies means that a placebo effect associated with valve implantation may have biased the outcomes, making the intervention appear more effective than it is.
				Secondary Clinical effectiveness Mortality	Mortality stratified by collateral ventilation (duckbill type valve)	**Duckbill type valve** Participants selected for intact fissures: n=211 (3 RCTs), OR 1.93 (95% CI 0.40 to 9.35) Participants not tested for fissure status: n=492 (2 RCTs), OR 0.85 (95% CI 0.33 to 2.22)			
				Primary Clinical effectiveness Change in forced expiratory volume in 1 second (FEV1)	% change in FEV_1 from baseline at end of follow-up	**Duckbill type valve** n=703 (5 RCTs), between group standardised mean difference (BGMD) 0.48 (95% CI 0.32 to 0.64) **Umbrella type valve** Wood et al 2014 (n=277): -2.11% for valves vs 0.04% for controls at 6 months, p=0.001, favouring controls. Ninane et al 2012 (n=73): 0.90 litres (SD 0.34) for valves and 0.87 l (SD 0.34) for controls at 3 months, p=0.065.			
				Secondary Clinical effectiveness Change in FEV_1 (MCID)	Proportion achieving minimal clinically important difference (MCID) in FEV_1 by end of follow up (definition	**Duckbill type valve** Davey et al 2015: 9 valve patients and 1 control reached MCID of ≥15%, p=0.0022 Valipour et al 2016: 34.9% of valve patients and 4% of controls			

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		group and 63 years for controls; 62% male; heterogeneous emphysema; mean FEV_1 31.6% predicted for treatment group and 31.8% for controls. 3 months follow-up. Wood et al 2014 (IBV): treatment n=142, control n=135; mean age 65 years in both groups; 57% male; heterogeneous emphysema; mean FEV_1 29.8% predicted in treatment group, 29.7% for controls. 6 months follow-up. Herth et al 2012 (VENT	valve placement (controls on standard medical care). Optimal care for all as per GOLD guidelines.		varied between studies)	reached MCID of ≥15%, p=0.0001 Klooster et al 2015: 72% of valve patients and 24% of controls reached MCID of ≥10%, p<0.001 Sciurba et al 2010: 28.6% of valve patients and 5.4% of controls reached MCID of ≥15%, p<0.001			Klooster et al 2015 was also at risk of bias due to outcome assessments not being blinded. These could lead to more favourable assessments of outcomes in the intervention groups.
				Secondary Clinical effectiveness Change in FEV_1	% change in FEV_1 stratified by follow-up (duckbill type valve)	**Duckbill type valve** 90 day: n=143 (2 RCTs), BGMD 0.77 (95% CI 0.43 to 1.11) 6 months: n=560 (3 RCTs), BGMD 0.40 (95% CI 0.22 to 0.58) 12 months: n=171 (1 RCT BGMD 0.33 (95% CI 0.01 to 0.65)			
				Secondary Clinical effectiveness Change in FEV_1	% change in FEV_1 stratified by emphysema distribution (duckbill type valve)	**Duckbill type valve** n=137 (2 RCTs), BGMD 16.36% (95% CI 9.02 to 23.70): a statistically significantly larger change in FEV_1 from baseline in patients with heterogeneous emphysema than with homogeneous emphysema, p=0.00001 (wording from NICE 2017 as not explained so clearly in Cochrane report).			

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		EU): treatment n=111, control n=60; mean age 60 years for both groups; 75% male; homogenous and heterogeneous emphysema; mean FEV_1 29% of predicted in treatment group, 30% for controls. 12 months follow-up. Ninane et al 2012: treatment n=37, control n=36; mean age 61 years for treatment group and 62 years for controls; 59% male; heterogeneous		Secondary Clinical effectiveness Change in FEV_1	% change in FEV_1 stratified by collateral ventilation (duckbill type valve)	**Duckbill type valve** Intact fissures: n=532 (3 RCTs), BGMD 18.15% (95% CI 11.81 to 24.48) Collateral ventilation present: n not given, (2 RCTs), BGMD 2.48% (95% CI -2.63 to 7.59) p=0.0002 for difference between change in FEV_1 for intact fissures vs collateral ventilation (data above)			
				Secondary Clinical effectiveness Change in FEV_1	% change in FEV_1 at 12 months follow-up stratified by lobar occlusion status (duckbill type valve)	**Duckbill type valve** Herth et al 2012 (n=171): 28% for those with complete lobar occlusion and 2% for those without, p=0.005 Sciurba et al 2010 (n=321): 20.6% for those with complete lobar occlusion and 5.2% for those without, p=0.006			
				Primary Clinical effectiveness Change in quality of life (QoL)	St Georges Respiratory Questionnaire (SGRQ)[11] change from baseline at end of follow-up	**Duckbill type valve** n=695 (5 RCTs), BGMD -7.29 (95% CI -11.12 to -3.45) Excluding the study with the best results (Klooster et al 2015), n=627, BGMD -5.34 (95% CI -7.43 to			

[11] The SGRQ is a 50-item validated patient questionnaire designed to measure health-related quality of life specifically in respiratory patients.

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		emphysema ; mean FEV_1 35% of predicted in treatment group, 32% for controls. 6 months follow-up. Sciurba et al 2010 (VENT US): treatment n=220, control n=101; mean age 65 years in both groups; 43% male; homogenous and heterogeneous emphysema ; mean FEV_1 30% of predicted in both groups. 12 months follow-up.				-3.24) **Umbrella type valve** n=350 (2 RCTs) BGMD 2.64 units (95% CI -0.28 to 5.56).			
				Secondary Clinical effectiveness Change in QoL	Proportion achieving MCID in SGRQ by end of follow up (definition varied between studies)	**Duckbill type valve** Davey et al 2015 (n=50): No difference between groups in proportion who reached MCID of -4 points, p=1.0 Valipour et al 2016 (n=93): 56.8% of valve patients and 25% of controls reached MCID of -4 points, p=0.003 And 45.9% of valve patients and 8.3% of controls reached the more stringent MCID of -8 points, p<0.0001 Klooster et al 2015 (n=68): 79% of valve patients and 33% of controls reached MCID of -4 points, p=0.001.			
				Secondary Clinical effectiveness Change in QoL	SGRQ change from baseline by follow-up time (duckbill type valve)	**Duckbill type valve** 90 days: n=135 (2 RCTs), BGMD -8,75 (95% CI -12.76 to -4.74) 6 months: n=560 (3 RCTs), BGMD -7.09 (95% CI -12.59 to -1.60)			

Endobronchial valves (“valves”) for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						12 months: n=492 (2 RCTs), BGMD -4.05 (95% CI -6.51 to -1.59)			
				Secondary Clinical effectiveness Change in QoL	SGRQ change from baseline by emphysema distribution (duckbill type valve)	**Duckbill type valve** Klooster et al 2015: (n=68) Heterogeneous emphysema: BGMD -19 (95% CI -31 to -6) Homogeneous emphysema: BGMD -12 (95% CI -21 to -4) p=0.005 for difference between homogenous and heterogeneous disease Valipour et at 2016: (n=93) for homogenous emphysema: BGMD -9.64 (95% CI -14.09 to -5.20), p<0.0001			
				Secondary Clinical effectiveness Change in QoL	SGRQ change from baseline by collateral ventilation (duckbill type valve)	**Duckbill type valve** Intact fissures: n=266 (4 RCTs), BGMD -9.03 (95% CI -5.98 to -12.07) Fissures not intact: n not stated, BGMD 0.00 (95% CI -5.48 to +5.48)			
				Secondary Clinical effectiveness Change in QoL	SGRQ change at 12 months follow-up stratified by lobar occlusion status (duckbill type valve)	**Duckbill type valve** Herth et al 2012 (n=171): mean improvement -4 units for those with complete lobar occlusion and +2 units (worsening QoL) for those without lobar occlusion, p=0.4			

Endobronchial valves (“valves”) for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Sciurba et al 2010 (n=321): -5.4 units for those with complete lobar occlusion and -0.3 units for those without complete lobar occlusion, p=0.12			
				Secondary Clinical effectiveness Change in QoL	COPD assessment test (CAT)[12] QoL score (duckbill type valve)	**Duckbill type valve** Davey et al 2015 (n=50) found no significant difference between groups in change from baseline, p=0.23 Valipour et al 2016 (n=93): BGMD -0.9 (95% CI -2.9 to 1.1)			
				Secondary Clinical effectiveness Change in QoL	mMRC[13] QoL score	**Duckbill type valve** Valipour et al 2016 (n=93): BGMD -0.57 (95% CI -0.98 to -0.16) Davey et al 2015 (n=50) found no significant difference in change from baseline between groups, p=0.40 Sciurba et al 2010 (n=321): BGMD -0.3 units			

[12] The COPD Assessment Test (CAT) is a validated questionnaire for people with COPD designed to measure the impact of COPD on a person's life, and how this changes over time.

[13] The mMRC scale ranges from 0-4 and is a validated tool used to establish levels of functional impairment or perceived impairment due to dyspnoea attributable to respiratory disease.

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						(95% CI -0.50 to -0.01) (favouring valves) **Umbrella type valve** Wood et al 2014 (n=240): BGMD at 6 months -0.10 (95% CI -0.34 to 0.14), p=0.43 Ninane et al 2012 (n=73): BGMD at 3 months -0.20 (95% CI -0.76 to 0.36), p=0.64			
				Secondary Clinical effectiveness Change in QoL	CCQ[14] QoL score (duckbill type valve)	**Duckbill type valve** Klooster et al 2015 (n=68): BGMD -0.74, p=0.002 (favouring valves)			
				Secondary Clinical effectiveness Change in QoL	SF-36[15] QoL score (umbrella type valve)	**Umbrella type valve** Wood et al 2014 (n=240): BGMD in physical component score 6 months -0.62 (95% CI -2.59 to 1.35), p=0.07 Ninane et al 2012 (n=73): BGMD not significant at 3 months for SF-36 mental component, p=0.83 and for SF-36 physical component, p=0.73.			

[14] The CCQ is an easy to complete QoL questionnaire which has been well-validated in COPD. It consists of 10 items (each scored between 0 and 6), divided into three domains (symptoms, functional, mental).

[15] SF-36 is a validated tool used to measure patient reported overall health status with questions in eight areas including physical role functioning and mental health. It is not specific to respiratory diseases.

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Primary Clinical effectiveness Change in lung function other than FEV_1	Mean change in residual volume (RV) from baseline	**Duckbill type valve** n=200 (3 RCTs) Valve group: -0.58 litres (95% CI -0.77 to -0.39) Control group: range -0.13 to +0.05 **Umbrella type valve** n=322 (2 RCTs) BGMD 0.38 litres (95% CI 0.12 to 0.65) favouring controls			
				Secondary Clinical effectiveness Change in lung function other than FEV_1	Proportion achieving MCID in RV reduction by end of follow up (definition varied between studies)	**Duckbill type valve** Davey et al 2015 (n=50): No difference between groups in % who reached MCID of 0.35 litre reduction in RV, p=0.24 Valipour et al 2016 (n=93): 44.2% of valve patients and 18% of controls reached MCID of -430 mls, p=0.006 Klooster et al 2015 (n=68): 71% of valve patients and 3% of controls reached MCID of -430 mls, p<0.001.			
				Primary Clinical effectiveness Change in lung function other than FEV_1	Mean change in total lung capacity (TLC) from baseline	**Duckbill type valve** n=107 (2 RCTs) Intervention group: -0.34 litres (95% CI -0.46 to -0.23) Control group: range -0.12 to +0.002 **Umbrella type valve**			

Endobronchial valves (“valves”) for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						n=322 (2 RCTs) BGMD 0.14 (95% CI -0.12 to 0.39)			
				Primary Clinical effectiveness Change in lung function other than FEV_1	Mean change in RV/TLC from baseline	**Duckbill type valve** n=118 (2 RCTs) Intervention group: -5.76 (95% CI -1.06 to -10.45) Control group: range -0.4 to -0.64 **Umbrella type valve** Ninane et al 2012 (n=73), significant BGMD favouring controls, p=0.01			
				Secondary Clinical effectiveness Change in lung function other than FEV_1	Proportion achieving MCID in RV/TLC by end of follow up	**Duckbill type valve** Klooster et al 2015 (n=68): 63% of valve patients and 9% of controls reached MCID of 4% reduction in RV/TLC, p<0.001.			
				Secondary Clinical effectiveness Change in lung function other than FEV_1	Mean change in forced vital capacity (FVC) from baseline (duckbill type valve)	**Duckbill type valve** Klooster et al 2015, n=68: BGMD 14.4% (standard deviation (SD) 27.8), favouring valves			
				Secondary Clinical effectiveness	Mean change in diffusion capacity of the lung for carbon monoxide	**Duckbill type valve** Davey et al 2015, n=50: Median improvement 0.30 mmol/min/kPa in treatment group vs 0 in			

Endobronchial valves (“valves”) for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Change in lung function other than FEV_1	(DLCO) from baseline (duckbill type valve)	control group, p=0.003			
				Primary Clinical effectiveness Change in exercise capacity	Mean change in 6 minute walk distance (6MWD) from baseline by end of follow-up	**Duckbill type valve** n=379 (4 RCTs) BGMD 38.12 metres (95% CI 8.68 to 67.56) **Umbrella type valve** n=316 (2 RCTs) BGMD -19.54 metres (95% CI -37.11 to -1.98), favouring controls			
				Secondary Clinical effectiveness Change in exercise capacity	Proportion achieving MCID in 6MWD by end of follow up (definition varied between studies)	**Duckbill type valve** Davey et al 2015 (n=50): 12 valve patients and 4 controls reached MCID of being able to walk ≥26 metres further, p=0.01 Valipour et al 2016 (n=93): 50% of valve patients and 14% of controls reached MCID of being able to walk ≥26 metres further, p=0.0002 Klooster et al 2015 (n=68): 88% of valve patients and 6% of controls reached MCID of being able to walk ≥26 metres further, p<0.001 Sciurba et al 2010 (n=321) found no difference between groups in reaching the MCID of 15%			

Endobronchial valves (“valves”) for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						improvement in 6MWD, p=0.28			
				Secondary Clinical effectiveness Change in exercise capacity	Mean change in 6 minute walk distance (6MWD) from baseline stratified for collateral ventilation status (duckbill type valve)	**Duckbill type valve** Herth 2012 and Sciurba 2010 separated results for patients with and without intact fissures and found no significant difference. Trials that selected patients with intact fissures (n=208, 3 RCTs) showed significantly higher BGMD 50.19 (95% CI 24.96 to 75.41) compared to the trial that did not (n=171, 1 RCT), BGMD 5.00 (95% CI -21.00 to 31.00) p=0.01			
				Primary Safety	**Adverse events (AEs)** Serious adverse events (SAEs) (as defined by the authors) by end of follow-up	**Duckbill type valve** (3 RCTs): 72 SAEs (n=297) in treatment group, 18 SAEs (n=185) in controls, OR 5.85 (95% CI 2.16 to 15.84, p=0.0005 Pneumonia distal to the valve was the most common SAE. Davey 2015 (n=50): no difference in COPD exacerbations, pneumonia or pneumothorax. 4 patients expectorated their valves (replaced in 3) and 2 needed valves removed.			

Endobronchial valves (“valves”) for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Valipour 2016 (n=93): 76.7% in valve group, and 40% of controls had COPD exacerbations, but no significant difference in exacerbation rates requiring hospitalisation (16.3% vs 12%, p value not given). 44% of valve group and 12% of controls had serious AEs leading to death or hospitalisation, and significantly more in the valve group had a pneumothorax (25.6% vs 0%, p<0.001). No pneumonia in the valve group. 5 patients had valve migration and/or replacement. Klooster 2015 (n=68): 23 serious AEs in treatment group vs 5 in controls, p<0.001. of 34 valve patients, pneumothorax in 6, pneumonia in 2, hospitalisation for COPD exacerbation in 4, and 7 had unacceptable AEs causing valves to be removed. 59 non-serious AEs in treatment group, 35 in controls, p<0.001. Herth 2012 (n=171): No overall significant			

Endobronchial valves (“valves”) for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						difference in serious complication rates. Those with pneumothorax lasting >7 days were patients with high lung volume reduction and more positive clinical response. 14 suffered valve expectoration, migration or aspiration. Sciurba 2010 (n=321): No significant difference in composite AEs at 6 and 12 months (p=0.08 and p=0.17) but difference approached significance at 90 days (4.2% in valve group, 0% in controls). Most common AE was pneumonia distal to the valve (4.2% at 12 months). Exacerbations requiring hospitalisation were significantly more common in valve group at 6 months but not 12 months (p=0.03 and p=0.84). Valves removed in 31 of 220 patients (14%). **Umbrella type valve** n=350 (2 RCTs): 26 AEs (n=179) in treatment group (143 per 1000), 8 AEs (n=171) in controls (47 per 1000), OR 3.41 (95% CI 1.48 to 7.84), p=0.004			

Endobronchial valves (“valves”) for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Most AEs were COPD exacerbations (18 in 179 valve patients), respiratory failure, pneumothorax and pneumonia. Procedural AEs were principally bronchospasms and dyspnoea.			
				Secondary Resource utilisation	**Hospital utilisation**	**Duckbill type valve** Klooster et al 2015 (n=68) reported median post-treatment hospital stay was 1 day (range 1-13) Procedure times were reported as 18 minutes (median, range 6-51), 33.8 minutes (mean) and 27 minutes (mean) in 3 different studies **Umbrella type valve** Wood et al 2014 (n=277): Median hospital stay: no difference between groups (1 day). Mean hospital stay 2.2 days (SD 6) for valve group and 1.0 day (SD 0) for controls. Ninane et al 2012 (n=73): No difference in days hospitalised: 1.1 days (SD 0.3), p=0.26 Mean procedure time 62 minutes (SD 17), controls 23 mins (SD 14), p<0.0001.			

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Wang et al 2017	S1 SRMA (search date not stated) of 10 RCTs, of which 7 were for valves; plus one combination analysis of two valve RCTs: Valipour et al 2016 (IMPACT) Klooster et al 2015 (STELVIO) Davey et al 2015 (BeLieVeR HIFi) Wood et al 2014 (IBV) Valipour et al	n=1053 (7 RCTs), of which n=703 for duckbill valve (5 RCTs) and n=350 for umbrella valve (2 RCTs) See van Agteren 2017 above for details.	5 RCTs used the "duckbill" or "endobronchial" valve. 2 RCTs used the "umbrella" or "intrabronchial" valve (Wood et al and Ninane et al). See van Agteren 2017 above for details.	Primary Clinical effectiveness in terms of minimal clinically important differences (MCIDs)	Minimal clinically important difference (MCID) in FEV_1 defined as change of ≥10%	**Duckbill type valve** n=703 (5 RCTs) 122 of 433 in treatment group and 33 of 270 controls reached MCID. Risk ratio (RR) 2.96 (95% CI 1.49 to 5.87), p=0.002	9	Direct Patient populations generally match the PICO specification except that it is not clear that patients had received pulmonary rehabilitation and for some studies it is not clear whether collateral ventilation was assessed pre-operatively.	This study combined results from trials with different durations of follow-up, which may affect the results obtained. Long term data were scarce with most studies limited to 12 months. Hence our understanding of longer term outcomes is limited. There was statistically significant heterogeneity between studies for some outcomes for the duckbill type valve, namely for FEV_1 p=0.05), 6MWD (p=0.003 and SGRQ (p=0.03). Although random effects modelling methods were used in the statistical analysis to allow for heterogeneity, the heterogeneity reduces the quality of the evidence. Both umbrella type valve studies (Wood et al 2014 and Ninane et al 2012) aimed to achieve partial lobar occlusion (bilaterally) in order to prevent lobar atelectasis from occurring, rather than total occlusion which was usually the aim in the duckbill valve studies. Apart from Davey et al 2015, Wood et al 2014 and Ninane et al 2012, which used sham procedures for control patients, the other studies were at high risk of bias from lack of blinding of participants and personnel. The lack of blinding in these studies means that a placebo effect associated with valve implantation may have biased the outcomes, making the intervention appear more effective than it is. Klooster et al 2015 was also at risk of bias due to outcome assessments not being blinded. These could lead to more favourable assessments of outcomes in the intervention groups.
				Primary Clinical effectiveness in terms of minimal clinically important differences (MCIDs)	MCID in 6MWD defined as change of ≥26 metres	**Duckbill type valve** n=703 (5 RCTs) 175 of 433 in treatment group and 60 of 270 controls reached MCID. RR 2.90 (95% CI 1.24 to 6.79), p=0.01			
				Primary Clinical effectiveness in terms of minimal clinically important differences (MCIDs)	MCID in SGRQ defined as change of ≥4 units	**Duckbill type valve** n=703 (5 RCTs) 174 of 433 in treatment group and 74 of 270 controls reached MCID. RR 1.53 (95% CI 1.22 to 1.92), p=0.0002			
				Primary Clinical effectiveness	MCID in mMRC defined as change of ≥1 point	**Duckbill type valve** n=585 (3 RCTs) 113 of 374 in treatment group and 26 of 211			

Endobronchial valves (“valves”) for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	2014 (VENT EU plus VENT US) Herth et al 2012 (VENT EU) Ninane et al 2012 Sciurba et al 2012 (VENT US)			in terms of minimal clinically important differences (MCIDs)		controls reached MCID. RR 2.53 (95% CI 1.71 to 3.76), p<0.00001			
				Secondary Clinical effectiveness in terms of absolute differences	FEV_1 absolute change (pooled weighted between group mean difference, %)	**Duckbill type valve** All patients: BGMD 11.44% (95% CI 6.11 to 16.77), p<0.0001 Patients with complete fissure or low collateral ventilation: BGMD 17.50% (95% CI 11.86 to 23.13), p<0.00001			
				Secondary Clinical effectiveness in terms of absolute differences	6MWD absolute change (pooled weighted between group mean difference, metres)	**Duckbill type valve** All patients: BGMD 33.86 (95% CI 11.54 to 56.19), p=0.003 Patients with complete fissure or low collateral ventilation: BGMD 50.17 (95% CI 25.04 to 75.29), p<0.0001 **Umbrella type valve** All patients: BGMD -18.77 metres (95% CI -35.27 to -2.28), p=0.03			

Endobronchial valves (“valves”) for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Secondary Clinical effectiveness in terms of absolute differences	SGRQ absolute change (pooled weighted between group mean difference, points)	**Duckbill type valve** All patients: BGMD -7.06 (95% CI -10.71 to -3.41), p=0.0001 Patients with complete fissure or low collateral ventilation: BGMD -8.55 (95% CI -12.83 to RQ-4.26), p<0.0001 **Umbrella type valve** All patients: BGMD +2.30 (95% CI -1.50 to +6.11), p=0.24			
				Secondary Clinical effectiveness in terms of absolute differences	mMRC absolute change (pooled weighted between group mean difference, points)	**Duckbill type valve** All patients: BGMD -0.35 (95% CI -0.56 to -0.14), p=0.0008 **Umbrella type valve** All patients: BGMD -0.08 (95% CI -0.29 to +0.13), p=0.47			
				Secondary Safety	Death	**Duckbill type valve** RR 1.56 (95% CI 0.47-5.18), p=0.47 **Umbrella type valve** RR 4.78 (95% CI 0.84 to 27.31), p=0.08			

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Secondary Safety	COPD exacerbation with hospitalisation	**Duckbill type valve** RR 2.01 (95% CI 1.19 to 3.40), p=0.01			
				Secondary Safety	Pneumonia	**Duckbill type valve** RR 2.17 (95% CI 0.86 to 5.49), p=0.10			
				Secondary Safety	Pneumothorax	**Duckbill type valve** RR 9.65 (95% CI 3.04 to 30.60), p=0.0001			
Randomised controlled trials (RCTs)									
Kemp et al 2017	P1 RCT, not blinded Multicentre, 17 sites across Europe June 2014 to June 2016	n=97 (65 valves, 32 controls) Eligibility criteria: ≥40 years, ex-smoker, severe emphysema on optimal medical management, post-bronchodilator FEV_1 15% to 45% predicted, TLC>100% predicted, RV≥180% predicted, 6MWD 150-450m, high resolution CT scan showing	Eligible patients underwent assessment during bronchoscopy for collateral ventilation (CV) and CV negative patients were immediately randomised to standard care or immediate placement of valves (same bronchoscopy procedure). Duckbill type valve inserted with intention of complete lobar occlusion. If >1 potential target lobe present, the lobe with highest	Primary Clinical effectiveness (MCID)	Improvement in post-bronchodilator FEV_1 of ≥12% at 3 months	55.4% of the valve group and 6.5% of controls, p<0.001	9	Direct Patients meet most of the PICO requirements except that they did not undergo mandatory pulmonary rehabilitation prior to trial entry.	225 subjects were screened, of which 125 met inclusion criteria for assessment of CV and 97 were assessed as CV negative and were therefore randomised. Valve patients are being followed up for 24 months but only results of 6 months follow-up were published at time of literature search. The relatively short follow-up reported limits our understanding of longer term outcomes. Results reported here are for an intention to treat analysis. Per protocol analysis resulted in very similar primary outcome results at 3 and 6 months. Results for secondary outcome measures are shown graphically for the 3 month follow-up. They appear very similar (with similar p values) to the results at 6 months which are presented here. The lack of blinding in this study means that a placebo effect associated with valve implantation may have biased the outcomes, making the intervention appear more effective. Although there were baseline differences in QoL and absolute (but not percent predicted) FEV_1, with these being worse in the valve group than in the control
				Primary Clinical effectiveness (MCID)	Improvement in post-bronchodilator FEV_1 of ≥12% at 6 months	56.3% of the valve group and 3.2% of controls, p<0.001			
				Secondary Clinical effectiveness	FEV_1, change from baseline at 6 months (mean +/- standard deviation (SD) and BGMD) (litres)	Valve group 0.14 +/-0.24, controls -0.09 +/- 0.14, BGMD 0.2 (95% CI 0.1 to -0.3*), p<0.001			
				Secondary Clinical effectiveness	FEV_1, percent predicted, change from baseline at 6 months (mean +/- SD and BGMD) (%)	Valve group 20.7 +/- 29.6, controls -8.6 +/- 13.0, BGMD 29.3 (95% CI 18.3 to -40.4*), p<0.001			

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		>10% difference in emphysema destruction scores between target and ipsilateral lobes (ie heterogeneous emphysema), absence of collateral ventilation. Baseline characteristics were similar in both groups, although the valve group reported a worse respiratory related QoL (p=0.042) and absolute (but not percent) predicted FEV_1 (p=0.008)	destruction score and lowest perfusion was assessed for CV first. If CV present or not assessable the secondary target lobe was evaluated. Valve patients discharged after 1 day in hospital unless complications. Target lobe volume reduction (TLVR) evaluated at 45 days. If <50% or incomplete lobar occlusion, repeat bronchoscopy and valve revision/replacement performed. Controls discharged post bronchoscopy to standard care.	Secondary outcome Clinical effectiveness	RV change from baseline at 6 months (mean +/- SD and BGMD) (litres)	Valve group -0.66 +/- 1.04, controls 0.01 +/- 0.79, BGMD -0.7 (95% CI -1.1 to -0.3), p=0.002			group, which could have affected outcomes, statistical analysis / modelling that was carried out to take account of these differences resulted in the same p values for all secondary endpoints, indicating that the group differences in outcomes are real and are not due to the groups having different baseline values. It is likely that the "-" sign against the two numbers marked with an * is an error.
				Secondary outcome Clinical effectiveness (MCID)	Proportion with reduction in RV ≥ 430mls	37/64 (57.8%) valve patients; 8/31 (25.8%) controls, p=0.003			
				Secondary outcome Clinical effectiveness	6MWD change from baseline at 6 months (mean +/- SD and BGMD) (metres)	Valve group 36.2 +/- 76.9, controls -42.5 +/- 68.2, BGMD 78.7 (95% CI 46.3 to 111.0), p<0.001			
				Secondary outcome Clinical effectiveness (MCID)	Proportion with increase in 6MWD ≥ 26 metres	33/63 (52.4%) valve patients; 4/31 (12.9%) controls, p<0.001			
				Secondary outcome Clinical effectiveness	SGRQ score change from baseline at 6 months (mean +/- SD and BGMD) (points)	Valve group -7.2 +/-15.1, controls -0.7 +/-10.4, BGMD -6.5 (95% CI -12.4 to -0.6), p=0.031			
				Secondary outcome Clinical	Proportion with reduction in SGRQ score of ≥ 4 points	35/62 (61.7%) valve patients; 11/32 (34.4%) controls, p=0.042			

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				effectiveness (MCID)					
				Secondary outcome Clinical effectiveness	mMRC grade change from baseline at 6 months (mean +/- SD and BGMD) (points)	Valve group -0.56 +/- 1.04, controls 0.00 +/- 0.86, BGMD -0.6 (95% CI -1.0 to -0.1), p=0.010			
				Secondary outcome Clinical effectiveness (MCID)	Proportion with decrease in mMRC of ≥ 1 point	29/64 (43.8%) valve patients; 7/31 (22.6%) controls, p=0.032			
				Secondary outcome Clinical effectiveness	BODE index[16] score change from baseline at 6 months (mean +/- standard deviation (SD) and BGMD) (points)	Valve group -0.97 +/- 2.01, controls 0.79 +/-1.17, BGMD -1.8 (95% CI -2.6 to -0.9), p<0.001			
				Secondary outcome Safety	Deaths	1 death in valve group, 0 in controls in first 6 months. Death was in hospital <30 days postop and related to pneumothorax			
				Secondary outcome Safety	Respiratory related SAEs	44 events in 31/65 valve patients (47.7%) vs 4 events in 3/32 control patients ((9.4%) in 6			

[16] The BODE index is a multidimensional grading system for predicting the risk of death among COPD patients using body mass index, degree of airflow obstruction, dyspnoea and 6MWD.

Endobronchial valves (“valves”) for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						months, p<0.001 Most common SAE in valve group was pneumothorax. Other respiratory related SAEs in first 30 days in valve group: dyspnoea (7.7%), COPD exacerbation (4.6%) and pneumonia (4.6%). Control group: 0% for each of these in first 30 days			
				Secondary outcome Safety	Pneumothorax	20 pneumothoraces in 19/65 valve patients (29.2%) vs 4 events in 3/32 control patients (9.4%) in 6 months, p<0.001 Median time to onset of pneumothorax: 1 day. In 14/19 patients pneumothorax required intervention and/or hospitalisation; 8 managed by observation only; 11 required chest drain; 1 operation; 1 died in hospital of cardiac arrest due to pneumothorax No difference in any outcome measure at 3 or 6 months in the valve group between patients who did and did not experience pneumothorax			

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Secondary outcome Safety	Secondary bronchoscopy for an adverse event	7 patients in valve group: 5 to remove valve due to pneumothorax; 1 to replace after 1 day due to expectoration; 1 for loss of effect			
Hartman et al 2016 Same RCT / patient group as Klooster et al 2015 – See van Agteren et al 2017 above for details	P1 RCT including crossover June 2011 to November 2014 Netherlands	n=43, 19 valve patients, 24 controls Klooster et al 2015 (STELVIO): n=34 for both groups; homogenous and heterogeneous emphysema. However, Hartman included only subgroup who wore the triaxial accelerometer for at least 94% of 4 full days at baseline and at 6 months (19 valve patients and 24 controls): 32% valve group and	Klooster et al 2015 (STELVIO): duckbill type valves (standard medical care in concordance with GOLD guidelines for controls)	Primary outcome Clinical effectiveness	Steps per day, mean increase in 6 months (mean increase in steps +/- SD)	Valve group (n=19) 1252 +/-1468, controls (n=24) -148 +/- 862; BGMD 1340 steps +/-380, p=0.001. % change from baseline 57.1% (SD 73.3) Including crossover: valve group (n=37) 47.5% +/- 56.9% increase in steps, p<0.001	7	Direct Mainly in line with PICO but patients did not necessarily have pulmonary rehabilitation prior to treatment (not mentioned) and no data on whether emphysema was homogenous or heterogeneous	This study uses data from an RCT that is included in the SRMAs by van Agteren et al 2017 and by Wang et al 2017 above (Klooster et al 2015). Respiratory outcomes for this study population are therefore included above and have not been repeated here. Only additional outcome measures not included in the SRMAs are described here. Results following cross over are not included here as they are no longer part of a RCT (randomisation is lost). The relatively small sample size and large number lost to follow-up limits the quality of this study. The authors report that there was no difference in baseline physical activity parameters between patients included and patients lost to follow-up (data not provided), but we do not know why some patients did not use the accelerometer or attend follow-up and there may have been a difference in the exercise capacity in this group. Duration of follow-up was limited to 6 months, so longer term outcomes are not known. Also by measuring physical activity 6 months apart, it was measured in 2 different seasons, which could have affected results. However, measurements for different patients were scattered throughout the year. Only some of the assessments were performed blind. Lack of blinding means that a placebo effect associated with valve implantation may have biased the outcomes, making the intervention appear more effective. Although the authors state that the improvement seen was without any specific encouragement on physical activity, details
				Primary outcome Clinical effectiveness	Locomotion duration, increase in % per day at 6 months (mean increase +/- SD)	Valve group (n=19) 1.15 +/- 1.46, controls (n=24) -0.13 +/- 0.93; BGMD 1.28 +/- 0.37, p=0.001. % change from baseline 36.4% (SD 49.7) Including crossover: valve group (n=37) 34.4% +/- 41.8% increase, p<0.001			
				Primary outcome Clinical effectiveness	Walk intensity, increase in average body acceleration (g) at 6 months (mean increase +/- SD)	Valve group (n=19) 0.0067 +/- 0.0141, controls (n=24) -0.0028 +/- 0.008; BGMD 0.00948 +/- 0.0036, p=0.014. % change from baseline 4.6% (SD 8.4)			

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		17% control group patients male, mean age 59 years in both groups; FEV_1 31.7% predicted in valve group and 29.5% predicted in controls; mean 6MWD 366m for valve patients and 388m for controls. After 6 months control patients (n=18/ 24) were crossed over and offered valve treatment. Baseline data not provided for these.				Including crossover: valve group (n=37) 3.1% +/- 7.6% increase, p=0.040			regarding what the patients were told about physical activity and whether or not they had had pulmonary rehabilitation are not provided. The triaxial accelerometer is a validated instrument for evaluating physical activity in patients with COPD. The authors report that the improvement in steps per day corresponds to the amount of steps that COPD patients lose in 3 years, and that it exceeds the MCID of 600-1100 steps per day.
				Primary outcome Clinical effectiveness	Sitting duration, increase in % per day at 6 months (mean increase +/- SD)	Valve group (n=19) 0.01 +/- 6.1, controls (n=24) 1.88 +/- 3.0; BGMD -1.86 +/-1.52, p=0.230. % change from baseline 1.44% (SD 19.0) Including crossover: valve group (n=37) -1.1% +/-15.7% (decrease), p=0.421			
				Primary outcome Clinical effectiveness	Inactivity duration, increase in % per day at 6 months (mean increase +/- SD)	Valve group (n=19) -1.1 +/- 3.2, controls (n=24) 0.39 +/- 3.0; BGMD -1.49 +/- 0.95, p=0.126. % change from baseline -1.3% (SD 3.9) Including crossover: valve group (n=37) -1.3% +/- 6.0% (decrease), p=0.171			
Brown et al 2012 Subset of	P1 Prospective multicentre RCT	n=421, valve group 289, controls 132 Homogenous and	Unilateral duckbill type valve placement (controls on standard medical care). Optimal	Primary outcome Clinical effectiveness	Reduction in target lobe volume at TLC	Valve patients (n=289) 0.45 litres (Standard Error (SE) 0.034), p<0.0001. Controls (n=132) 0.005 l (SE 0.012), p=0.70	7	Direct Mainly in line with PICO but no mention	The authors' premise is that endobronchial valves are effective because by reducing the volume of the more severely damaged lung, more healthy lung is able to expand and function better. They sought to evaluate whether there was an expansion in volume of other more healthy areas of lung when valves

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
patient group of VENT RCT, see van Agteren et al 2017 above for details.	Jan 2003 to Dec 2006.	heterogeneous emphysema Age, gender and baseline FEV_1 not stated. p values indicate valve and control groups well matched with respect to baseline TLC, RV and RV/TLC eg RV 4.92 in valve group and 4.86 in controls, p=0.76	care for all as per GOLD guidelines. In treated patients one-way valves were placed in the segmental airways of the most diseased lobe to cause lobar occlusion and prevent air from entering these portions of the lung while still allowing air to exit. Inspiratory and expiratory CT imaging used to determine lung volumes and density pre and 6 months (+/- 0.5 months) post treatment.	Secondary outcome Clinical effectiveness	Reduction in target lobe RV for valve patients with >50% target lobe volume reduction	Valve patients (n=49) 1.09 l (SE 0.058), p<0.0001		of whether patients had pulmonary rehabilitation prior to treatment, and no breakdown by whether emphysema was homogenous or heterogeneous	reduced the volume of the treated lobes. Although the results suggest that when the most damaged lobes are treated with valves and reduce in volume, the other lobes expand, this study does not provide evidence that lung function improves as a result of this. This study used data from the VENT RCTs. However the numbers of patients do not match either the VENT US (Sciurba et al 2010) or the VENT EU (Herth et al 2012) trials. Baseline demographic and lung function data such as age, gender and FEV_1, are not provided and hence it is not possible to know how generalizable the results are. Some data are missing, for example 52 patients had >50% reduction in target lobe volume but results were available for 49 patients, and there are no data on how those who were not evaluated may have differed. There is no indication that assessors were blinded in this study. Although assessment of lung volumes on CT scans was semi-automated, there was some manual editing and therefore a small potential for bias.
					Increase in ipsilateral lobe RV for valve patients with >50% target lobe volume reduction	Valve patients (n=49) 0.481 l (SE 0.047), p<0.0001 Control group no significant change, p>0.2			
					Increase in contralateral lobe RV for valve patients with >50% target lobe volume reduction	Valve patients (n=49) 0.06 l (SE 0.040), p=0.16 Control group no significant change			
					Reduction in whole lung RV for valve patients with >50% target lobe volume reduction	Valve patients (n=49) 0.555 litres (SE 0.087), p<0.0001 Control group no significant change, p>0.2			
					Reduction in low attenuation relative area (CT scan indication of reduction in air in lung) on expiration for valve patients with >50% target lobe	Valve patients (n=49) 4.8 percentage points (SE 1.2) Control group no significant change, p>0.2			

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
					volume reduction				
					Reduction in RV/TLC for valve patients with >50% target lobe volume reduction	Valve patients (n=49) 4.5 percentage points (SE 1.3) Control group no significant change, p>0.2			
Cost effectiveness studies									
Pietzch et al 2014	S2 Secondary analysis of a subset of data from VENT EU (Herth et al 2012) and VENT US (Sciurba et al 2010) trials (see above) 23 clinical sites in the US and 23 in	n=73, 37 valve patients, 36 matched controls. Valve patients were a subset of the 76 patients from the base RCTs who had complete fissures isolating the target lobe and high heterogeneity between the target lobe and other lobes in the same lung (≥15% difference in emphysema	Complete occlusion/exclusion of target lobe using duckbill type valve	Primary Cost effectiveness	Cost effectiveness of duckbill type valve (no cost-effectiveness data for umbrella type valve found)	**Duckbill type valve:** Assuming average use of 3.08 valves per participant to achieve full occlusion of target lobe and initial cost of valve placement of EUR 9,581,discounted costs were estimated at (3%/year discount rate applied): 5 years: EUR 20,734 for valve patients and EUR 10,435 for controls. 10 years: EUR 25,857 for valve patients and EUR 15,432 for controls. Considering total incremental discounted (3%/yr) QALYs gained by treatment of 0.22 at 5 years and 0.41 at 10 years, the incremental cost-effectiveness ratio	5	Direct Mainly in line with PICO but patients did not all have pulmonary rehabilitation prior to inclusion in trials.	This study only included patients in the treatment group where the valves had been effective in occluding the air flow to the target lobe (37 of 76 patients with complete fissures and high heterogeneity of emphysema). The objective of the studies had been to occlude the most severely affected portions of lung, but this this was not successful in all patients (see Brown et al 2012 above). While fissure completeness and heterogeneity can be assessed pre-operatively, "successful lobar exclusion" cannot, and hence the true cost of valve treatment should be based on all patients who had valve treatment, including those where it failed to completely occlude air flow to the target lobe. As the latter patients are likely to have had poorer outcomes, the true cost effectiveness of valve treatment is likely to be lower than that calculated by this study (and true ICERs higher). NB: It is not clear from the report how patients were selected for inclusion, in particular how occlusion status was known, though use of the word "successful" implies that it was post valve insertion. Only direct medical costs are included, and not effects on indirect costs such as wages, travel, caregivers. If these are lower in treated patients, their inclusion might increase the calculated cost effectiveness of valve treatment (lower ICER)

Endobronchial valves ("valves") for lung volume reduction (LVR) vs maximal medical therapy in severe emphysema									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	Europe	%). Patients from this group were only included in the analysis if they had complete lobar exclusion[17] (37 patients). Mean age 62.24 years for valve group and 62.08 years for controls; 23% valve group and 19% controls male; FEV_1 28% predicted in valve patients, 30% in control group.				(ICER) was EUR 46,322 per QALY gained at 5 years and EUR 25,142 per QALY gained at 10 years.			Extrapolation to 5 and 10 years was based on observations in the 12 months post treatment. Although this took account of different stages of disease in different patients at the time of treatment and disease progression rates seen, it is possible that the longer term effects of valves are different. Late pneumothorax, infection requiring valve removal and loss of atelectasis were not considered because of the paucity of evidence available regarding these possible later complications. The lack of blinding in the RCTs that this study is based on means that a placebo effect associated with valve implantation may have biased the outcomes, making the intervention appear more effective than it is.

[17] Complete lobar exclusion occurs where valve placement successfully occludes all air flow to the target lobe.

8. Grade of evidence tables

For clarity, the evidence is presented in two tables. One relates to the studies of the use of the duckbill type of valve to completely occlude the most severely affected areas of lung, whereas the other relates to studies of the use of the umbrella type of valve to partially occlude bronchi bilaterally. Outcomes for these two groups of studies were very different and it is not clear whether this relates to the different types of valves used or the different treatment strategies.

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Mortality	van Agteren et al 2017	9	Direct	A	The effect of treatment on overall mortality is important, particularly for a treatment which, while improving some measures such as lung function, also results in serious adverse events and complications. Overall mortality by end of follow-up was analysed for five randomised controlled trials (RCTs) in two systematic reviews and meta-analyses (SRMAs), by van Agteren et al (2017) and by Wang et al (2017). The former provided additional analyses and is therefore quoted here: the combined odds ratio (OR) for mortality by the end of follow-up was 1.07 (95% confidence interval (CI) 0.47-2.43), p=0.86. In the postoperative period, and at 90 days, 6 and 12 months there was also no statistically significant difference in mortality between valve treated patients and controls. Additionally, valve treatment had no statistically significant effect on mortality in neither patients with intact fissures (an indicator that they do not have collateral ventilation (CV)), nor those for whom CV was not tested. (van Agteren et al, 2017) (CV is where air enters a lobe of the lung through a passage other than the normal airway.) This means that these studies do not provide evidence of a positive or negative effect of valve treatment on mortality. The evidence relating to mortality was graded by van Agteren et al (2017) as moderate quality. Studies varied in the types of patients included (heterogeneous versus homogenous emphysema) and few patients were followed up for more than 12 months. Hence any difference in mortality related to heterogeneity of emphysema or difference over a longer time frame was not assessed.
	Wang et al 2017	9	Direct		
	Kemp et al 2017	9	Direct		

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Lung function – increase in forced expiratory volume in one second (FEV_1) from baseline	van Agteren et al 2017	9	Direct	A	FEV_1 is used as a measure of the severity of emphysema and to monitor response to treatment. If emphysema has caused large areas of the lung to lose their elasticity, less air can be exhaled quickly (in the first second of expiration) and hence FEV_1 is lower. If valve treatment allows less damaged, more elastic areas of lung to expand in place of more damaged lung, FEV_1 might increase, indicating an improvement in lung function. The best evidence for this outcome measure mainly comes from the SRMAs by van Agteren et al (2017) and Wang et al (2017). Wang et al found that the mean improvement in FEV_1 by the end of follow-up for valve treated patients was 11.44% greater than for control patients (BGMD) and that this difference was statistically significant ($p<0.0001$). Statistically significant differences were also seen at 90 days, 6 and 12 months (van Agteren et al 2017). The improvement in FEV_1 was significantly larger in patients with heterogeneous emphysema compared to homogenous emphysema (BGMD 16.36%, p=0.00001), in patients without CV compared to with CV (p=0.0002), and in those where the valves resulted in complete lobar occlusion compared to incomplete occlusion (p=0.005 and p=0.006 in two studies) (van Agteren et al 2017). Wang et al (2017) considered the minimal difference in FEV_1 that is clinically meaningful to the patient (MCID) as an increase of ≥10%. They found that this was achieved significantly more frequently in treated patients than controls (risk ratio (RR) 2.96, p=0.002). This suggests that the degree of improvement in lung function that results from this treatment is clinically important to patients. The significant improvement in FEV_1 in treated patients was described (by van Agteren et al 2017) as low quality evidence because results were combined from trials that did and did not attempt to exclude patients with CV and there was a wide range between studies in the mean improvement, with considerably better results in one of the studies.
	Wang et al 2017	9	Direct		
	Kemp et al 2017	9	Direct		
Lung function – change in residual volume (RV) from baseline	van Agteren et al 2017	9	Direct	A	RV is the amount of air left in the lungs after full expiration and effectively represents the volume of “dead space” in the lung which does not help with gas exchange as air does not flow in and out. The damage and loss of elasticity in emphysema increases the RV. The largest study for this outcome measure was van Agteren et al’s (2017) meta-analysis. They found a statistically significant 0.58 litre reduction in RV in treated patients (95% CI -0.77 to -0.39) and no significant change in controls.

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
	Kemp et al 2017	9	Direct		This suggests that valve treatment reduces the RV in the lobe of lung that is treated, hence reducing the amount of lung that is effectively dead space and not helping with gas exchange. The effect of the smaller increase in RV of the other nearby lobe on lung function is not clear. The minimum reduction in RV of the target lobe is defined in studies as either 350 mls or 430 mls and 2 of 3 studies found that a clinically important reduction was seen significantly more often in treated patients than in controls (van Agteren et al 2017). van Agteren et al graded the evidence relating to RV as moderate quality. Given the mixed results and the evidence that a reduction in RV in one lobe can increase the RV in another, it is difficult to assess the true impact of changes in this measure on patients.
	Brown et al 2012	7	Direct		
Lung function - Change in total lung capacity (TLC) from baseline	van Agteren et al 2017	9	Direct	A	TLC includes the useful capacity of the lung and the RV or “dead space”. Emphysema damages lung and reduces its elasticity resulting in hyperinflation. This increases the TLC and RV while reducing overall lung function. van Agteren et al (2017) found a statistically significant reduction in TLC (by 0.34 litres) in valve treated patients and not in controls. No indication was given in the studies of the minimum change in TLC that is clinically important and so we do not know whether the observed reduction in TLC is linked to a clinically important improvement in lung function. van Agteren et al graded the evidence for this outcome as moderate quality. The result is in line with the finding of a reduction in RV in valve treated patients and may mean that a higher proportion of lung is functional, thus increasing overall lung function. However, the finding on its own is not evidence of an improvement in lung function following valve treatment.
	Brown et al 2012	7	Direct		

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Lung function - Decrease in ratio of RV to TLC (RV/TLC) from baseline	van Agteren et al 2017	9	Direct	A	A reduction in RV/TLC means that a larger proportion of the air in the lungs can be exhaled and therefore a higher proportion may be useable for gas exchange. This may therefore improve gas exchange and reduce symptoms of breathlessness. van Agteren et al (2017) reported a significant reduction in RV/TLC in valve treated patients of 5.76% (95% CI 1.06 to 10.45), with much smaller changes in controls. van Agteren et al (2017) report a study which defined the MCID in RV/TLC as a 4% reduction and found that this was achieved in significantly more treated patients than controls (63% vs 9%, p<0.001), suggesting that the changes observed are clinically important to patients. Results for RV/TLC varied between studies and the quality of evidence for this measure was graded as low (by van Agteren et al 2017). However, the analysis used a random effects model, which attempts to take account of the between study heterogeneity.
	Brown et al 2012	7	Direct		
Lung function – Forced vital capacity (FVC)	van Agteren et al 2017	9	Direct	B	The FVC is the amount of air a person can forcefully and quickly exhale after taking a deep breath, and therefore is another indicator of the functional capacity of the lungs. van Agteren et al (2017) found one RCT that reported on this measure and found a greater improvement in FVC in the treated group than in controls (BGMD 14.4%, standard deviation (SD) 27.8). This suggests a benefit from valve treatment, but the amount of change that is clinically important to patients was not reported and hence the importance of this observation is not known. This measure was reported by only one relatively small study (n=68) with no p value or CI reported and so its significance is not clear.
Lung function – Increase in diffusion capacity of the lung for carbon monoxide (DLCO)	van Agteren et al 2017	9	Direct	B	Emphysema damages lung tissue, reducing the diffusion capacity of the lung for oxygen and hence causing breathlessness. DLCO is a measure of this diffusion capacity of the lung for gases. van Agteren et al (2017) found one RCT that reported on this measure and found a significantly greater improvement in DLCO in the treated group than in controls (p=0.003). This should result in better oxygenation of the blood and reduced breathlessness in valve treated patients. However, the amount of change that is clinically important to patients was not reported and hence the relative importance of this is not known.

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					DLCO was reported by only one relatively small study (n=50), and further studies would add confidence to our understanding of the effect of valves on DLCO.
Exercise capacity – improvement in 6 minute walk distance (6MWD)	van Agteren et al 2017	9	Direct	A	Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. The distance that a patient can walk in six minutes is a useful indicator of how severely their capacity for exercise is limited as it helps to indicate their capacity to do everyday tasks. The test is usually performed on a treadmill. The improvement in 6MWD was significantly greater in valve treated patients than controls (BGMD 38.12 metres, 95% CI 8.68 to 67.56) (van Agteren et al 2017). Although two trials separated results for patients with and without intact fissures and found no significant difference for this measure, when results of the three trials which selected only patients with intact fissures were compared with the two trials that did not, there was significantly more improvement in 6MWD in the former (p=0.01) (van Agteren et al 2017). A 26 metre improvement in 6MWD was considered the MCID by most RCTs and the SRMA by Wang et al (2017) found that this was achieved in a significantly higher proportion of valve treated patients (175/433) compared to controls (60/270) (p=0.01), indicating that this effect of valves is important for patients. van Agteren et al (2017) graded the quality of evidence found for this measure as low because of the heterogeneity in the results between studies. However, the analysis used a random effects model, which attempts to take account of the heterogeneity.
	Wang et al 2017	9	Direct		
	Kemp et al 2017	9	Direct		
Exercise capacity – increase in steps per day at 6 months	Hartman et al 2016	7	Direct	B	Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. Change in the number of steps per day is an indication of whether a patient does more exercise following valve treatment, which might indicate that the treatment enables them to exercise more. Hartman et al (2016) found a significant increase in steps per day six months post valve treatment compared to controls (BGMD 1340 steps, p=0.001). Steps increased in treated patients and decreased in controls. This suggests that valve treatment increased the amount of exercise patients did each day. This could mean that they were able to live a more active life, do more, and keep more physically fit. However, no indication was given of the minimum difference that would be important

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					to patients. This result should be treated with caution as it is based on a relatively small (n=43) unblinded (patients knew which treatment they had received) RCT with a high drop-out rate. A placebo effect of valve treatment in encouraging patients to be more active cannot be ruled out, although the authors state that the improvement was seen without any specific encouragement on physical activity. No information is provided regarding whether patients had pulmonary rehabilitation prior to treatment.
Exercise capacity – increase in locomotion duration at 6 months	Hartman et al 2016	7	Direct	B	Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. Change in the percentage of a day spend moving/walking is an indication of whether a patient does more exercise following valve treatment, which might indicate that the treatment enables them to exercise more. Hartman et al (2016) found a significant increase in the percentage of a day spent walking for valve treated patients compared to controls (BGMD 1.28%, p=0.001), which was equivalent to an average 36.4% increase from baseline. (1.28% of 24 hours is 18.4 minutes.) This suggests that valve treatment increased the amount of exercise patients did each day. This could mean that they were able to live a more active life, do more, and keep more physically fit. However, no indication was given of the minimum difference that would be important to patients. This result should be treated with caution as it is based on a relatively small (n=43) unblinded RCT with a high drop-out rate. A placebo effect of valve treatment in encouraging patients to be more active cannot be ruled out, although the authors state that the improvement was seen without any specific encouragement on physical activity. No information is provided regarding whether patients had pulmonary rehabilitation prior to treatment.
Exercise capacity – increase in walk intensity (average body acceleration) at 6 months	Hartman et al 2016	7	Direct	B	Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. Change in walking intensity is an indication of whether treated patients do more intensive exercise following valve treatment, which might indicate that the treatment enables them to do more intense activity. Hartman et al (2016) found a significant increase in walk intensity in valve treated patients compared to controls (BGMD 0.00948g, p=0.014; mean increase 4.6%). Mean walk intensity had increased in the valve group and decreased in controls.

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					This suggests that valve treatment increased the intensity of exercise that patients did at six months. This could mean that they were able to do more intense exercise. However, no indication was given of the minimum difference that would be important to patients. This result should be treated with caution as it is based on a relatively small (n=43) unblinded RCT with a high drop-out rate. A placebo effect of valve treatment in encouraging patients to be more active cannot be ruled out, although the authors state that the improvement was seen without any specific encouragement on physical activity. No information is provided regarding whether patients had pulmonary rehabilitation prior to treatment.
Exercise capacity – increase in sitting duration at 6 months	Hartman et al 2016	7	Direct	B	Lung damage and breathlessness restricts the capacity of patients with severe emphysema to exercise and be physically active. A change in the percentage of each day spent sitting might indicate whether a patient does more exercise or physical activity following valve treatment, which might indicate that the treatment enables them to be more physically active. Hartman et al (2016) found no significant difference between valve and control patients for this measure (p=0.230). Although the study found no significant effect on time spent sitting, this does not mean that there was no effect of treatment on exercise capacity, for example on the time spent walking or doing more intensive exercise. This result should be treated with caution as it is based on a relatively small (n=43) unblinded RCT with a high drop-out rate, and no information is provided regarding whether patients had pulmonary rehabilitation prior to treatment.

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Exercise capacity – increase in duration of inactivity at 6 months	Hartman et al 2016	7	Direct	B	Lung damage and breathlessness restricts the capacity of patients with severe emphysema to exercise and be physically active. A decrease in the proportion of each day that a treated patient is inactive might indicate that they are doing more exercise or physical activity, which might indicate that the treatment has enabled them to be more physically active. Hartman et al (2016) found no significant difference between valve and control patients for this measure (p=0.126). Although the study found no significant effect on time spent inactive, this does not mean that there was no effect of treatment on exercise capacity, for example on the time spent doing more intensive exercise. This result should be treated with caution as it is based on a relatively small (n=43) unblinded RCT with a high drop-out rate, and no information is provided regarding whether patients had pulmonary rehabilitation prior to treatment.
Quality of life – change in St George's Respiratory Questionnaire (SGRQ) score from baseline	van Agteren et al 2017	9	Direct	A	The SGRQ is a 50-item validated patient questionnaire designed to measure health-related quality of life specifically in respiratory patients. Valve treatment aims to improve patient quality of life (QoL) by improving lung function, reducing breathlessness and increasing exercise capacity. The best evidence for this outcome measure comes from the SRMA by van Agteren et al (2017) which found a statistically significant improvement in SGRQ score in valve treated patients compared to controls by the end of follow-up (BGMD -7.29 (95% CI -11.12 to -3.45). The difference was also statistically significant at 90 days, 6 and 12 months. The improvement in SGRQ score was statistically significantly greater in patients with heterogeneous emphysema compared to homogenous emphysema (p=0.005) in 1 RCT although there was a significant improvement in SGRQ in both groups and another RCT also found a statistically significant improvement in those with homogenous emphysema (p<0.0001). The improvement in SGRQ was significant in patients with intact fissures (BGMD -9.03, 95% CI -5.98 to -12.07), but not in those whose fissures were not intact (BGMD 0.00). No significant difference was found for this outcome measure relating to whether or not lobar occlusion was complete. (van Agteren et al 2017) The MCID for SGRQ was considered to be an improvement of 4 points or more. This was achieved significantly more frequently in treated patients than controls by end of follow-up (174/433 valve patients vs
	Wang et al 2017	9	Direct		
	Kemp et al 2017	9	Direct		

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					74/270 controls, RR 1.53, p=0.0002), suggesting that the improvement in QoL is meaningful to patients. (Wang et al 2017) The significant improvement in SGRQ was described as low quality evidence (van Agteren et al 2017) because results varied between studies (heterogeneity). However, when the authors reanalysed the data omitting results from the trial that had found the greatest benefit, the result was still positive, suggesting that the improvement in QoL is real, although there could be some bias related to the lack of concealment of the treatment group (blinding) in some of the RCTs included in the SRMA potentially resulting in a placebo effect.
Quality of life – change in COPD[18] assessment test (CAT) score from baseline	van Agteren et al 2017	9	Direct	B	The COPD Assessment Test (CAT) is a validated questionnaire for people with COPD designed to measure the impact of COPD on a person's life, and how this changes over time. Valve treatment aims to improve patient QoL by improving lung function, reducing breathlessness and increasing exercise capacity, No significant effect of valve treatment on this measure of QoL was found in two RCTs (p=0.23 in one and 95% CI -1.50 to +6.11 in the other RCT) (van Agteren et al 2017). Using this measure valve treatment was not shown to improve QoL. Different measures of QoL measure different aspects of functioning and some may be more relevant to patients with severe emphysema. The reason for the negative result may be that aspects of QoL measured by this tool are not affected by valve treatment or because it is based on two relatively small RCTs that were analysed separately (n=50 and n=93).
Quality of life – change in Modified Medical Research Council Dyspnoea Scale (mMRC) score from baseline	van Agteren et al 2017	9	Direct	A	The mMRC scale ranges from 0 to 4 and is a validated tool used to establish levels of functional impairment or perceived impairment due to dyspnoea attributable to respiratory disease. It consists of six phrases describing how much breathlessness interferes with daily activities.

[18] COPD, or chronic obstructive pulmonary disease, is a condition usually found in smokers. Patients have a combination of chronic bronchitis and emphysema.

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
	Wang et al 2017	9	Direct		The SRMA by Wang et al (2017) found a statistically significant improvement in mMRC in valve treated patients compared to controls (BGMD -0.35, p=0.0008, n not provided). Wang et al (2017) quote the MCID for mMRC as a change of 1 or more points, and a significantly higher proportion of valve treated patients achieved this level of improvement (113/374 valve patients vs 26/ 211 controls, RR 2.53, p<0.00001). This suggests that the size of the effect of valve treatment on QoL is meaningful to patients. The mMRC, with only five levels and six questions, is not likely to be as discriminatory as the SGRQ. However, a significant effect of valves was found despite this.
	Kemp et al 2017	9	Direct		
Quality of life – change in Clinical COPD Questionnaire (CCQ) score from baseline	van Agteren et al 2017	9	Direct	B	The CCQ is an easy to complete QoL questionnaire which has been well-validated in COPD. It consists of 10 items (each scored between 0 and 6), divided into three domains (symptoms, functional, mental). One RCT found a significant improvement in the valve treated group compared to controls on this QoL measure (n=68, BGMD -0.74, p=0.002) (van Agteren et al 2017). There is no indication of the MCID relating to this outcome measure, making it difficult to know if the improvement is important to patients. This result is based on one relatively small study. However, taken together with the evidence from other respiratory disease QoL measures, it suggests a positive effect of valve treatment on QoL.
Quality of life – change in SF-36 score from baseline	van Agteren et al 2017	9	Direct	B	SF-36 is a validated tool used to measure patient reported overall health status with questions in eight areas including physical role functioning and mental health. It is not specific to respiratory diseases. van Agteren et al (2017) report that neither of the two studies that assessed the effect of valves on patients' SF-36 scores found a significant effect (p=0.07 for effect on physical component score in one study and p=0.93 and p=0.73 for effect on mental health in two studies). This outcome measure does not suggest that overall physical functioning or mental health are improved by valve treatment in patients with severe emphysema. This outcome measure is not developed specifically for patients with breathlessness and may therefore be less sensitive to the types of changes that matter to patients with severe emphysema than some of the validated QoL measures developed specifically for people with

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					COPD.
Disease severity index – BODE index	Kemp et al 2017	9	Direct	B	The BODE index is a multidimensional grading system for predicting the risk of death among COPD patients using body mass index, degree of airflow obstruction, dyspnoea and 6MWD. Kemp et al (2017) found a significantly greater improvement in this measure in valve patients compared to controls at six months (BGMD -1.8, p<0.001). This suggests that valve treatment improves overall severity of emphysema. However, it is not clear what the MCID is and whether the size of the change is likely to be meaningful to patients. This result is based on one relatively small study (n=97), but the combination of this result with the other outcome measures above relating to lung function, exercise capacity and QoL increases confidence that valve treatment benefits patients.
Duration of hospital treatment	van Agteren et al 2017	9	Direct	B	The difference in duration of hospital treatment for those receiving valve treatment compared to maximal medical therapy may be important to patients as well as to commissioners. Median post treatment hospital stay was one day (range 1-13 days) from one RCT (n=68), and mean or median procedure times reported in three RCTs were 18, 27 and 33.8 minutes (van Agteren et al 2017). No comparison with control patients was reported. The hospital stay and duration of procedure appear relatively short. The lack of a comparison with control patients and the lack of data comparing longer term duration of hospital stay in treated patients vs controls, for example due to admissions for adverse events that might be linked to treatment, makes it difficult to come to any conclusion regarding the effect of valves on overall duration of hospital treatment.
Adverse events – serious adverse events (SAEs) as defined by authors of each RCT	van Agteren et al 2017	9	Direct	A	Assessing SAEs related to a treatment is important, particularly if the treatment appears to be clinically effective in reducing symptoms. The best data on SAEs comes from the SRMA by van Agteren et al (2017) who found significantly more SAEs in valve patients than controls (72/297 valve patients vs 18/185 controls, OR 5.85, p=0.0005), and in one RCT these led to death or hospitalisation in 44% of valve patients vs 12% of controls. The importance to patients of these SAEs relative to the clinical
	Kemp et al 2017	9	Direct		

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					benefits of valve treatment is not clear. The RCTs included in this analysis defined SAEs differently, and the severity and impact of different AEs can vary considerably. Little information was provided on this, which makes it difficult to interpret the significance of this finding for patients.
Adverse events – COPD exacerbations	Wang et al 2017	9	Direct	A	Most patients with emphysema have COPD, a combination of chronic bronchitis and emphysema. They tend to suffer from acute episodes of increased respiratory symptoms known as exacerbations of COPD. The SRMA by Wang et al (2017) found a significantly higher RR of COPD exacerbation with hospitalisation in patients treated with valves compared to controls (RR 2.01, p=0.01). COPD exacerbations are likely to be important to patients, but the relative importance of these compared to the benefits of valve treatment are not known. van Agteren et al (2017) reviewed the same RCTs as Wang et al but did not meta-analyse the data. Their report suggests that there was variation between the studies in this outcome, making the conclusion by Wang et al less reliable.
	van Agteren et al 2017	9	Direct		
	Kemp et al 2017	9	Direct		
Adverse events – pneumothorax	Wang et al 2017	9	Direct	A	Pneumothorax occurs when air leaks from the lung into the chest cavity around the lung. If severe, enough air can leak out to exert pressure on the lung and make it collapse. The SRMA by Wang et al (2017) reported a significantly higher RR of pneumothorax in patients treated with valves compared to controls (RR 9.65, p=0.0001). The importance of this finding to patients is not known. It is likely to depend on the severity and longer term effects of the pneumothorax. One RCT suggested that patients with a pneumothorax lasting more than 7 days were also those more likely to have a more positive clinical response to valve treatment (van Agteren et al 2017). Kemp et al (2017) report that there was no difference in any outcome measure at 3 or 6 months in the valve group between patients who did and did not experience a pneumothorax. Although pneumothorax is a serious and potentially life threatening SAE, the balance of this risk with potential benefits of valve treatment is not clear.
	van Agteren et al 2017	9	Direct		
	Kemp et al 2017	9	Direct		

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Adverse events - pneumonia	Wang et al 2017	9	Direct	A	Pneumonia is a relatively common complication of emphysema due to damage to the lungs and increased RV which mean that secretions/mucous and infections are less easily cleared. Atelectasis (collapse) of the target lobe in valve treatment could result in increased susceptibility to infection/pneumonia. The SRMA by Wang et al (2017) reported no significant difference in the rate of pneumonia in valve treated patients compared to controls (RR 2.17, p=0.10). This result is reassuring for patients, given the theoretical increased risk of pneumonia in valve treated lung where airflow to a lobe has been occluded. The result is surprising because pneumonia distal to the valve was reported as the most common SAE following valve treatment (van Agteren et al 2017), but this could be because pneumonia is also relatively common in emphysema patients not treated with valves.
	van Agteren et al 2017	9	Direct		
	Kemp et al 2017	9	Direct		
Adverse events – valve expectoration, migration and removal/replacement	van Agteren et al 2017	9	Direct	A	Expectoration, migration and removal/replacement of valves are important because they are likely to require further bronchoscopic procedures, with their associated risks. Removal may be due to unacceptable adverse effects of lack of effect. van Agteren et al (2017) reported on this outcome for the five RCTs separately. Overall, of 433 patients treated, 23 suffered valve expectoration, migration or aspiration and 40 had their valves removed. The importance of these findings for patients is difficult to assess as the effects of these events on other patient outcomes were not described. The numbers of these events appeared to vary considerably between the five RCTs included in van Agteren et al (2017)'s report, reducing the reliability of these findings. For example the variation may be due to variation in surgical technique or in patient pathways (e.g. threshold for valve removal) and the results may not be generalisable.
	Kemp et al 2017	9	Direct		
Cost effectiveness	Pietzch et al 2014	5	Direct	C	Cost effectiveness is measured as the cost of each additional quality adjusted life year gained by the treatment (incremental cost effectiveness ratio or ICER). It is the ratio of the extra cost of valve treatment (including follow-up and treatment of AEs) above the cost for those having maximal medical therapy, to the additional QALYs gained due to treatment. Pietzch et al (2014) considered the incremental QALYs gained to be

Use of Duckbill Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					0.22 at five years and 0.41 at ten years, and the overall costs to be EUR 20,734 (£18,453[19]) for valve patients and EUR 10,435 (£9,287) for controls at five years; and EUR 25,857 (£23,013) for valve patients and EUR 15,432 (£13,734) for controls at ten years (discounted at 3% per year), giving ICERs of EUR 46,322 (£41,227) per QALY gained at five years and EUR 25,142 (£22,376) per QALY gained at ten years. This suggests that by ten years, but not by five years, the procedure is cost effective at the threshold considered to be affordable by NICE of £30,000 per QALY. However, concerns about the quality of this study make this result unreliable and mean that the true ICER may be higher. This is because this study is based on data from two RCTs where 76 patients had complete fissures and heterogeneous emphysema. However the cost effectiveness study only included 37 of these patients – those with complete lobar occlusion. Data was not included for the 39 patients where "successful lobar exclusion" was not achieved, even though the objective of the RCTs had been to occlude the most severely affected areas of lung. The true cost of valve treatment should be based on all patients who had valve treatment that was aimed at excluding the target lobe. As patients where complete occlusion was not successful are likely to have had poorer outcomes while still incurring the costs of treatment and its complications, the true cost effectiveness of valve treatment is likely to be lower than that calculated by this study (and true ICERs higher). Furthermore, the lack of blinding in the RCTs that this study is based on means that a placebo effect associated with valve implantation may have biased the outcomes, making the intervention appear more effective than it is. Also, extrapolation to five and ten years was based on observations in the 12 months post treatment and may not be reliable. Late pneumothorax, infection requiring valve removal and loss of atelectasis were not considered because of the paucity of evidence available regarding these possible later complications. Only direct medical costs were included in the analysis, and not effects on indirect costs such as wages, travel and caregivers, which, if lower in treated patients, might increase the apparent cost effectiveness of valve treatment (lower ICER), The cost effectiveness calculations in this study should be treated with extreme caution given the issues described above.

[19] Based on currency conversion rate of EUR 1 = £0.89 as current on 12th Jan 2018.

Use of Umbrella Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Mortality	van Agteren et al 2017	9	Direct	A	The effect of treatment on overall mortality is important, particularly for a treatment which, while improving some measures such as lung function, also results in serious adverse events and complications. Overall mortality by end of follow-up was analysed for two randomised controlled trials (RCTs) in two systematic reviews and meta-analyses (SRMAs). van Agteren et al (2017) found the combined odds ratio (OR) for mortality by the end of follow-up to be 4.95 (95% CI 0.85 to 28.94, p=0.08). This means that these studies do not provide evidence of a positive or negative effect of valve treatment on mortality. The evidence relating to mortality was graded by van Agteren et al (2017) as moderate quality. Patients with both heterogeneous and homogenous emphysema were included and patients were followed up for only 12 months. Any difference in mortality relating to heterogeneity of emphysema or over more than 12 months was not assessed. Both RCTs included a sham procedure for control patients to try to reduce bias relating to a placebo effect of treatment.
	Wang et al 2017	9	Direct		
Lung function – increase in forced expiratory volume in one second (FEV_1) from baseline	van Agteren et al 2017	9	Direct	B	FEV_1 is used as a measure of the severity of emphysema and to monitor response to treatment. If emphysema has caused large areas of the lung to lose their elasticity, less air can be exhaled quickly (in the first second of expiration) and hence FEV_1 is lower. If valve treatment allows less damaged, more elastic areas of lung to expand in place of more damaged lung, FEV_1 might increase, indicating an improvement in lung function. The SRMA by van Agteren et al (2017) reported results separately for the two RCTs: one found no significant difference in FEV_1 at three months (0.90 litres for valves vs 0.87 for controls, p=0.065); the other study found a change in FEV_1 statistically significantly in favour of controls at six months (2.11% decrease in FEV1 in valve patients and 0.04% increase in controls, p=0.001). This suggests that valve treatment results in worsening of lung function, as measured by FEV_1, compared to maximal medical therapy. van Agteren et al (2017) graded the evidence relating to FEV_1 as moderate quality. The deleterious effect of valves on FEV_1 could be due to the type of valves used or the strategy for their use. Whereas the studies of duckbill type valves aimed to completely occlude the most severely affected areas of lung, the RCTs of umbrella type valves aimed to only partially occlude the lung lobes bilaterally.

Use of Umbrella Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Lung function – change in residual volume (RV) from baseline	van Agteren et al 2017	9	Direct	B	RV is the amount of air left in the lungs after full expiration and effectively represents the volume of "dead space" in the lung which does not help with gas exchange as air does not flow in and out. The damage and loss of elasticity in emphysema increases the RV. Results from two RCTs found a 0.38 litre greater reduction in RV in control patients compared to valve treated patients (95% CI 0.12 to 0.65) (van Agteren et al 2017). This suggests that valve treatment performs worse than maximal medical therapy alone in reducing RV in severe emphysema. van Agteren et al (2017) graded the evidence relating to RV as high quality. The deleterious effect of valves on RV could be due to the type of valves used or the strategy for their use. Whereas the studies of duckbill type valves aimed to completely occlude the most severely affected areas of lung, the RCTs of umbrella type valves aimed to only partially occlude the lung lobes bilaterally.
Lung function - Change in total lung capacity (TLC) from baseline	van Agteren et al 2017	9	Direct	B	TLC includes the useful capacity of the lung and the RV or "dead space". Emphysema damages lung and reduces its elasticity resulting in hyperinflation. This increases the TLC and RV while reducing overall lung function. Valve treatment was not found to make a significant difference to TLC compared to maximal medical therapy (between group mean difference (BGMD) 0.14, 95% CI -0.12 to 0.39) (van Agteren et al 2017). This suggests that valve treatment does not have a significant impact on TLC in people with severe emphysema. van Agteren et al (2017) graded the evidence relating TLC as moderate quality. The lack of effect of valves on TLC could be due to the type of valves used or the strategy for their use. Whereas the studies of duckbill type valves aimed to completely occlude the most severely affected areas of lung, the RCTs of umbrella type valves aimed to only partially occlude the lung lobes bilaterally.

Use of Umbrella Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Lung function - Decrease in ratio of RV to TLC (RV/TLC) from baseline	van Agteren et al 2017	9	Direct	B	A reduction in RV/TLC means that a larger proportion of the air in the lungs can be exhaled and therefore a higher proportion is used for gas exchange. This may therefore improve gas exchange and reduce symptoms of breathlessness. A significantly greater reduction in RV/TLC was found in the control group compared to treated patients in one RCT, suggesting a negative effect of the valves (p=0.01) (van Agteren et al 2017). This suggests that valve treatment performs worse than maximal medical therapy alone in reducing RV/TLC in severe emphysema. This result is based on one relatively small RCT (n=73) and is therefore not of high quality. The deleterious effect found of valves on RV/TLC could be due to the type of valves used or the strategy for their use. Whereas the studies of duckbill type valves aimed to completely occlude the most severely affected areas of lung, the RCTs of umbrella type valves aimed to only partially occlude the lung lobes bilaterally.
Exercise capacity – improvement in 6 minute walk distance (6MWD)	van Agteren et al 2017	9	Direct	A	Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. The distance that a patient can walk in six minutes is a useful indicator of how severely their capacity for exercise is limited as it helps to indicate their capacity to do everyday tasks. The test is usually performed on a treadmill. van Agteren et al (2017) found significantly less improvement in 6MWD in valve patients compared to controls (n=316, BGMD -19.54 metres, 95% CI -37.11 to -1.98). This suggests that valve treatment results in reduced exercise capacity compared to maximal medical therapy alone in patients with severe emphysema. van Agteren et al (2017) graded the evidence relating to 6MWD as moderate quality. The negative effect found for valves on 6MWD could be due to the type of valves used or the strategy for their use. Whereas the studies of duckbill type valves aimed to completely occlude the most severely affected areas of lung, the RCTs of umbrella type valves aimed to only partially occlude the lung lobes bilaterally.
	Wang et al 2017	9	Direct		
Quality of life – change in St George's Respiratory	van Agteren et al 2017	9	Direct	A	The SGRQ is a 50-item validated patient questionnaire designed to measure health-related quality of life specifically in respiratory patients. Valve treatment aims to improve patient quality of life (QoL) by

Use of Umbrella Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Questionnaire (SGRQ) score from baseline	Wang et al 2017	9	Direct		improving lung function, reducing breathlessness and increasing exercise capacity. No significant effect of valve treatment was found for SGRQ by end of follow up (BGMD 2.64 units, 95% CI -0.28 to 5.56) (van Agteren et al 2017). This suggests that valve treatment does not improve QoL for patients with severe emphysema compared to maximal medical therapy. van Agteren et al (2017) graded the evidence relating to SGRQ as high quality. The lack of effect on QoL found for valve treatment could be due to the type of valves used or the strategy for their use. Whereas the studies of duckbill type valves aimed to completely occlude the most severely affected areas of lung, the RCTs of umbrella type valves aimed to only partially occlude the lung lobes bilaterally.
Quality of life – change in Modified Medical Research Council Dyspnoea Scale (mMRC) score from baseline	van Agteren et al 2017	9	Direct	A	The mMRC scale ranges from 0 to 4 and is a validated tool used to establish levels of functional impairment or perceived impairment due to dyspnoea attributable to respiratory disease. It consists of six phrases describing how much breathlessness interferes with daily activities. The meta-analysis by Wang et al (2017) of the two RCTs found no statistically significant effect of valve treatment on mMRC (BGMD -0.08, 95% CI -0.29 to +0.13, p=0.47). This suggests that valve treatment does not improve QoL for patients with severe emphysema compared to maximal medical therapy. The lack of effect on QoL found for valve treatment could be due to the type of valves used or the strategy for their use. Whereas the studies of duckbill type valves aimed to completely occlude the most severely affected areas of lung, the RCTs of umbrella type valves aimed to only partially occlude the lung lobes bilaterally.
	Wang et al 2017	9	Direct		
Duration of hospital treatment	van Agteren et al 2017	9	Direct	B	The difference in duration of hospital treatment for those receiving valve treatment compared to maximal medical therapy may be important to patients as well as to commissioners. van Agteren (2017) reported results from two RCTs separately: in one RCT mean hospital stay was 2.2 days (standard deviation (SD) 6.6) in the valve group and 1.0 days (SD 0) for controls. The other study reported no difference between groups (1.1 days, p=0.26). The mean procedure time was 62 minutes (SD 17).

Use of Umbrella Type Endobronchial Valves vs. Maximal Medical Therapy for Severe Emphysema					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					The hospital stay and duration of procedure appear relatively short. There is conflicting evidence as to whether hospital stay is longer for valve patients. The lack of data comparing longer term duration of hospital stay in treated patients vs controls, for example due to admissions for adverse events that might be linked to treatment, makes it difficult to come to any conclusion regarding the effect of valve treatment on overall duration of hospital treatment.
Adverse events – adverse events (AEs) as defined by authors of each RCT	van Agteren et al 2017	9	Direct	B	Assessing AEs related to a treatment is important, particularly if other outcome measures are positive. There were significantly more AEs in patients treated with valves than controls (26 AEs in 179 valve patients (143 per 1000) vs 8 AEs in 171 controls (47 per 1000), p=0.004). The most frequent serious AEs were COPD exacerbations (18 in 179 valve patients, number in controls not stated), respiratory failure, pneumothorax and pneumonia. Procedural AEs were principally bronchospasms and dyspnoea. (van Agteren et al 2017). The longer term impact and importance to patients of these SAEs is not clear. The severity and impact of different AEs can vary considerably and was not discussed, which makes it difficult to interpret the significance of this finding for patients.

9. Literature Search Terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Symptomatic pulmonary emphysema with demonstrable hyperinflation, persisting after pulmonary rehabilitation Pre-operative assessment of collateral ventilation and heterogeneity
I – Intervention Which intervention, treatment or approach should be used?	Lung volume reduction by endobronchial valve placement.
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Maximal medical therapy.
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	<u>Critical to decision-making:</u> Clinical effectiveness: - Clinical effectiveness and safety outcomes including: - Health related quality of life: absolute reductions/improvements and percentage change mean difference (SF 36, SGRQ) - Respiratory physiology: absolute and percentage change mean difference (FEV1 and RV) - Survival rates at 30 days, 90 days, one year and five year <u>Important to decision-making:</u> - Post-operative complications, including post-procedure pneumothorax readmission with procedural complication (e.g. pneumothorax, chest infection, valve displacement) - Readmission rate for COPD exacerbation or other COPD related admission - MRC Dyspnoea scale - Exercise capacity: absolute increase and increase percentage mean difference in 6 min walk test or shuttle walk test - Cost-effectiveness
Assumptions / limits applied to search	
Inclusion criteria: English language papers in peer reviewed journals from last 10 years. Include case series where n>50 Exclusion criteria: limited case series n <50, case reports, patients with coexisting malignancy, pulmonary fibrosis or pulmonary hypertension.	

10. Search Strategy

We searched PubMed, Embase, Cochrane Library, TRIP and NHS Evidence limiting the search to papers published in England from **1st January 2007 to 23rd November 2017**. We excluded conference abstracts, commentaries, letters, editorials and case reports. For each of the main databases searches were carried out for “endobronchial valves” and for “intrabronchial valves” and these are entitled “Search 1” and “Search 2” respectively below.

Embase search:

#	
▲	**Search 1**
1	*chronic obstructive lung disease/ or exp lung emphysema/
2	((sever* or serious* or advanced) adj5 (emphysema or copd or chronic obstructive pulmonary disease or chronic obstructive lung disease)).ti,ab.
3	(emphysema or copd or chronic obstructive pulmonary disease or chronic obstructive lung disease).ti.
4	1 or 2 or 3
5	((lung or pulmonary) adj5 volume reduc*).ti,ab.
6	((lung volume or pulmonary volume) adj5 reduc*).ti,ab.
7	lvr.ti,ab.
8	5 or 6 or 7
9	((bronchial* or endobronchial* or endo-bronchial or one-way or oneway or zephyr or duckbill) adj5 valve?).ti,ab.
10	8 and 9
11	elvr.ti,ab.
12	((bronchial* or endobronchial* or endo-bronchial or one-way or oneway) adj5 (lung volume reduction or pulmonary volume reduction)).ti,ab.
13	10 or 11 or 12
14	4 and 13
15	conference*.pt.
16	14 not 15
17	limit 16 to (english language and yr="2007 -Current")
18	from 17 keep 1-146

#	
▲	**Search 2**
1	*chronic obstructive lung disease/ or exp lung emphysema/
2	((sever* or serious* or advanced) adj5 (emphysema or copd or chronic obstructive pulmonary disease or chronic obstructive lung disease)).ti,ab.
3	(emphysema or copd or chronic obstructive pulmonary disease or chronic obstructive lung disease).ti.
4	1 or 2 or 3
5	((lung or pulmonary) adj5 volume reduc*).ti,ab.
6	((lung volume or pulmonary volume) adj5 reduc*).ti,ab.
7	lvr.ti,ab.
8	5 or 6 or 7
9	((intrabronchial* or intra-bronchial* or unilateral* or bilateral*) adj5 valve*).ti,ab.

10 8 and 9
11 ((intrabronchial* or intra-bronchial* or unilateral* or bilateral*) adj5 (lung volume reduction or pulmonary volume reduction)).ti,ab.
12 10 or 11
13 4 and 12
14 conference*.pt.
15 13 not 14
16 limit 15 to (english language and yr="2007 -Current")

11. Evidence Selection

- Total number of publications reviewed: 53
- Total number of publications considered potentially relevant: 14
- Total number of publications selected for inclusion in this briefing: 6

12. References

Brown MS, Kim HJ, Abtin FG, Strange C, Galperin-Aizenberg M, Pais R, et al. 2012. Emphysema lung lobe volume reduction: effects on the ipsilateral and contralateral lobes. *Eur Radiol.* 22(7):1547-55.

Eberhardt R, Gompelmann D, Schuhmann M, Reinhardt H, Ernst A, Heussel CP, et al. 2012. Complete unilateral vs partial bilateral endoscopic lung volume reduction in patients with bilateral lung emphysema. *Chest.* 142(4):900-8.

Hartman JE, Klooster K, Slebos DJ, Ten Hacken NH. 2016. Improvement of physical activity after endobronchial valve treatment in emphysema patients. *Respir Med.* 117:116-21.

Kemp SV, Slebos DJ, Kirk A, Kornaszewska M, Carron K, Ek L, et al. 2017. A Multicenter RCT of Zephyr(R) Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM). *Am J Respir Crit Care Med.* 2017 Sep 08.

National Institute for Health and Care Excellence (NICE) Interventional Procedures Programme. 2013. Interventional procedure overview of insertion of endobronchial valves for lung volume reduction in emphysema. *NICE.* July 2015. https://www.nice.org.uk/guidance/ipg600/documents/overview-2 (accessed 18 January 2018).

National Institute for Health and Care Excellence (NICE) Interventional Procedures Programme. 2013. Endobronchial valve insertion to reduce lung volume in emphysema Interventional procedures guidance [IPG600]. *NICE.* December 2017. https://www.nice.org.uk/guidance/ipg600 (accessed 18 January 2018).

NHS Choices. Chronic obstructive pulmonary disease (COPD). *NHS Choices.* 5th September 2016. https://www.nhs.uk/conditions/chronic-obstructive-pulmonary-disease-copd/ (accessed 17 Jan 2018).

Pietzsch JB, Garner A, Herth FJ. 2014. Cost-effectiveness of endobronchial valve therapy for severe emphysema: a model-based projection based on the VENT study. *Respiration.* 88(5):389-98.

Public Health England. 2015. Chronic smoking-related lung disease blights over 1 million lives in England. *Public Health England.* Press release 29 December 2015. https://www.gov.uk/government/news/chronic-smoking-related-lung-disease-blights-over-1-million-lives-in-england (accessed 17 Jan 2018).

van Agteren JEM, Hnin K, Grosser D, Carson KV, Smith BJ. 2017. Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews.* 2017, Issue 2.

Wang Y, Lai TW, Xu F, Zhou JS, Li ZY, Xu XC, et al. 2017. Efficacy and safety of bronchoscopic lung volume reduction therapy in patients with severe emphysema: a meta-analysis of randomized controlled trials. *Oncotarget.* 29;8(44):78031-43.