MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
28-29 July 20

Agenda Item No	5.2
National Programme	Internal Medicine
Clinical Reference Group	Specialised Respiratory
URN	1622

Title
Lung volume reduction by surgery or endobronchial valve for severe emphysema in adults.

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
NHS England is proposing that some forms of lung volume reduction for adults with severe emphysema are routinely commissioned. NHS England does not have a commissioning policy in place for adults with severe emphysema who may benefit from lung volume reduction. There are two approaches; surgical reduction or the use of endobronchial valves. However, there has been partial adoption of both approaches in most hospitals leading to unequal access in England and adoption of one approach over another without full consideration of the published evidence. This policy proposition aims to address both these points by providing evidence for lung reduction and evidence on the benefits and risks of both approaches as well as considering different types of endobronchial valves available. Severe emphysema is a form of chronic obstructive pulmonary disease (COPD) which is a national priority within the NHS Long Term Plan for respiratory diseases. The proposition includes commissioning some types of valves but does not propose to commission coils. The proposition was previously considered for prioritisation by CPAG in May 2019 and November 2019 and is being resubmitted for the third time. The updated proposition includes a revised equality and health inequalities impact assessment (EHIA) report and integrated impact assessment which more accurately assesses current and future demand.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy to include both lung volume reduction surgery and endobronchial “duck bill” type valves.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality and health Inequalities Impact Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and health Inequalities Impact Assessment Report

The Benefits of the Proposition		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	**Benefit of open surgery compared to maximal medical therapy** 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. Over five years (4.3 years median follow-up), Naunheim et al (2006) reported a total mortality rate of 0.11 deaths per person-year in the lung volume reduction surgery (LVRS) group and 0.13 in the control group. This represents a statistically significant overall relative risk (RR) of 0.85 (p=0.02). The lowest mortality rate (overall RR = 0.57; p=0.01) was seen amongst patients with upper lobe predominant emphysema and low exercise capacity at baseline (excluding those at high-risk). This group of patients represented a quarter of the trial's population. These results show that LVRS improves overall survival compared to medical management. Patients with upper lobe predominant

		emphysema and low exercise capacity at baseline were shown to have the highest improvement in survival after LVRS. These results are based on a well-conducted randomised controlled trial (RCT) with a large sample size (1,218) and long follow-up of 5 years. One issue to note is that 30% of the LVRS group had VATS rather than open surgery which may have affected the results. Overall, however, the results provide good evidence of an increase in overall survival. It is an important result because it suggests that there is a benefit in overall longer-term survival despite the high initial risk of mortality post-surgery.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy The greater than 30 day mortality risk is the chance of a patient dying more than 30 days after having lung volume reduction surgery (LVRS). Death occurring in this time period is less likely to be associated with complications of surgery and more likely to be associated with emphysema or other diseases occurring over the follow-up period of the trial. Over 12 months, Goldstein et al (2003) reported that 2/28 (7%) patients died of respiratory failure more than 30 days after surgery (at 285 and 334 days after surgery) in the VATS group and 1/27 (4%) patient died of respiratory failure (at 117 days after randomisation) in the control group. No confidence intervals or p-values were reported, but it is likely to represent a non-significant difference due to the small sample size. This means that although the trial observed a higher risk of dying greater than 30 days after VATS compared to control, it is not known if this is a true difference due to the small numbers enrolled in the trial. The results should be treated with caution as they are based on a randomised controlled trial (RCT) with a relatively small sample size (n=55) and therefore it is likely not to have the power to detect small differences between the groups. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Over a follow-up period of 31.9 months, in the non-randomised comparison, McKenna et al (2004) reported an overall mortality rate of 0.1 deaths per person-year for video assisted thorascopic surgery (VATS) patients and 0.08 for median sternotomy (MS) patients. This equates to a statistically non-significant risk ratio of 1.18 (p=0.42). Results for the randomised comparison were not reported. These results suggest that there is no difference in the overall death rate between VATS and MS in patients with severe emphysema.

		These results should be treated with caution as although based on relatively large numbers (n=511) there may not be sufficient power to detect small differences of clinical significance. In addition, the results are based on a non-randomised comparison therefore the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy 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.
		Benefit of duckbill endobronchial valves compared to control 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.

2.	Progression free survival	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
3.	Mobility	**Benefit of open surgery compared to maximal medical therapy** The six-minute walk distance (6MWD) is defined as the distance that a patient can walk in six minutes, usually on a treadmill. 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 capacity for exercise is limited and it helps to indicate capacity to do everyday tasks. Miller et al (2005) reported a statistically significant mean difference between LVRS and medical management group of 148.8 feet (95% CI 24.3 to 273.2; p=0.019) in favour of LVRS at six months. A 26 metre (85 feet) improvement is most widely considered to be the minimal change that is clinically important to patients (MCID) for 6MWD (Jones et al 2014). Therefore, these results show that LVRS offers a clinically meaningful improvement in exercise capacity as measured by the 6MWD for up to six months in patients with severe emphysema. These results are based on a meta-analysis of two RCTS with a relatively small pooled sample size (n=93) and short follow-up of six months and therefore there is a large range of uncertainty around the estimated effect size with a possibility of the true effect being lower than the MCID. In addition, it was not possible to blind the patients to their allocated treatment in the trials so patients in the intervention group may be more likely to try harder in the tests and hence bias the results in favour of LVRS. Therefore, these results should be treated with caution

		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in 6MWD of 66 metres (95% CI 32 to 101; p=0.0002) in favour of VATS. These results suggest that VATS offers a greater improvement in 6MWD of 66 metres compared to medical management in patients with severe emphysema at 12 months. This is of clinical significance, with a difference of 26 metres in patients with severe COPD being identified as the minimal difference that is clinically important to patients (MCID) (Jones et al 2014). These results should be treated with caution as they are based on a single RCT with a relatively small sample size (n=55) and short follow-up of 12 months, therefore there is a large range of uncertainty around the estimated effect size and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. Furthermore, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to try harder in the tests and hence bias the results in favour of LVRS.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) In a non-randomised comparison, McKenna et al (2004) found no significant difference in the percentage of patients with an improvement in 6MWD (the cut-off point used to define improvement was not reported) at 12 months (37% of VATS patients vs 44% of MS patients; p=0.09) and 24 months (25% of VATS patients vs 33% of MS patients; p=0.11). Results for the randomised comparison were not reported. These results suggest that there is no difference in improvement in exercise capacity, as measured by the 6MWD, with VATS compared to MS for patients with severe emphysema. These results should be treated with caution as stated in No. 1. In addition, it was not possible to blind the patients to their allocated treatment so patients in one of the groups may be more likely to try harder in the tests and hence bias the results.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy 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 (6MWD) 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.
		Benefit of duckbill endobronchial valves compared to control 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.
4.	Self-care	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported

		Benefit of duckbill endobronchial valves compared to control Not reported
5.	Usual activities	**Benefit of open surgery compared to maximal medical therapy** St. George's Respiratory Questionnaire (SGRQ) is a validated, disease related, self-administered, measure of quality of life (QoL). It contains 50-items covering symptoms, activities and psychosocial impact. The best study, Naunheim et al (2016), reported on the percentage of patients with a clinically significant improvement in SGRQ which is defined as a decrease in SGRQ score of >8 units over five years. Amongst all patients (n=1,218), 40%, 32%, 20%, 10%, and 13% of lung volume reduction surgery (LVRS) patients improved in SGRQ at 1, 2, 3, 4, and 5 years respectively compared to 9%, 8%, 8%, 4%, and 7% control patients. This represents odds ratios (ORs) of 6.50 ($p<0.001$), 5.27 ($p<0.001$), 3.06 ($p<0.001$), 2.63 ($p=0.05$) and 2.16 ($p=0.12$) at 1, 2, 3, 4, and 5 years respectively. An average initial improvement (time point not defined) of 10.7 units in surviving LVRS patients and a decline of 2.2 units in control patients were reported. Mean values were not reported for other time points. Minimal clinically important differences (MCID) range from 2 to 8 points in the literature (Jones et al 2014). Naunheim et al (2016) used a greater than 8-point decrease to define a change that is clinically important to patients. Therefore, these results show that LVRS offers clinically meaningful improvements in QoL as measured by the SGRQ for up to four years. LVRS patients were three times more likely to show an improvement in SGRQ than those in the control group at four years. These results are based on a well-conducted randomised controlled trial (RCT) with a large sample size (1,218) and long follow-up of five years. One issue is that it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely give positive responses and hence bias the results in favour of LVRS. Furthermore, 30% of the LVRS group had video assisted thoracoscopic surgery (VATS) rather than open surgery which may have affected the results. However, overall these results provide good evidence that open LVRS benefits patients in terms of QoL.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy VATS aims to improve patient QoL by improving lung function, reducing breathlessness and increasing exercise capacity. At six months, Mineo et al (2004) reported a statistically significant mean difference (in change from baseline) between the groups in SGRQ score overall of 7.6 in favour of VATS ($p=0.0001$). Confidence intervals were not reported. Long-term results for the VATS group only, show an improvement in SGRQ score from baseline with mean (SE) overall scores of 29.0 (3.5), 30.5 (3.6), 31.0 (3.5), 31.6 (5.2) at 1, 2, 3 and 4 years respectively compared to a baseline mean (SE) score of 38.5 (4.6)

		These were all statistically significant improvements from baseline with p-values of <0.01, 0.01, 0.03 and 0.03 at 1, 2, 3 and 4 years respectively. These results suggest that VATS improves QoL by 7.6 points more than medical management as measured by SGRQ in the short-term. This is likely to be a clinically meaningful difference to patients with severe emphysema, with MCID ranging from 2 to 8 points in the literature, with 4 being the average (Jones et al 2014). The longer-term results show an improvement in SF-36 score from baseline up to four years, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months. These results are taken from a small RCT (n=60) therefore there is a large range of uncertainty around the estimated effect sizes. In addition, the long-term impacts are not certain as from six months patients were allowed to cross over to LVRS and an intention to treat analysis was not carried out. Furthermore, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to give positive responses and hence bias the results in favour of LVRS.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) In a non-randomised comparison, McKenna et al (2004) found no statistically significant difference in the percentage of patients with an improvement in the SGRQ (defined as a decrease in SGRQ score of >8 units from baseline) at 12 months (55% of VATS patients vs 67% of MS patients; p=0.23) and 24 months (52% of VATS patients vs 53% of MS patients; p=0.73). Results for the randomised comparison were not reported. The results suggest that there is no evidence of a difference in QoL as measured by SGRQ between VATS and open surgery in patients with severe emphysema up to two years. These results should be treated with caution as stated in No. 1. In addition, it was not possible to blind the patients to their allocated treatment, so patients in one of the groups may be more likely to try harder in the tests and hence bias the results.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Valve treatment aims to improve patient quality of life (QoL) by 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
		Benefit of duckbill endobronchial valves compared to control 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 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.
6.	Pain	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported

		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
7.	Anxiety / Depression	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
8.	Replacement of more toxic treatment	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported

		Benefit of duckbill endobronchial valves compared to control Not reported
9.	Dependency on care giver / supporting independence	**Benefit of open surgery compared to maximal medical therapy** The percentage of patients hospitalised or living in a nursing or rehabilitation facility after surgery is an important indicator of independent living. The ability to live independently is an important component of QoL. Naunheim et al (2006) reported that 28.1%, 14.3%, 6.7%, and 3.3% of LVRS patients were hospitalised or living in a nursing or rehabilitation facility (or unavailable for interview but not known to be dead) at 1, 2, 4 and 8 months, respectively compared to 2.2%, 3.3%, 3.2% and 3.7% of control patients. These represented statistically significant differences between the groups at 1 to 4 months, but not at 8 months where only a 0.4% difference was observed. There is evidence to suggest that patients are more likely to be hospitalised or living in a nursing or rehabilitation facility up to four months after surgery, but no significant difference was seen longer-term at eight months between LVRS and medical management. These results are based on a well-conducted RCT with a large sample size (1,218) and therefore provide good evidence of a reduction in independence up to eight months after surgery. However only results up to eight months are provided so long-term effects on independence are not known. Furthermore, 30% of the LVRS group had VATS rather than open surgery which may have affected the results.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy The modified Medical Research Council Dyspnoea Scale (mMRC) ranges from 0-4 and is a validated tool used to establish levels of functional impairment or perceived impairment due to dyspnoea (breathlessness) attributable to respiratory disease. It consists of six phrases describing how much breathlessness interferes with daily activities. At six months, Mineo et al (2004) reported a statistically significant mean difference (in change from baseline) between the groups in mMRC score of 1.2 in favour of VATS ($p<0.0001$). Confidence intervals were not reported. Long-term results for the VATS group only, show an improvement in mMRC score from baseline with mean (SE) overall scores of 1.9 (0.1), 1.92 (0.20), 2.04 (0.10), 2.46 (0.10) at 1, 2, 3 and 4 years respectively compared to a baseline mean (SE) score of 3.3 (0.1). These were all statistically significant improvements from baseline with p-values of <0.001, <0.0001, 0.0001 and 0.002 at 1, 2, 3 and 4 years respectively. These results suggest that VATS improves dyspnoea as measured by the mMRC by 1.2 points more than medical management in patients with severe emphysema in the short-term. It is not known if this

		difference is clinically meaningful to patients as the mMRC scale, although widely used, is reported to have poor evaluative properties to assess changes in dyspnoea (Jones et al 2014). The longer-term results show an improvement in mMRC score from baseline up to four years, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months. These results are taken from a small RCT (n=60) as stated in No. 5.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) The ability to live independently is an important component of QoL. This outcome was not defined by McKenna et al (2004), but it is likely to refer to the percentage of patients not hospitalised or living in a nursing or rehabilitation facility. In the randomised comparison, McKenna et al (2004), reported there was a statistically significant difference in the percentage of patients living independently at 30 days after surgery in favour of VATS (87.3% of VATS patients vs 62.3% of MS patients, p=0.001). The difference at four months was statistically non-significant (90.1% of VATS patients vs 83.1% of MS patients, p=0.24). The baseline figures were not given. The results suggest that VATS patients are more likely to live independently in the month after surgery compared to patients having open surgery, but this difference disappears by four months after surgery. These results are based on a well conducted randomised controlled trial (RCT) with a moderate sample size (n=148) and overall provide good evidence that VATS patients are more likely to live independently within 30 days of surgery compared to open surgery patients.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy 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.
		Benefit of duckbill endobronchial valves compared to control

		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.
10.	Safety	**Benefit of open surgery compared to maximal medical therapy** Assessing complications arising during surgery is important as if serious and/or common they may outweigh the benefits associated with LVRS. An earlier publication of the National Emphysema Treatment Trial (NET) trial on safety and effectiveness of LVRS by open surgery compared to video assisted thoracoscopic surgery (VATS) reported that 7% of open LVRS patients who were not at high-risk (n=359) had intraoperative complications which included arrhythmia (1.7%), uncontrolled air leak (0.8%), hypoxaemia (0.8%), hypercapnia (0.8%), hypotension (0.3%), cardiac arrest (0.3%), and other complications (3.3%). Only percentages were reported, not number of patients (McKenna et al 2004). The mean blood loss during open LVRS was 138.0 ml and 3.1% of patients needed a transfusion. These results suggest a moderate complication rate during open LVRS in patients with severe emphysema. However, the severity and long-term impact of this are not discussed, which makes it difficult to interpret the significance of this finding for patients. These results are taken from a large group of patients having open LVRS (n=359) from a well conducted RCT and therefore provide good evidence of complications associated with open LVRS.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Total complications occurring over the follow-up period are important as if shown to be serious and/or common they may outweigh the benefits associated with VATS. During the 12-month follow-up period after hospital, Goldstein et al (2003) reported that 4/28 LVRS patients (14%) required subsequent hospital admissions (due to colitis, pneumonia, respiratory failure & empyema) and there were no hospital admissions for control patients. Other than this, Goldstein et al (2003) reported that the only morbidities encountered were ischaemic heart disease (one surgical and one control subject) and respiratory infections (30 surgical and 35 control subjects).

		These results suggest a relatively high readmission rate (14%) associated with VATS. This has implications for the patient as well as hospital resources. These results are taken from a relatively small single RCT so therefore there will be a large range of uncertainty around these rates. In addition the trial included a small number of open surgery cases (number not known) so some of the admissions may not be associated with VATS surgery.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) McKenna et al (2004) reported that intraoperative complications included hypotension, arrhythmia, hypoxaemia, hypercapnia, cardiac arrest and uncontrolled air leak. In the non-randomised comparison, McKenna et al (2004), found a statistically significant mean difference in the percentage of patients with intraoperative complications of 6.8% (13.8% of VATS group and 7.0% of MS group; p=0.02). However, the randomised comparison showed a non-significant difference (no figures reported). Hypoxaemia was the only complication that was significantly different between the two groups with a higher rate seen in the VATS group (5.3% in VATS compared to 0.8% in MS; p=0.04) for the non-randomised comparison, but it was found to be non-significant in the randomised comparison (p=0.25). Therefore, the evidence is unclear regarding any difference in intraoperative complications between the two groups. These results should be treated with caution as although the randomised comparison was based on a moderate number (n=148) there may not be sufficient power to detect small differences of clinical significance. In addition, for the non-randomised comparison results the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Assessing adverse events (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.
		Benefit of duckbill endobronchial valves compared to control Assessing serious adverse events (SAEs) related to a treatment is important, particularly if the treatment appears to be clinically effective in reducing symptoms. The best data on SAEs (as defined by study authors) 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). The importance to patients of these SAEs relative to the clinical 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
11.	Delivery of intervention	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported

Other health metrics determined by the evidence review		
No	**Outcome measure**	**Summary from evidence review**
1.		**Benefit of open surgery compared to maximal medical therapy**

	Lung function – forced expiratory volume in one second (FEV1) from baseline	Forced expiratory volume in one second (FEV1) is the maximal quantity of air a patient can exhale in one second. It 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 FEV1 is lower. It is expressed in litres or as percentage of predicted value (% predicted) based on age, size, sex and race. The study with the longest follow-up, Hillerdal et al (2005) reported a statistically significant mean difference (of changes from baseline) between the groups of 0.23 litres (95% CI 0.14 to 0.31) for FEV1 at six months and 0.19 litres (95% CI 0.09 to 0.28) at 12 months in favour of LVRS. An increase of 0.1 litres is widely considered to be an MCID (Jones et al 2014). Therefore, these results show that LVRS offers a clinically meaningful improvement in lung function as measured by FEV1 up to 12 months in patients with severe emphysema. These results are based on a RCT with a relatively small sample size (n=106) and short follow-up of 12 months hence there is a large range of uncertainty around the estimated effect sizes and the long-term impacts are not known.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in FEV1 of 0.3 L (95% CI 0.1 to 0.5; p=0.0003) in favour of VATS. These results suggest that VATS offers a greater improvement in FEV1 compared to medical management in the short-term (up to 12 months) by 0.3 litres in patients with severe emphysema. A difference of 0.1 litres is considered to be a MCID and therefore even at the lower limit of the confidence interval, this would be considered a clinically significant difference (Jones et al 2014). These results are based on an RCT with a relatively small sample size (n=55) and short follow-up of 12 months and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy

		If valve treatment allows less damaged, more elastic areas of lung to expand in place of more damaged lung, FEV1 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 FEV1 at three months (0.90 litres for valves vs 0.87 for controls, p=0.065); the other study found a change in FEV1 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 FEV1, compared to maximal medical therapy. van Agteren et al (2017) graded the evidence relating to FEV1 as moderate quality. The deleterious effect of valves on FEV1 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.
		Benefit of duckbill endobronchial valves compared to control Not reported
2	Lung function - Forced expiratory volume in one second, % predicted	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in FEV1 of 11% predicted in favour of VATS ($p<0.05$). Confidence intervals were not reported. These results suggest that VATS offers a greater improvement in FEV1 % predicted compared to medical management in the short-term (up to 12 months) by 11% in patients with severe emphysema. This difference is of clinical significance as a difference of 5-10% is considered to be a MCID (Jones et al 2014). These results should be treated with caution as stated in Table 1 No.3 (Goldstein 2003).
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy

		In a non-randomised comparison, McKenna et al (2004) found a statistically significant difference in the percentage of patients with an improvement in FEV1 % predicted (the cut-off point used to define improvement was not reported) in favour of open surgery (51% of VATS patients vs 60% of MS patients; p=0.05) at 12 months. However, no evidence of a difference was seen at 24 months (40% of VATS patients vs 47% of MS patients; p=0.12). Results for the randomised comparison were not reported. These results suggest a greater proportion of open surgery patients showed improvements in FEV1 in the short-term (up to 12 months) compared to VATS patients, but there was no evidence of a difference between the groups in the longer-term (up to 24 months). Absolute values were not reported so it was not possible to determine whether the differences seen at 12 months were clinically meaningful to patients. These results should be treated with caution as stated in Table 1 No. 1 (McKenna 2004).
		Benefit of duckbill endobronchial valves compared to control 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 FEV1 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 FEV1 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 FEV1 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 FEV1 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.
3	Lung function - FEV_1/FVC, %	**Benefit of open surgery compared to maximal medical therapy** Not reported

		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy The FEV1/FVC ratio is the amount of air exhaled in the first second divided by all of the air exhaled during maximal exhalation. It is widely used in clinical practice to differentiate obstructive (e.g. low FEV1/FVC ratio with normal FVC) from restrictive (e.g. normal FEV1/FVC ratio and low FVC) lung disease. Emphysema is an obstructive lung disease, with lower FEV1/FVC ratio indicating more severe disease. At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in FEV1/FVC of 3% in favour of VATS ($p<0.05$). Confidence intervals were not reported. These results suggest that VATS offers a greater improvement in FEV1/FVC compared to medical management in the short-term (up to 12 months). However, no value for the MCID was found in the papers that were reviewed so it is not clear if this effect is clinically meaningful. These results should be treated with caution as stated in Table 1 No. 3.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
4	Lung function – change in residual volume (RV) from baseline	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy 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.
		Benefit of duckbill endobronchial valves compared to control 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. 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.
5	Lung function - Change in total lung capacity (TLC) from baseline	**Benefit of open surgery compared to maximal medical therapy** Total lung capacity (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. The study with the longest follow-up, Hillerdal et al (2005), reported a statistically significant mean difference (of changes from baseline) of -0.36 litres (95% CI -0.80 to -0.08) at 6 months and -0.48 litres (95%CI -0.91 to -0.05) at 12 months in favour of LVRS. These results show that open LVRS offers a reduction in TLC in patients with severe emphysema. However, no MCID could be found in the papers reviewed so it is not clear if these changes are of clinical importance.

		These results are based on a RCT with a relatively small sample size as stated in Table 2 No. 1.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in TLC of -15% in favour of VATS ($p<0.05$). Confidence intervals were not reported These results suggest that VATS offers a greater reduction in TLC compared to medical management in patients with severe emphysema. However, no value for the minimal difference that is clinically important (MCID) was found so it is not clear if these changes are of clinical importance. These results should be treated with caution as stated in Table 1 No.3 (Goldstein 2003).
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy 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.
		Benefit of duckbill endobronchial valves compared to control 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.
6	Lung function - Functional residual capacity	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Functional residual capacity (FRC) is the volume of air in the lungs after a normal relaxed expiration. It is a measure of elasticity of the lungs. The damage and loss of elasticity in emphysema increases the FRC resulting in reduced overall lung function. At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in FRC of -41% in favour of VATS ($p<0.05$). Confidence intervals were not reported. These results suggest that VATS offers a greater reduction in FRC compared to medical management in patients with severe emphysema up to 12 months. However, no value for MCID was found so it is not clear if these changes are of clinical importance. These results should be treated with caution as stated in Table 1 No.3 (Goldstein 2003).
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
7	Lung function – Residual volume, litres	**Benefit of open surgery compared to maximal medical therapy** Residual volume (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. Lung damage and loss of elasticity in emphysema increases the RV. The study with the longest follow-up, Hillerdal et al (2005), reported a non-significant mean difference (of changes from baseline) between the groups of -0.94 litres (95% CI -1.37 to 0.52) at six months and a significant mean difference of -1.00 litres (95% CI -1.37 to -0.62) at 12 months in favour of LVRS.

		These results show that there is evidence to support a reduction in RV with open LVRS at 12 months but the results at six months are uncertain. Reductions of 350 ml and 430 ml have been defined in studies as MCIDs (van Agteren et al 2017) which would mean that the 12 month reduction of 1 litres would be clinically meaningful to patients. These results are based on a single RCT as stated in Table 2 No.1.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy At six months, Mineo et al (2004) found a statistically significant mean difference (in change from baseline) between the groups in RV of -1.4 litres in favour of VATS ($p<0.0001$). Confidence intervals were not reported. Long-term results for the VATS group only, show an improvement in RV from baseline with a mean (standard error (SE)) RV of 4.2 litres (0.1), 4.57 litres (0.10), 4.73 litres (0.10), 4.92 litres (0.10) at 1, 2, 3 and 4 years respectively compared to a baseline mean (SE) of 5.5 litres (0.1). These were all statistically significant improvements from baseline with p-values of <0.001, <0.0001, <0.0001 and <0.0001 at 1, 2, 3 and 4 years respectively. These results suggest that there is evidence to support a greater reduction in RV with VATS compared to medical management, in the short-term (up to six months) in patients with severe emphysema. Reductions of 350 ml and 430 ml have been defined in studies as MCIDs (van Agteren et al 2017) which would mean that the reduction of 1.4 litres found between the two groups is likely to be clinically meaningful to patients. The longer-term results show an improvement in RV from baseline for up to four years, but it is not known how this compares to patients in the control group as control patients were allowed to cross over to LVRS from six months. These results are taken from a small RCT (n=60) as stated in Table 1 No.5.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
8	Lung function – Residual	**Benefit of open surgery compared to maximal medical therapy** Not reported

	volume, % predicted	**Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy** At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in RV as a % of predicted RV of -47% in favour of VATS (95% CI -71 to -23; p=0.0002) These results suggest that VATS offers a reduction in RV in patients with severe emphysema However, no value for MCID was found so it is not clear if these changes are of clinical importance. These results should be treated with caution as stated in Table 1 No. 3.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
9	Lung function - Decrease in ratio of RV to TLC (RV/TLC) from baseline	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy 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. At three months, Clarenbach et al (2015) found a statistically significant mean difference (in change from baseline) between the groups in RV/TLC of -7.8% (95% CI -13.6 to -1.9; p=0.011) in favour of VATS. These results suggest that VATS reduces RV/TLC by 7.8% more than medical management in patients with severe emphysema in the short-term (up to three months). This reduction is likely to be clinically meaningful to patients as an MCID of 4% was found in the literature (van Agteren et al 2017). These results should be treated with caution as they are taken from a single RCT with a relatively small sample size (n=30) with a short follow-up (3-months) and therefore there is a large range of uncertainty around the estimated effect size and the long-term impacts are not

		known. In addition, the groups were not balanced at baseline with the control group likely to have a worse prognosis (older, more pack years of smoking and greater cardiovascular medication use) which could bias the results in favour of VATS.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy 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.
		Benefit of duckbill endobronchial valves compared to control 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.
10	Lung function – Forced vital capacity (FVC), litres	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Forced vital capacity (FVC) is the maximal volume of air forcefully expired after taking a deep breath. It is an indicator of the functional capacity of the lungs and is expressed in litres or as percentage of predicted.

		At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in FVC of 0.7 litres in favour of VATS ($p<0.05$). Confidence intervals were not reported. These results suggest that VATS offers a greater improvement in FVC compared to medical management in the short-term (up to 12 months) in patients with severe emphysema. However, no value for the MCID was found in the papers that were reviewed so it is not clear if this effect is clinically meaningful. These results should be treated with caution as stated in Table 1 No. 3.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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.
11	Lung function - Forced vital capacity, % predicted	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy At 12 months, Goldstein et al 2003 found a statistically significant mean difference in FVC as a % of predicted FVC (adjusted for baseline scores) between the groups of 18% in favour of VATS ($p<0.05$). Confidence intervals were not reported. These results suggest that VATS offers a greater improvement in FVC % predicted compared to medical management in the short-term (up to 12 months). However, no value for the MCID was found in the papers that were reviewed so it is not clear if this effect is clinically meaningful. These results should be treated with caution as stated in Table 1 No.3.

		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
12	Lung function – Vital capacity, litres	**Benefit of open surgery compared to maximal medical therapy** Vital capacity (VC) is the maximum amount of air a person can expel from the lungs after a maximum inhalation and is another indicator of lung function. Hillerdal et al (2005) reported a statistically significant mean difference (of changes from baseline) of 0.45 litres (95% CI 0.18 to 0.72) for VC at six months and 0.39 litres (95% CI 0.13 to 0.65) at 12 months in favour of LVRS. These results show that open LVRS offers an increase in VC in patients with severe emphysema. However, no MCID was found in the literature so it is not clear if these improvements are clinically important. These results are based on a single RCT as stated in Table 2 No.1.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
13	Lung function – Partial	**Benefit of open surgery compared to maximal medical therapy** Not reported

	pressure of oxygen in arterial blood	**Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy** Partial pressure of oxygen in arterial blood (PaO2) is the pressure of oxygen dissolved in the arterial blood. It is a measure of how well oxygen is able to move from the airspaces of the lungs into the blood. An increase in PaO2 signifies an improvement in condition. At six months, Mineo et al (2003) found a statistically significant mean difference (in change from baseline) between the groups in PaO2 of 0.9 kPa in favour of VATS ($p<0.002$). Confidence intervals were not reported. Long-term results for the VATS group only, show an improvement in PaO2 from baseline with a mean (SE) PaO2 of 9.5 kPa (0.1), 9.8 kPa (0.1), 9.5 kPa (0.1), 9.3 kPa (0.1) at 1, 2, 3 and 4 years respectively compared to a baseline mean (SE) of 5.5 (0.1). The 1 and 4-year results were statistically significant improvements from baseline with p-values seen of <0.01, >0.05, >0.05 and 0.04 at 1, 2, 3 and 4 years respectively (Mineo et al 2004). Evidence was found of an effect of VATS on PaO2 compared to medical management in the short-term (up to six months) in patients with severe emphysema. However, no value for the MCID was found in the papers that were reviewed so it is not clear of this effect is clinically meaningful. The longer-term results show some improvement in PaO2 from baseline, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months. These results are taken from a small RCT (n=60) as stated in Table 1 No. 5.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
14	Lung function – Partial pressure of carbon dioxide in arterial blood	**Benefit of open surgery compared to maximal medical therapy** Carbon dioxide (CO2) is produced through metabolic processes in the body and enters the blood. The lungs help to remove the CO2 from the blood. Partial pressure of carbon dioxide in arterial blood (PaCO2) is the pressure of CO2 dissolved in the arterial blood and is a measure of how well the lungs are able to remove CO2 from the blood. A reduction in PaCO2 signifies an improvement in lung function.

		Miller et al (2005) reported a statistically significant mean difference for PaCO2 of -3.7183 mm Hg (95% CI -6.960 to -0.477; p=0.025) in favour of LVRS. These results suggest that LVRS offers a reduction in PaCO2 in patients with severe emphysema. However, no value for MCID so it is not clear if these improvements are clinically meaningful to patients. These results are based on a meta-analysis of 2 RCTS with a relatively small pooled sample size (n=93) and short follow-up of six months. There is a wide range of uncertainty around the effect size and the long-term impacts are not known
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy At six months, Mineo et al (2003) found a statistically non-significant mean difference (in change from baseline) between the groups in PaCO2 of -0.1 kPa. Confidence intervals and p-values were not reported. These results suggest that there is no evidence of a difference in PaCO2 between VATS and medical management in patients with severe emphysema at six months. These results are taken from a small RCT (n=60) as stated in Table 1 No. 5.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
15	Lung function – Diffusion capacity of the lung for carbon monoxide (DLCO)	**Benefit of open surgery compared to maximal medical therapy** Emphysema damages lung tissue, reducing the diffusion capacity of the lung for oxygen and hence causing breathlessness. The diffusion capacity of the lung for carbon monoxide (DLCO) is a measure of this diffusion capacity of the lung for gases. Miller et al (2005) reported a non-significant mean difference for DLCO of 0.9810 mL/min/mm Hg (95% CI -0.334 to 2.296; p=0.144). LVRS was not shown to improve DLCO in patients with severe emphysema.

		These results are based on a meta-analysis of 2 RCTS as stated in Table 2 No. 14.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy At 12 months, Goldstein et al (2003) found a non-significant mean difference (adjusted for baseline scores) between the groups in DLCO of 4% predicted. Confidence intervals were not reported. These results do not provide evidence of a difference in DLCO between VATS and medical management in patients with severe emphysema at 12 months. The results should be treated with caution as stated in Table 1 No.3.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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. 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.
16	Endothelial function – Flow-mediated dilatation of the brachial artery, %	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Flow-mediated dilatation of the brachial artery (FMD) can be used to assess endothelial function, which has been shown to be predictive of cardiovascular risk. There is a theory that airflow obstruction and systemic inflammation in emphysema may contribute to endothelial dysfunction thereby increasing the risk of cardiovascular disease in patients with emphysema.

		At three months, Clarenbach et al (2015) reported a statistically significant mean difference (in change from baseline) between the groups in FMD of 2.9% (95% CI 2.1 to 3.6; p<0.001). These results suggest that LVRS patients have a greater increase in endothelial function by 2.9% as measured by FMD compared to control patients in the short term. This is likely to be a clinically meaningful effect size as the relative risk of cardiovascular events has been shown to increase by 13% per 1% decrease in FMD (Clarenbach et al 2015). These results should be treated with caution as they are taken from a single RCT with a relatively small sample size (n=30) with a short follow-up (3-months) and therefore there is a large range of uncertainty around the estimated effect size and the long-term impacts are not known.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
17	Endothelial function - Nitroglycerine-mediated dilatation, %	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Nitroglycerine-mediated dilatation (NMD) can be used to assess endothelial function which has been shown to be predictive of cardiovascular risk. There is a theory that airflow obstruction and systemic inflammation in emphysema may contribute to endothelial dysfunction thereby increasing the risk of cardiovascular disease in patients with emphysema. At three months, Clarenbach et al (2015) reported a statistically non-significant mean difference (in change from baseline) between the groups in NMD of -1.7% (95% CI -5.9 to 2.5; p=0.412). These results suggest that there is no evidence of a difference in endothelial function as measured by NMD between VATS and medical management in patients with severe emphysema in the short-term. These results should be treated with caution as they are taken from a single RCT with a relatively small sample size (n=30) with a short follow-up (3-months) therefore it may not have the power to detect

		small differences in effect size that could still be of clinical significance and the long-term impacts are not known
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
18	Systemic inflammation – High sensitive C-reactive protein, mg/L	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy High sensitive C-reactive protein (CRP) is a marker for systemic inflammation which occurs in emphysema and is associated with atherosclerosis (hardening and narrowing of the arteries due to build-up of fatty plaques) and an increased risk of cardiovascular disease. At three months, Clarenbach et al (2015) reported a statistically non-significant mean difference (in change from baseline) between the groups in CRP of 0 mg/L (95% CI -0.9 to 0.6; p=0.942). These results suggest that there is no evidence of a difference in systemic inflammation as measured by CRP between VATS and medical management in patients with severe emphysema in the short-term. These results should be treated with caution as they are taken from a single RCT with a relatively small sample size (n=30) as stated in Table 2 No. 17.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported

19	Exercise capacity - Submaximal endurance time, min	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise. Submaximal endurance time is a measure of integrated cardiopulmonary and physical performance. It is determined by a submaximal, constant power exercise test using a cycle ergometer. Submaximal cycle endurance time was not defined by Goldstein et al (2003). At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups of 7.3 minutes (95% CI 3.9 to 10.8; p<0.0001) in favour of VATS. These results suggest that VATS offers a greater improvement in exercise capacity as assessed by submaximal endurance time compared to medical management in patients with severe emphysema. It is not clear whether these results are clinically meaningful to patients as no value for the MCID was found in the papers that were reviewed. These results should be treated with caution as stated in Table 1 No. 3.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
20	Exercise capacity - Number of steps per 24 hours, number	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. An increase in the number of steps per 24 hours is an indication of whether a patient does more exercise following VATS, which might indicate that the surgery enables them to exercise more.

		At three months, Clarenbach et al (2015) found a statistically non-significant mean difference (in change from baseline) between the groups of 120 steps (95% CI 0 to 667; p=0.100). These results suggest that there is no evidence of a difference in exercise capacity as measured by number of steps per 24 hours between VATS and medical management in patients with severe emphysema in the short-term. These results should be treated with caution as they are taken from a single RCT with a relatively small sample size (n=30) as stated in Table 2 No. 17. In addition, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to be more motivated to take more steps and hence bias the results in favour of LVRS. Furthermore, the number of steps in 24 hours may be influenced by many factors, not just lung function, so other measures of exercise capacity may provide more robust measures.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
21	Exercise capacity – Maximum work, Watts	**Benefit of open surgery compared to maximal medical therapy** A measure of integrated cardiopulmonary and physical performance. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. The maximum work load is the highest work level reached (measured in Watts) and maintained for a full minute. It is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks. The best study, Naunheim et al (2016), reported on the percentage of patients with an improvement in maximum exercise capacity (defined as increase in maximum work of >10 Watts). Amongst all patients (n=1,218), 23%, 15%, and 9% of LVRS patients improved in maximum exercise capacity at 1, 2 and 3 years respectively compared to 5%, 3%, and 1% of control patients. This represents statistically significant ORs of 5.79 (p<0.001), 5.06 (p<0.001), 7.43 (p<0.001) at 1, 2 and 3 years respectively in favour of LVRS. An average initial improvement (time point not defined) of 5.4 Watts in surviving LVRS patients and a decline by 4.4 Watts in control patients were reported. Naunheim et al (2016) used 10 Watts or greater increase to define a change that is clinically important to patients. Therefore, these results

		show that LVRS offers clinically meaningful improvements in exercise capacity as measured by cycle ergometer maximum exercise capacity tests for up to three years. These results are based on a well-conducted RCT with a large sample size (1,218) as stated in Table 1 No. 5 (Naunheim 2016). However, overall these results provide good evidence that open LVRS benefits patients in terms of exercise capacity.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Maximum work load is a measure of integrated cardiopulmonary and physical performance. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. The maximum work load is the highest work level reached (measured in Watts) and maintained for a full minute. It is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks. At six months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) of 13 Watts (95% CI 6 to 20; p=0.0003) in favour of VATS. The results for 12 months were not reported. These results suggest that VATS offers a greater improvement in maximum work load of 13 Watts compared to medical management in patients with severe emphysema at six months. Naunheim et al (2016) used 10 Watts or a greater increase to define a change that is clinically important to patients. Therefore, these results suggest that VATS offers clinically meaningful improvements in exercise capacity as measured by cycle ergometer maximum exercise capacity tests in the short-term (up to six months). These results should be treated with caution as they are based on a single RCT with a relatively small sample size (n=55) as stated in Table 1 No. 3.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) This is a measure of integrated cardiopulmonary and physical performance. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. The maximum work load is the highest work level reached (measured in Watts) and maintained for a full minute. It is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks. In a non-randomised comparison, McKenna et al (2004) found a statistically significant difference in the percentage of patients with an improvement in maximum work (defined as increase in maximum work of greater than 10 Watts from baseline) in favour of open surgery at 12 months (41% of VATS patients vs 46% of MS patients; p=0.05) and at

		24 months (26% of VATS patients vs 35% of MS patients; p=0.03). Results for the randomised comparison were not reported. The results suggest a greater improvement in exercise capacity with open surgery compared to VATS as measured by cycle ergometer maximum exercise capacity tests up to two years. Although the absolute values are not reported, the difference between the groups is likely to be clinically meaningful as to improve patients had to have an increase in maximum work of greater than 10 Watts from baseline, which the authors define as clinically significant. These results should be treated with caution as stated in Table 1 No. 3 (McKenna 2004).
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
22	Exercise capacity – Incremental shuttle walking distance, metres	**Benefit of open surgery compared to maximal medical therapy** The incremental shuttle walking distance (ISWD) is a progressive exercise test where patients walk 10 metres at a set speed. After each 10 metres, the speed is increased in a standardised manner until point of intolerance. It measures total distance walked. Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. The ISWD is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks. Hillerdal et al (2005) found a statistically significant mean difference (of changes from baseline) between the groups of 104 metres (95% CI 57 to 151) at six months and 90 metres (95% CI 47 to 133) at 12 months in favour of LVRS. An MCID for ISWD is considered to be 47.5 metres (Jones et al 2014). Therefore, these results show that LVRS offers a clinically meaningful improvement in exercise capacity as measured by the ISWD up to 12 months in patients with severe emphysema. These results are based on an RCT with a relatively small sample size (n=106) as stated in Table 2 No. 1. In addition, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to try harder in the tests and hence bias the results in favour of LVRS. Therefore, these results should be treated with caution.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported

		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
23	Exercise capacity – increase in steps per day at 6 months	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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 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.
24	Exercise capacity – increase in locomotion duration at 6 months	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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 as stated in Table 2 No. 23.
25	Exercise capacity – increase in walk intensity (average body acceleration) at 6 months	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported

		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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. 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 as stated in Tabel 2 No. 23.
26	Exercise capacity – increase in sitting duration at 6 months	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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 as stated in Table 2 No. 23.
27	Exercise capacity – increase in duration of inactivity at 6 months	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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) as stated in Table 2 No. 23.
28	Body weight, kg	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Weight loss, muscle wasting, as well as muscle dysfunction are recognised as important problems in emphysema, contributing to morbidity and mortality. Therefore body weight gain is an important outcome for patients. At six months, Mineo et al (2004) reported a statistically significant mean difference (in change from baseline) between the groups in body

		weight of 4.5 kg in favour of VATS (p<0.0001). Confidence intervals were not reported. The results suggest a greater effect of VATS on body weight gain compared to medical management in patients with severe emphysema in the short-term. However, it is not clear whether this difference is clinically meaningful to patients as no value for the MCID for body weight or BMI was found (Wouter et al 2005). These results are taken from a small RCT (n=60) as stated in Table 1 No. 5.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
29	Oxygen dependent patients, %	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Emphysema can limit the ability of the lungs to absorb sufficient oxygen leading to low PaO2, which is a risk for complications such as pulmonary hypertension and can affect breathlessness and patients' exercise capacity and QoL. Mineo et al (2004) reported that oxygen dependency was considered whenever PaO2 was 8.64kPa or less, but no further details were provided on the type of oxygen dependency (e.g. short-term for an exacerbation or long-term). At six months, Mineo et al (2004) reported a statistically significant difference in percentage of oxygen dependent patients (from changes from baseline) between the groups of 51.7% in favour of VATS (p=0.02). Confidence intervals were not reported. At baseline 63.3% of VATS patients and 60.0% of control patients were dependent on oxygen and this reduced to 7.1% in VATS patients and 55.5% in control patients at six months after surgery or randomisation. The results appear to suggest a large difference in the percentage of patients requiring oxygen of some type between the groups after surgery. This will have an impact on the QoL of patients and healthcare resources.

		These results are taken from a small RCT (n=60) as stated in Table 1 No. 5.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
30	Steroid dependent patients, %	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Steroids reduce inflammation caused by emphysema and can improve symptoms in patients with severe emphysema. However they have side effects which can affect QoL such as sore mouth, infections and weight gain. Mineo et al (2004) defined steroid dependency as having an oral methylprednisolone intake of 8 or more mg per day for a minimum of one month within the last year's pre-treatment. At six months, Mineo et al (2004) reported a statistically non-significant difference in the percentage of steroid dependent patients (from changes from baseline) between the groups of 34.6% in favour of VATS. Confidence intervals or p-values were not reported. At baseline, 73.3% of VATS patients and 80.0% of control patients were dependent on steroids and this reduced to 14.2% in VATS patients and 55.5% in control patients at six months after surgery or randomisation. Thus no evidence was found of an effect of VATS on steroid dependency compared to medical management in the short-term. These results are taken from a relatively small RCT (n=60) As stated in Table 1 No. 5. Furthermore, the paper's definition of steroid dependency is unclear, but seems to imply that to be considered dependent on steroids, the patient had to be on steroids for at least a month within the last year, so for the six month results, this would include six months prior to surgery and six months post surgery.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported

		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
31	Treatment failure	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Treatment failure was considered by Goldstein et al (2003) to be death or a functional decline in quality of life (QoL) defined as a consistent reduction of one or more units in two Chronic Respiratory Questionnaire (CRQ) domains (a disease specific QoL measure) from which the patient did not recover. Goldstein et al (2003), reported that by 12 months 7/28 (25%) patients in the VATS group had treatment failure (four died and three experienced functional decline) compared to 17/27 (63%) patients in the control group (one died and 16 experienced functional decline). A hazard ratio of 3.1 (95% CI 1.3 to 7.6; p=0.01) at 12 months in favour of VATS was found. The results suggest that patients undergoing VATS are three times less likely to experience treatment failure at one year compared to medical management alone in patients with severe emphysema. The results are based on an RCT with a relatively small sample size (n=55) as stated in Table 1 No. 3.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
32	Mortality – 30-day risk	**Benefit of open surgery compared to maximal medical therapy** The 30-day mortality risk is the chance of a patient dying within 30 days after having LVRS. It is used as a measure of risk of death related to surgery. The effect of treatment on mortality is important, particularly

		for a treatment which, while improving some measures such as lung function, also results in serious adverse events and complications. In an earlier analysis of the NET trial (Naunheim et al 2016), Fishman et al (2003) reported that among the 1,078 patients who were not at high risk (excluding those with FEV1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted), the 30-day mortality risk was 2.2% in the LVRS group compared with 0.2% in the control group ($p<0.001$). Results for all the patients in the trial and for the high-risk patients alone were not reported. There is evidence to suggest an increased risk of early mortality within 30 days after open LVRS in patients with severe emphysema. These results are based on a well-conducted RCT with a large sample size (1,218). One issue to note is that 30% of the LVRS group had VATS rather than open surgery which may have affected the results. Overall, however, the results provide good evidence of an increased risk of early mortality associated with open LVRS.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Goldstein et al (2003) reported that 2/28 (7%) patients died of respiratory failure within 30 days (at days 7 and 15) in the video assisted thoracoscopic surgery (VATS) group compared with 0/27 patients in the control group. No confidence intervals or p-values were reported, but it is likely to represent a non-significant difference due to the small sample size. This means that although the trial observed a higher risk of dying within 30 days of VATS compared to control, it is not known if this is a true difference between the groups due to the small numbers enrolled in the trial. The results should be treated with caution as they are based on a single randomised controlled trial (RCT) with a relatively small sample size (n=55) as stated in Table 1 No. 3.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) In a non-randomised comparison including all patients having LVRS by video assisted thoracoscopic surgery (VATS) or open surgery by median sternotomy (MS), McKenna et al (2004) found no statistically significant difference in the 30-day mortality risk (2.0% for VATS vs 2.8% for MS; $p=0.76$). Results for the randomised comparison were not reported. However, the authors state that similar results were seen in the randomised comparison. The results suggest that there is no evidence of a difference in risk of mortality within 30 days of LVRS between VATS and open surgery.

		These results should be treated with caution as although based on relatively large numbers (n=511) as stated in Table 1 No. 1.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
33	Mortality – 90-day risk, %	**Benefit of open surgery compared to maximal medical therapy** The 90-day mortality risk is the chance of a patient dying within 90 days after having LVRS. It is used as a measure of risk of death that might be related to surgery. The effect of treatment on mortality is important, particularly for a treatment which, while improving some measures such as lung function, also results in serious adverse events and complications. In an earlier analysis of the National Emphysema Treatment Trial (NETT; Naunheim et al 2016), Fishman et al (2003) reported a 90-day mortality risk amongst all patients of 7.9% (95% CI 5.9 to 10.3) in the LVRS group and 1.3% (95% CI 0.6 to 2.60) in the control group. This represents a statistically significant higher risk with LVRS ($p<0.001$). Amongst non-high-risk patients, the risk was 5.2% (95% CI 3.5 to 7.4) in the LVRS group and 1.5% (95% CI 0.6 to 2.9) in the control group ($p=0.001$), and amongst high-risk patients it was 28.6% (95% CI 18.4 to 40.6) in LVRS group and 0% (95% CI 0 to 5.1) in control group. There is evidence to suggest an increased risk of mortality within 90-days of open LVRS. The risk was deemed too high for patients defined as high-risk (those with FEV1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted) and these patients were stopped from being recruited into the trial partway through the trial. These results are based on a well-conducted RCT with a large sample size (1,218) as stated in Table 2 No. 32.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) In a non-randomised comparison, McKenna et al (2004) found a statistically non-significant difference in 90-day mortality risk between VATS and MS (4.6% for VATS vs 5.9% for MS; $p=0.67$). Results for the randomised comparison were not reported.

		The results suggest that there is no evidence of a difference in risk of mortality within 90 days of LVRS between VATS and open surgery in patients with severe emphysema. These results should be treated with caution as although based on relatively large numbers (n=511) as stated in Table 1 No. 1.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
34	Mortality – In hospital risk, %	**Benefit of open surgery compared to maximal medical therapy** The risk of dying in hospital during LVRS or in hospital stay after LVRS. It is used as a measure of risk of death related to surgery. The effect of treatment on mortality is important, particularly for a treatment which, while improving some measures such as lung function, also results in serious adverse events and complications. The study with the slightly larger sample size, Hillerdal et al (2005) reported a in hospital mortality risk of 6/53 (12%) caused by pneumonia and respiratory failure (on days 9, 15, 19, 42, 49, and 71) in the LVRS group. No results for the control group were reported for the same time period. This result suggests a high rate of death in hospital after LVRS. However, this result is higher than the 30-day mortality rate reported in Naumheim et al 2006 of 2.2% (see above) which is based on larger numbers and is likely to be a more accurate figure. The results from Hillerdal et al are only based on 53 LVRS patients and it is not known whether they differ significantly to the mortality rate for control patients for the same time period so should be treated with caution.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported

		Benefit of duckbill endobronchial valves compared to control Not reported
35	Quality of Life-Chronic Respiratory Disease Questionnaire	**Benefit of open surgery compared to maximal medical therapy** Chronic Respiratory Disease Questionnaire (CRDQ) is a patient reported, disease specific measure of QoL which focuses on four domains: dyspnoea, fatigue, emotional function, and mastery (patients' sense of being in control of their lives and their health problem). At six months, Miller et al (2005) found statistically significant improvements with LVRS compared to medical management in all four domains of the CRDQ which included dyspnoea (md = 1.56; 95 CI 0.80 to 2.32; p=0.001), fatigue (md=1.17; 95 CI 0.62 to 1.71; p=0.001), mastery (md = 1.19; 95 CI 0.63 to 1.74; p= 0.001) and emotion (md = 0.87; 95 CI 0.28 to 1.46; p=0.004). The difference observed between the two groups across all the CRDQ domains at six months was greater than the widely reported MCID of 0.5 (Goldstein et al 2005). Therefore, there is evidence to support a clinically meaningful improvement in QoL as measured by CRDQ with open LVRS in the short-term. These results are based on a meta-analysis of two RCTS with a relatively small pooled sample size (n=93) as stated in Table 1 No. 3.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
36	Quality of life – change in COPD assessment test (CAT) score from baseline	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported

		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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).
37	Quality of life – change in Clinical COPD Questionnaire (CCQ) score from baseline	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy VATS aims to improve patient QoL by improving lung function, reducing breathlessness and increasing exercise capacity. Goldstein et al (2003) reported a significant treatment effect in favour of VATS in each of the CRQ domains at 3, 6, 9 & 12 months (all p<0.0001). At 12 months, a mean difference (adjusted for baseline scores) of 1.9 (95% CI 1.3 to 2.6; p<0.0001) was found for dyspnoea, 1.5 (95% CI 0.9 to 2.1; p<0.0001) for emotional function, 2.0 (95% CI 1.4 to 2.6; p<0.0001) for fatigue, and 1.8 (95% CI 1.2 to 2.5; p<0.0001) for mastery. These results suggest that VATS improves QoL as measured by CRQ more than medical management in patients with severe emphysema up to 12 months. The difference in scores between the two groups for all the CRQ domains were greater than the widely reported MCID of 0.5

		and hence are likely to represent clinically meaningful differences to patients (Goldstein et al 2003). These results should be treated with caution as they are based on a single RCT with a relatively small sample size (n=55) as stated in Table 1 No. 3.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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.
38	Quality of life – change in SF-36 score from baseline	**Benefit of open surgery compared to maximal medical therapy** The Medical Outcomes Study 36-item Short Form (SF-36) is a widely used, validated, generic measure of health status which assesses quality of life (QoL) across eight domains, which are both physically and emotionally based. The eight domains are physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health. Scores are presented as a scale from 0 to 100. A high score indicates a more favourable health state. It is not specific to respiratory diseases. The study with the longest follow-up, Hillerdal et al (2005), found statistically significant mean differences (of changes from baseline) between the groups for physical functioning (mean difference (md) = 17.1; 95% confidence intervals (95% CI) 9.8 to 24.5), role physical (md = 20.5; 95% CI 3.1 to 37.9), general health (md = 6.8; 95% CI 0.2 to 13.4) and vitality (md = 11.0; 95% CI 1.3 to 20.6), all in favour of LVRS at six months. Further improvements were seen at 12 months, with statistically significant mean differences (of changes from baseline) between the groups of 19.7 (95% CI 12.1 to 27.3) for physical functioning, 25.2 (95% CI 7.7 to 42.6) for role physical, 9.7 (95% CI 3.2 to 16.2) for general health, 11.4 (95% CI 1.2 to 21.6) for vitality, 21.0 (95% CI 6.2

		to 35.7) for social functioning and 13.6 (95% CI 5.2 to 22.0) for mental health, all in favour of LVRS. These results show that LVRS improves QoL in the majority of the domains measured by the SF-36 up to 12 months. No standard MCID has been established for SF-36. One of the included studies in this review defined 5 to be a small change in score and 10 to be a moderate-to-large change in score (Miller et al 2005), and based on this definition, there is evidence to suggest a moderate to large clinically significant effect on QoL with LVRS. These results are based on an RCT with a relatively small sample size (n=106) as stated in Table 2 No. 1. Furthermore, SF-36 is a general measure of QoL so may be less responsive than measures of QoL specifically for people with respiratory disease. Therefore, these results should be treated with caution.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy VATS aims to improve patient QoL by improving lung function, reducing breathlessness and increasing exercise capacity. At six months, Mineo et al (2004) reported a statistically significant mean difference (in change from baseline) between the groups of 14.1 in overall SF-36 score in favour of VATS (p=0.0001). Confidence intervals were not reported. Statistically significant mean differences (in change from baseline) between the groups at six months were seen in the specific domains of physical functioning (md = 22.4; p=0.001), general health (md = 15.6; p<0.0001), social functioning (md = 14.1; p=0.004), role limitations due to emotional problems (md = 27.9; p=0.02), mental health (md = 11.3; p=0.003) and physical component summary (md = 5.1; p=0.01) in favour of VATS. Long-term results for the VATS group only, show an improvement in SF-36 score from baseline with mean (SE) overall scores of 63.2 (1.8), 61.1 (3.1), 60.2 (2.2), 56.3 (3.1) at 1, 2, 3 and 4 years respectively compared to a baseline mean (SE) score of 51.1 (2.2). These were all statistically significant improvements from BL with p-values of <0.01, 0.01, 0.02 and 0.05 at 1, 2, 3 and 4 years respectively. These results suggest that VATS offers a greater improvement in QoL as measured by SF-36 compared to medical management in the short-term. However, it is not clear whether these improvements are clinically meaningful as no value for the MCID was found in the papers that were reviewed. The longer-term results show an improvement in SF-36 score from baseline up to four years, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months. These results are taken from a small RCT (n=60) as stated in Table 1 No. 5. Finally, SF-36 is a general measure of QoL, so may be less

		responsive than measures of QoL specifically for people with respiratory disease.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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 COPD.
39	Quality of life – Nottingham Health Profile Score	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy The Nottingham Health Profile (NHP) is a measure of QoL, which contains 38 dichotomic-choice questions relating to eight domains: mobility, energy, pain, social isolation, sleep disturbance, and emotional reactions. It ranges from 0 (best score) to 100 (worst score). VATS aims to improve patient QoL by improving lung function, reducing breathlessness and increasing exercise capacity. At six months, Mineo et al (2004) found a non-significant mean difference (in change from baseline) between the groups in overall NHP score of 10.8. Confidence intervals and p-values were not reported. Long-term results for the VATS group only, show an improvement in NHP score from baseline with mean (SE) overall scores of 17.2 (2.3), 19.7 (3.1), 22.2 (2.3), 27.1 (3.1) reported at 1, 2, 3 and 4 years respectively compared to a baseline mean (SE) score of 29.7 (3.6). With the exception of the 4-year result, these were all statistically significant improvements from baseline with p-values of <0.01, 0.02, 0.03 and >0.05 at 1, 2, 3 and 4 years respectively.

		Therefore no evidence was found of an effect of VATS on QoL as measured by NHP compared to medical management in the short-term. The longer-term results show an improvement in NHP score from baseline up to three years, but it is not known how this compares to patients in the control group, as patients were allowed to cross over to LVRS from six months. These results are taken from a relatively small RCT (n=60) as stated in Table 1 No. 5.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
40	Quality of life - Quality of Wellbeing Scale	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) The Quality of Wellbeing Scale consists of 71 items which measure overall health status and QoL over the previous three days in four areas: physical activities, social activities, mobility, and symptom/problem complexes. In a non-randomised comparison, McKenna et al (2004) found no significant difference in the percentage of patients with an improvement in the Quality of Wellbeing Scale (the cut-off point used to define improvement was not reported) at 12 months (40% of VATS patients vs 44% of MS patients; p=0.45) and 24 months (36% of VATS patients vs 31% of MS patients; p=0.81). Results for the randomised comparison were not reported. The results suggest that there is no evidence of a difference in QoL as measured by the Quality of Wellbeing Scale between VATS and open surgery in patients with severe emphysema up to two years.

		These results should be treated with caution as although based on relatively large numbers (n=511) as stated in Table 1 No. 3.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
41	Disease severity index – BODE index	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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.
42	Hospital utilisation - Operating time, minutes	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy

		Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Operating times are an important outcome in terms of healthcare resources and also there is a greater risk of complications with longer times under general anaesthetic. In a randomised comparison, McKenna et al (2004), found the mean operating time to be 8.8 minutes shorter for open surgery compared to VATS, but the difference was not statistically significant (p=0.30). No further details were given. The non-randomised comparison showed a statistically significant difference of 21.4 minutes shorter (p=0.001) for open surgery compared to VATS. The mean time was 126.7 minutes for VATS and 105.0 minutes for MS in the non-randomised comparison. Overall, based on this trial, the evidence is unclear as to whether there is a real difference in operating times between the two groups. The randomised comparison may lack the power to detect small differences and the non-randomised comparison may introduce bias as the two groups may not be comparable at baseline. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
43	Hospital utilisation - Length of Intensive Care Unit stay, days	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Length of stay in an intensive care unit (ICU) for patients who survived at least 30 days after LVRS is an important outcome in terms of use of hospital resources and as an indication of complications associated with surgery.

		McKenna et al (2004) reported the percentage of VATS and MS patients who stayed in ICU for 0-1 days (65.1% of VATS patients vs 43.1% of MS patients), 2 days (6.6% of VATS patients vs 15.3% of MS patients), 3-29 days (24.3% of VATS patients vs 36.2% of MS patients) and □30days (2% of VATS patients vs 2.3% of MS patients). A statistically significant difference in the distribution of days was seen between the two groups for this non-randomised comparison ($p<0.001$), but not for the randomised comparison ($p=0.76$). Therefore, the evidence is unclear regarding differences in the length of stay in ICU after surgery between VATS and open surgery patients. These results should be treated with caution as although the randomised comparison was based on a moderate number (n=148) there may not be sufficient power to detect small differences of clinical significance. In addition, some of the results are based on a non-randomised comparison therefore the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
44	Length of hospital stay	**Benefit of open surgery compared to maximal medical therapy** Length of hospital stay after surgery is an important indicator of the length of recovery after LVRS and use of hospital resources. It is also important as it will impact on a patient's QoL. Miller et al (2005) reported that the median length of hospital stay after surgery was 22 days (range 4 to 161 days) in the CLVR trial and 12 days (range 4 to 57) in the OBEST trial. The results show that patients tend to have relatively long stays in hospital after surgery of around 2-3 weeks. These results are based on a meta-analysis of two RCTS with a relatively small pooled sample size (n=93) and hence there is a wide range of lengths of hospital stay observed. In addition, the difference in median length of stay between the two trials suggests that it may vary markedly between hospitals or healthcare systems.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy The most recent trial, Clarenbach et al (2015) reported an average hospitalisation time of 14 days (range = 7 to 28).

		This suggests that patients are likely to be in hospital for around two weeks after VATS which is a relatively long hospital stay. These results are taken from relatively small RCTs based in Italy and Switzerland and therefore may not be applicable to the UK.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy 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). 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.
		Benefit of duckbill endobronchial valves compared to control 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
45	Hospital admissions	**Benefit of open surgery compared to maximal medical therapy** This is a measure of the number of LVRS patients readmitted into hospital after surgery and the number of control patients admitted into hospital during the trial period.

		Over a six-month period, Miller et al (2005) reported that 18/30 (60%) LVRS patients had 27 readmissions in the CLVR trial and 3/24 (12.5%) LVRS patients had three readmissions in the OBEST trial. In the control groups, 14/28 (50%) of control patients had 38 hospitalisations in the CLVR trial and 1/11 (9%) control patients in the OBEST trial. No confidence intervals or p-values were reported so it is not clear whether there was a significant difference in hospital admissions between the groups. In addition, no details on reason for admission were given. Given the relatively small numbers and lack of p-values or confidence intervals it is not possible to say whether LVRS is associated with an increase in hospital admissions compared to medical care or not. These results are based on a meta-analysis of 2 RCTS with a relatively small pooled sample size (n=93) and short follow-up of six months and hence there is likely to be a wide range of uncertainty around the observed difference.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
46	Complications – postoperative, %	**Benefit of open surgery compared to maximal medical therapy** An earlier publication of the NET trial on safety and effectiveness of LVRS by open surgery compared to video assisted thoracoscopic surgery (VATS) reported that 58.4% of open LVRS patients who were not at high-risk (n=359) had postoperative complications within 30 days after LVRS. These included arrhythmia (21.3%), pneumonia (20.1%), tracheostomy (9.2%), failure to wean from ventilation (6.1%), urinary retention (4.2%), failure of early extubation (3.1%), atrial fibrillation (2.5%), reoperation for air leak (2.2%), readmission within 72 hours after discharge (2.2%), sepsis (2%), epidural catheter complications (1.1%), mediastinitis (0.8%), sternal debridement (0.8%) and pulmonary embolus (0.6%). In addition, air leak at completion of open LVRS occurred in 54.3% of patients. Out of those patients with data on air leak after completion (n=339), 46% of patients had air leak for seven or more days.

		Out of 354 open LVRS patients who were not at high risk, 43.5% were in the intensive care unit (ICU) for one day or less, 15.3% for two days, 36.2% for 3 to 29 days, 2.3% for 30 days or more and 2.8% were dead within 30 days of LVRS. The reason for not including the full 359 patients is not reported. Out of 357 open LVRS patients who were not at high risk, 76.2% did not need mechanical ventilation after LVRS, 6.4% required one day, 6.2% for 2-14 days, 7.6% for 15-29 days, 0.8% for 30 days or more and 2.8% were dead within 30 days of LVRS. The reason for not including the full 359 patients is not reported. Only percentages were reported, not number of patients having complications. These results suggest a high rate of complications within 30 days after open LVRS with 58.4% of patients having a complication. Air leak is particularly high with just over a half of patients (54%) having air leak on completion of LVRS, followed by arrhythmia (21.3%) and pneumonia (20.1%). Three quarters of patients (76.2%) did not require mechanical ventilation after LVRS and 58.4% of patients were in ICU for two days or less. The importance of some of these complications to patients and to long term outcomes is not clear. These results are taken from a large group of patients having open LVRS (n=359) from a well conducted RCT and therefore provide good evidence of complications associated with open LVRS. However, the results reported for the duration of air leak, ICU stay and mechanical ventilation should be treated with caution as when calculating the percentages, it appears that data for patients who died within 30 days of surgery were excluded from the numerator but were included in the denominator which would make the results smaller than the true result, but should still reflect the true pattern of distribution for the lengths of complications
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Assessing complications arising after surgery is important as if serious and/or common they may outweigh the benefits associated with VATS. McKenna et al (2004) reported that post-operative complications included arrhythmia, pneumonia, tracheostomy, failure of early extubation, reoperation for air leak and failure to wean from ventilation amongst others. McKenna et al (2004) found no evidence of a difference in the percentage of patients who had a postoperative complication between the groups in the 30 days after surgery (52% of VATS group and 58.2% of open surgery group, p=0.2 for the non-randomised comparison; p=0.1 for the randomised comparison).

		Looking at individual complications, in the randomised comparison a significantly greater percentage of patients with a failure to wean off ventilation in the MS groups compared to VATS (0% of VATS patients vs 7.8% of MS patients, p=0.03) was observed, but not in the non-randomised comparison. In addition, in the non-randomised comparison, a significantly greater percentage of patients with the need to reoperate for air leak in the VATS group compared to MS (5.9% of VATS group and 2.2% of MS group; p=0.05) was observed, but not in the non-randomised comparison. In a separate assessment of air leak, in the non-randomised comparison, a significantly higher incidence of air leak at closure of VATS compared to MS was found in patients (65.8% in VATS vs 54.3% in MS; p=0.01). However, there was no difference between groups in the number of days with air leak (p=0.74). Air leak on seven or more days occurred in 46% of MS patients compared to 49% of VATS patients (p=0.48). When the analysis was restricted to randomised patients, there was no difference between groups in the presence of air leak at closure or in the number of days with air leak. Therefore, there was very little evidence of a difference in postoperative complications between VATS and open surgery, with a reliable difference only observed for failure to wean off ventilation. The results for individual complications should be treated with caution, as despite a non-significant result seen for postoperative complications overall between the two groups, many significance tests for individual postoperative complications for the randomised comparison and again for the non-randomised comparison were conducted, therefore it is possible these are false positive results due to multiple testing. Furthermore, although the randomised comparisons were based on a moderate number (n=148) there may not be sufficient power to detect small differences of clinical significance. In addition, for the non-randomised comparison results the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
47	Adverse events – Complications during hospitalisation	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Goldstein et al (2003) reported 4/28 (14%) patients experiencing serious complications during hospitalisation after LVRS. Two patients

		required prolonged ventilation, one of whom sustained a non-fatal cardiac arrest, one had significant bleeding, and one patient had a sternal dehiscence (wound rupture along the surgical incision along the sternum which is often accompanied with infection of the deep soft tissues). Other complications during hospitalisation for surgery included prolonged air leakage of greater than seven days (n=10; one subject required re-operation for air leak), benign dysrhythmias (n=6), respiratory tract infections (n=6), transient confusion (n=6), small bowel ileus (n=2), vocal cord dysfunction (n=2), and transient ischaemic attack (n=1). These results suggest a high complication rate (14%) associated with VATS. However the severity and long-term impact of this are not discussed, which makes it difficult to interpret the significance of this finding for patients. These results are taken from a relatively small RCT so there is likely to be a large range of uncertainty around the estimated risks. In addition the trial included a small number of open surgery cases (number not known) so some of the complications such as sternal dehiscence may not be associated with VATS surgery.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
48	Adverse events – Early (□30 days) complications	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Early complications occurring 30 days or less after surgery are important as if serious and/or common they may outweigh the benefits associated with VATS. Mineo et al (2004) found a statistically significant difference ($p<0.00001$) in early morbidity between the two groups. In the VATS group, 16/30 (53%) patients had 19 non-fatal early complications (11 prolonged air leaks, 3 atrial fibrillation, 2 pneumonias, 1 empyema, 1 transient ischemic attack, and 1 transient Horner's syndrome). No early morbidity was reported for the control group.

		These results suggest a very high early complication rate (53%) associated with VATS. However the severity and long-term impact of this are not discussed, which makes it difficult to interpret the significance of this finding for patients. These results are taken from a single relatively small RCT (n=60) so there is likely to be a large range of uncertainty around the estimated risks.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
49	Adverse events – Late (>30 days) complications	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Late complications occurring more than 30 days after surgery are important as if serious and/or common they may outweigh the benefits associated with VATS. Mineo et al (2004) found a non-significant difference in late morbidity between the groups. In the VATS group, 3/10 (30%) patients had late complications (1 persistent intercostal neuralgia, 1 pneumonia requiring hospitalisation, and 1 loculated pneumothorax requiring reoperation) and 4/30 (15%) patients in the control group (3 worsening hypoxemia & 1 pneumonia, all required hospitalisation). These results suggest that there is no difference in adverse events occurring more than 30 days after surgery or randomisation. The results should be treated with caution as they are based on a single trial of small numbers (n=60) and control patients were allowed to cross over to surgery from six months (12 patents crossed over to VATS due to unsatisfactory improvements) and these patients were excluded from the analysis.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported

		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
50	Adverse events – COPD exacerbations	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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
51	Adverse events – pneumothorax	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported

		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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.
52	Adverse events - pneumonia	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control

		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.
53	Adverse events – valve expectoration, migration and removal/replacement	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control 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.
54	Costs - Mean hospital and physician costs, $	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) In a time of finite resources, it is important to determine whether there are any differences in costs for the two types of surgery. McKenna et al (2004) compared hospital and physician costs associated with an admission for LVRS based on Medicare claims data. No further information was provided on included costs. In the randomised comparison, McKenna et al (2004) analysed costs for patients with Medicare data available randomised to VATS (n=67) and to open surgery (n=45) by MS. They found no evidence of a difference in costs ($7,138 less for the VATS group compared with the MS group (95% CI on difference $5,900 to $20,177; p=0.28)) between the two groups for hospital and physician costs. Actual costs were not provided for each group for the randomised comparison, only differences in costs between the groups were provided. McKenna et al (2004) also compared costs for all 489 patients with Medicare data available having LVRS (343 MS patients and 146 VATS patients) in a non-randomised comparison. The mean costs for LVRS and associated hospital stay was $30,350 (standard deviation (sd) = $37,219) for VATS and $38,557 (sd = $40,519) for MS). The mean hospital and physician costs for the LVRS admission was $8,207 significantly less for the VATS group compared with the MS group (95% CI on difference $917 to $16,035; p=0.03). Therefore the evidence is unclear regarding any difference in costs of VATS compared to open surgery, with a randomised comparison finding no significant difference, while a lower quality non-randomised comparison with more patients found a significant difference. These results should be treated with caution as there is a wide range of uncertainty around the cost estimates. In addition, the costs are from a US perspective and are over 10 years old so have limited applicability to the UK today.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported

		Benefit of duckbill endobronchial valves compared to control Not reported
55	Costs - Mean total costs during the 6 months after surgery, $	**Benefit of open surgery compared to maximal medical therapy** Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) In the randomised comparison, McKenna et al (2004) analysed costs for patients with Medicare data available randomised to VATS (n=67) and to open surgery (n=45) by MS. They found evidence of a significant difference in total costs of $6,500 less for the VATS group (95% CI on difference $4,295 to $8,705; p=0.001) compared to open surgery. Actual costs were not provided for each group for the randomised comparison, only differences in costs between the groups were provided. McKenna et al (2004) also compared total costs for all 489 patients with Medicare data available having LVRS (343 MS patients and 146 VATS patients) in a non-randomised comparison. The mean total costs during the six months after surgery were $51,053 (sd=$4,502) for VATS and $61,481 (sd=$3,189) for open surgery. The difference in mean total costs during the six months after surgery were significantly less by $10,428 for the VATS group (95% CI on difference $9786 to $109,062; p=0.005) compared to open surgery. These results suggest a lower cost is incurred during the six months after surgery for VATS compared to open surgery. These results should be treated with caution as there is a wide range of uncertainty around the cost estimates. In addition, the costs are from a US perspective and are over 10 years old so have limited applicability to the UK today.
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Not reported
56	Cost effectiveness	**Benefit of open surgery compared to maximal medical therapy** Cost effectiveness is measured as the cost of each additional quality adjusted life year (QALY) gained by the treatment (incremental cost

		effectiveness ratio or ICER). It is the ratio of the extra cost of LVRS (including follow-up and treatment of adverse events) above the cost for those having maximal medical therapy, to the additional QALYs gained due to surgery. Ramsey et al (2007), reported that the cost-effectiveness of LVRS vs medical therapy was found to be $140,000 per QALY gained (95% CI 40,155 to 239,359) at five years, and was projected to be $54,000 per QALY gained (confidence intervals not reported) at ten years. The cost-effectiveness of LVRS in patients with upper-lobe predominant emphysema and low exercise capacity at baseline (patient sub-group with greatest benefits) was $77,000 per QALY gained at five years and was projected to be $48,000 per QALY gained at ten years (confidence intervals not reported). The results show that the costs associated with LVRS are high and the cost-effectiveness is low. These results are based on a well conducted large RCT with long follow-up (up to five years). However, large uncertainty remains around the 10-year cost per QALYs as they are based on estimates of survival and QoL taken from data up to five years. In addition, the sub-group results are based on small numbers so will also have wide confidence intervals. Furthermore, the costs are from a US perspective and are over ten years old so may not be applicable to today's patients or to the UK NHS. The costs included medical goods and services, time spent in treatment, transportation to and from health-care facilities and time spent by family and friends caring for the patient, and some of these would not usually be included in cost-effectiveness studies carried out for the UK NHS.
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy Not reported
		Benefit of video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery (median sternotomy) Not reported
		Benefit of umbrella endobronchial valves compared to maximal medical therapy Not reported
		Benefit of duckbill endobronchial valves compared to control Pietzch et al (2014) considered the incremental QALYs gained to be 0.22 at five years and 0.41 at ten years, and the overall costs 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), 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.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
The original proposition received full support of the Internal Medicine Business Meeting on 10th April 2019 and final sign off at the National Programme of Care (NPOC) Board on 25 April 2019. The revised proposition which includes the updated EHIA, associated Consultation Report and Impact Assessment was considered by the Internal Medicine Work Programme Assurance Group and signed off through Chair's action 8 June 2020.

The Internal Medicine National Programme of Care noted that severe emphysema / COPD is a national priority within the NHS England Long Term Plan (LTP) and it is expected that with the focus on earlier diagnosis that referrals will increase overtime. It was noted that the LTP will promote smoking cessation and cardiac rehabilitation which the Policy Working Group had noted as important interventions prior to consideration of LVR. (added 21st October 2019). The LTP team have provided a letter supporting the importance of managing advanced lung disease. The updated proposition includes a revised EHIA report which highlights this cohort may face several health inequalities. The integrated impact assessment has been revised to more accurately describe the current demand and activity levels. Hence the proposition assumes a lower level of growth than when considered previously by CPAG. The NPoC also supports requesting an additional “Treatment Function Code” to ensure accurate data collection going forward.