# Amalgamated CPAG Summary Report for Clinical Panel – Lung volume reduction for severe emphysema

There are two types of endobronchial valves: the duckbill type was used in the studies to completely occlude the most severely affected areas of the lung, whereas the umbrella type of valve was used in the studies to partially occlude bronchi bilaterally. Reported outcomes for studies of the two types of valve differ markedly; it is not clear whether this arises from the different types of valves used or the different treatment strategies. Therefore, results for the two types of valve are presented separately.

## SUMMARY OF CONCLUSIONS FROM RAPID EVIDENCE REVIEWS

| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** |
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| The evidence about open lung volume reduction surgery (LVRS) compared to medical management is dominated by one well-conducted, large RCT with relatively long follow-up. | The included evidence on video-assisted thoracoscopic lung volume reduction surgery (VATS) versus maximal medical therapy consists of three randomised controlled trials. All had relatively small sample sizes and short follow-up periods. | One small trial was included of VATS compared to open surgery. | Evidence included two systematic reviews with meta-analysis (SRMAs) of seven RCTs of endobronchial valves for patients with severe emphysema. Five were of duckbill valves and two of umbrella valves. There were three further RCTs, two of which are based on patients included in the SRMAs. |
| The evidence suggests that open LVRS is likely to be an effective intervention for improving quality of life, exercise capacity and lung function in the short-term in selected patients with severe emphysema, with some sustained benefits shown in quality of life and exercise capacity in the longer term. Despite the early mortality and complications observed with open LVRS, overall long-term survival appears to be improved.<br><br>Patients with upper lobe predominant emphysema and low exercise capacity were reported to benefit most from open LVRS.<br><br>However, the cost-effectiveness of open LVRS, even for the sub-group of patients with greatest benefit, appears to be low. Furthermore, the cost-effectiveness estimates are based on the healthcare system in the United States and may not be applicable to the UK NHS. | The literature suggests that VATS has a benefit of clinical importance over medical management on quality of life, exercise capacity and lung function, but the extent of the effect on mortality and morbidity associated with the procedure is unclear. In addition, no evidence was found on the cost-effectiveness of VATS. | The relative clinical effectiveness and safety of these two approaches remain uncertain, but the evidence suggests that they are probably broadly similar. VATS is associated with a shorter hospital stay and lower overall costs. No evidence was found about the two procedures' relative cost effectiveness. | *Duckbill valves*<br>There is evidence that duckbill valves improve lung function, exercise capacity and quality of life in patients with heterogeneous emphysema, when used to occlude more severely affected lobes of lung which have no collateral ventilation. However, there is a relatively high incidence of serious adverse events related to the procedure and there is no reliable evidence that the procedure is cost effective.<br><br>*Umbrella valves*<br>Current evidence does not support the use of umbrella valves. |

**Overall conclusion**

Although there were methodological issues with the studies, the evidence was fairly consistent in suggesting that open LVRS, VATS and duckbill type valves can all provide clinically important improvements in lung function, quality of life and exercise capacity, at least in the short term. Open LVRS appears to improve long-term survival, but otherwise no mortality benefits have been found. VATS and open surgery appear of similar effectiveness, though VATS is associated with lower overall costs. Although the hospital stay for the valve insertion procedure is shorter than for surgery, there were no direct comparisons between surgery and valves so we do not know whether one is more effective or has a different overall cost than the other.

All three techniques can result in adverse events, sometimes serious, and there were no direct comparisons between surgery and valves so we do not know if one is safer than the other. The comparison between open surgery and VATS did not find any significant differences with respect to safety.

There was no evidence that any of the techniques has acceptable cost-effectiveness.

Thus, apart from patients with a collateral ventilation, who should not be treated with valves, no good evidence was found to favour any one of the three techniques above either of the other two.

## SUMMARY OF EVIDENCE

| **SURVIVAL**<br>The proportion of participants alive at intervals after treatment | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| 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).<br><br>In an earlier analysis of the NET trial (Naunheim et al 2016), Fishman et al (2003) reported that among the | Over 12 months, Goldstein et al (2003) reported that 2/28 (7%) patients died of respiratory failure more than 30 days after surgery in the video-assisted thoracoscopic lung volume reduction surgery (VATS) group and 1/27 (4%) patient died of respiratory failure 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 | In a non-randomised comparison, McKenna et al (2004) found no statistically significant difference in the 30-day mortality risk (2.0% for VATS vs 2.8% for open surgery; p=0.76). Results for the randomised comparison were not reported. However, the authors state that similar results were seen in the randomised comparison. They also reported a statistically non-significant difference in 90-day mortality risk between VATS and open surgery (4.6% for VATS vs 5.9% for open surgery; | *Duckbill valves*<br>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 | Open surgery is associated with longer survival than maximal medical therapy. Patients with upper lobe predominant emphysema and low exercise capacity at baseline were shown to have the highest improvement in survival after LVRS. There is no evidence that VATS and endobronchial valves prolong survival versus maximal medical therapy, nor that VATS is superior to open surgery.<br><br>There is evidence to suggest an increased risk of early mortality within 30 and 90 days after open LVRS in patients with severe emphysema.<br><br>The results for open surgery are likely to be reliable, though 30% of the LVRS |

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| 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.<br><br>The same analysis 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 (p<0.001).<br>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.<br><br>Hillerdal et al (2005) reported an in-hospital mortality risk of 6/53 (12%) caused by pneumonia and respiratory failure in the LVRS group. No results for the control group were reported for the same time period. | size.<br><br>Goldstein et al (2003) also reported that 2/28 (7%) patients died of respiratory failure within 30 days in the 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. | p=0.67). Results for the randomised comparison were not reported.<br><br>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 VATS patients and 0.08 for open surgery patients. This equates to a statistically non-significant risk ratio of 1.18 (p=0.42). Results for the randomised comparison were not reported. | 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 patients with intact fissures (an indicator that they do not have collateral ventilation (CV)), nor in those for whom CV was not tested (van Agteren et al, 2017). CV occurs when air enters a lobe of the lung through a passage other than the normal airway.<br><br>*Umbrella valves*<br>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). | group had VATS rather than open surgery which may have affected the results.<br><br>The result for VATS versus open surgery 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.<br><br>The results for VATS versus maximal medical therapy are based on small numbers and may result from a lack of statistical power, rather than a definite lack of effect.<br><br>For endobronchial valves, no significant effect on mortality was found, but for duckbill type valves this result may have been affected by the variety of patients included (homogenous and heterogeneous emphysema) in the studies and few patients followed up for more than 12 months. |

| **MOBILITY**<br>The distance a patient can walk in six minutes (6MWD) | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| Miller et al (2005) reported a statistically significant mean difference between LVRS and medical management of 148.8 feet (95% CI 24.3 to 273.2; p=0.019) in favour of LVRS at six months. | 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. | 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 open surgery patients; p=0.09) and 24 months (25% of VATS patients vs 33% of open surgery patients; p=0.11). Results for the randomised comparison were not reported. | *Duckbill valves*<br>The improvement in 6MWD was significantly greater in valve-treated patients than controls (between group mean difference (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).<br><br>*Umbrella valves*<br>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). | 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). These results therefore indicate that a clinically meaningful improvement in exercise capacity follows open surgery, VATS and duckbill valve insertion. Medical management appears better than umbrella valve insertion for this outcome. There is no difference in improvement in exercise capacity, as measured by the 6MWD, with VATS compared to open surgery.<br><br>There are important doubts about the reliability of all these results. For open surgery and duckbill valves, the range of uncertainty around the estimated effect size means that the true effect may be lower than the MCID. Patients were aware of their allocated treatment so those in the intervention group may be more likely to try harder in the tests and hence bias the results in favour of interventional treatment. An unknown proportion of patients allocated to VATS underwent open surgery, impeding interpretation of the results. van Agteren et al (2017) graded the quality of evidence found for this measure for duckbill valves as low because of the heterogeneity in the results between studies. For umbrella valves, the study quality was graded as moderate.<br><br>Although the comparison of VATS and open surgery is 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 with homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias. In addition, it was not possible to blind the patients to their allocated treatment, so patients in one of the groups may have been more likely to try harder in the tests and hence bias the results. |

| **USUAL ACTIVITIES**<br>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. | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| The best study, Naunheim et al (2016), reported the proportion of patients with a clinically significant improvement in SGRQ, defined in this study 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 | 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. | 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 open surgery patients; p=0.23) and 24 months (52% of VATS patients vs 53% of open surgery patients; p=0.73). Results for the randomised comparison were not reported. | *Duckbill valves*<br>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.<br><br>The improvement in SGRQ score was statistically significantly greater in patients with heterogeneous emphysema compared to homogenous emphysema (p=0.005) in one 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).<br><br>The improvement in SGRQ was significant in patients with intact fissures (BGMD - | Minimal clinically important differences (MCID) range from 2 to 8 points in the literature, with 4 being the average (Jones et al 2014). These results therefore indicate a clinically meaningful improvement in exercise capacity follows open surgery, VATS and duckbill valve insertion. Medical management appears equivalent to umbrella valve insertion, and VATS to open surgery, for this outcome.<br><br>The results for open surgery are likely to be reliable, though patients were aware of their allocated treatment, so those in the intervention group may be more likely to give positive responses and hence bias the results in favour of interventional treatment. Also, 30% of the LVRS group had VATS rather than open surgery which may have affected the results.<br><br>The results for VATS versus medical management are also suggestive of benefit, though they are taken from a relatively small RCT (n=60) with 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.<br><br>The results for VATS versus open surgery 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 |

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| decline of 2.2 units in control patients were reported. Mean values were not reported for other time points. | | | 9.03, 95% CI -5.98 to -12.07), but not in those whose fissures were not intact (BGMD 0.00).<br><br>*Umbrella valves*<br>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). | could introduce bias. In addition, it was not possible to blind the patients to their allocated treatment, so patients in one of the groups may have been more likely to try harder in the tests and hence bias the results.<br><br>The result for duckbill valves is less reliable. The significant improvement reported for duckbill valves 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.<br><br>The result for umbrella valves is more reliable. van Agteren et al (2017) graded this evidence as high quality. |

| **HOSPITALISATION OR RESIDENCE IN A NURSING OR REHABILITATION FACILITY**<br>The percentage of patients hospitalised, living in a nursing or rehabilitation facility or living independently after surgery | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| 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. | Not reported | 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 open surgery patients, p=0.001). The difference at four months was statistically non-significant (90.1% of VATS patients vs 83.1% of open surgery patients, p=0.24). The baseline figures were not given. | Not reported | 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 than with medical management, but no significant difference was seen at eight months. VATS patients are more likely to live independently one month after treatment compared to patients having open surgery, but this difference disappears by four months after surgery.<br><br>These results are likely to be reliable, being based on well-conducted RCTs with sample sizes of 1,218 and 148.) However only results up to eight and four months respectively are provided so long-term effects on independence are not known. Furthermore, in Naunheim et al (2006), 30% of the LVRS group had VATS rather than open surgery which may have affected the results. |

| **IMPAIRMENT DUE TO DYSPNOEA**<br>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.<br><br>The BODE index (Body-mass index, airflow Obstruction, Dyspnoea, and Exercise) 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. | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| Not reported | 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. | Not reported | *Duckbill valves*<br>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 reported).<br>A significantly higher proportion of valve treated patients achieved an improvement in mMRC score of at least 1 point (113/374 valve patients vs 26/211 controls, RR 2.53, p<0.00001).<br><br>Kemp et al (2017) found a significantly greater improvement in BODE in valve patients compared to controls at six months (BGMD -1.8, p<0.001).<br><br>*Umbrella valves*<br>The meta-analysis by Wang et al (2017) of the two RCTs found no statistically significant effect of valve treatment on mMRC (BGMD<br>-0.08, 95% CI -0.29 to +0.13, p=0.47). | Wang et al (2017) quote the MCID for mMRC as a change of 1 or more points. The papers did not report a MCID for BODE.<br><br>On this basis, VATS and duckbill valves are materially more effective than medical management on the mMRC measure, while umbrella valves made no significant difference. The lack of an MCID makes the BODE result hard to interpret.<br><br>The results suggest that valve treatment improves dyspnoea. This result for BODE 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.<br><br>The VATS results<br>are of limited reliability. They are from a relatively small RCT (n=60). 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.<br><br>The results for endobronchial valves are considered reliable. |

| **SAFETY**<br>The incidence of adverse events (AEs) after treatment. | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| The National Emphysema Treatment Trial (NETT) reported that 7% of open LVRS patients who were not at high-risk (n=359)[1] 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%) (McKenna et al 2004). The mean blood loss during open LVRS was 138.0 ml and 3.1% of patients needed a transfusion.<br><br>This trial 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%), | Goldstein et al (2003) reported 4/28 (14%) patients experiencing serious complications during hospitalisation after LVRS[2]. 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).<br><br>During the 12-month follow-up period after discharge, Goldstein et al (2003) reported that 4/28 LVRS patients (14%) | 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 open surgery 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 open surgery; p=0.04) for the non-randomised comparison, but it was found to be non-significant in the randomised comparison (p=0.25).<br><br>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).<br><br>McKenna et al (2004) reported that post-operative complications included | *Duckbill valves*<br>The best data on serious adverse events (as defined by study authors) comes from the SRMA by van Agteren et al (2017) who found significantly more serious AEs in valve patients than controls (72/297 valve patients vs 18/185 controls, OR 5.85, p=0.0005). These authors reported that, of 433 patients treated, 23 suffered valve expectoration, migration or aspiration and 40 had their valves removed.<br><br>The SRMA by Wang et al (2017) reported significantly higher RRs of COPD exacerbation with | These results indicate rates of adverse events in the populations studied in the papers.<br><br>There was no consistent evidence of a difference in complications between VATS and open surgery.<br><br>Duckbill valves are associated with higher rates of complications than medical treatment.<br><br>However, the results have limited value. Although the nature of the complications of open surgery is enumerated, their severity and long-term impact are not discussed, which makes it difficult to interpret the significance of this finding for patients. For the other interventions, there is less information.<br><br>The VATS versus medical management results are taken from relatively small RCTs so therefore there will be a large range of uncertainty around these rates. In addition, Goldstein et al (2003) included a small number of open surgery cases (number not known) so some of the admissions may not be associated with VATS surgery. The two groups in McKenna et al (2004) may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown |

[1] High risk defined as patients with FEV1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted.
[2] Goldstein et al (2003) stated that surgery was performed by VATS or, less often, by median sternotomy/open surgery, at the discretion of the surgeon, but the paper did not report exact numbers.

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| 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.<br><br>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 all 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. | 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).<br><br>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.<br><br>Mineo et al (2004) also reported 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). | arrhythmia, pneumonia, tracheostomy, failure of early extubation, reoperation for air leak and failure to wean from ventilation amongst others.<br><br>Looking at individual complications, in the randomised comparison a significantly greater percentage of patients with a failure to wean off ventilation in the open surgery group compared to VATS (0% of VATS patients vs 7.8% of open surgery 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 open surgery (5.9% of VATS group and 2.2% of open surgery group; $p=0.05$) was observed, but not in the non-randomised comparison.<br><br>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 open surgery was found in patients (65.8% in VATS vs 54.3% in open surgery; $p=0.01$). 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 open surgery 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. | hospitalisation and of pneumothorax in patients treated with valves compared to controls (RR 2.01, $p=0.01$ and RR 9.65, $p=0.0001$ respectively). They reported no significant difference in the rate of pneumonia in valve treated patients compared to controls (RR 2.17, $p=0.10$).<br><br>*Umbrella valves*<br>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). | confounding factors that could introduce bias.<br><br>van Agteren et al (2017) reviewed the same RCTs as Wang et al but did not meta-analyse the data for individual AEs. Their report suggests that there was variation between the studies, for example of COPD exacerbation rates, making the conclusions reached by Wang et al less reliable.<br><br>The numbers of valve expectorations, migrations and aspirations varied 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.<br><br>The results comparing rates of individual complications after VATS versus open surgery 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 that there are false positive results due to multiple testing. Furthermore, although the randomised comparisons were based on a moderate number of patients (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. |

**QUALITY OF LIFE**

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. SF-36 is not specific to respiratory diseases.

The 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). Treatment failure is defined as death or a consistent reduction of one or more units in two CRDQ domains.

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).

The Quality of Wellbeing Scale (QWS) 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.

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.

The Clinical COPD Questionnaire (CCQ) is a QoL questionnaire which has been validated in COPD. It consists of 10 items (each scored between 0 and 6), divided into three domains (symptoms, functional, mental).

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| The study with the longest follow-up, Hillerdal et al (2005), found statistically significant mean differences in changes in SF-36 scores 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; | 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.<br><br>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 | 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 | *Duckbill valves*<br>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 | 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). The widely reported MCID for the CRDQ is 0.5 (Goldstein et al 2005).<br><br>Based on this definition, there is evidence from the SF-36 studies that open surgery and VATS yield a moderate to large clinically significant effect on QoL. Duckbill valves appear to have no effect on quality of life and this outcome was not reported for umbrella valves.<br><br>The open surgery and VATS trials indicate a clinically meaningful improvement in QoL as measured by CRDQ with both these interventions. The results suggest that patients undergoing VATS are nearly three times less likely to |

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| 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.<br><br>Further improvements were seen at 12 months, with statistically significant mean differences in 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.<br><br>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). | 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.<br><br>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 baseline with p-values of <0.01, 0.01, 0.02 and 0.05 at 1, 2, 3 and 4 years respectively.<br><br>Goldstein et al (2003) reported a significant treatment effect in favour of VATS in each of the CRDQ 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.<br><br>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 in QoL, defined as a consistent reduction of one or more units in two CRDQ domains from which the patient did not recover) compared to 17/27 (63%) patients in the control | months (40% of VATS patients vs 44% of open surgery patients; p=0.45) and 24 months (36% of VATS patients vs 31% of open surgery patients; p=0.81). Results for the randomised comparison were not reported. | p=0.73 for effect on mental health in two studies).<br><br>No significant effect of valve treatment on the CAT 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).<br><br>One RCT found a significant improvement in the valve-treated group compared to controls on CCQ (n=68, BGMD -0.74, p=0.002) (van Agteren et al 2017).<br><br>*Umbrella valves*<br>Not reported | experience treatment failure at one year compared to medical management alone in patients with severe emphysema. No results relating to the CRDQ were reported for endobronchial valves.<br><br>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.<br><br>The results suggest that there is no 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. Nor is there an apparent effect from duckbill valves as measured with the CAT score. The lack of a MCID for the CCQ makes the result on that measure for duckbill valves hard to interpret.<br><br>These results should all be interpreted with caution:<br><br>In all the studies except for one of the five RCTs of duckbill valves and the two of umbrella valves (which used sham procedures for controls), patients were not blinded to their allocated treatment, so patients in the intervention group may have been more likely to give positive responses relating to QoL and hence bias the results in favour of LVRS.<br><br>*SF-36 results*<br>The results for open surgery are based on an RCT with a relatively small sample size (n=106) and short follow-up of 12 months, therefore there is a large range of uncertainty around the estimated effect sizes and the long-term impacts are not known. Furthermore, SF-36 is a general measure of QoL so may be less responsive than measures of QoL specifically for people with respiratory disease.<br><br>For VATS, it is not known how longer-term results compare to patients in the control group as patients were allowed to cross over to LVRS from six months and an intention-to-treat analysis was not carried out.. These results are taken from a small RCT (n=60) therefore there is likely to be a large range of uncertainty around the estimated effect sizes.<br>*CRDQ results* |

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| | group (one died and 16 experienced functional decline in QoL). 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.<br><br>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. | | | The results for open surgery 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 sizes and the long-term impacts are not known.<br><br>The VATS results for CRDQ are based on a single RCT with a relatively small sample size (n=55) and short follow-up of 12 months so the long-term impacts are not known. In addition, although the majority of patients had VATS, some had open surgery (exact numbers not reported), and this may influence the results.<br><br>*NHP results*<br>The results for VATS are taken from a relatively small RCT (n=60), therefore it may not have the power to detect small differences in effect size. 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.<br><br>*QWS results*<br>The results of comparing VATS and open surgery are based on relatively large numbers (n=511), but 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.<br><br>*CAT results*<br>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 relating to the CAT for duckbill valve treatment may be that these valves do not improve QoL or 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). |

**EXERCISE CAPACITY AND ENDURANCE**

Maximum work load is a measure of integrated cardiopulmonary and physical performance, and is the highest work level reached (measured in watts) and maintained for a full minute. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. It is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks.

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.

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. The total distance walked is measured.

Walk intensity is defined as average body acceleration.

Results for the distance a patient can walk in six minutes (six minute walk distance) are reported above under mobility.

| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
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| 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 | At six months, Goldstein et al (2003) found a statistically significant mean difference in maximum exercise capacity, measured as maximum work (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.<br><br>At 12 months, Goldstein et al (2003) found a statistically significant mean | 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 of greater than 10 Watts from baseline in favour of open surgery at 12 months (41% of VATS patients vs 46% of open surgery patients; p=0.05) and at 24 months (26% of VATS patients vs | *Duckbill valves*<br>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.<br><br>These authors also reported a significant increase in the percentage of a day spent walking six months after treatment for | Naunheim et al (2016) used 10 Watts or greater increase in maximum work to define a change that is clinically important to patients. No MCID value for submaximal endurance time was found.<br><br>The results for open surgery and VATS indicate clinically meaningful improvements in exercise capacity/maximum work as measured by cycle ergometer maximum exercise capacity tests. There also appears to be an improvement in submaximal endurance time but its clinical meaning is unclear. VATS was not shown to affect the number of steps per 24 hours. Open surgery appears more effective than VATS in improving exercise capacity.<br><br>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.<br><br>There is no MCID reported for steps per day, percentage of the day spent walking, walking intensity or duration of sitting or of inactivity, making the results for duckbill valves hard to interpret.<br><br>The results for open surgery are likely to be reliable. They are based on a well-conducted RCT with a large sample size (1,218) and long follow-up of five years. However, 30% of the LVRS group had VATS rather than open surgery which may |

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| 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.<br><br>Hillerdal et al (2005) found a statistically significant mean difference of changes from baseline ISWD 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. | difference in submaximal endurance time (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.<br><br>At three months, Clarenbach et al (2015) found a statistically non-significant mean difference in the number of steps per 24 hours (in change from baseline) between the groups of 120 steps (95% CI 0 to 667; p=0.100). | 35% of open surgery patients; p=0.03). Results for the randomised comparison were not reported. | valve treated patients compared to controls (BGMD 1.28%, p=0.001), which was equivalent to an average 36.4% increase from baseline.<br><br>These authors also reported a significant increase in walk intensity at six months in valve treated patients compared to controls (BGMD 0.00948g, p=0.014; mean increase 4.6%). They reported no significant difference between valve and control patients for duration of sitting (p=0.230) or duration of inactivity (p=0.126) at six months.<br><br>*Umbrella valves*<br>Not reported | have affected 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.<br><br>This lack of blinding is a potential limitation of all the studies of open surgery and of VATS.<br><br>The VATS versus medical management 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 patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results.<br><br>The VATS versus open surgery results should also be treated with caution as although based on relatively large numbers (n=511), 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.<br><br>The ISWD results for open surgery should be treated with caution. They are based on an RCT with a relatively small sample size (n=106) and short follow-up of 12 months and hence there is a large range of uncertainty around the estimated effect sizes and the long-term impacts are not known.<br><br>The results for duckbill valves should be treated with caution as they are 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. |

| **LUNG FUNCTION – FORCED EXPIRATORY VOLUME IN ONE SECOND**<br>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 FEV1/FVC ratio is the amount of air exhaled in the first second divided by all of the air exhaled during maximal exhalation. | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| 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. | 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 litres (95% CI 0.1 to 0.5; p=0.0003) in favour of VATS. They also 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.<br><br>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. | 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 open surgery patients; p=0.05) at 12 months. However, no significant difference was seen at 24 months (40% of VATS patients vs 47% of open surgery patients; p=0.12). Results for the randomised comparison were not reported. | *Duckbill valves*<br>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 reported a BGMD in FEV1 by the end of follow-up for valve treated patients of 11.4% greater than for control patients (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).<br><br>An increase of ≥10% was achieved significantly more frequently in treated patients than controls (risk ratio (RR) 2.96, p=0.002). | An increase of 0.1 litres in $FEV_{1,}$ and of 5 to 10% in % predicted $FEV_{1,}$ is considered to be an MCID (Jones et al 2014). No MCID value for FEV1/FVC ratio was found in the papers reviewed.<br><br>On this basis, the results indicate that LVRS and VATS offer a clinically meaningful improvement in lung function as measured by FEV1 up to 12 months in patients with severe emphysema. VATS also appears to improve FEV1/FVC ratio, but the clinical meaning of the change is unclear.<br><br>Wang et al (2017) considered the minimal difference in FEV1 that is clinically meaningful to the patient (MCID) as an increase of ≥10%. On this basis, the duckbill valve also produces a clinically meaningful improvement. By contrast, the umbrella valve appears to worsen lung function.<br><br>For the comparison of VATS and open surgery, absolute values were not reported so it was not possible to determine whether the differences seen in favour of open surgery at 12 months were clinically meaningful to patients. By 24 months, no significant difference was apparent.<br><br>The results for open surgery and VATs are based on a RCT with a relatively small sample size (n=106 and n=55 respectively) 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. In addition, for the VATS results, although the majority of patients had VATS, some had open surgery (exact numbers not reported), and this may influence the results.<br><br>The comparison of VATS and open surgery should be |

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| | | | *Umbrella valves*<br>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). | 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.<br><br>For duckbill valves, van Agteren et al (2017) graded the evidence relating to FEV1 as low quality 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. The trials of umbrella valves were of moderate quality. |

| **LUNG FUNCTION – TOTAL LUNG CAPACITY AND RESIDUAL VOLUME**<br>Total lung capacity (TLC) comprises vital capacity (VC) (the maximum amount of air a person can expel from the lungs after a maximum inhalation) and the residual volume (RV) (what is left in the lungs after forced expiration). Functional residual capacity (FRC) is the volume of air in the lungs after a normal relaxed expiration. Emphysema damages lung and reduces its elasticity resulting in hyperinflation. This increases TLC, RV and FRC while reducing VC and overall lung function. | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| The study with the longest follow-up, Hillerdal et al (2005), reported a statistically significant mean difference in TLC (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.<br><br>These authors also reported a non-significant mean | At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in:<br>• TLC of -15% in favour of VATS (p<0.05).<br>• RV as a proportion of predicted RV of -47% in favour of VATS (95% CI -71% to -23%; p=0.0002).<br>• FRC of **-**41% in favour of VATS (p<0.05).<br>• Forced VC of 0.7 litres in favour of VATS (p<0.05).<br>• Forced VC as a % of | Not reported | *Duckbill valves*<br>van Agteren et al (2017) found a statistically significant reduction in TLC (by 0.34 litres) in valve treated patients and not in controls.<br><br>They also 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. These authors further reported a significant reduction in RV to TLC ratio in duckbill-valve-treated patients of 5.76% (95% CI 1.06% to 10.45%), with | No MCID for change in TLC or VC could be found in the papers reviewed so it is not clear if the changes reported are of clinical importance. Reductions in RV of 350 ml and 430 ml have been defined in studies as MCIDs (van Agteren et al 2017) and van Agteren et al (2017) report a study which defined the MCID for RV to TLC ratio as a 4% reduction.<br><br>Open LVRS, VATS and duckbill valves appear to bring about a reduction in TLC, but it is not clear if these changes are of clinical importance. Umbrella valves appear to have no effect on TLC.<br><br>Open LVRS, VATS and duckbill valves appear to bring about a clinically important reduction in RV. Umbrella valves appear to reduce RV less than maximal medical management. VATS is reported also to improve FRC. |

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| difference (of changes from baseline) in RV 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.<br><br>They also 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. | predicted forced VC of 18% in favour of VATS (p<0.05).<br><br>Confidence intervals were not reported.<br><br>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.<br><br>At three months, Clarenbach et al (2015) found a statistically significant mean difference (in change from baseline) between the groups in RV to TLC ratio of -7.8% (95% CI -13.6% to -1.9%; p=0.011) in favour of VATS. | | much smaller changes in controls, and significantly more treated patients than controls (63% vs 9%, p<0.001) achieved a reduction of at least 4% in RV to TLC ratio.<br><br>van Agteren et al (2017) found one RCT that reported a greater improvement in forced VC in the treated group than in controls (BGMD 14.4%, standard deviation (SD) 27.8).<br><br>*Umbrella valves*<br>Valve treatment was not reported to make a significant difference to TLC compared to maximal medical therapy (BGMD 0.14 litres, 95% CI -0.12 litres to 0.39 litres) (van Agteren et al 2017).<br><br>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).<br><br>A significantly greater reduction in RV/TLC was found in the control group compared to treated patients in one RCT, also suggesting a negative effect of the valves (p=0.01) (van Agteren et al 2017). | VATS and duckbill valves also appear to bring about a clinically important improvement in RV/TLC ratio, while umbrella valves worsen it. This outcome measure was not reported for open surgery.<br><br>Open surgery improves vital capacity, but it is not clear whether this is clinically meaningful. This is also true of the VC results with duckbill valves and the forced VC results for VATS, which are also of unknown statistical significance.<br><br>van Agteren et al graded the evidence for duckbill valves as moderate quality for TLC and RV, and that for umbrella valves as moderate and high quality for TLC and RV respectively. All of the other results should be treated with caution.<br><br>Hillerdal et al (2005) and Goldstein et al (2003) had relatively small sample sizes (n=106 and n=55 respectively) 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. In addition, although the majority of patients in the study by Goldstein et al had VATS, some had open surgery (exact numbers not reported) and this may influence the results.<br><br>Mineo et al (2004) was also a small RCT (n=60), therefore there is likely to be 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.<br><br>Clarenbach et al (2015) also had 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. |

| **LUNG FUNCTION – DIFFUSION OF CARBON MONOXIDE AND PARTIAL PRESSURE OF OXYGEN AND CARBON DIOXIDE**<br>The diffusion capacity of the lung for carbon monoxide (DLCO) is a measure of how easily gases pass between the lung and air within it.<br><br>Partial pressure of a gas in arterial blood ($PaO_2$ and $PaCO_2$) is the pressure of the gas dissolved in the arterial blood and is a measure of how well the lungs are able to transport the gas to and from the blood. | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| 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), and a statistically significant mean difference for $PaCO_2$ of -3.7183 mm Hg (95% CI -6.960 to -0.477; p=0.025) in favour of LVRS. | 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.<br><br>At six months, Mineo et al (2003) found a statistically significant mean difference (in change from baseline) between the groups in $PaO_2$ 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 $PaO_2$ from baseline with a mean (SE) $PaO_2$ 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).<br><br>These authors also reported a non-significant mean difference (in change from baseline) between the groups in $PaCO_2$ of -0.1 kPa. Confidence intervals and p-values were not reported. | Not reported | *Duckbill valves*<br>van Agteren et al (2017) found one RCT that reported a significantly greater improvement in DLCO in the treated group than in controls (p=0.003).<br><br>*Umbrella valves*<br>Not reported | No values for MCID were found for any of these outcomes.<br><br>LVRS and VATS were not shown to improve DLCO in patients with severe emphysema, while duckbill valves are reported to improve this. However, LVRS appears to bring about a reduction in $PaCO_2$ in patients with severe emphysema, while VATS appears not to improve $PaCO_2$ but may improve $PaO_2$. However, it is not clear if these improvements are clinically meaningful to patients.<br><br>The results should all be treated with caution. Those for open surgery 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. There is a wide range of uncertainty around the effect size and the long-term impacts are not known.<br><br>The results for VATS are also based on RCTs with a relatively small sample size (n=55 and n=60) which therefore do not have the power to detect small differences between the groups. In addition, although the majority of patients had VATS in Goldstein et al (2003), some had open surgery (exact numbers not reported) and this may influence the results. In Mineo et al (2003), 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 reported.<br><br>The result in duckbill valves 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. |

| **ENDOTHELIAL FUNCTION**<br>Flow- and nitroglycerine-mediated dilatation of the brachial artery (FMD and 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. | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| Not reported | 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). They also 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). | Not reported | *Duckbill valves*<br>Not reported<br><br>*Umbrella valves*<br>Not reported | 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). However, there is no evidence of a difference in endothelial function as measured by NMD between VATS and medical management.<br><br>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. |

| **SYSTEMIC INFLAMMATION**<br>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. | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| Not reported | At three months, Clarenbach et al (2015) reported a statistically non-significant mean difference (in change | Not reported | *Duckbill valves*<br>Not reported | These results indicate that there is no difference in systemic inflammation as measured by CRP between VATS and medical management in patients with severe emphysema in the short-term. |

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| | from baseline) between the groups in CRP of 0 mg/L (95% CI -0.9 to 0.6; p=0.942). | | *Umbrella valves*<br>Not reported | 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 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. |

| **BODY WEIGHT**<br>Weight loss and muscle wasting are recognised as important problems in emphysema, contributing to morbidity and mortality. Therefore body weight gain is an important outcome for patients. | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| Not reported | 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. | Not reported | *Duckbill valves*<br>Not reported<br><br>*Umbrella valves*<br>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).<br><br>These results are taken from a small RCT (n=60) therefore there is likely to be 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. |

| **OXYGEN DEPENDENCY**<br>Mineo et al (2004) defined oxygen dependency as a $PaO_2$ of 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). | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| Not reported | 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 | Not reported | *Duckbill valves*<br>Not reported | The results appear to suggest a large difference in the percentage of patients requiring oxygen of some type between the groups after surgery. |

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| | 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% of VATS patients and 55.5% of control patients at six months after surgery or randomisation. | | *Umbrella valves*<br>Not reported | These results are taken from a small RCT (n=60) therefore there is likely to be 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. |

| **STEROID DEPENDENCY**<br>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 before treatment. Steroids have adverse effects, so reducing patients' need for steroids is desirable. | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| Not reported | 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% of VATS patients and 55.5% of control patients at six months after surgery or randomisation. | Not reported | *Duckbill valves*<br>Not reported<br><br>*Umbrella valves*<br>Not reported | The results indicate that there is no effect of VATS on steroid dependency compared to medical management in the short-term.<br><br>These results are taken from a small RCT (n=60) therefore there is likely to be 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. |

| **HOSPITAL UTILISATION – OPERATING TIME, RE-ADMISSIONS, DURATION OF TREATMENT AND LENGTH OF STAY**<br>Duration of procedure, of intensive care and of admission, and the number of patients readmitted into hospital after surgery | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| Over a six-month period, Miller et al (2005) reported that 18/30 (60%) LVRS patients had 27 readmissions in the | The most recent trial, Clarenbach et al (2015) reported an average hospitalisation | 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 | *Duckbill valves*<br>Median post-treatment hospital stay was one day (range 1 to 13 days) from one RCT (n=68), and mean or | 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.<br><br>The results show that patients tend to have relatively long stays in |

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| 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.<br><br>The authors also 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. | time of 14 days (range = 7 to 28). | 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 open surgery in the non-randomised comparison.<br><br>These authors also reported the percentage of VATS and open surgery patients who stayed in ICU for 0-1 days (65.1% of VATS patients vs 43.1% of open surgery patients), 2 days (6.6% of VATS patients vs 15.3% of open surgery patients), 3 to 29 days (24.3% of VATS patients vs 36.2% of open surgery patients) and more than 30 days (2% of VATS patients vs 2.3% of open surgery 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). | 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.<br><br>*Umbrella valves*<br>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). | hospital after open surgery of around 2-3 weeks, 14 days after VATS and 1 to 2 days after valve insertion.<br><br>It is unclear as to whether there is an important difference in operating times and duration of ICU stay between VATS and open surgery.<br><br>The results for open surgery 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.<br><br>The results for VATS versus medical treatment are taken from relatively small RCTs based in Italy and Switzerland and therefore may not be applicable to the UK.<br><br>The comparison of VATS and open surgery 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.<br><br>For valves, 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 about overall duration of hospital treatment. |

| COSTS AND COST UTILITY<br>Incremental cost effectiveness ratio (ICER) is the ratio of the extra cost of the intervention, including follow-up and treatment of adverse events, above the cost for those having maximal medical therapy, to the additional quality-adjusted life-years (QALYs) gained due to surgery. | | | | |
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| ***Open surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to maximal medical therapy*** | ***Video-assisted thoracoscopic lung volume reduction surgery compared to open lung volume reduction surgery*** | ***Endobronchial valves compared to maximal medical therapy*** | ***Summary and outline critique*** |
| Ramsey et al (2007), reported that the cost-effectiveness of LVRS vs medical therapy was $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 | Not reported | 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 open surgery. They found no evidence of a difference in hospital and physician costs ($7,138 less for the VATS group compared with the open surgery 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.<br><br>McKenna et al (2004) also compared hospital and physician costs for all 489 patients with Medicare data available having LVRS (343 open surgery patients and 146 VATS patients) in a non-randomised comparison. The mean costs for the procedure and associated hospital stay was $30,350 (standard deviation (sd) = $37,219) for VATS and $38,557 (sd = $40,519) for open surgery). The mean hospital and physician costs for the LVRS admission | *Duckbill valves*<br>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 €20,734 (£18,453[3]) for valve patients and €10,435 (£9,287) for controls at five years; and €25,857 (£23,013) for valve patients and €15,432 (£13,734) for controls at ten years (discounted at 3% per year), giving ICERs of €46,322 (£41,227) per QALY gained at five years and €25,142 (£22,376) per QALY gained at ten years.<br><br>*Umbrella valves*<br>Not reported | The results show that the costs associated with LVRS are high and the cost-effectiveness is low. The results for duckbill valves suggest 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.<br><br>The evidence is unclear regarding any difference in hospital and physician 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. However, the results suggest a lower cost is incurred during the six months after surgery for VATS compared to open surgery.<br><br>The results for open surgery versus medical care should be treated with caution. They 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.<br><br>These results for open surgery versus VATS should also be treated |

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

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| emphysema and low exercise capacity at baseline (the 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). | | was $8,207 significantly less for the VATS group compared with the open surgery group (95% CI on difference $917 to $16,035; p=0.03).<br><br>In the six months after surgery, McKenna et al (2004) analysed costs for patients with Medicare data available randomised to VATS (n=67) and to open surgery (n=45) by open surgery. 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.<br><br>These authors also compared total costs for all 489 patients with Medicare data available having lung volume reduction (343 open surgery 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. | | 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.<br><br>Concerns about the quality of the study of duckbill valves make its result unreliable and mean that the true ICER may be higher than reported. 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 in whom 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).<br><br>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 and the reduce the ICER. |