NHS England

# Evidence review: Lung volume reduction using video assisted thoracoscopic surgery for severe emphysema

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Prepared by: Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

## Contents

# 1 Introduction

**Indication and epidemiology**

- Chronic obstructive pulmonary disease (COPD) is a progressive chronic lung disease that is characterised by varying degrees of chronic bronchitis (chronic inflammation of the central airways) and emphysema (van Agteren et al 2016).
- Emphysema is characterised by damaged lung parenchyma with loss of its elasticity, resulting in hyperinflation of the lung, reduced airflow, reduced capacity for efficient gas exchange between the alveoli and the blood, and breathlessness (van Agteren 2016).
- There is no single diagnostic test for COPD, with a diagnosis relying on clinical judgement based on a combination of history, physical examination and confirmation of the presence of airflow obstruction using spirometry (NICE 2010).
- Patients with COPD commonly have increasing breathlessness (particularly a feature of emphysema), a persistent chesty cough with phlegm (chronic bronchitis), frequent chest infections and persistent wheezing, and patients may suffer from weight loss and tiredness. The symptoms usually get gradually worse over time and make daily activities increasingly difficult, although treatment can help slow the progression. For many patients there are periods when symptoms get suddenly worse (exacerbations), particularly during the winter (NHS Choices, 2016).
- According to Public Health England, over one million people in England live with COPD, around 25,000 deaths each year are attributable to COPD, and there were over 113,000 emergency hospital admissions in England due to COPD in 2013/14 (Public Health England, 2015).
- In most cases emphysema results predominantly from cigarette smoke or other noxious particles such as air pollutants, which lead to oxidative stress, chronic inflammation and gradual destruction of lung tissue (van Agteren et al 2016).
- Emphysema can be broadly described as homogeneous or heterogeneous in the way it affects the lungs, although the degree of heterogeneity varies markedly between patients. Typically, heterogeneity refers to variation between the lobes of the lungs (interlobar), but it can also be within a lobe (intralobar) (van Agteren et al 2017).
- Conventional treatment for COPD involves short and long-acting bronchodilators, sometimes in combination with inhaled steroids, pulmonary rehabilitation, oxygen supplementation, and a focus on smoking cessation. At more advanced stages of the disease patients respond less well to conventional medical treatment and medical treatment options are limited (van Agteren et al 2017, NICE 2017).

**The intervention**

- Lung volume reduction surgery (LVRS) is a palliative treatment that aims to remove the most diseased and least functional part of the lungs.
- LVRS aims to improve lung function, quality of life (QoL) and exercise capacity by some combination of:

    i) Increasing pulmonary elastic recoil pressure resulting in increased expiratory

airflow,

ii) Reducing the degree of hyperinflation, resulting in improved mechanics of diaphragm and chest wall movement, and

iii) Reducing lung heterogeneity, leading to improved alveolar gas exchange and increased effectiveness of ventilation (van Agteren et al 2016).

- LVRS reduces the volume of the lung usually via surgical stapling to cut and seal the tissue. Computed tomography (CT) and perfusion scanning are used to identify the most diseased lung tissue (NICE 2005).

- The two most common techniques used for LVRS are video-assisted thoracoscopic surgery (VATS) and open surgery by median sternotomy (MS). Another surgical approach, thoracotomy, is performed to a lesser extent (van Agteren et al 2016, NICE 2005).

- MS involves cutting through the sternum to open the chest, whereas VATS is less invasive and involves making a number of small incisions in both sides of the chest to allow the insertion of instruments into the chest between the ribs. A thoracotomy involves making an incision between the ribs on one side of the chest and separating the ribs to access the lung (NICE 2005).

- Endobronchial valves are being used increasingly as a treatment option for a subset of patients with emphysema, for example for patients without collateral ventilation. This involves placing small one-way valves in some airways leading to damaged parts of the lungs (NICE 2017).

**Existing national policies and guidance**

- The National Institute for Health and Care Excellence (NICE) published interventional procedures guidance on lung volume reduction surgery for advanced emphysema (IPG114) in February 2005 (NICE 2005).

- NICE's recommendations are as follows:

*"Current evidence on the safety and efficacy of lung volume reduction surgery for advanced emphysema appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance."*

*"Clinicians wishing to use lung volume reduction surgery for advanced emphysema should ensure that patients are fully informed about the risks of the procedure and the likelihood of deterioration in the longer term. Use of the Institute's information for the public is recommended."*

*"Patient selection is important because mortality is increased in patients with the most seriously compromised lung function. The Institute has issued a clinical guideline on chronic obstructive pulmonary disease."*

*"The procedure should be undertaken by a multidisciplinary team that includes a respiratory physician, specialists in pulmonary rehabilitation and a thoracic surgeon."*

## 2 Summary of results

- This evidence review is based on four randomised controlled trials (RCTs), three of which compared LVRS by VATS to medical management for severe emphysema (Goldstein et al 2003, Mineo et al 2004 and Clarenbach et al 2012), and one of which compared VATS to open surgery (McKenna et al 2004). No studies were found comparing VATS to endobronchial valves.
- The RCTs range in size from 30 patients to 148 patients and mean follow-up times of three months to 32 months.
- The intervention group was solely VATS in all of the trials except for Goldstein et al (2003) which stated that surgery was performed by VATS or, less often, by MS at the discretion of the surgeon, but the paper did not report exact numbers.
- The control group for the trials were mostly usual medical care including pulmonary rehabilitation (Goldstein et al 2003, McKenna et al 2004 and Mineo et al 2004). Clarenbach et al (2015) reported that the control group were placed on a waiting list for LVRS and no further interventions were mentioned, but presumably usual medical care was provided.
- The most commonly reported outcomes relate to mortality, lung function, QoL, exercise capacity and adverse events.

Comparing VATS to medical management:

- Two trials reported on mortality (Goldstein et al 2003 and Mineo et al 2004), and no significant differences between VATS and medical management were observed up to 12 months, although the trials were likely to be underpowered to detect anything other than a large difference due to the relatively small numbers in the trials.
- In Goldstein et al (2003), 2/28 (7%) patients died of respiratory failure within 30 days of VATS compared with 0/27 (0%) patients in the control group. More than 30 days after surgery, a further 2/28 (7%) patients died in the VATS group and 1/27 (4%) in the control group, all of respiratory failure.
- In Mineo et al (2004), 2/30 (7%) patients died in the VATS group compared with 1/30 (3%) in the control within six months after surgery.
- A primary outcome in Goldstein et al (2003) was treatment failure, defined as death or 'functional decline' (a consistent reduction of >1 unit in two Chronic Respiratory Questionnaire (CRQ) QoL domains from which they did not recover). They found evidence to suggest that patients undergoing VATS were three times less likely to experience treatment failure at 12 months compared to medical management alone (hazard ratio = 3.1 (95% CI 1.3 to 7.6; p=0.01).
- QoL was measured by CRQ in Goldstein et al (2003). They found a significant treatment effect in favour of VATS in each of the CRQ domains at 3, 6, 9 & 12 months (all p<0.0001). Across all domains and at each time-point, the mean differences (adjusted for baseline scores) between the groups were greater than the widely reported minimal clinically important difference (MCID) of 0.5 (Jones et al 2014). At 12 months, this equated to a mean difference between the groups of 1.9 (95% CI 1.3 to 2.6) for dyspnoea, 1.5 (95% CI 0.9 to 2.1) for emotional function, 2.0 (95% CI 1.4 to 2.6) for fatigue and 1.8 (95% CI 1.2 to 2.5) for mastery in favour of VATS.
- QoL was the primary outcome measure reported in Mineo et al (2004). The RCT included three different measures of QoL as well as the modified Medical Research Council Dyspnoea Scale (mMRC). It found statistically and clinically significant greater

improvements with VATS in QoL as measured by the St George's Respiratory Questionnaire (SGRQ) with a mean difference (in change from baseline) between the groups of 7.6 points (p=0.0001) at six months. Significant improvements were also seen with VATS for QoL measured by the Short Form 36 item (SF-36) (md = 14.1 points; p=0.0001) and the SF-36 specific domains of physical functioning (md = 22.4; p=0.001), general health (md = 15.6; p<0.0001), social functioning (md = 14.1; p=0.004), role limitations due to emotional problems (md = 27.9; p=0.02), mental health (md = 11.3; p=0.003) and physical component summary (md = 5.1; p=0.01) compared to medical management at six months. A non-significant difference was seen for the Nottingham Health Profile (NHP) score. A statistically significant mean difference of 1.2 in mMRC score was seen in favour of VATS (p<0.0001) at six months. The trial also looked at the long-term effects of changes from baseline for the VATS group only, up to four years. It found statistically significant improvements in NHP score from baseline up to three years and in SGRQ, SF-36 and mMRC scores up to four years for VATS patients.

- There is evidence to suggest that exercise capacity is improved with VATS compared to medical management. A significant improvement in the six-minute walk distance (6MWD) was found. At six months, Mineo et al (2004) found a 61 metres greater improvement in the VATS group compared to the control group (p<0.0002) and Goldstein et al (2003) found a 66 metres (95% CI 32 to 101; p=0.0002) mean difference (adjusted for baseline scores) between the groups at 12 months. This is of clinical significance as a difference of 26 metres in patients with severe COPD is considered to be the MCID (Jones et al 2014). Goldstein et al (2003) also found significant improvements in submaximal endurance time (md = 7.3 mins (95% CI 3.9 to 10.8; p<0.0001) at 12 months and maximal workload (md = 13 watts (95% CI 6 to 20; p=0.0003) at six months.
- Many lung function outcomes were reported across the trials. The most commonly used parameter in clinical practice, forced expiratory volume in one second ($FEV_1$), improved significantly more with VATS than medical therapy. All three trials showed statistically and clinically significant improvements in percentage predicted $FEV_1$, ranging from 10-14% reported at 3-12 months after VATS (p<0.001 in all cases).
- Other measures of lung function, including forced vital capacity (FVC), $FEV_1$/FVC, forced residual capacity (FRC), total lung capacity (TLC), residual volume (RV), RV/TLC and partial pressure of oxygen in arterial blood ($PaO_2$), also showed statistically significant changes that favoured VATS over medical therapy across the trials.
- Little evidence was found for significant differences in diffusion capacity for carbon monoxide (DLCO) and partial pressure of carbon dioxide in arterial blood ($PaCO_2$) between VATS and medical therapy.
- Goldstein et al (2003), reported serious complications during hospitalisation in 4/28 (14%) patients after VATS (two patients required prolonged ventilation, one of whom sustained a non-fatal cardiac arrest, one had significant bleeding, and one had a sternal dehiscence). Combining Goldstein et al (2003) and Mineo et al (2004), other complications included prolonged air leak in 21/58 (36%), dysrhythmia in 9/58 (16%), respiratory tract infection in 9/58 (16%) including one empyema, and transient ischaemic attack in 2/58 (3%).
- There was no evidence to suggest an increase in early or late complications after surgery (Mineo et al 2004). However, Goldstein et al (2003), reported that there were four hospital readmissions (due to colitis, pneumonia, respiratory failure & emphysema) in the VATS group and no admissions in the control group.
- The average hospital stay after surgery was 14 days where reported.
- No cost-effectiveness analyses were found.

Comparing VATS to open surgery:

- The only study found for this comparison (McKenna et al 2004) consisted of a randomised comparison of 71 VATS and 77 MS patients and a non-randomised comparison of 152 VATS and 359 MS patients. However, few outcomes were reported for the randomised comparison. It had a mean follow-up time of 32 months.
- No evidence was found of a difference in mortality within 30 days (2.0% for VATS vs 2.8% for MS; p=0.76), within 90-days (4.6% for VATS vs 5.9% for MS; p=0.67), or overall (risk ratio=1.18; p=0.42) between the two approaches for the non-randomised comparison.
- Lung function as measured by percentage of patients with an improvement in $FEV_1$ (cut-off for improvement not defined) significantly differed between the groups in favour of open surgery at 12 months (51% of VATS patients vs 60% of MS patients; p=0.05 for non-randomised comparison). However, there was no evidence of a sustained difference at 24 months (40% of VATS patients vs 47% of MS patients; p=0.12 for non-randomised comparison). No absolute values were reported.
- No evidence was seen of a difference in exercise capacity as measured by percentage of patients with an improvement in 6MWD (cut-off for improvement not defined) between VATS and open surgery at 12 months (37% of VATS patients vs 44% of MS patients; p=0.09) and 24 months (25% of VATS patients vs 33% of MS patients; p=0.11) for non-randomised comparison. No absolute values were reported.
- However, a statistically significant difference in the percentage of patients with an improvement in maximum work as measured by cycle ergometry (defined as increase in maximum work of greater than 10 Watts from baseline) in favour of open surgery was seen at 12 months (41% of VATS patients vs 46% of MS patients; p=0.05) and at 24 months (26% of VATS patients vs 35% of MS patients; p=0.03) for non-randomised comparison. No absolute values were reported.
- No evidence was seen of a difference in QoL as measured by SGRQ and Quality of Wellbeing at 12 and 24 months between VATS and open surgery.
- Hospital stay after surgery significantly differed between the two approaches by six days in favour of VATS (mean length = 13 days for VATS vs 19 days for MS patients; md = 6 days; p=0.02; randomised comparison).
- 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% in favour of open surgery (13.8% of VATS group and 7.0% of MS group; p=0.02). However, the difference (figure not reported) was non-significant in the randomised comparison.
- No evidence was seen for a difference in the percentage of patients who had a postoperative complication (52% of VATS group and 58.2% of MS group, p=0.2 for non-randomised comparison; p=0.1 for randomised).
- McKenna et al (2004) analysed Medicare claims data for the patients randomised to VATS (n=67) and to open surgery (n=45). They found non-significant differences in mean hospital and physician costs for the LVRS admission (md = $7,138; 95% CI $5,900 to $20,177; p=0.28). Mean total costs (medical and related non-medical) during the six months after surgery were $6,500 significantly lower for the VATS group (95% CI $4295 to $8,705; p=0.001).

Overall:

- The results suggest that VATS is an effective intervention for improving QoL, exercise capacity, and lung function in patients with severe emphysema in the short-term.

Uncertainty remains about the risk of death and serious complications associated with the surgery.

- It is still unclear whether there is a difference in effectiveness and safety between VATS and open surgery as the majority of results were statistically non-significant. However, this would suggest if there are any differences between the approaches, they are likely to be relatively small. Hospital stay was shorter for VATS and costs appear lower, although the costs reported are from over ten years ago and from a US setting.
- Overall, the results should be treated with caution as the included trials were relatively small. In addition, a couple of the trials were unbalanced in respect to known prognostic factors at baseline which may have introduced bias. Finally, the trials comparing VATS to medical management had short follow-up times of up to 12 months before cross-over, so the long-term effectiveness of VATS is not known.

## 3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: PubMed, Embase, Cochrane, TRIP and NHS Evidence (see section 10 for search strategy).
- The search dates for publications were between 1st of January 2002 and 15th of January 2018
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for potential inclusion in this review with the exception of non-randomised controlled trials and case series, because sufficient RCT evidence was found.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long-term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).

## 4 Results

Four papers are included in this rapid evidence review. These report on three RCTs comparing LVRS by VATS to medical management (Clarenbach et al 2015, n=30; Mineo et al 2004, n=60; Goldstein et al 2003, n=55) and one RCT comparing VATS to open surgery (McKenna et al 2004, randomised comparison n=148 & non-randomised n=511). No papers were found comparing VATS to endobronchial valves.

Given the RCT evidence found, case series were excluded as they provide much lower quality evidence. In addition, systematic reviews and RCTs which combined data from VATS and open surgery were excluded where the proportion of patients for whom LVRS had been carried out by VATS was less than 70% of the total or the paper did not report results for VATS separately.

The mean follow-up period of the included trials ranged from three months to 32 months. Two of the RCTs allowed control patients to cross over to surgery after a predefined time point (Clarenbach et al 2015 at three months & Mineo et al 2004 at six months) and hence only results up to this point could be used in the comparison with medical management.

The trials reported on a range of outcomes including mortality, QoL, exercise capacity, lung function and adverse events. Full details of the study designs and outcomes are summarised in the evidence tables in section 7.

One paper included a cost analysis of VATS compared to open surgery.

**Question 1: In people with severe emphysema, what is the evidence for the clinical effectiveness and safety for lung volume reduction using video assisted thoracoscopic surgery (VATS) compared to maximal medical therapy, lung volume reduction using endobronchial valves or open surgery?**
**a) Do the benefits reach clinically meaningful differences?**

The outcomes measured include mortality, lung function, exercise capacity, QoL and adverse events.

**VATS compared to medical management**

**Mortality: ≤30-day mortality**
This outcome was reported in one RCT.
Goldstein et al (2003) reported that 2/28 (7%) patients died of respiratory failure within 30 days (at days 7 & 15) 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.
The RCT evidence is inadequate to reliably estimate operative mortality following VATS as numbers are too small. Of note, the 30-day mortality after LVRS by VATS for severe emphysema was 3/152 (2.0%) in the VATS arm of the non-randomised comparison of McKenna et al (2004) discussed later for VATS compared to open surgery results.

**Mortality: >30-day mortality**
This outcome was reported in two RCTs.

Over 12 months, Goldstein et al (2003) reported that 2/28 (7%) patients died of respiratory failure more than 30 days after surgery (at 285 and 334 days after surgery) in the VATS group and 1/27 (4%) patients died of respiratory failure (at 117 days after randomisation) in the control group. No confidence intervals or p-values were reported, but it is likely to represent a non-significant difference due to the small sample size.

Within six months, before patients were allowed to cross over, Mineo et al (2004) reported 2/30 (7%) patients died in the VATS group compared with 1/30 (3%) in the control group. This difference was statistically non-significant (p-value not reported).

The RCT evidence is inadequate to reliably estimate mortality more than 30 days after surgery as numbers are too small.

**Treatment failure**
Treatment failure (defined as death or functional decline (a consistent reduction of >1 unit in two CRQ[1] domains from which they did not recover) was reported in one RCT.

Goldstein et al (2003), reported that by 12 months 7/28 (25%) patients in the VATS group had treatment failure (four died and three experienced functional decline) compared to 17/27 (63%) patients in the control group (one died and 16 experienced functional decline). A hazard ratio of 3.1 (95% CI 1.3 to 7.6; p=0.01) at 12 months in favour of VATS treatment was found.

There is evidence to suggest that patients undergoing VATS are three times less likely to experience treatment failure at one year compared to medical management alone.

**Lung function - Forced expiratory volume in one second ($FEV_1$), litres**
This outcome was reported in two RCTs.

At six months, Mineo et al (2004) found a statistically significant mean difference (in change from baseline) between the groups in $FEV_1$ of 0.5 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 $FEV_1$ from baseline with a mean (standard error (SE)) $FEV_1$ of 1.2 litres (0.07), 1.15 litres (0.10), 1.03 litres (0.10), 0.91 litres (0.10) at 1, 2, 3 and 4 years respectively compared to a baseline mean (SE) of 0.8 litres (0.06). With the exception of the 4-year result, these were all statistically significant improvements from baseline with p-values of <0.001, 0.0001, 0.01 and >0.05 at 1, 2, 3 and 4 years respectively (Mineo et al 2004).

At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in $FEV_1$ of 0.3 litres (95% CI 0.1 to 0.5; p=0.0003) in favour of VATS (mean(SE) = 1.0(0.1) in VATS and 0.7(0.1) in control).

Evidence was found of an effect of VATS on $FEV_1$, compared to controls, in the short-term (up to 12 months). The MCID for $FEV_1$ has been reported as ≥0.1 litres (Jones et al 2014), which suggests that the effects observed in both trials were clinically significant. The longer-term results show an improvement in $FEV_1$ 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.

**Lung function - Forced expiratory volume in one second ($FEV_1$), % predicted**
This outcome was reported in three RCTs.

At three months, Clarenbach et al (2015) reported a statistically significant mean difference (in change from baseline) between the groups in $FEV_1$ of 9.7% (95% CI 4.9 to 14.5; p=<0.001) in favour of VATS.

At six months, Mineo et al (2004) found a statistically significant mean difference (in change from baseline) between the groups in $FEV_1$ of 14.3% (p<0.0001) in favour of VATS. Confidence intervals were not reported.

[1] CRQ is a patient reported, disease specific measure of QoL which focuses on four domains: dyspnoea, fatigue, emotional function, and mastery

At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in $FEV_1$ of 11% ($p \leq 0.5$) in favour of VATS (mean(SE) = 41(2) in VATS and 30(2) in control. Confidence intervals were not reported.

The MCID for % predicted $FEV_1$ has been reported as 5% or more (Jones et al 2014), which suggests that the observed changes in these trials are clinically significant.

**Lung function – Forced vital capacity (FVC), litres**
This outcome was reported in two RCTs.

At six months, Mineo et al (2004) found a statistically significant mean difference (in change from baseline) between the groups in FVC of 0.4 litres ($p<0.0001$) in favour of VATS. Confidence intervals were not reported.

Long-term results for the VATS group only, show an improvement in FVC from baseline with a mean (SE) FVC of 2.7 litres (0.1), 2.72 litres (0.10), 2.66 litres (0.10), 2.56 litres (0.10) at 1, 2, 3 and 4 years respectively compared to a baseline mean (SE) of 2.5 litres (0.1). With the exception of the 4-year result, these were all statistically significant improvements from baseline with p-values of <0.05, 0.001, 0.01 and >0.05 at 1, 2, 3 and 4 years respectively (Mineo et al 2004).

At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in FVC of 0.7 litres in favour of VATS (mean(SE) = 2.9(0.1) in VATS and 2.2(0.1) in control). Confidence intervals were not reported.

Evidence was found of an effect of VATS on FVC, compared to controls, in the short-term (up to 12 months). However, no value for the MCID was found in the papers that were reviewed so it is not clear if this effect is clinically meaningful. The longer-term results show an improvement in FVC 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.

**Lung function – Forced vital capacity (FVC), % predicted**
This outcome was reported in three RCTs.

At three months, Clarenbach et al (2015) reported a statistically significant mean difference (in change from baseline) between the groups in FVC of 15.5% (95% CI 3.7 to 27.3; p=0.012) in favour of VATS.

At six months, Mineo et al (2004) found a statistically significant mean difference (in change from baseline) between the groups in FVC of 13.7% ($p<0.0001$) in favour of VATS. Confidence intervals were not reported.

At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in FVC of 18% in favour of VATS (mean(SE) = 88(3) in VATS and 70(3) in control). Confidence intervals were not reported.

FVC % predicted mean differences ranged between 13.7% to 18% across the trials. It is not clear whether this represents a clinically significant difference as no value for the MCID was found in the papers that were reviewed.

**Lung function - $FEV_1$/FVC, %**
This outcome was reported in one RCT.

At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in $FEV_1$/FVC of 3% in favour of VATS (mean(SE) = 33(1) in VATS and 30(1) in control). Confidence intervals were not reported.

It is not clear whether this represents a clinically significant difference as no value for the MCID was found in the papers that were reviewed.

**Lung function – Total lung capacity (TLC), % predicted**
This outcome was reported in two RCTs.

At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in TLC of -15% predicted in favour of VATS (mean(SE) = 134(4) in VATS and 149(4) in control). Confidence intervals were not reported.

In the smaller RCT, Clarenbach et al (2015) found a statistically non-significant mean difference (in change from baseline) between the groups in TLC of -6% predicted at three months (95% CI -15.0 to 2.0; p=0.131).

It is not clear whether this represents a clinically significant difference as no value for the MCID was found in the papers that were reviewed.

**Lung function – Forced residual capacity (FRC), % predicted**
This outcome was reported in one RCT.

At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in FRC of **-**41% in favour of VATS (mean(SE) = 171(11) in VATS and 212(10) in control). Confidence intervals were not reported.

It is not clear whether this represents a clinically significant difference as no value for the MCID was found in the papers that were reviewed.

**Lung function - Residual volume (RV), litres**
This outcome was reported in one RCT.

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 (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 (Mineo et al 2004).

Evidence was found of an effect of VATS on RV, compared to controls, in the short-term (up to six months). Reductions of 350 ml and 430 ml have been defined in studies as MCIDs (van Agteren et al 2017) which would mean that the reduction of 1.4 litres found between the two groups would be clinically meaningful to patients. The longer-term results show an improvement in RV from baseline up to four years, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months.

**Lung function - Residual volume (RV), %**
This outcome was reported in three RCTs.

At three months, Clarenbach et al (2015) reported a statistically non-significant mean difference (in change from baseline) between the groups in RV of -40.4% (95% CI -81.3 to 0.47; p=0.052).

At six months, Mineo found a statistically significant mean difference (in change from baseline) between the groups in RV of -58.8% (p<0.0001) in favour of VATS. Confidence intervals were not reported.

At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in RV of -47% in favour of VATS (95% CI -71 to -23; p=0.0002; mean(SE) = 192(9) in VATS and 239(8) in control).

RV % predicted mean differences ranged between 40.4% to 58.8% across the trials. It is not clear whether this represents a clinically significant difference as no value for the MCID was found in the papers that were reviewed.

**Lung function - RV/TLC ratio, %**
This outcome was reported in one RCT.

At three months, Clarenbach et al (2015) found a statistically significant mean difference (in change from baseline) between the groups in RV/TLC of -7.8% (95% CI -13.6 to -1.9; p=0.011) in favour of VATS.

This reduction is likely to be clinically meaningful to patients as an MCID of a reduction of 4% was found in the literature (van Agteren et al 2017).

**Lung function – Diffusion capacity of lung for carbon monoxide (DLCO)**
This outcome was reported in three trials.

Two trials found no evidence of an improvement in DLCO with VATS. At three months, Clarenbach et al (2004) found a non-significant mean difference (in change from baseline) between the groups in DLCO of 4.8% predicted (95% CI -0.2 to 9.9; p=0.061). 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 (mean(SE) = 37(2) in VATS and 33(2) in control). Confidence intervals were not reported.

At six months, Mineo et al (2004) reported a statistically significant mean difference (in change from baseline) between the groups in DLCO of 0.1 mmol/kPa$^{-1}$/min$^{-1}$ in favour of VATS. Confidence intervals were not reported.

On balance, there is little evidence of a clinically significant improvement in DLCO with VATS.

**Lung function – Partial pressure of oxygen in arterial blood ($PaO_2$), kPa**
This outcome was reported in one RCT.

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 kPa (0.1). The 1 and 4-year results were statistically significant improvements from baseline with p-values seen of <0.01, >0.05, >0.05 and 0.04 at 1, 2, 3 and 4 years respectively (Mineo et al 2004).

Evidence was found of an effect of VATS on $PaO_2$, compared to controls, in the short-term (up to six months). However, no value for the MCID was found in the papers that were reviewed so it is not clear of this effect is clinically meaningful. The longer-term results show some improvement in $PaO_2$ from baseline, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months.

**Lung function – Partial pressure of carbon dioxide in arterial blood ($PaCO_2$), kPa**
This outcome was reported in one RCT.

At six months, Mineo et al (2003) found a statistically 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.

There was no evidence found of a difference in $PaCO_2$ between the two groups.

**Endothelial function - Flow-mediated dilatation of the brachial artery (FMD), %**
This outcome was reported by one RCT.

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) in favour of LVRS.

There is evidence to suggest that endothelial function as measured by FMD increased in patients after LVRS. The authors state that this is a clinically meaningful effect size.

**Endothelial function - Nitroglycerine-mediated dilatation (NMD), %**
This outcome was reported by one RCT.

At three months, Clarenbach et al (2015) reported a statistically non-significant mean difference (in change from baseline) between the groups in NMD of -1.7% (95% CI -5.9 to 2.5; p=0.412).

No evidence was found of a difference in endothelial function between the two groups as measured by NMD.

**Systemic inflammation - High-sensitive C-reactive protein (CRP), mg/L**
This outcome was reported by one RCT.

At three months, Clarenbach et al (2015) reported a statistically non-significant mean difference (in change from baseline) between the groups in CRP of 0 mg/L (95% CI -0.9 to 0.6; p=0.942).

No evidence was found of a difference in systemic inflammation between the two groups as measured by CRP.

**Exercise capacity – Six minute walk distance (6MWD), metres**
This outcome was reported in two RCTs.

At six months, Mineo et al (2004) found a statistically significant mean difference (in change from

baseline) between the groups in 6MWD of 61 metres (p<0.0002) in favour of VATS. Confidence intervals were not reported.

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.

This is of clinical significance as a difference of 26 metres in patients with severe COPD is considered a MCID (Jones et al 2014).

**Exercise capacity – Maximal workload, Watts[2]**
This outcome was reported in one RCT.

At six months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) of 13 Watts (95% CI 6 to 20; p=0.0003) in favour of VATS. The results for 12 months were not reported.

Naunheim et al (2006) used 10 Watts or greater to define an increase that is clinically important to patients. Therefore, these results suggest that VATS offers clinically meaningful improvements in exercise capacity as measured by cycle ergometer maximum exercise capacity tests in the short-term (up to six months).

**Exercise capacity – Submaximal endurance time, minutes[3]**
This outcome was reported in one RCT.

At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups of 7.3 minutes (95% CI 3.9 to 10.8; p<0.0001) in favour of VATS.

It is not clear whether this represents a clinically significant difference as no value for the MCID was found in the papers that were reviewed.

**Exercise capacity – Number of steps per 24 hours, number**
This outcome was reported in one RCT.

At three months, Clarenbach et al (2015) found a statistically non-significant mean difference (in change from baseline) between the groups of 120 steps (95% CI 0 to 667; p=0.100).

No evidence was found of a difference in steps per 24 hours between the two groups.

**QoL – Chronic Respiratory Questionnaire (CRQ) score[4]**
This outcome was reported in one RCT.

Goldstein et al (2003) reported a significant treatment effect in favour of VATS in each of the CRQ domains at 3, 6, 9 & 12 months (all p<0.0001).

[2] A measure of integrated cardiopulmonary and physical performance. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. The maximum work load is the highest work level reached (measured in Watts) and maintained for a full minute.

[3] A measure of integrated cardiopulmonary and physical performance. It is determined by a submaximal, constant power exercise test using a cycle ergometer. Submaximal cycle endurance time was not defined by Goldstein et al 2003.

[4] CRQ is a patient reported, disease specific measure of QoL which focuses on four domains: dyspnoea, fatigue, emotional function, and mastery

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.

The magnitude of the effect was greater than the widely reported MCID of 0.5 in all domains and at all time points (Jones et al 2014).

**QoL – Nottingham Health Profile (NHP) score[5]**
This outcome was reported in one RCT.

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 BL with p-values of <0.01, 0.02, 0.03 and >0.05 at 1, 2, 3 and 4 years respectively.

Thus no evidence was found of an effect of VATS on QoL as measured by NHP, compared to controls, 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.

**QoL – St George's Respiratory Questionnaire (SGRQ)[6]**
This outcome was reported in one RCT.

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.

Evidence was found of an effect of VATS on QoL as measured by SGRQ, compared to controls, in the short-term. MCID ranges from 2 to 8 points in the literature, with 4 being the average (Jones et al 2014). Therefore, this is evidence of a clinically significant improvement in QoL. The longer-term results show an improvement in SGRQ score from baseline up to four years, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months.

[5] 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).
[6] SGRQ is a 50-item questionnaire developed to measure QoL in patients with diseases of airways obstruction. It contains three sections investigating symptoms, activity and impact of these limitations on mood state.

**QoL – Short Form 36 item (SF-36)[7]**
This outcome was reported in one RCT.

At six months, Mineo et al (2004) reported a statistically significant mean difference (in change from baseline) between the groups of 14.1 in overall SF-36 score in favour of VATS (p=0.0001). Confidence intervals were not reported.

Statistically significant mean differences (in change from baseline) between the groups at six months were seen in the specific domains of physical functioning (md=22.4; p=0.001), general health (md = 15.6; p<0.0001), social functioning (md = 14.1; p=0.004), role limitations due to emotional problems (md = 27.9; p=0.02), mental health (md = 11.3; p=0.003) and physical component summary (md = 5.1; p=0.01) in favour of VATS.

Long-term results for the VATS group only, show an improvement in SF-36 score from baseline with mean (SE) overall scores of 63.2 (1.8), 61.1 (3.1), 60.2 (2.2), 56.3 (3.1) at 1, 2, 3 and 4 years respectively compared to a baseline mean (SE) score of 51.1 (2.2). These were all statistically significant improvements from baseline with p-values of <0.01, 0.01, 0.02 and 0.05 at 1, 2, 3 and 4 years respectively.

Evidence was found of an effect of VATS on QoL as measured by SF-36, compared to controls, in the short-term. However, it is not clear whether this represents a clinically significant difference as no value for the MCID was found in the papers that were reviewed. The longer-term results show an improvement in SF-36 score from baseline up to four years, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months.

**QoL – Modified Medical Research Council Dyspnoea Scale (mMRC)[8]**
This outcome was reported in one RCT.

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.

Evidence was found of an effect of VATS on dyspnoea as measured by mMRC, compared to controls, in the short-term. It is not known if this difference is clinically meaningful to patients as the mMRC scale, although widely used, has been reported to have poor evaluative properties to assess changes in dyspnoea (Jones et al 2014). The longer-term results show an improvement in SF-36 score from baseline up to four years, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months.

[7] The SF-36 is a widely used, validated, generic measure of health status which assesses 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; general health. Scores are presented as a scale from 0 to 100. A high score indicates a more favourable health state.
[8] The mMRC ranges from 0-4 and is a validated tool used to establish levels of functional impairment or perceived impairment due to dyspnoea attributable to respiratory disease. It consists of six phrases describing how much breathlessness interferes with daily activities.

**Body weight, kg**
This outcome was reported in one RCT.

At six months, Mineo et al (2004) reported a statistically significant mean difference (in change from baseline) between the groups in body weight of 4.5kg in favour of VATS ($p<0.0001$). Confidence intervals were not reported.

Evidence was found of an effect of VATS on body weight gain, compared to controls, in the short-term. However, it is not clear whether this represents a clinically significant difference as no value for the MCID for body weight or body mass index was found in the papers that were reviewed (Wouters et al 2005).

**Oxygen dependent patients, %**
This outcome was reported in one RCT.

At six months, Mineo et al (2004) reported a statistically significant difference in the percentage of oxygen dependent patients (from changes from baseline) between the groups of 51.7% in favour of VATS ($p=0.02$). Confidence intervals were not reported. At baseline 63.3% of LVRS patients and 60.0% of control patients were dependent on oxygen and this reduced to 7.1% in VATS patients and 55.5% in control patients at six months after surgery or randomisation.

This appears to be a large difference in the percentage of patients requiring oxygen between the groups. However, no details were provided on the type of oxygen therapy, other than oxygen dependency was considered whenever $PaO_2$ was 8.64 kPa or less.

**Steroid dependent patients, %**[9]
This outcome was reported in one RCT.

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.

Thus no evidence was found of an effect of VATS on steroid dependency, compared to controls, in the short-term.

**Hospital utilisation – Length of hospital stay**
This outcome was reported in two RCTs.

Both, Clarenbach et al (2015) and Mineo et al (2004) reported average hospitalisation times of 14 days in the VATS group. Clarenbach et al (2015) had a mean of 14 days (range = 7 to 28) and Mineo et al (2004) was 13.6 days (+/- 7.1).

**Adverse events – Complications during hospitalisation**
This outcome was reported in two RCTs.

Goldstein et al (2003) reported 4/28 (14%) patients experiencing serious complications during hospitalisation after VATS. Two patients required prolonged ventilation, one of whom sustained a non-fatal cardiac arrest, one had significant bleeding, and one had a sternal dehiscence. Other complications during hospitalisation for surgery included prolonged air leakage lasting over 7 days

[9] Steroid dependency was defined by an oral methylprednisolone intake of ≥ 8 mg/day for ≥ 1 month within the last year pre-treatment.

(n=10), 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).

Clarenbach et al (2015) reported two cases where a pneumothorax had to be drained after removal of thoracic drainage and resolved without further complication and one case where a persistent fistula had to be oversealed 14 days after surgery.

**Adverse events – Early complications (≤30 days after surgery)**
This outcome was reported in one RCT

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 seen in the control group.

**Adverse events – Late complications (>30 days after surgery)**
This outcome was reported in one RCT

Mineo et al (2004) found a non-significant difference in late morbidity between the groups. In the VATS group, 3/30 (10%) 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).

**Adverse events – Total complications after hospital discharge**
This outcome was reported in one RCT

During the 12-month follow-up period after hospital discharge, there were four subsequent admissions reported (colitis, pneumonia, respiratory failure & empyema) for LVRS patients and none for the control group. 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).

**<u>VATS compared to open surgery</u>**

One RCT was found which compared VATS to open surgery (McKenna et al 2004). It is part of the large National Emphysema Treatment Trial (NETT) which compared LVRS (n=608) to medical management (n=610) (Naunheim et al 2006). Six out of 17 centres in NETT further randomised the LVRS intervention arm to VATS (n=71) or MS (n=77). This formed the randomised comparison reported in McKenna et al (2004). The remaining centres either performed MS only (eight centres) or VATS only (three centres). The addition of these patients to the randomised group formed the non-randomised comparison in the trial (VATS = 152 & MS = 359). The trial excluded high risk patients ($FEV_1$ % predicted of ≤20% and either homogeneous emphysema or DLCO ≤20% predicted) who were stopped from being randomised into NETT partway through as they were deemed to be at high risk of death with little benefit (n=140). The main results of NETT comparing LVRS to medical management did not report results separately for VATS and hence were not included in this RER for the VATS to medical management comparison.
The following outcomes were reported in McKenna et al (2004):

**Mortality – 30-day mortality risk**
McKenna et al (2004) found no statistically significant difference in 30-day mortality risk (2.0% for VATS vs 2.8% for MS; p=0.76 for non-randomised comparison).

Results for the randomised comparison were not reported.

Thus no evidence was found of a difference in risk of mortality within 30 days of LVRS between VATS and open surgery.

**Mortality – 90-day mortality risk**
McKenna et al (2004) found no statistically significant difference in 90-day mortality risk (4.6% for VATS vs 5.9% for MS; p=0.67 for non-randomised comparison).

Results for the randomised comparison were not reported.

Thus no evidence was found of a difference in risk of mortality 90 days after LVRS between VATS and open surgery.

**Mortality – Overall mortality rate**
Over a mean follow-up period of 31.9 months, McKenna et al (2004), found no statistically significant difference in overall mortality (rate of 0.1 deaths per person-year for VATS patients and 0.08 for MS patients; risk ratio=1.18; p=0.42 for non-randomised comparison).

Results for the randomised comparison were not reported.

Thus no evidence was found of a difference in overall death rate between VATS and open surgery.

**Lung function - Forced expiratory volume in one second ($FEV_1$), % predicted**
At 12 months, McKenna et al (2004) found a statistically significant difference in the percentage of patients with an improvement in $FEV_1$ % predicted (the cut-off point used to define improvement was not reported) in favour of open surgery (51% of VATS patients vs 60% of MS patients; p=0.05 for non-randomised comparison). No evidence of a difference in the percentage with an improvement was seen at 24 months (40% of VATS patients vs 47% of MS patients; p=0.12 for non-randomised comparison).

Results for the randomised comparison were not reported.

The absolute $FEV_1$% results were not reported so it is not possible to determine whether this is a clinically important result.

**Exercise capacity – Maximum work, Watts**
McKenna et al (2004) found a statistically significant difference in the percentage of patients with an improvement in maximum work (defined as increase in maximum work of greater than 10 Watts from baseline) in favour of open surgery at 12 months (41% of VATS patients vs 46% of MS patients; p=0.05 for non-randomised comparison) and at 24 months (26% of VATS patients vs 35% of MS patients; p=0.03 for non-randomised comparison).

Results for the randomised comparison were not reported.

There is evidence to support a clinically significant greater improvement in exercise capacity with open surgery compared to VATS as measured by cycle ergometer maximum exercise capacity

tests.

**Exercise capacity – Six minute walk distance (6MWD)**
McKenna et al (2004) found no significant difference in the percentage of patients with an improvement in 6MWD (the cut-off point used to define improvement was not reported) at 12 months (37% of VATS patients vs 44% of MS patients; p=0.09 for non-randomised comparison) and 24 months (25% of VATS patients vs 33% of MS patients; p=0.11 for non-randomised comparison).

Results for the randomised comparison were not reported.

Thus no evidence was found of a difference in exercise capacity, as measured by 6MWD, between VATS and open surgery.

**QoL – St George's Respiratory Questionnaire (SGRQ)**
McKenna et al (2004) found no significant difference in the percentage of patients with an improvement in the SGRQ (defined as a decrease in SGRQ score of >8 units from baseline) at 12 months (55% of VATS patients vs 67% of MS patients; p=0.23 for non-randomised comparison) and 24 months (52% of VATS patients vs 53% of MS patients; p=0.73 for non-randomised comparison).

Results for the randomised comparison were not reported.

Thus no evidence was found of a difference in QoL as measured by SGRQ between VATS and open surgery.

**QoL – Quality of Wellbeing[10]**
McKenna et al (2004) found no significant difference in the percentage of patients with an improvement in the Quality of Wellbeing Scale (the cut-off point used to define improvement was not reported) at 12 months (40% of VATS patients vs 44% of MS patients; p=0.45 for non-randomised comparison) and 24 months (36% of VATS patients vs 31% of MS patients; p=0.81 for non-randomised comparison).

Results for the randomised comparison were not reported.

Thus no evidence was found of a difference in QoL as measured by the Quality of Wellbeing Scale between VATS and open surgery.

**QoL – Living independently**
In the randomised comparison of McKenna et al (2004), there was a significant difference in the percentage of patients living independently (not defined) at 30 days after surgery in favour of VATS (87.3% of VATS patients vs 62.3% of MS patients, p=0.001). The difference at four months was statistically non-significant (90.1% of VATS patients vs 83.1% of MS patients, p=0.24). Baseline results were not given.

The results suggest that VATS patients are more likely to live independently in the month after surgery compared to patients having open surgery.

[10] The Quality of Wellbeing Scale consists of 71 items which measure overall health status and QoL over the previous three days in four areas: physical activities, social activities, mobility, and symptom/problem complexes.

**Hospital utilisation – Operating time, minutes**
In the randomised comparison of McKenna et al (2004), the mean operating time was 8.8 minutes shorter for MS than for VATS, but the difference was not statistically significant (p=0.30). No further details were given.

The non-randomised comparison showed a statistically significant difference of 21.4 minutes shorter (p=0.001) for MS than for VATS (mean time was 126.7 minutes for VATS and 105.0 minutes for MS.

**Hospital utilisation – Length of hospital stay, days**
In the randomised comparison of McKenna et al (2004), there was a statistically significant difference in the length of hospital stay of six days in favour of VATS (mean length was 13 days for VATS patients vs 19 days for MS patients; mean difference = 6 days; p=0.02).

A reduction of six days in hospital stay is a clinically significant benefit to patients' QoL and to hospital utilisation and costs.

**Hospital utilisation – Length of intensive care unit (ICU) stay, days**
Length of stay in ICU for patients who survived at least 30 days after LVRS.

McKenna et al (2004) reported the percentage of VATS and MS patients who stayed in ICU for 0-1 days (65.1% of VATS patients vs 43.1% of MS patients), 2 days (6.6% of VATS patients vs 15.3% of MS patients), 3-29 days (24.3% of VATS patients vs 36.2% of MS patients) and ≥30days (2% of VATS patients vs 2.3% of MS patients). A statistically significant difference in the distribution of days was seen between the two groups for this non-randomised comparison (p<0.001), but not for the randomised comparison (p=0.76).

Therefore, the evidence is unclear regarding length of stay in ICU.

**Adverse events - intraoperative complications, %**
Intraoperative complications included hypotension, arrhythmia, hypoxaemia, hypercapnia, cardiac arrest and uncontrolled air leak.

In the non-randomised comparison, McKenna et al (2004), found a statistically significant mean difference in the percentage of patients with intraoperative complications of 6.8% (13.8% of VATS group and 7.0% of MS group; p=0.02). However, the randomised comparison showed a non-significant difference (no figures reported). Hypoxaemia was the only complication that was significantly different between the two groups with a higher rate seen in the VATS group (5.3% in VATS compared to 0.8% in MS; p=0.04) for the non-randomised comparison, but it was found to be non-significant in the randomised comparison (p=0.25).

Therefore, there is little evidence of a difference in intraoperative complications between the two groups.

**Adverse events - postoperative complication, %**
Post-operative complications, occurring during the 30 days after LVRS, included arrhythmia, pneumonia, tracheostomy, failure of early extubation, reoperation for air leak and failure to wean amongst others.

McKenna et al (2004) found no evidence of a difference in the percentage of patients who had a postoperative complication (52% of VATS group and 58.2% of open surgery group, p=0.2 for the

non-randomised comparison; p=0.1 for the randomised comparison).

Looking at individual complications, in the randomised comparison a significantly greater percentage of patients with a failure to wean off ventilation in the MS groups compared to VATS (0% of VATS patients vs 7.8% of MS patients, p=0.03) was observed, but not in the non-randomised comparison. In addition, in the non-randomised comparison, a significantly greater percentage of patients with the need to reoperate for air leak in the VATS group compared to MS (5.9% of VATS group and 2.2% of MS group; p=0.05) was observed, but not in the non-randomised comparison. These results should be treated with caution, as despite a non-significant result seen for postoperative complications overall between the two groups, the authors conducted significance tests for 15 individual postoperative complications for the randomised comparison and again for the non-randomised comparison therefore it is possible these are false positive results due to multiple testing.

In a separate assessment of air leak in the non-randomised comparison, a significantly higher incidence of air leak at closure of VATS compared to MS was found (65.8% in VATS vs 54.3% in MS; p=0.01). However, there was no difference between groups in the number of days with air leak in those alive 30 days after surgery (p=0.74). Air leak on seven or more days occurred in 46% of MS patients compared to 49% of VATS patients (p=0.48). When the analysis was restricted to randomised patients, there was no difference between groups in the presence of air leak at closure or in the number of days with air leak.

There is little evidence of a difference in postoperative complications between the two groups, with a reliable difference only observed for failure to wean off ventilation. Multiple testing was carried out and differences found in the non-randomised comparison tended not to be seen in the randomised comparison.

**<u>VATS compared to endobronchial valves</u>**

No studies were found comparing VATS to endobronchial valves. An ongoing trial (CELEB) was found which aims to compare LVRS (approach not stated) and the bronchoscopic placement of endobronchial valves (BLVR) in patients with heterogeneous emphysema. The trial includes patients from three centres in the UK and is expected to run until March 2019.

**b) Are there any subgroups of patients who are likely to derive the greatest benefit from the intervention(s)?**

None of the trials reported on differences seen between subgroups of patients such as heterogeneous and homogenous emphysema patients, and those with and without collateral ventilation.

The trial comparing VATS to open surgery (McKenna et al 2004) reported that no predictors of differential mortality by approach were identified. No further details were given.

McKenna et al (2004) is part of the NET trial, which included subgroup comparisons of four predefined subgroups of patients characterised by distribution of emphysema (upper-lobe versus non-upper-lobe predominant) in combination with baseline exercise capacity (high versus low). However, these results were not reported specifically for VATS patients (30% of the LVRS group had VATS and 70% MS) and hence no subgroup analysis relevant to this RER is available from the NET trial.

**c) Are there any condition and intervention specific exclusions that reduce the patients ability to benefit or that reduce the duration of that benefit**

As described earlier, McKenna et al (2004) is part of the NET trial which, after the trial started, stopped randomising patients with $FEV_1 \leq$ 20% predicted and either a homogeneous distribution of emphysema or a DLCO≤ 20% predicted, as these patients were deemed to be at high risk for death after LVRS, with a low probability of functional benefit (Naunheim et al 2006). McKenna et al (2004) excludes these high-risk patients and therefore its results are only applicable to those patients not defined as high risk.

Two trials (Goldstein et al 2003 & Mineo et al 2004) excluded patients with homogenous emphysema so their results are only applicable to patients with heterogeneous emphysema.

One trial (Goldstein et al 2003) found that VATS patients who experienced treatment failure (death or functional decline (a consistent reduction of >1 unit in two CRQ domains from which they did not recover) had a lower baseline TLCO (difference = 12% predicted (95% CI –23 to –1); p = 0.05) and lower 6MWD (difference = –99 metres (95% CI –170 to –27); p=0.05) than those who did not. They did not find any baseline differences in QoL, lung volumes, expiratory flows, arterial blood gas tensions, age, or body mass index between those who had treatment failure and those who did not.

**2. Is there any evidence of cost effectiveness of LVRS using VATS compared to maximal medical support?**

No cost-effectiveness analyses were found for VATS compared to medical management.

A cost analysis was found for VATS compared to open surgery from a US perspective (McKenna et al 2004).

McKenna et al (2004) analysed costs for patients with Medicare data available randomised to VATS (n=67) and to open surgery (n=45). They found a non-significant difference in LVRS and associated hospital stay costs (includes hospital and physician costs) for the LVRS admission of $7,138 less for the VATS group compared with the MS group (95% CI $5,900 to $20,177; p=0.28). In addition, mean total costs during the six months after surgery were $6,500 significantly lower for the VATS group (95% CI $4,295 to $8,705; p=0.001). Total costs were described as including all medical and related nonmedical costs incurred during the six months after surgery. Actual costs were not provided for each group for the randomised comparison, only differences in costs between the groups were provided.

They also compared costs for all 489 patients with Medicare data available having LVRS (343 MS patients and 146 VATS patients) in a non-randomised comparison. The mean costs for LVRS and associated hospital stay was $30,350 (standard deviation (sd) = $37,219) for VATS and $38,557 (sd = $40,519) for MS. The mean total costs for during the six months after surgery were $51,053 (sd=$4,502) for VATS and $61,481 (sd=$3,189). Differences were greater with mean hospital and physician costs for the LVRS admission at $8,207 less for the VATS group compared with the MS group (95% CI $917 to $16,035; p=0.03)and mean total costs during the six months after surgery were $10,428 lower for the VATS group (95% CI $9786 to $109,062; p=0.005).

**3. What is the evidence of cost-effectiveness for LVRS using VATS compared to lung volume reduction by endobronchial valves for those who are eligible for both?**

No cost-effectiveness analyses were found for VATS compared to endobronchial valves.

## 5 Discussion

VATS compared to maximal medical management

Three RCTS were found comparing VATS to medical management with a total of 145 patients with severe emphysema (Goldstein et al 2003, Mineo et al 2004 and Clarenbach et al 2015). The trials had similarly strict eligibility criteria with the exception of Clarenbach et al (2015) which included patients with homogenous and heterogeneous emphysema whereas homogenous emphysema patients were excluded from the other two trials.

The PICO for this RER stated that the patient population of interest is people with "symptomatic pulmonary emphysema with demonstrable hyperinflation, persisting after pulmonary rehabilitation". Only Goldstein et al (2003) reported a prerequisite of pulmonary rehabilitation prior to enrolment in the trials. Patients were enrolled in a six-week programme of rehabilitation that included supervised exercises, education, psychosocial support and medication optimisation. In this trial pulmonary rehabilitation offered an additional opportunity to select patients suitable for LVRS.

The intervention group was solely VATS in all of the trials except for Goldstein et al (2003) which stated that surgery was performed by VATS or, less often, by MS at the discretion of the surgeon, but the paper did not report exact numbers.

The control group for the trials were mostly usual medical care including pulmonary rehabilitation (Goldstein et al 2003, McKenna et al 2004 and Mineo et al 2004). Clarenbach et al (2015) reported that the control group were placed on a waiting list for LVRS and no further interventions were mentioned, but presumably usual medical care was provided.

The RCTs have relatively small sample sizes ranging from 30 to 60 patients meaning that they do not have the power to detect small differences in effect size.

The randomisation methods are not described in detail in the papers, so it is difficult to assess the extent of selection bias. Clarenbach et al (2015) had an imbalance between the two groups at baseline with the control group potentially having a worse prognosis (older patients, more pack years of smoking and greater cardiovascular medication use), which most likely occurred due to the small numbers randomised. The authors attempted to adjust for this imbalance for some outcome measures, but not for the lung function outcomes so these are likely to be biased in favour of VATS.

Two of the trials have a cross-over design. Clarenbach et al (2015) allowed patients to cross over at three months and Mineo et al (2004) allowed patients who did not improve to cross over from six months. Clarenbach et al (2015) only reports results at three months. Mineo et al (2004) reports between group comparisons up to one year and changes from baseline for the VATS group only, for up to four years for select outcomes. Only the six month results have been used for between group comparison in this RER as intention-to-treat analyses were not carried out, instead cross-over patients were excluded from the analysis for post six month results. This could

lead to an imbalance in prognostic factors between the two groups with the potential to introduce selection bias in favour of the control group, because patients that did not improve have been removed from this group. The longer-term results where available have been included for uncontrolled comparisons. Goldstein et al (2003) did not allow cross-over and had the longest robust follow-up of 12 months.

Unsurprisingly, patients were not blinded to allocation as none of the trials included a sham procedure for control patients. This lack of blinding could introduce performance bias and a placebo effect in favour of VATS, particularly for the subjective QoL outcomes and motivational dependent exercise capacity outcomes, thus exaggerating the apparent effectiveness of the intervention. Two trials reported that outcome assessors were blinded, but in practice this would have been difficult to achieve as patients could disclose their allocation. Also some of the LVRS patients would have been recovering in hospital or were discharged with clear signs of surgery. However, this is unlikely to introduce significant detection bias as the outcomes assessed by the research assistants were mostly objective.

A further issue is that two of the trials started recruitment over 20 years ago and it is likely that patient selection for LVRS, surgical procedures and medical management have improved since then, affecting the applicability of these results to today's patients.

Despite these limitations, the evidence appears to suggest that VATS is likely to be an effective intervention for improving QoL, exercise capacity and lung function in patients with severe emphysema in the short term (at least 12 months). Uncertainty remains though regarding the risk of mortality and morbidity associated with the surgery and regarding its longer term effectiveness.

<u>VATS compared to open surgery</u>

One RCT was found which compared VATS to open surgery (McKenna et al 2004). The paper included patients randomised to the LVRS group in the National Emphysema Treatment Trial (NETT) which compared LVRS to medical management (Naunheim et al 2006). Some of the centres in NETT further randomised LVRS patients to VATS and MS which formed the randomised comparison for McKenna et al (2004) (n=148). Other centres either only performed VATS solely or MS solely, and the addition of these patients to the randomised patients formed the non-randomised comparison (VATS = 152 patients & MS = 359 patients).

McKenna et al (2004) included patients with severe emphysema, persisting after pulmonary rehabilitation as the main paper for NETT states that before randomisation, eligible patients completed six to ten weeks of pulmonary rehabilitation supervised by study personnel. Patients with heterogeneous and homogeneous emphysema were included.

The trial is generally well conducted, but with the issues associated with lack of blinding of patients and outcome assessors discussed above. The main flaw with the trial is that despite having a randomised comparison, the paper mainly reports the non-randomised comparison results, presumably because the randomised comparison lacked statistical power. However, this is likely to introduce selection bias in favour of open surgery as the VATS group had a greater proportion of homogenous emphysema at baseline and this difference was not adjusted for in the analyses. Patients with homogeneous emphysema were found to be at higher risk of death and benefit less from LVRS than patients with heterogeneous emphysema in NETT. In addition, there may also be an imbalance in other, unknown confounding factors.

The majority of the results are statistically non-significant, so it is not known whether this is evidence of no difference between the LVRS approaches, or there is a difference that the trial does not have the power to detect. However, it would suggest that if there are differences

between the approaches, they are likely to be relatively small. The trial did show with reasonable certainty that VATS is associated with a shorter hospital stay and lower total costs (medical and related nonmedical costs) incurred during the six months after surgery although these costs are from a US setting and are over ten years old.

VATS compared to endobronchial valves
No studies were found comparing VATS to endobronchial valves for severe emphysema.

## 6 Conclusion

The included evidence on VATS for severe emphysema consists of several randomised controlled trials with relatively small sample sizes and short follow-up periods.

The literature suggests a benefit of VATS over medical management on QoL, exercise capacity and lung function of clinical importance, but the extent of the effect on mortality and morbidity associated with surgery is still unclear. In addition, no evidence was found on the cost-effectiveness of VATS.

The evidence is less clear for VATS compared to open surgery. Differences in clinical effectiveness and safety between the approaches remain uncertain, but the evidence suggests that they might be comparable. VATS is associated with a shorter hospital stay and lower overall costs.

No evidence was found on the clinical and cost-effectiveness of VATS compared to endobronchial valves.

## 7 Evidence Summary Table

For abbreviations see list after each table

| Use of video assisted thoracoscopic lung volume reduction surgery Vs. maximal medical therapy to treat severe emphysema | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| Clarenbach et al (2015)<br><br>Switzerland | P1 Randomised controlled trial<br><br>Single centre<br><br>Cross-over for all control patients at 3 months<br><br>Follow-up = 3 months | n=30<br><br>Patients aged 40-75 with severe emphysema (homogenous or heterogeneous)<br><br>BL characteristics:<br><br>Age, mean (sd): 60.9 (10.4) in LVRS group and 65.1 (6.1) years in control<br><br>Male/female ratio: 8/6 in lung volume reduction surgery (LVRS) group and 9/4 in control<br><br>$FEV_1$ % pred, mean (sd): 27.8 (7.2) in LVRS group and 26.2 (5.9) in control<br><br>TLC % pred, mean (sd): 137.2 (19.8) in | Intervention (n=15) = immediate video assisted thoracoscopic surgery (VATS)<br><br>Bilateral n=7<br>Unilateral n=8<br><br>Control (n=15) = VATS after a delay of 3 months | Primary<br><br>Clinical effectiveness | Flow-mediated dilatation (FMD), % | At BL (mean, SD):<br>VATS (n=14) = 2.4 (1.3)<br>Control (n=13) = 2.0 (0.9)<br><br>At 3 months (mean, SD):<br>VATS (n=14) = 4.8 (1.7)<br>Control (n=13) = 1.5 (1.0)<br><br>BGMD (between group mean difference) in change from BL to 3 months = 2.9 (95% CI 2.1 to 3.6; p=<0.001) | 7 | Direct | Short follow-up of 3 months as control group given VATS after 3 months.<br><br>Patients not blinded. Not reported whether outcome assessor was blind to allocation.<br><br>Most likely due to the small numbers randomised, there is an imbalance between the 2 groups with the control group likely to have a worse prognosis (older, more pack years of smoking and greater cardiovascular medication use).<br>The authors attempted to adjust for this imbalance, but only for the primary outcomes and mean blood pressure. Therefore, the secondary outcomes of lung function are likely to biased in favour of VATS.<br><br>Intention-to-treat analysis was not carried out. However, this does not pose a major problem as there was only one patient lost to follow-up and one withdrawal in the VATS group and one lost to follow-up in the control group.<br><br>No mortality data reported. |
| | | | | | Nitroglycerine-mediated dilatation (NMD), % | At BL (mean, SD):<br>VATS (n=14) = 15.9 (8.9)<br>Control (n=13) = 11.3 (3.1)<br><br>At 3 months (mean, SD):<br>VATS (n=14) = 15.4 (7.0)<br>Control (n=13) = 1.2 (4.7)<br><br>BGMD in change from BL to 3 months = -1.7 (95% CI -5.9 to 2.5; p=0.412) | | | |
| | | | | | High-sensitive C-reactive protein (CRP), mg/L | At BL (median, first & third quartiles):<br>VATS (n=14) = 2.0 (0.8 to 2.5)<br>Control (n=13) = 1.3 (0.8 to 1.9)<br><br>At 3 months (median, first & third quartiles):<br>VATS (n=14) = 1.7 (0.7 to 2.6)<br>Control (n=13) = 1.8 (0.8 to 3.3)<br><br>BGMD in change from BL to 3 months = -0.0 (95% CI -0.9 to 0.6; p=0.942) | | | |

| Use of video assisted thoracoscopic lung volume reduction surgery Vs. maximal medical therapy to treat severe emphysema | | | | | | | | | |
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| | | LVRS and 124.5 (9.1) in control.<br><br>RV/TLC ratio: 67.9 (6.1) in LVRS group and 66.7 (5.6) in control<br><br>DLCO % pred, median (first & third quartiles): 35 (27-39) in LVRS and 33 (31-38) in control<br><br>Significant differences seen between the groups (see critical appraisal column) | | Secondary<br><br>Clinical effectiveness | Forced expiratory volume in one second ($FEV_1$), % pred | At BL (mean, SD):<br>VATS (n=14) = 28 (7.2)<br>Control (n=13) = 26 (5.9)<br><br>At 3 months (mean, SD):<br>VATS (n=14) = 36 (9.4)<br>Control (n=13) = 25 (6.5)<br><br>BGMD in change from BL to 3 months = 9.7 (95% CI 4.9 to 14.5; p=<0.001) in favour of VATS | | | |
| | | | | | Forced vital capacity (FVC), % pred | At BL (mean, SD):<br>VATS (n=14) = 69 (13.4)<br>Control (n=13) = 68 (15.7)<br><br>At 3 months (mean, SD):<br>VATS (n=14) = 85 (15.8)<br>Control (n=13) = 69 (16.3)<br><br>BGMD in change from BL to 3 months = 15.5 (95% CI 3.7 to 27.3; p=0.012) in favour of VATS | | | |
| | | | | | Total lung capacity (TLC), % pred | At BL (mean, SD):<br>VATS (n=14) = 137 (19.8)<br>Control (n=13) = 125 (9.1)<br><br>At 3 months (mean, SD):<br>VATS (n=14) = 127 (20.3)<br>Control (n=13) = 121 (13.7)<br><br>BGMD in change from BL to 3 months = -6.0 (95% CI -15.0 to 2.0; p=0.131) | | | |
| | | | | | Residual volume (RV), % pred | At BL (mean, SD):<br>VATS (n=14) = 251 (62.5)<br>Control (n=13) = 222 (26.9)<br><br>At 3 months (mean, SD):<br>VATS (n=14) = 202 (39.8)<br>Control (n=13) = 213 (38.6)<br><br>BGMD in change from BL to 3 months = -40.4 (95% CI -81.3 TO 0.47; p=0.052) | | | |

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| | | | | | RV/TLC ratio, % | At BL (mean, SD):<br>VATS (n=14) = 68 (6.1)<br>Control (n=13) = 67 (5.6)<br><br>At 3 months (mean, SD):<br>VATS (n=14) = 60 (7.6)<br>Control (n=13) = 67 (7.8)<br><br>BGMD in change from BL to 3 months = -7.8 (95% CI -13.6 to -1.9; p=0.011) in favour of VATS | | | |
| | | | | | Diffusion capacity of the lung for carbon monoxide (DLCO), % pred | At BL (mean, 1st and 3rd quartiles):<br>VATS (n=14) = 35 (27 to 39)<br>Control (n=13) = 33 (31 to 38)<br><br>At 3 months (mean, SD):<br>VATS (n=14) = 40 (33 to 48)<br>Control (n=13) = 33 (30 to 36)<br><br>BGMD in change from BL to 3 months = 4.8 (95% CI -0.2 to 9.9; p=0.061) | | | |
| | | | | | 6 minute walk distance (6MWD), metres | At BL (mean, SD):<br>VATS (n=14) = 325 (114)<br>Control (n=13) = 392 (120)<br><br>At 3 months (mean, SD):<br>VATS (n=14) = 287 (98)<br>Control (n=13) = 311 (94)<br><br>BGMD in change from BL to 3 months = 25 (95% CI 0 to 87, p=0.123) | | | |
| | | | | | Number of steps per 24h, number | At BL (mean, 1st and 3rd quartiles):<br>VATS (n=14) = 2,245 (1,135 to 6,690)<br>Control (n=13) = 2,770 (1,463 to 4,036)<br><br>At 3 months (mean, SD):<br>VATS (n=14) = 2,179 (1,545 to 6,486)<br>Control (n=13) = 2,353 (1,368 to 3,699) | | | |

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| | | | | | | BGMD in change from BL to 3 months = 120 (95% CI 0 to 667; p=0.100) | | | |
| | | | | | Average hospitalisation time, days | VATS: Mean (range) = 14 (7-28) days<br>Controls: not reported | | | |
| | | | | Secondary<br><br>Safety | Complications | VATS: 2 cases of pneumothorax<br>1 case of persistent fistula<br>Controls: not reported | | | |
| Mineo et al (2004)<br><br>Italy | P1 Randomised controlled trial<br><br>Recruitment 1996-1999<br><br>Single centre<br><br>Cross-over allowed at 6 months<br><br>Median follow-up time not | n=60<br><br>Patients with severe emphysema<br><br>BL characteristics:<br>Age, mean (sd): in LVRS group = 61.9 (7.3) and in control group = 64.1 (5)<br><br>Male to female ratio: in LVRS group = 29:1 and in control group = 28:1<br><br>$FEV_1$ % predicted, mean (sd): in the LVRS group = | Intervention (n=30) = VATS<br><br>Bilateral n=17<br>Unilateral n=13<br><br>Control (n=30) = comprehensive rehabilitation programme directed to optimise ability to perform daily-living activities by improving exercise capacity | Primary<br><br>Clinical effectiveness<br>Primary | QoL as measured by the Nottingham Health Profile (NHP)[11] | At BL (mean, SE):<br>VATS (n=30) = 29.7 (3.6)<br>Control (n=30) = 33.0 (4.0)<br><br>At 6 months (mean, SE):<br>VATS (n=28) = 16.0 (3.2)<br>Control (n=27) = 30.1 (4.1)<br><br>BGMD in change from BL to 6 months = 10.8 (p=ns)<br><br>Long-term results for VATS group only:<br>Mean (SE) overall NHP score was 17.2 (2.3), 19.7 (3.1), 22.2 (2.3), 27.1 (3.1) at 1, 2, 3 and 4 years respectively in the VATS group. With the exception of the 4-year result, these were all statistically significant improvements from BL with p-values of <0.01, 0.02, 0.03 and >0.05 at 1, 2, 3 and 4 years respectively. | 7 | Direct | Patients with bullous emphysema were not excluded from entry, but no patient included had giant bullae.<br><br>Patients not blinded. Outcome assessors were blind to allocation.<br><br>Patients allowed to cross over from 6 months.<br><br>6 patients crossed over to LVRS at 6 months and a further 6 patients at 12 months due to unsatisfactory improvements.<br><br>No intention to treat analysis carried out. Instead these patients were excluded from the analysis for post 6-month results. This could lead to an imbalance in prognostic factors between the two groups with the potential to introduce selection bias in favour of control group, because patients that did not improve have |
| | | | | | QoL as measured by the Medical Outcomes Study | Overall SF-36:<br>At BL (mean, SE):<br>VATS (n=30) = 51.1 (2.2)<br>Control (n=30) = 49.1 (2.9) | | | |

[11] 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).

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| | reported | 30.2 (1.9) and in the control group = 31.4 (2.7)<br><br>RV % pred, mean (sd): in LVRS group = 240.1 (5.9) and in the control group = 237.2 (5.5)<br><br>DLCO ($mmol.kPa^{-1}.min^{-1}$), mean (sd): in the LVRS group = 2.7 (0.1) and in the control group = 2.8 (0.1)<br><br>$PaCO_2$ (kPa), mean (sd): in the 5.3 (0.1) in LVRS group and control group = 5.3 (0.1)<br><br>No significant differences seen between the two groups | | | Short Form 36 item (SF-36)[12] | At 6 months (mean, SE):<br>VATS (28) = 67.4 (2.0)<br>Control (27) = 51.3 (3.0)<br><br>BGMD in change from BL to 6 months = 14.1 (p=0.0001) in favour of VATS.<br><br>Specific domains, BGMD in change from BL to 6 months:<br>physical functioning: 22.4 (p=0.001), general health: 15.6 (p<0.0001)<br>social functioning: 14.1(p=0.004)<br>role emotional: 27.9 (p=0.02)<br>mental health: 11.3 (p=0.003)<br>physical component summary: 5.1 (p=0.01)<br>All in favour of VATS.<br><br>BGMD in change from BL to 6 months in physical role, bodily pain and vitality domains were non-significant.<br><br>Long-term results for VATS group only:<br>Mean (SE) overall SF-36 score was 63.2 (1.8), 61.1 (3.1), 60.2 (2.2), 56.3 (3.1) at 1, 2, 3 and 4 years respectively in the VATS group. These were all statistically significant improvements from BL with p-values of <0.01, 0.01, 0.02 and 0.05 at 1, 2, 3 and 4 years respectively. | | | been removed from this group.<br><br>For this reason, only results for 6 months have been extracted in detail. Results for 12 months are available for both groups and 2, 3 and 4-year results are also available for VATS group only.<br><br>Mean differences of change from BL at 6 months between the 2 groups have been calculated by Solutions for Public Health (SPH). Only the p-values were reported in the paper for these mean differences at 6-months (not for 12-month results). |
| | | | | | QoL as measured by the St George's Respiratory | Overall SGRQ:<br>At BL (mean, SE):<br>VATS (n=30) = 38.5 (4.6)<br>Control (n=30) = 37.9 (4.9) | | | |

[12] SF-36 is a widely used, validated, generic measure of health status which assesses 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; general health. Scores are presented as a scale from 0 to 100. A high score indicates a more favourable health state.

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| | | | | | Questionnaire (SGRQ)[13] | At 6 months (mean, SE):<br>VATS (28) = 24.6 (3.6)<br>Control (27) = 31.6 (5.2)<br><br>BGMD in change from BL to 6 months = 7.6 (p=0.0001) in favour of VATS.<br><br>Specific domains, BGMD in change from BL to 6 months:<br>Activity: 14.5 (p=0.0001) in favour of VATS.<br><br>BGMD in change from BL to 6 months for symptoms and impact domains were non-significant.<br><br>Long-term results for VATS group only:<br>Mean (SE) overall SGRQ score was 29.0 (3.5), 30.5 (3.6), 31.0 (3.5), 31.6 (5.2) at 1, 2, 3 and 4 years respectively in the VATS group. These were all statistically significant improvements from BL with p-values of <0.01, 0.01, 0.03 and 0.03 at 1, 2, 3 and 4 years respectively. | | | |
| | | | | Secondary<br><br>Clinical effectiveness | Modified Medical Research Council (mMRC) Dyspnoea Scale[14] | At BL (mean, SE):<br>VATS (n=30) = 3.3 (0.1)<br>Control (n=30) = 3.3 (0.1)<br><br>At 6 months (mean, SE):<br>VATS (28) = 1.7 (0.1)<br>Control (27) = 2.9 (0.1)<br><br>BGMD in change from BL to 6 months = 1.2 (p<0.0001) in favour of VATS. | | | |

[13] SGRQ is a 50-item questionnaire developed to measure QoL in patients with diseases of airways obstruction. It contains three sections investigating symptoms, activity and impact of these limitations on mood state.

[14] mMRC ranges from 0-4 and is a validated tool used to establish levels of functional impairment or perceived impairment due to dyspnoea attributable to respiratory disease. It consists of six phrases describing how much breathlessness interferes with daily activities.

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| | | | | | | Long-term results for VATS group only:<br>Mean (SE) mMRC score was 1.9 (0.1), 1.92 (0.20), 2.04 (0.10), 2.46 (0.10) at 1, 2, 3 and 4 years respectively in the VATS group. These were all statistically significant improvements from BL with p-values of <0.001, <0.0001, 0.0001 and 0.002 at 1, 2, 3 and 4 years respectively. | | | |
| | | | | | $FEV_1$, litres | At BL (mean, SE):<br>VATS (n=30) = 0.8 (0.06)<br>Control (n=30) = 0.8 (0.03)<br><br>At 6 months (mean, SE):<br>VATS (28) = 1.3 (0.1)<br>Control (27) = 0.8 (0.04)<br><br>BGMD in change from BL to 6 months = 0.5 (p<0.0001) in favour of VATS.<br><br>Long-term results for VATS group only:<br>Mean (SE) $FEV_1$ was 1.2 (0.07), 1.15 (0.10), 1.03 (0.10), 0.91 (0.10) at 1, 2, 3 and 4 years respectively in the VATS group. With the exception of the 4-year result, these were all statistically significant improvements from BL with p-values of <0.001, 0.0001, 0.01 and >0.05 at 1, 2, 3 and 4 years respectively. | | | |
| | | | | | $FEV_1$, % pred | At BL (mean, SE):<br>VATS (n=30) = 30.2 (1.9)<br>Control (n=30) = 31.4 (2.7)<br><br>At 6 months (mean, SE):<br>VATS (28) = 44.3 (2.9)<br>Control (27) = 31.2 (2.5)<br><br>BGMD in change from BL to 6 months = 14.3 (p<0.0001) in favour of VATS. | | | |

| Use of video assisted thoracoscopic lung volume reduction surgery Vs. maximal medical therapy to treat severe emphysema | | | | | | | | | |
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| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | | Long-term results not reported. | | | |
| | | | | | FVC, litres | At BL (mean, SE):<br>VATS (n=30) = 2.5 (0.1)<br>Control (n=30) = 2.5 (0.06)<br><br>At 6 months (mean, SE):<br>VATS (28) = 2.9 (0.1)<br>Control (27) = 2.5 (0.06)<br><br>BGMD in change from BL to 6 months = 0.4 (p<0.0001) in favour of VATS.<br><br>Long-term results for VATS group only:<br>Mean (SE) FVC was 2.7 (0.1), 2.72 (0.10), 2.66 (0.10), 2.56 (0.10) at 1, 2, 3 and 4 years respectively in the VATS group. With the exception of the 4-year result, these were all statistically significant improvements from BL with p-values of <0.05, 0.001, 0.01 and >0.05 at 1, 2, 3 and 4 years respectively. | | | |
| | | | | | FVC, % pred | At BL (mean, SE):<br>VATS (n=30) = 66.6 (2.9)<br>Control (n=30) = 65.2 (2.9)<br><br>At 6 months (mean, SE):<br>VATS (28) = 80.3 (3.0)<br>Control (27) = 65.2 (2.8)<br><br>BGMD in change from BL to 6 months = 13.7 (p<0.0001) in favour of VATS.<br><br>Long-term results not reported. | | | |
| | | | | | RV, litres | At BL (mean, SE):<br>VATS (n=30) = 5.5 (0.1)<br>Control (n=30) = 5.1 (0.1)<br><br>At 6 months (mean, SE):<br>VATS (28) = 4.1 (0.1) | | | |

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| | | | | | | Control (27) = 5.1 (0.1)<br><br>BGMD in change from BL to 6 months= -1.4 (p<0.0001) in favour of VATS.<br><br>Long-term results for VATS group only:<br>Mean (SE) RV was 4.2 (0.1), 4.57 (0.10), 4.73 (0.10), 4.92 (0.10) at 1, 2, 3 and 4 years respectively in the VATS group. These were all statistically significant improvements from BL with p-values of <0.001, <0.0001, <0.0001 and <0.0001 at 1, 2, 3 and 4 years respectively. | | | |
| | | | | | RV, % pred | At BL (mean, SE):<br>VATS (n=30) = 240.1 (5.9)<br>Control (n=30) = 237.2 (5.5)<br><br>At 6 months (mean, SE):<br>VATS (28) = 182.2 (5.3)<br>Control (27) = 238.1 (5.5)<br><br>BGMD in change from BL to 6 months = -58.8 (p<0.0001) in favour of VATS.<br><br>Long-term results not reported. | | | |
| | | | | | DLCO, mmol·kPa−1·min−1 | At BL (mean, SE):<br>VATS (n=30) = 2.7 (0.1)<br>Control (n=30) = 2.8 (0.1)<br><br>At 6 months (mean, SE):<br>VATS (28) = 2.7 (0.1)<br>Control (27) = 2.7 (0.1)<br><br>BGMD in change from BL to 6 months = 0.1 (p<0.01) in favour of VATS.<br><br>Long-term results not reported. | | | |
| | | | | | Partial pressure of oxygen in arterial blood | At BL (mean, SE):<br>VATS (n=30) = 9.0 (0.1)<br>Control (n=30) = 8.5 (0.1) | | | |

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| | | | | | $(PaO)_2$, kPa | At 6 months (mean, SE):<br>VATS (28) = 9.7 (0.1)<br>Control (27) = 8.3 (0.1)<br><br>BGMD in change from BL to 6 months = 0.9 (p<0.002) in favour of VATS.<br><br>Long-term results for VATS group only:<br>Mean (SE) $PaO_2$ was 9.5 (0.1), 9.8 (0.1), 9.5 (0.1), 9.3 (0.1) at 1, 2, 3 and 4 years respectively in the VATS group. The 1 and 4-year results were statistically significant improvements from BL with p-values seen of <0.01, >0.05, >0.05 and 0.04 at 1, 2, 3 and 4 years respectively. | | | |
| | | | | | Partial pressure of carbon dioxide in arterial blood ($PaCO_2$), kPa | At BL (mean, SE):<br>VATS (n=30) = 5.3 (0.1)<br>Control (n=30) = 5.3 (0.1)<br><br>At 6 months (mean, SE):<br>VATS (28) = 5.2 (0.1)<br>Control (27) = 5.3 (0.1)<br><br>BGMD in change from BL to 6 months = -0.1 (p=ns)<br><br>All long-term results were statistically non-significant. | | | |
| | | | | | 6MWD, metres | At BL (mean, SE):<br>VATS (n=30) = 380 (7.8)<br>Control (n=30) = 376 (7.3)<br><br>At 6 months (mean, SE):<br>VATS (28) = 473 (13)<br>Control (27) = 408 (8.4)<br><br>BGMD in change from BL to 6 months = 61 (p<0.0002) in favour of VATS. | | | |

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| | | | | | | Long-term results not reported. | | | |
| | | | | | Body weight, kg | At BL (mean, SE):<br>VATS (n=30) = 65.0 (1.9)<br>Control (n=30) = 66.9 (1.5)<br><br>At 6 months (mean, SE):<br>VATS (28) = 68.4 (1.8)<br>Control (27) = 65.8 (1.3)<br><br>BGMD in change from BL to 6 months = 4.5 (p<0.0001) in favour of VATS. | | | |
| | | | | | Oxygen dependent patients, % | At baseline:<br>VATS (n=30) = 63.3<br>Control (n=30) = 60.0<br><br>At 6 months:<br>VATS (28) = 7.1<br>Control (27) = 55.5<br><br>BGMD in change from BL to 6 months = 51.7 (p<0.02) in favour of VATS. | | | |
| | | | | | Steroid dependent users, % | At baseline:<br>VATS (n=30) = 73.3<br>Control (n=30) = 80.0<br><br>At 6 months:<br>VATS (28) = 14.2<br>Control (27) = 55.5<br><br>BGMD in change from BL to 6 months = 34.6 (p=ns) | | | |
| | | | | Secondary<br><br>Safety | Mortality | Within 6 months:<br>VATS: 2 deaths (7%) - one in-hospital death due to multidrug-resistant *Pseudomonas aeruginosa* pneumonia & one 4 months after VATS due to pneumonia and respiratory failure<br>Control: 1 death (3%) | | | |

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| | | | | | | Difference non-significant<br><br>Long-term results not reported. | | | |
| | | | | | Complications | Early (≤30 days) morbidity:<br>VATS: 16 patients (53%) had 19 non-fatal complications<br>(11 prolonged air leaks, 3 atrial fibrillation, 2 pneumonia, 1 empyema, 1 transient ischemic attack, and 1 transient Horner's syndrome).<br>Control: 0 patients<br>Statistically significant difference ($p<0.00001$) in early morbidity between the 2 groups.<br><br>Mean hospital stay for VATS group was 13.6 (+/- 7.1) days.<br><br>Late (>30 days) morbidity:<br>VATS: 3 patients (10%) - 1 persistent intercostal neuralgia, 1 pneumonia requiring hospitalization, and 1 loculated pneumothorax requiring reoperation<br>Control: 4 patients (13%) - 3 worsening hypoxemia & 1 pneumonia, all required hospitalisation<br>Statistically non-significant difference in late morbidity between the groups.<br><br>Long-term results not reported. | | | |
| Goldstein et al (2003)<br><br>Canada | P1 Randomised controlled trial<br><br>Recruitment | n=55<br><br>Non-smoking patients who were clinically stable, aged <75 years with severe emphysema | Intervention (n=28) = LVRS mostly performed by VATS (exact numbers not given). | Primary<br><br>Clinical effectiveness | QoL as measured by the Chronic Respiratory Questionnaire (CRQ)[15] | When comparing values for each group at each time point, a significant treatment effect in favour of LVRS was found in each of the CRQ domains (dyspnoea, fatigue, emotional function and mastery) at 3, 6, 9 & 12 months (all $p<0.0001$).<br><br>The magnitude of the effect was greater than the minimal important difference of 0.5 in all domains. | 8 | Direct | Excludes homogenous emphysema.<br><br>All patients were enrolled in a six month programme of rehabilitation that included supervised exercises, education and psychosocial support before randomisation.<br><br>Method of randomisation appears |

[15] CRQ is a patient reported, disease specific measure of QoL which focuses on four domains: dyspnoea, fatigue, emotional function, and mastery.

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| | 1997-2001<br><br>No cross-over between the groups<br><br>Follow-up = 3, 6, 9, 12 months. Median follow-up time not reported | ($FEV_1$ <40% predicted, $FEV_1$/FVC<0.7) of heterogeneous distribution.<br><br>BL characteristics: Age, mean (SE) = 64.9 (0.91)<br><br>Males = 33 (60%)<br><br>$FEV_1$ % pred, mean (SE) = 32 (1.38)<br><br>RV % pred, mean (SE) = 240 (7.89)<br><br>TLC % pred, mean (SE) = 146 (2.64)<br><br>TLCO % pred, mean (SE) = 35 (1.63)<br><br>$PaCO_2$ (kPa), mean (SE) = 5.9 (0.1)<br><br>No differences between the groups. | Bilateral n= 20<br>Unilateral n= 8<br><br>Comparator (n=27) = ongoing medical management | | | Differences between groups at 12 months (only reported graphically for other time points):<br>Dyspnoea = 1.9 (95% CI 1.3 to 2.6; p<0.0001)<br>Emotional function = 1.5 (95% CI 0.9 to 2.1; p<0.0001)<br>Fatigue = 2.0 (95% CI 1.4 to 2.6; p<0.0001)<br>Mastery = 1.8 (95% CI 1.2 to 2.5; p<0.0001) | | | adequate.<br><br>Patients not blinded. Outcome assessors blind to allocation.<br><br>The paper does not report whether an intention-to-treat analysis was carried out. This is not such an issue as there was no cross over between the groups or withdrawals from the trial.<br><br>Only a few confidence intervals reported.<br><br>Mean differences at 12 months calculated by SPH. They do not represent differences in change scores from baseline as the p-values reported correspond to differences in 12-month endpoints. The mean values at follow-up points reported in the paper were adjusted for the baseline score.<br><br>Although, the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported). |
| | | | | | Treatment failure (defined as death or functional decline (a consistent reduction of >1 unit in two CRQ domains from which they did not recover)) | LVRS group = 7/28 (25%)<br>4 died and 3 experienced functional decline<br><br>Control group = 17/27 (63%)<br>1 died and 16 experienced functional decline<br><br>Difference between the groups<br>HR = 3.1 (95% CI 1.3 to 7.6; p=0.01) at 12 months in favour of surgical treatment<br><br>Surgical subjects who experienced treatment failure had a lower baseline TLCO (difference –12% predicted (95% CI –23 to –1); p = 0.05) and lower 6-minute walking distance (difference –99 metres (95% CI –170 to –27); p=0.05) than those who did not, with no other baseline differences in QoL, lung volumes, expiratory flows, arterial blood gas tensions, age, or body mass index. | | | |
| | | | | Secondary<br><br>Clinical effectiveness | TLC, % pred | At 12 months<br>LVRS = 134 (4)<br>Control = 149 (4)<br>BGMD (adjusted for BL score) = -15 (p<0.05) in favour of LVRS | | | |
| | | | | | Functional residual capacity (FRC), % pred | At 12 months (mean (S.E)):<br>LVRS = 171 (11)<br>Control = 212 (10)<br>BGMD (adjusted for BL score) = -41 (p<0.05) | | | |

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| | | | | | RV, % pred | At 12 months (mean (S.E)):<br>LVRS = 192 (9)<br>Control = 239 (8)<br>BGMD (adjusted for BL score) = - 47 (95% CI -71 to -23; p=0.0002) in favour of LVRS | | | |
| | | | | | FVC, litres | At 12 months (mean (S.E)):<br>LVRS = 2.9 (0.1)<br>Control = 2.2 (0.1)<br>BGMD (adjusted for BL score) = 0.7 (p<0.05) | | | |
| | | | | | FVC, % pred | At 12 months (mean (S.E)):<br>LVRS = 88 (3)<br>Control = 70 (3)<br>BGMD (adjusted for BL score) = 18 (p<0.05) | | | |
| | | | | | $FEV_1$, litres | At 12 months (mean (S.E)):<br>LVRS = 1.0 (0.1)<br>Control = 0.7 (0.1)<br>BGMD (adjusted for BL score) = 0.3 (95% CI 0.1 to 0.5, p=0.0003) in favour of LVRS | | | |
| | | | | | $FEV_1$, % pred | At 12 months (mean (S.E)):<br>LVRS = 41 (2)<br>Control = 30 (2)<br>BGMD (adjusted for BL score) = 11 (p<0.05) | | | |
| | | | | | $FEV_1$/FVC, % | At 12 months (mean (S.E)):<br>LVRS = 33 (1)<br>Control = 30 (1)<br>BGMD (adjusted for BL score) = 3 (p<0.05) | | | |
| | | | | | Transfer factor for the lung for carbon monoxide (TLCO), % pred | At 12 months (mean (S.E)):<br>LVRS = 37 (2)<br>Control = 33 (2)<br>BGMD (adjusted for BL score) = 4 (non-significant) | | | |
| | | | | | 6MWD, metres | At 12 months (mean (S.E)):<br>LVRS = 389 (13)<br>Control = 323 (12)<br>BGMD = 66 (95% CI 32 to 101; p=0.0002) in | | | |

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| | | | | | | favour of LVRS | | | |
| | | | | | Submaximal endurance time, minutes[16] | At BL (mean (SE)):<br>LVRS = 6.9 (95% CI 4.5 to 9.3)<br>Control = 6.6 (95% CI 4.7 to 8.4)<br><br>BGMD (adjusted for BL score) at 12 months = 7.3 (95% CI 3.9 to 10.8, p<0.0001)<br><br>Results for other time points not reported. | | | |
| | | | | | Maximal workload, Watts[17] | At BL (mean, (SE)):<br>LVRS = 37 (95% CI 32 to 42)<br>Control = 34 (95% CI 28 to 39)<br><br>BGMD (adjusted for BL score) at 6 months = 13 (95% CI 6 to 20, p=0.0003)<br><br>Results for other time points not reported. | | | |
| | | | | Secondary<br><br>Safety | Mortality | ≤30-day mortality:<br>LVRS: 2 patients died of respiratory failure (days 7 & 15).<br>Control: 0 deaths<br><br>>30-day mortality (over 12-month f/up period):<br>LVRS: 2 patients died of respiratory failure (285 and 334 days after surgery).<br>Control: 1 patient died of respiratory failure (117 days after randomisation). | | | |
| | | | | | Complications over 12-month follow-up period | LVRS:<br><br>There were four serious complications. Two patients required prolonged ventilation, one of whom sustained a non- fatal cardiac arrest, one | | | |

[16] A measure of integrated cardiopulmonary and physical performance. It is determined by a submaximal, constant power exercise test using a cycle ergometer. Submaximal cycle endurance time was not defined by Goldstein et al 2003.

[17] A measure of integrated cardiopulmonary and physical performance. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. The maximum work load is the highest work level reached (measured in Watts) and maintained for a full minute.

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| | | | | | | had significant bleeding, and one had a sternal dehiscence.<br><br>Other complications during hospitalisation for surgery included prolonged air leakage >7 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>After discharge from hospital there were four subsequent admissions (colitis, pneumonia, respiratory failure, emphysema).<br><br>One patient developed ischaemic heart disease.<br>30 patients developed respiratory infections.<br><br>Control:<br>There were no hospital admissions.<br><br>One patient developed ischaemic heart disease.<br>35 patients developed respiratory infections. | | | |

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| McKenna et al (2004)<br><br>NETT<br><br>USA | P1 Randomised controlled trial<br><br>Multi-centre<br><br>Mean follow-up time = 31.9 months | Patients enrolled in National Emphysema Treatment Trial (NETT) who were randomised to intervention group (LVRS) and who were not defined as high risk ($FEV_1$ % predicted of ≤20% and either homogeneous emphysema or DLCO ≤20% predicted).<br><br>NETT eligibility criteria: Patients with bilateral severe emphysema (homogenous and heterogeneous) judged suitable for LVRS. | Randomised comparison: video assisted thoracoscopic surgery (VATS) (n=71) vs open surgery by median sternotomy (MS) (n=77)<br><br>Non-randomised comparison: VATS (n=152) vs MS (n=359) | Primary<br><br>Clinical effectiveness | Maximum work, Watts Assessed by cycle ergometry | Non-randomised results<br><br>% patients with improvement (defined as increase in maximum work of >10 Watts) at 12 months:<br>VATS (n=134): 41%<br>MS (n=310) = 46%<br>Difference significant in favour of MS (p=0.05)<br><br>% patients with improvement (defined as increase in maximum work of >10 Watts) at 24 months:<br>VATS (n=99): 26%<br>MS (n=230) = 35%<br>Difference significant in favour of MS (p=0.03) | 8 | Direct | Before randomisation, eligible patients completed 6 to 10 weeks of pulmonary rehabilitation.<br><br>6 out of 17 centres in NETT (n=1,218) which compared LVRS to medical management, further randomised the LVRS intervention arm to VATS (n=71) or MS (n=77). The remaining centres either performed MS only (8 centres) or VATS only (3 centres). The trial excluded high risk patients ($FEV_1$ % predicted of ≤20% and either homogeneous emphysema or DLCO ≤20% predicted) who were stopped from being randomised into NETT partway through as they were deemed too high risk for little benefit (n=140).<br><br>Despite having a randomised comparison, this paper reports mainly on the non-randomised comparison which compared all VATS patients to all MS patients in NETT.<br><br>The non-randomised groups were comparable at BL except the MS group had a larger proportion of patients with heterogeneous emphysema.<br><br>The non-randomised results may be biased in favour of MS as the VATS group had a higher proportion of homogenous emphysema patients (49% vs 39%) and these patients are thought to be higher risk and benefit less from LVRS than patients with heterogeneous emphysema. This difference was not adjusted for in the analyses. In addition, there may be differences other than the surgery approach between the centres offering VATS only or MS only e.g. surgeon expertise, although the paper reports that all centres had similar percentages of 30-day mortality and postoperative complications.<br><br>The most likely reason for reporting on the non-randomised comparison would be to increase the power as the p-values reported for the smaller randomised comparison are mostly non-significant. |
| | | | | Secondary<br><br>Clinical effectiveness | Living independently, % | Randomised results<br><br>BL results not provided<br><br>By 30 days after surgery:<br>VATS = 87.3<br>MS = 62.3<br>Difference significant (p=0.001) in favour of VATS<br><br>After 4 months:<br>VATS = 90.1<br>MS = 83.1 | | | |

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| | | Randomised comparison: n = 148<br><br>Authors state that the two randomised groups were comparable at BL.<br><br>Non-randomised comparison: n =511<br><br>BL characteristics for non-randomised comparison: Age, mean (sd): in VATS group = 66.3 (6.7) and in MS group = 67.3 (6.0)<br><br>No (%) female: in VATS group = 65 (43) and in MS group = 154 (43)<br><br>No. (%) of patients with heterogeneous | | | | Difference non-significant (p=0.24)<br><br>Non-randomised results<br><br>BL results not provided<br><br>By 30 days after surgery:<br>VATS = 80.9<br>MS = 70.5<br>Difference significant (p=0.02) in favour of VATS<br><br>After 4 months:<br>VATS = 90.8<br>MS = 87.5<br>Difference non-significant (p=0.36) | | | No CI reported, only p-values.<br><br>Method of randomisation not described so not possible to determine likelihood of selection bias.<br><br>BL characteristics not given for the randomised groups.<br><br>Patients not blinded. Not stated whether outcome assessors were blinded.<br><br>Histograms of changes from BL to 12 months and 24 months were shown for % of patients with improvements in exercise capacity, $FEV_1$, 6MWD and QoL outcomes for the non-randomised comparison. However, absolute values are not reported. Some of the cut-offs for improvements were not defined so it is not possible to determine clinical significance. |
| | | | | | $FEV_1$, % pred | Non-randomised results<br><br>% patients with positive improvement (not defined) at 12 months:<br>VATS (n=134): 51%<br>MS (n=310) = 60%<br>Difference significant in favour of MS (p=0.05)<br><br>% patients with positive improvement (not defined) at 24 months:<br>VATS (n=99): 40%<br>MS (n=230) = 47%<br>Difference non-significant (p=0.12) | | | |

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| | | emphysema : in VATS group = 77 (51%) and 218 (61%) in MS group.<br><br>$FEV_1$ % predicted, mean (sd): in VATS group = 28.6 (7.1) and in MS group = 27.9 (6.6)<br><br>TLC, % pred, mean (sd): in VATS group = 127.6 (15.3) and in MS group = 127.2 (15.0)<br><br>RV % pred, mean (sd): in VATS group = 219.6 (47.7) and in MS group = 212.2 (44.5)<br><br>DLCO, % pred, mean (sd), mean | | | | | | | | |
| | | | | | QoL - St. Georges Respiratory Questionnaire (SGRQ) | Non-randomised results<br><br>% patients with positive improvement (defined as a decrease in SGRQ score of >8 units from baseline)) at 12 months:<br>VATS (n=134): 55%<br>MS (n=310) = 67%<br>Difference non-significant (p=0.23)<br><br>% patients with positive improvement (defined as a decrease in SGRQ score of >8 units from baseline) at 24 months:<br>VATS (n=99): 52%<br>MS (n=230) = 53%<br>Difference non-significant (p=0.73) | | | |
| | | | | | QoL – Quality of Well Being Scale[18] | Non-randomised results<br><br>% patients with positive improvement (not defined) at 12 months:<br>VATS (n=134): 40%<br>MS (n=310) = 44% | | | |

[18] The Quality of Wellbeing Scale consists of 71 items which measure overall health status and QoL over the previous three days in four areas: physical activities, social activities, mobility, and symptom/problem complexes.

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| | | (sd): in VATS group = 28.4 (9.6) and in MS group = 29.5 (9.2)<br><br>$PaCO_2$ (mmHg), mean (sd): in VATS group = 42.8 (6.0) and in MS group = 42.8 (5.5) | | | | Difference non-significant (p=0.45)<br><br>% patients with positive improvement at 24 months:<br>VATS (n=99): 36%<br>MS (n=230) = 31%<br>Difference non-significant (p=0.81) | | | |
| | | | | | Six minute walk distance (feet) | Non-randomised results<br><br>% patients with positive improvement (not defined) at 12 months:<br>VATS (n=134): 37%<br>MS (n=310) = 44%<br>Difference non-significant (p=0.09)<br><br>% patients with positive improvement at 24 months:<br>VATS (n=99): 25%<br>MS (n=230) = 33%<br>Difference non-significant (p=0.11) | | | |
| | | | | Primary<br><br>Safety | 30-day mortality risk, % | Non-randomised results<br><br>VATS= 2.0%<br>MS = 2.8%<br>Difference statistically non-significant (p=0.76)<br><br>Authors state similar | | | |

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| | | | | | | results seen for randomised comparison (no details provided). | | | |
| | | | | | 90-day mortality risk, % | Non-randomised results<br><br>VATS = 4.6%<br>MS = 5.9%<br>Difference statistically non-significant (p=0.67)<br><br>Authors state similar results seen for randomised comparison (no details provided). | | | |
| | | | | | Overall mortality rate, deaths per person-year | Mean follow-up = 31.9 months<br>During follow-up 39 VATS patients and 79 MS patients died.<br><br>Non-randomised results<br><br>VATS = 0.1<br>MS = 0.08<br>Risk ratio for deaths in VATS group = 1.18 (p=0.42)<br><br>No predictors of differential mortality by approach were identified. | | | |
| | | | | Secondary<br><br>Safety | Intraoperative complications, % | Non-randomised results<br><br>Proportion of patients with intraoperative complications: | | | |

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| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | | VATS = 13.8%<br>MS = 7.0%<br>Difference is statistically significant (p=0.02)<br><br>Only intraoperative complications that were significantly different were:<br>Hypoxemia:<br>VATS = 5.3%<br>MS = 0.8%<br>p=0.004<br><br>There was no difference between the MS and VATS groups in mean blood loss (138.0 vs 127.4 mL, respectively; p=0.55) or need for transfusion (3.1% vs 3.3%; p=0.99)<br><br>No statistically significant differences seen for randomised comparison (no results provided). | | | |
| | | | | | Postoperative complications, % | Randomised results<br><br>Failure to wean was the only significantly different postoperative complication.<br>VATS = 0%<br>MS = 7.8%<br>p=0.03<br><br>Total number of postoperative | | | |

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| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | | complications were non-significant (p=0.1) between the groups (no results provided).<br><br>Non-randomised results<br><br>Proportion of patients with postoperative complications:<br>VATS = 52.0%<br>MS = 58.2%<br>Difference is statistically non-significant (p=0.2)<br><br>Postoperative complications that were significantly different:<br><br>Reoperation for air leak:<br>VATS = 5.9%<br>MS = 2.2%<br>p=0.05<br><br>Air leak at closure:<br>VATS = 65.8%<br>MS = 54.3%<br>p=0.01<br>There was no difference between groups in the number of days with air leak (p=0.74).<br>Air leak on seven or more days occurred in 46% of MS patients compared to 49% of VATS patients (p=0.48). | | | |

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| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | | However, for the randomised comparison there was no difference between groups in the presence of air leak at closure or in the number of days with air leak. | | | |
| | | | | | Operating time, minutes | Randomised results<br><br>Mean operating time was 8.8 minutes shorter for MS than for VATS, but the difference was not statistically significant (p=0.30). No further details given.<br><br>Non-randomised results<br><br>VATS = 126.7 minutes<br>MS = 105.0 minutes<br>Mean difference = 21.7 minutes shorter for MS than for VATS (p=0.001) | | | |
| | | | | | Length of hospital stay, days | Randomised results<br><br>Mean length (SD)<br>VATS (n=67) = 13 (15)<br>MS (n=75) = 19 (15)<br>p=0.02<br><br>Median length<br>VATS = 9<br>MS = 15<br>p<0.001 | | | |
| | | | | | Length of Intensive Care | Randomised results | | | |

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| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | Unit (ICU) stay for patients who survived at least 30 days after LVRS, days | Difference between the groups was statically non-significant (p=0.76). No results provided.<br><br>Non-randomised comparison<br><br>0-1 days in ICU:<br>VATS = 65.1%<br>MS = 43.1%<br><br>2 days in ICU:<br>VATS = 6.6%<br>MS = 15.3%<br><br>3-29 days in ICU:<br>VATS = 24.3%<br>MS = 36.2%<br><br>≥30days on ICU:<br>VATS = 2.0%<br>MS = 2.3%<br><br>Difference in distribution was statically significant (p<0.001) | | | |
| | | | | Secondary<br><br>Costs | Mean hospital and physician costs, $ | For those patients with Medicare data available<br><br>Randomised results<br>VATS n = 67<br>MS n = 45.<br>$7138 less for the VATS group compared with the MS group (95% CI $5900 to | | | |

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| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | | $20,177; p=0.28).<br><br>Non-randomised results<br>VATS n = 146<br>Mean costs (SD) = $30,350 (35,219)<br>Median costs = $19,947<br><br>MS n = 343<br>Mean costs (SD) = $38,557 (40,519)<br>Median costs = $30,350<br>LVRS admission was $8207 less for the VATS group compared with the MS group (95% CI $917 to $16,035; p=0.03) | | | |
| | | | | | Mean total costs during the 6 months after surgery, $ | For those patients with Medicare data available<br><br>Randomised results<br>VATS n=67<br>MS n=45.<br>$6500 lower for the VATS group (95% CI $4295 to $8,705; p=0.001).<br><br>Non-randomised results<br>VATS n = 146<br>Mean costs (SD) = $51,053 (4,502)<br><br>MS n = 343<br>Mean costs (SD) = | | | |

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| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | | $61,481 (3,189)<br><br>$10,428 lower for the VATS group (95% CI $9786 to $109,062; p=0.005). | | | |

## 8 Grade of Evidence Table

For abbreviations see list after each table

| Use of video assisted thoracoscopic lung volume reduction surgery Vs. maximal medical therapy to treat severe emphysema | | | | | | |
|---|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** | |
| Mortality- ≤30-day mortality | Goldstein et al (2003) | 8 | Direct | B | The 30-day mortality risk is the chance of a patient dying within 30 days after having lung volume reduction surgery (LVRS). It is used as a measure of risk of death related to surgery. The effect of treatment on mortality is important, particularly for a treatment which, while improving some measures such as lung function, also results in serious adverse events and complications.<br><br>Goldstein et al (2003) reported that 2/28 (7%) patients died of respiratory failure within 30 days (at days 7 and 15) in the video assisted thoracoscopic surgery (VATS) group compared with 0/27 patients in the control group. No confidence intervals or p-values were reported, but it is likely to represent a non-significant difference due to the small sample size.<br><br>This means that although the trial observed a higher risk of dying within 30 days of VATS compared to control, it is not known if this is a true difference between the groups due to the small numbers enrolled in the trial.<br><br>The results should be treated with caution as they are based on a single randomised controlled trial (RCT) with a relatively small sample size (n=55) and therefore it is likely not to have the power to detect small differences between the groups. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. | |
| Mortality - >30-day mortality | Goldstein et al (2003) | 8 | Direct | A | The greater than 30 day mortality risk is the chance of a patient dying more than 30 days after having LVRS. Death occurring in this time period is less likely to be associated with complications of surgery and more likely to be associated with emphysema or other diseases occurring over the follow-up period of the trial.<br><br>Over 12 months, Goldstein et al (2003) reported that 2/28 (7%) patients died of respiratory failure more than 30 days after surgery (at 285 and 334 days after surgery) in the VATS group and 1/27 (4%) patient died of respiratory failure (at 117 days after randomisation) in the control group. No confidence intervals or p-values were reported, but it is likely to represent a non-significant difference due to the small sample size.<br><br>This means that although the trial observed a higher risk of dying greater than 30 days after VATS compared to control, it is not known if this is a true difference due to the small numbers enrolled in the trial.<br><br>The results should be treated with caution as they are based on an RCT with a relatively small sample size (n=55) and therefore it is likely not to have the power to detect small differences between the groups. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. | |
| | Mineo et al (2004) | 7 | Direct | | | |
| Treatment failure | Goldstein et al (2003) | 8 | Direct | B | Treatment failure was considered by Goldstein et al (2003) to be death or a functional decline in quality of life (QoL) defined as a consistent reduction of one or more units in two Chronic Respiratory Questionnaire (CRQ) domains (a disease specific QoL measure) from which the patient did not recover. | . |

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| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | | | | | Goldstein et al (2003), reported that by 12 months 7/28 (25%) patients in the VATS group had treatment failure (four died and three experienced functional decline) compared to 17/27 (63%) patients in the control group (one died and 16 experienced functional decline). A hazard ratio of 3.1 (95% CI 1.3 to 7.6; p=0.01) at 12 months in favour of VATS was found.<br><br>The results suggest that patients undergoing VATS are three times less likely to experience treatment failure at one year compared to medical management alone in patients with severe emphysema.<br><br>The results are based on an 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 sizes and the long-term impacts are not known. In addition, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to give positive responses in the CRQ and hence bias the results in favour of VATS. Furthermore, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. |
| Lung function – Total lung capacity, % predicted | Goldstein et al (2003) | 8 | Direct | A | Total lung capacity (TLC) includes the useful capacity of the lung and the residual volume (RV) or “dead space”. Emphysema damages the lung and reduces its elasticity resulting in hyperinflation. This increases the TLC and RV while reducing overall lung function.<br><br>At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in TLC of -15% in favour of VATS (p<0.05). Confidence intervals were not reported<br><br>These results suggest that VATS offers a greater reduction in TLC compared to medical management in patients with severe emphysema. However, no value for the minimal difference that is clinically important (MCID) was found so it is not clear if these changes are of clinical importance.<br><br>These results should be treated with caution as they are based on an RCT with a relatively small sample size (n=55) and short follow-up of 12 months, therefore there is likely to be a large range of uncertainty around the estimated effect size and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. |
| | Clarenbach et al (2015) | 7 | Direct | | |
| Lung function - Functional residual capacity, % predicted | Goldstein et al (2003) | 8 | Direct | B | Functional residual capacity (FRC) is the volume of air in the lungs after a normal relaxed expiration. It is a measure of elasticity of the lungs. The damage and loss of elasticity in emphysema increases the FRC resulting in reduced overall lung function.<br><br>At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in FRC of -41% in favour of VATS (p<0.05). Confidence intervals were not reported.<br><br>These results suggest that VATS offers a greater reduction in FRC compared to medical management in patients with severe emphysema up to 12 months. However, no value for MCID was found so it is not clear if these changes are of clinical importance.<br><br>These results should be treated with caution as they are based on a single RCT with a relatively small sample size (n=55) and short follow-up of 12 months, therefore there is likely to be a large range of uncertainty around the |

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| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | | | | | estimated effect size and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. |
| Lung function – Residual volume, % predicted | Goldstein et al (2003) | 8 | Direct | A | RV is the amount of air left in the lungs after full expiration and effectively represents the volume of "dead space" in the lung which does not help with gas exchange as air does not flow in and out. The damage and loss of elasticity in emphysema increases the RV.<br><br>At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in RV as a % of predicted RV of -47% in favour of VATS (95% CI -71 to -23; p=0.0002)<br><br>These results suggest that VATS offers a reduction in RV in patients with severe emphysema<br>However, no value for MCID was found so it is not clear if these changes are of clinical importance.<br><br>These results should be treated with caution as they are based on an RCT with a relatively small sample size (n=55) and short follow-up of 12 months therefore there is a large range of uncertainty around the estimated effect size and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. |
| | Clarenbach et al (2015) | 7 | Direct | | |
| | Mineo et al (2004) | 7 | Direct | | |
| Lung function - Residual volume, litres | Mineo et al (2004) | 7 | Direct | B | RV is the amount of air left in the lungs after full expiration and effectively represents the volume of "dead space" in the lung which does not help with gas exchange as air does not flow in and out. The damage and loss of elasticity in emphysema increases the RV.<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>These results suggest that there is evidence to support a greater reduction in RV with VATS compared to medical management, in the short-term (up to six months) in patients with severe emphysema. Reductions of 350 ml and 430 ml have been defined in studies as MCIDs (van Agteren et al 2017) which would mean that the reduction of 1.4 litres found between the two groups is likely to be clinically meaningful to patients. The longer-term results show an improvement in RV from baseline for up to four years, but it is not known how this compares to patients in the control group as control patients were allowed to cross over to LVRS from six months.<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, where patients are analysed in the groups they were randomised to regardless of whether they actually had the allocation, was not carried out. |
| Lung function - Forced vital capacity, litres | Goldstein et al (2003) | 8 | Direct | A | Forced vital capacity (FVC) is the maximal volume of air forcefully expired after taking a deep breath. It is an indicator of the functional capacity of the lungs and is expressed in litres or as percentage of predicted.<br><br>At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) |
| | Mineo et al (2004) | 7 | Direct | | |

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| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | | | | | between the groups in FVC of 0.7 litres in favour of VATS ($p<0.05$). Confidence intervals were not reported.<br><br>These results suggest that VATS offers a greater improvement in FVC compared to medical management in the short-term (up to 12 months) in patients with severe emphysema. However, no value for the MCID was found in the papers that were reviewed so it is not clear if this effect is clinically meaningful.<br><br>These results should be treated with caution as they are based on an RCT with a relatively small sample size (n=55) and short follow-up of 12 months, therefore there is likely to be a large range of uncertainty around the estimated effect size and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. |
| Lung function - Forced vital capacity, % predicted | Goldstein et al (2003) | 8 | Direct | A | Forced vital capacity (FVC) is the maximal volume of air forcefully expired after taking a deep breath. It is an indicator of the functional capacity of the lungs and is expressed in litres or as percentage of predicted.<br><br>At 12 months, Goldstein et al 2003 found a statistically significant mean difference in FVC as a % of predicted FVC (adjusted for baseline scores) between the groups of 18% in favour of VATS ($p<0.05$). Confidence intervals were not reported.<br><br>These results suggest that VATS offers a greater improvement in FVC % predicted compared to medical management in the short-term (up to 12 months). However, no value for the MCID was found in the papers that were reviewed so it is not clear if this effect is clinically meaningful.<br><br>These results should be treated with caution as they are based on an RCT with a relatively small sample size (n=55) and short follow-up of 12 months, therefore there is likely to be a large range of uncertainty around the estimated effect size and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. |
| | Clarenbach et al (2015) | 7 | Direct | | |
| | Mineo et al (2004) | 7 | Direct | | |
| Lung function - Forced expiratory volume in one second, litres | Goldstein et al (2003) | 8 | Direct | A | Forced expiratory volume in one second ($FEV_1$,) is the maximum volume of air a patient can exhale in one second. It is expressed in litres or as percentage of predicted value based on age, size, sex and race. It is the most frequently used parameter to measure pulmonary function in emphysema patients<br><br>At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in $FEV_1$ of 0.3 L (95% CI 0.1 to 0.5; p=0.0003) in favour of VATS.<br><br>These results suggest that VATS offers a greater improvement in $FEV_1$ compared to medical management in the short-term (up to 12 months) by 0.3 litres in patients with severe emphysema. A difference of 0.1 litres is considered to be a MCID and therefore even at the lower limit of the confidence interval, this would be considered a clinically significant difference (Jones et al 2014).<br><br>These results are based on an RCT with a relatively small sample size (n=55) and short follow-up of 12 months and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. |
| | Mineo et al (2004) | 7 | Direct | | |
| Lung function - Forced expiratory volume in one second, % predicted | Goldstein et al (2003) | 8 | Direct | A | Forced expiratory volume in one second ($FEV_1$) is the maximum volume of air a patient can exhale in one second. It is expressed in litres or as percentage of predicted value based on age, size, sex and race. It is the most |

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| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | Clarenbach et al (2015) | 7 | Direct | | frequently used parameter to measure pulmonary function in emphysema patients.<br><br>At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in $FEV_1$ of 11% predicted in favour of VATS ($p<0.05$). Confidence intervals were not reported.<br><br>These results suggest that VATS offers a greater improvement in $FEV_1$ % predicted compared to medical management in the short-term (up to 12 months) by 11% in patients with severe emphysema. This difference is of clinical significance as a difference of 5-10% is considered to be a MCID (Jones et al 2014).<br><br>These results should be treated with caution as they are based on an RCT with a relatively small sample size (n=55) and short follow-up of 12 months therefore there is likely to be a large range of uncertainty around the estimated effect size and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. |
| | Mineo et al (2004) | 7 | Direct | | |
| Lung function - $FEV_1$/FVC, % | Goldstein et al (2003) | 8 | Direct | B | The $FEV_1$/FVC ratio is the amount of air exhaled in the first second divided by all of the air exhaled during maximal exhalation. It is widely used in clinical practice to differentiate obstructive (e.g. low $FEV_1$/FVC ratio with normal FVC) from restrictive (e.g. normal $FEV_1$/FVC ratio and low FVC) lung disease. Emphysema is an obstructive lung disease, with lower $FEV_1$/FVC ratio indicating more severe disease.<br><br>At 12 months, Goldstein et al (2003) reported a statistically significant mean difference (adjusted for baseline scores) between the groups in $FEV_1$/FVC of 3% in favour of VATS ($p<0.05$). Confidence intervals were not reported.<br><br>These results suggest that VATS offers a greater improvement in $FEV_1$/FVC compared to medical management in the short-term (up to 12 months). However, no value for the MCID was found in the papers that were reviewed so it is not clear if this effect is clinically meaningful.<br><br>These results should be treated with caution as they are based on a single RCT with a relatively small sample size (n=55) and short follow-up of 12 months, therefore there is likely to be a large range of uncertainty around the estimated effect size and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. |
| Lung function – Diffusion capacity of the lung for carbon monoxide, % predicted | Goldstein et al (2003) | 8 | Direct | A | Emphysema damages lung tissue, reducing the diffusion capacity of the lung for oxygen and carbon dioxide and hence causing breathlessness. The diffusion capacity of the lung for carbon monoxide (DLCO) is a measure of this diffusion capacity of the lung for gases.<br><br>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>These results do not provide evidence of a difference in DLCO between VATS and medical management in patients with severe emphysema at 12 months.<br><br>The results should be treated with caution as they are based on a RCT with a relatively small sample size (n=55) and therefore it does not have the power to detect small differences between the groups. In addition, although the |
| | Clarenbach et al (2015) | 7 | Direct | | |
| | Mineo et al (2004) | 7 | Direct | | |

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| | | | | | majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. |
| Lung function - RV/TLC ratio, % | Clarenbach et al (2015) | 7 | Direct | B | A reduction in RV/TLC means that a larger proportion of the air in the lungs can be exhaled and therefore a higher proportion may be useable for gas exchange. This may therefore improve gas exchange and reduce symptoms of breathlessness.<br><br>At three months, Clarenbach et al (2015) found a statistically significant mean difference (in change from baseline) between the groups in RV/TLC of -7.8% (95% CI -13.6 to -1.9; p=0.011) in favour of VATS.<br><br>These results suggest that VATS reduces RV/TLC by 7.8% more than medical management in patients with severe emphysema in the short-term (up to three months). This reduction is likely to be clinically meaningful to patients as an MCID of 4% was found in the literature (van Agteren et al 2017).<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. 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 – Partial pressure of oxygen in arterial blood, kPa | Mineo et al (2004) | 7 | Direct | B | Partial pressure of oxygen in arterial blood ($PaO_2$) is the pressure of oxygen dissolved in the arterial blood. It is a measure of how well oxygen is able to move from the airspaces of the lungs into the blood. An increase in $PaO_2$ signifies an improvement in condition.<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>Evidence was found of an effect of VATS on $PaO_2$ compared to medical management in the short-term (up to six months) in patients with severe emphysema. However, no value for the MCID was found in the papers that were reviewed so it is not clear of this effect is clinically meaningful. The longer-term results show some improvement in $PaO_2$ from baseline, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months.<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. |
| Lung function – Partial pressure of carbon dioxide in arterial blood, kPa | Mineo et al (2004) | 7 | Direct | B | Partial pressure of carbon dioxide ($CO_2$) in arterial blood ($PaCO_2$) is the pressure of $CO_2$ dissolved in the arterial blood. It is a measure of how well $CO_2$ is able to move out of the body. A reduction in $PaCO_2$ signifies an improvement in condition. |

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| | | | | | At six months, Mineo et al (2003) found a statistically 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.<br><br>These results suggest that there is no evidence of a difference in $PaCO_2$ between VATS and medical management in patients with severe emphysema at six months.<br><br>These results are taken from a small RCT (n=60) therefore it may not have the power to detect small differences in effect size that could still be of clinical significance. 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. |
| Endothelial function - Flow-mediated dilatation of the brachial artery, % | Clarenbach et al (2015) | 7 | Direct | B | Flow-mediated dilatation of the brachial artery (FMD) can be used to assess endothelial function, which has been shown to be predictive of cardiovascular risk. There is a theory that airflow obstruction and systemic inflammation in emphysema may contribute to endothelial dysfunction thereby increasing the risk of cardiovascular disease in patients with emphysema.<br><br>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).<br><br>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).<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. |
| Endothelial function - Nitroglycerine-mediated dilatation, % | Clarenbach et al (2015) | 7 | Direct | B | Nitroglycerine-mediated dilatation (NMD) can be used to assess endothelial function which has been shown to be predictive of cardiovascular risk. There is a theory that airflow obstruction and systemic inflammation in emphysema may contribute to endothelial dysfunction thereby increasing the risk of cardiovascular disease in patients with emphysema.<br><br>At three months, Clarenbach et al (2015) reported a statistically non-significant mean difference (in change from baseline) between the groups in NMD of -1.7% (95% CI -5.9 to 2.5; p=0.412).<br><br>These results suggest that there is no evidence of a difference in endothelial function as measured by NMD between VATS and medical management in patients with severe emphysema in the short-term.<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) 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. |
| Systemic inflammation – High sensitive C-reactive protein, mg/L | Clarenbach et al (2015) | 7 | Direct | B | 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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| | | | | | At three months, Clarenbach et al (2015) reported a statistically non-significant mean difference (in change from baseline) between the groups in CRP of 0 mg/L (95% CI -0.9 to 0.6; p=0.942).<br><br>These results suggest that there is no evidence of a difference in systemic inflammation as measured by CRP between VATS and medical management in patients with severe emphysema in the short-term.<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 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. |
| Exercise capacity - Six minute walk distance, m | Goldstein et al (2003)<br>Mineo et al (2004) | 8<br>7 | Direct<br>Direct | A | The six-minute walk distance (6MWD) is defined as the distance that a patient can walk in six minutes usually on a treadmill. Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. The distance that a patient can walk in six minutes is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks.<br><br>At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups in 6MWD of 66 m (95% CI 32 to 101; p=0.0002) in favour of VATS.<br><br>These results suggest that VATS offers a greater improvement in 6MWD of 66 m compared to medical management in patients with severe emphysema at 12 months. This is of clinical significance with a difference of 26 m in patients with severe COPD being identified as a MCID (Jones et al 2014).<br><br>These results should be treated with caution as they are based on a single RCT with a relatively small sample size (n=55) and short follow-up of 12 months, therefore there is a large range of uncertainty around the estimated effect size and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. Furthermore, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to try harder in the tests and hence bias the results in favour of LVRS. |
| Exercise capacity - Submaximal endurance time, min | Goldstein et al (2003) | 8 | Direct | B | Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise. Submaximal endurance time is a measure of integrated cardiopulmonary and physical performance. It is determined by a submaximal, constant power exercise test using a cycle ergometer. Submaximal cycle endurance time was not defined by Goldstein et al (2003).<br><br>At 12 months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) between the groups of 7.3 minutes (95% CI 3.9 to 10.8; p<0.0001) in favour of VATS.<br><br>These results suggest that VATS offers a greater improvement in exercise capacity as assessed by submaximal endurance time compared to medical management in patients with severe emphysema. It is not clear whether these results are clinically meaningful to patients as no value for the MCID was found in the papers that were reviewed.<br><br>These results should be treated with caution as they are based on a single RCT with a relatively small sample size (n=55) and short follow-up of 12 months therefore there is a large range of uncertainty around the estimated effect |

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| | | | | | size and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS, some had open surgery (exact numbers not reported) and this may influence the results. Furthermore, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to try harder in the tests and hence bias the results in favour of LVRS. |
| Exercise capacity – Maximum work load, Watts | Goldstein et al (2003) | 8 | Direct | B | Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise. Maximum work load is a measure of integrated cardiopulmonary and physical performance. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. The maximum work load is the highest work level reached (measured in Watts) and maintained for a full minute. It is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks.<br><br>At six months, Goldstein et al (2003) found a statistically significant mean difference (adjusted for baseline scores) of 13 Watts (95% CI 6 to 20; p=0.0003) in favour of VATS. The results for 12 months were not reported.<br><br>These results suggest that VATS offers a greater improvement in maximum work load of 13 Watts compared to medical management in patients with severe emphysema at six months. Naunheim et al (2016) used 10 Watts or a greater increase to define a change that is clinically important to patients. Therefore, these results suggest that VATS offers clinically meaningful improvements in exercise capacity as measured by cycle ergometer maximum exercise capacity tests in the short-term (up to six months).<br><br>These results should be treated with caution as they are based on a single RCT with a relatively small sample size (n=55) and short follow-up of 12 months, therefore there is a large range of uncertainty around the estimated effect size and the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS some had open surgery (exact numbers not reported) and this may influence the results. Furthermore, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to try harder in the tests and hence bias the results in favour of LVRS. |
| Exercise capacity - Number of steps per 24 hours, number | Clarenbach et al (2015) | 7 | Direct | B | Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. An increase in the number of steps per 24 hours is an indication of whether a patient does more exercise following VATS, which might indicate that the surgery enables them to exercise more.<br><br>At three months, Clarenbach et al (2015) found a statistically non-significant mean difference (in change from baseline) between the groups of 120 steps (95% CI 0 to 667; p=0.100).<br><br>These results suggest that there is no evidence of a difference in exercise capacity as measured by number of steps per 24 hours between VATS and medical management in patients with severe emphysema in the short-term.<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 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. In addition, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to be more motivated to take more steps and hence bias the results in favour of LVRS. Furthermore, the number of steps in 24 hours may be influenced by many factors, not just lung function, so other measures of exercise capacity may provide more robust measures. |

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| QoL - Chronic Respiratory Questionnaire (CRQ) score | Goldstein et al (2003) | 8 | Direct | B | Chronic Respiratory Questionnaire (CRQ) 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). VATS aims to improve patient QoL by improving lung function, reducing breathlessness and increasing exercise capacity.<br><br>Goldstein et al (2003) reported a significant treatment effect in favour of VATS in each of the CRQ domains at 3, 6, 9 & 12 months (all p<0.0001). At 12 months, a mean difference (adjusted for baseline scores) of 1.9 (95% CI 1.3 to 2.6; p<0.0001) was found for dyspnoea, 1.5 (95% CI 0.9 to 2.1; p<0.0001) for emotional function, 2.0 (95% CI 1.4 to 2.6; p<0.0001) for fatigue, and 1.8 (95% CI 1.2 to 2.5; p<0.0001) for mastery.<br><br>These results suggest that VATS improves QoL as measured by CRQ more than medical management in patients with severe emphysema up to 12 months. The difference in scores between the two groups for all the CRQ domains were greater than the widely reported MCID of 0.5 and hence are likely to represent clinically meaningful differences to patients (Goldstein et al 2003).<br><br>These results should be treated with caution as they are based on a single RCT with a relatively small sample size (n=55) and short follow-up of 12 months so the long-term impacts are not known. In addition, although the majority of LVRS patients had VATS some had open surgery (exact numbers not reported) and this may influence the results. Furthermore, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to give positive responses and hence bias the results in favour of LVRS. |
| QoL - Nottingham Health Profile score | Mineo et al (2004) | 7 | Direct | B | The Nottingham Health Profile (NHP) is a measure of QoL, which contains 38 dichotomic-choice questions relating to eight domains: mobility, energy, pain, social isolation, sleep disturbance, and emotional reactions. It ranges from 0 (best score) to 100 (worst score). VATS aims to improve patient QoL by improving lung function, reducing breathlessness and increasing exercise capacity.<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.<br><br>Therefore no evidence was found of an effect of VATS on QoL as measured by NHP compared to medical management in the short-term. The longer-term results show an improvement in NHP score from baseline up to three years, but it is not known how this compares to patients in the control group, as patients were allowed to cross over to LVRS from six months.<br><br>These results 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. Furthermore, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to |

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| | | | | | give positive responses and hence bias the results in favour of LVRS. |
| QoL - Short Form 36 item score | Mineo et al (2004) | 7 | Direct | B | The SF-36 is a widely used, validated, generic measure of health status which assesses 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; general health. Scores are presented as a scale from 0 to 100. A high score indicates a more favourable health state. VATS aims to improve patient QoL by improving lung function, reducing breathlessness and increasing exercise capacity.<br><br>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 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 BL with p-values of <0.01, 0.01, 0.02 and 0.05 at 1, 2, 3 and 4 years respectively.<br><br>These results suggest that VATS offers a greater improvement in QoL as measured by SF-36 compared to medical management in the short-term. However, it is not clear whether these improvements are clinically meaningful as no value for the MCID was found in the papers that were reviewed. The longer-term results show an improvement in SF-36 score from baseline up to four years, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months.<br><br>These results are taken from a small RCT (n=60) therefore there is a large range of uncertainty around the estimated effect sizes. In addition, the long-term impacts are not certain as from six months patients were allowed to cross over to LVRS and an intention to treat analysis was not carried out. Furthermore, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to give positive responses and hence bias the results in favour of LVRS. Finally, SF-36 is a general measure of QoL, so may be less responsive than measures of QoL specifically for people with respiratory disease. |
| QoL - St George's Respiratory Questionnaire score | Mineo et al (2004) | 7 | Direct | B | St George's Respiratory Questionnaire (SGRQ) is a validated, disease related, self-administered, measure of QoL. It contains 50-items covering symptoms, activities and psychosocial impact. VATS aims to improve patient QoL by improving lung function, reducing breathlessness and increasing exercise capacity.<br><br>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 |

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| | | | | | baseline with p-values of <0.01, 0.01, 0.03 and 0.03 at 1, 2, 3 and 4 years respectively.<br><br>These results suggest that VATS improves QoL by 7.6 points more than medical management as measured by SGRQ in the short-term. This is likely to be a clinically meaningful difference to patients with severe emphysema, with MCID ranging from 2 to 8 points in the literature, with 4 being the average (Jones et al 2014). The longer-term results show an improvement in SF-36 score from baseline up to four years, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months.<br><br>These results are taken from a small RCT (n=60) therefore there is a large range of uncertainty around the estimated effect sizes. In addition, the long-term impacts are not certain as from six months patients were allowed to cross over to LVRS and an intention to treat analysis was not carried out. Furthermore, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to give positive responses and hence bias the results in favour of LVRS. |
| QoL - Modified Medical Research Council Dyspnoea Scale score | Mineo et al (2004) | 7 | Direct | B | The modified Medical Research Council Dyspnoea Scale (mMRC) ranges from 0-4 and is a validated tool used to establish levels of functional impairment or perceived impairment due to dyspnoea (breathlessness) attributable to respiratory disease. It consists of six phrases describing how much breathlessness interferes with daily activities.<br><br>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.<br><br>These results suggest that VATS improves dyspnoea as measured by the mMRC by 1.2 points more than medical management in patients with severe emphysema in the short-term. It is not known if this difference is clinically meaningful to patients as the mMRC scale, although widely used, is reported to have poor evaluative properties to assess changes in dyspnoea (Jones et al 2014). The longer-term results show an improvement in mMRC score from baseline up to four years, but it is not known how this compares to patients in the control group as patients were allowed to cross over to LVRS from six months.<br><br>These results are taken from a small RCT (n=60) therefore there is a large range of uncertainty around the estimated effect sizes. In addition, the long-term impacts are not certain as from six months patients were allowed to cross over to LVRS and an intention to treat analysis was not carried out. Furthermore, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to give positive responses and hence bias the results in favour of LVRS. |
| Body weight, kg | Mineo et al (2004) | 7 | Direct | B | Weight loss, muscle wasting, as well as muscle dysfunction are recognised as important problems in emphysema, contributing to morbidity and mortality. Therefore body weight gain is an important outcome for patients.<br><br>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. |

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| | | | | | 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 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 dependent patients, % | Mineo et al (2004) | 7 | Direct | B | Emphysema can limit the ability of the lungs to absorb sufficient oxygen leading to low $PaO_2$, which is a risk for complications such as pulmonary hypertension and can affect breathlessness and patients' exercise capacity and QoL. Mineo et al (2004) reported that oxygen dependency was considered whenever $PaO_2$ was 8.64kPa or less, but no further details were provided on the type of oxygen dependency (e.g. short-term for an exacerbation or long-term).<br><br>At six months, Mineo et al (2004) reported a statistically significant difference in percentage of oxygen dependent patients (from changes from baseline) between the groups of 51.7% in favour of VATS (p=0.02). Confidence intervals were not reported. At baseline 63.3% of VATS patients and 60.0% of control patients were dependent on oxygen and this reduced to 7.1% in VATS patients and 55.5% in control patients at six months after surgery or randomisation.<br><br>The results appear to suggest a large difference in the percentage of patients requiring oxygen of some type between the groups after surgery. This will have an impact on the QoL of patients and healthcare resources.<br><br>These results are taken from a small RCT (n=60) therefore there is a large range of uncertainty around the estimated effect sizes. In addition, the long-term impacts are not certain as from six months patients were allowed to cross over to LVRS and an intention to treat analysis was not carried out. |
| Steroid dependent patients, % | Mineo et al (2004) | 7 | Direct | B | Steroids reduce inflammation caused by emphysema and can improve symptoms in patients with severe emphysema. However they have side effects which can affect QoL such as sore mouth, infections and weight gain. Mineo et al (2004) defined steroid dependency as having an oral methylprednisolone intake of 8 or more mg per day for a minimum of one month within the last year's pre-treatment.<br><br>At six months, Mineo et al (2004) reported a statistically non-significant difference in the percentage of steroid dependent patients (from changes from baseline) between the groups of 34.6% in favour of VATS. Confidence intervals or p-values were not reported. At baseline, 73.3% of VATS patients and 80.0% of control patients were dependent on steroids and this reduced to 14.2% in VATS patients and 55.5% in control patients at six months after surgery or randomisation.<br><br>Thus no evidence was found of an effect of VATS on steroid dependency compared to medical management in the short-term.<br><br>These results are taken from a relatively small RCT (n=60) therefore it may not have the power to detect small differences in effect size that may still be clinically significant. 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, the paper's definition of steroid dependency is unclear, but seems to imply that to be considered |

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| | | | | | dependent on steroids, the patient had to be on steroids for at least a month within the last year, so for the six month results, this would include six months prior to surgery and six months post surgery. |
| Hospitalisation utilisation – Hospital stay, days | Clarenbach et al (2015) | 7 | Direct | A | The length of hospital stay after surgery is an important outcome as it indicates the length of time it takes to recover from an operation and will have an impact to patients' QoL and hospital resources.<br><br>The most recent trial, Clarenbach et al (2015) reported an average hospitalisation time of 14 days (range = 7 to 28).<br><br>This suggests that patients are likely to be in hospital for around two weeks after VATS which is a relatively long hospital stay.<br><br>These results are taken from relatively small RCTs based in Italy and Switzerland and therefore may not be applicable to the UK. |
| | Mineo et al (2004) | 7 | Direct | | |
| Adverse events – Complications during hospitalisation | Goldstein et al (2003) | 8 | Direct | A | Assessing complications related to surgery is important as if serious and/or common they may outweigh the benefits associated with VATS.<br><br>Goldstein et al (2003) reported 4/28 (14%) patients experiencing serious complications during hospitalisation after LVRS. Two patients required prolonged ventilation, one of whom sustained a non-fatal cardiac arrest, one had significant bleeding, and one patient had a sternal dehiscence (wound rupture along the surgical incision along the sternum which is often accompanied with infection of the deep soft tissues). Other complications during hospitalisation for surgery included prolonged air leakage of greater than seven days (n=10; one subject required re-operation for air leak), benign dysrhythmias (n=6), respiratory tract infections (n=6), transient confusion (n=6), small bowel ileus (n=2), vocal cord dysfunction (n=2), and transient ischaemic attack (n=1).<br><br>These results suggest a high complication rate (14%) associated with VATS. However the severity and long-term impact of this are not discussed, which makes it difficult to interpret the significance of this finding for patients.<br><br>These results are taken from a relatively small RCT so there is likely to be a large range of uncertainty around the estimated risks. In addition the trial included a small number of open surgery cases (number not known) so some of the complications such as sternal dehiscence may not be associated with VATS surgery. |
| | Clarenbach et al (2015) | 7 | Direct | | |
| Adverse events – Early (≤30 days) complications | Mineo et al (2004) | 7 | Direct | B | Early complications occurring 30 days or less after surgery are important as if serious and/or common they may outweigh the benefits associated with VATS.<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>These results suggest a very high early complication rate (53%) associated with VATS. However the severity and long-term impact of this are not discussed, which makes it difficult to interpret the significance of this finding for patients.<br><br>These results are taken from a single relatively small RCT (n=60) so there is likely to be a large range of |

| Use of video assisted thoracoscopic lung volume reduction surgery Vs. maximal medical therapy to treat severe emphysema | | | | | |
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| | | | | | uncertainty around the estimated risks. |
| Adverse events – Late (>30 days) complications | Mineo et al (2004) | 7 | Direct | B | Late complications occurring more than 30 days after surgery are important as if serious and/or common they may outweigh the benefits associated with VATS.<br><br>Mineo et al (2004) found a non-significant difference in late morbidity between the groups. In the VATS group, 3/10 (30%) patients had late complications (1 persistent intercostal neuralgia, 1 pneumonia requiring hospitalisation, and 1 loculated pneumothorax requiring reoperation) and 4/30 (15%) patients in the control group (3 worsening hypoxemia & 1 pneumonia, all required hospitalisation).<br><br>These results suggest that there is no difference in adverse events occurring more than 30 days after surgery or randomisation.<br><br>The results should be treated with caution as they are based on a single trial of small numbers (n=60) and control patients were allowed to cross over to surgery from six months (12 patents crossed over to VATS due to unsatisfactory improvements) and these patients were excluded from the analysis. |
| Adverse events – Total complications | Goldstein et al (2003) | 8 | Direct | B | Total complications occurring over the follow-up period are important as if shown to be serious and/or common they may outweigh the benefits associated with VATS.<br><br>During the 12-month follow-up period after hospital, Goldstein et al (2003) reported that 4/28 LVRS patients (14%) required subsequent hospital admissions (due to colitis, pneumonia, respiratory failure & empyema) and there were no hospital admissions for control patients. Other than this, Goldstein et al (2003) reported that the only morbidities encountered were ischaemic heart disease (one surgical and one control subject) and respiratory infections (30 surgical and 35 control subjects).<br><br>These results suggest a relatively high readmission rate (14%) associated with VATS. This has implications for the patient as well as hospital resources.<br><br>These results are taken from a relatively small single RCT so therefore there will be a large range of uncertainty around these rates. In addition the trial included a small number of open surgery cases (number not known) so some of the admissions may not be associated with VATS surgery. |

| Use of video assisted thoracoscopic lung volume reduction surgery Vs. open lung volume reduction surgery (median sternotomy) to treat severe emphysema | | | | | |
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| Mortality - 30-day risk | McKenna et al (2004) | 8 | Direct | B | The 30-day mortality risk is the chance of a patient dying within 30 days after having lung volume reduction surgery (LVRS). It is used as a measure of risk of death related to surgery. The effect of treatment on mortality is important, particularly for a treatment which, while improving some measures such as lung function, also results in |

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| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | | | | | serious adverse events and complications.<br><br>In a non-randomised comparison including all patients having LVRS by video assisted thoracoscopic surgery (VATS) or open surgery by median sternotomy (MS), McKenna et al (2004) found no statistically significant difference in the 30-day mortality risk (2.0% for VATS vs 2.8% for MS; p=0.76). Results for the randomised comparison were not reported. However, the authors state that similar results were seen in the randomised comparison.<br><br>The results suggest that there is no evidence of a difference in risk of mortality within 30 days of LVRS between VATS and open surgery.<br><br>These results should be treated with caution as although based on relatively large numbers (n=511) there may not be sufficient power to detect small differences that are still 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. |
| Mortality – 90-day risk | McKenna et al (2004) | 8 | Direct | B | The 90-day mortality risk is the chance of a patient dying within 90 days after having LVRS. It is used as a measure of risk of death that might be related to surgery. The effect of treatment on mortality is important, particularly for a treatment which, while improving some measures such as lung function, also results in serious adverse events and complications.<br><br>In a non-randomised comparison, McKenna et al (2004) found a statistically non-significant difference in 90-day mortality risk between VATS and MS (4.6% for VATS vs 5.9% for MS; p=0.67). Results for the randomised comparison were not reported.<br><br>The results suggest that there is no evidence of a difference in risk of mortality within 90 days of LVRS between VATS and open surgery in patients with severe emphysema.<br><br>These results should be treated with caution as although based on relatively large numbers (n=511) there may not be sufficient power to detect small differences that are still 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. |
| Mortality – Overall rate | McKenna et al (2004) | 8 | Direct | B | The effect of treatment on overall mortality is important, particularly for a treatment which, while improving some measures such as lung function, also results in serious adverse events and complications.<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 MS patients. This equates to a statistically non-significant risk ratio of 1.18 (p=0.42). Results for the randomised comparison were not reported.<br><br>These results suggest that there is no difference in the overall death rate between VATS and MS in patients with severe emphysema. |

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| | | | | | These results should be treated with caution as although based on relatively large numbers (n=511) there may not be sufficient power to detect small differences of clinical significance. In addition, the results are based on a non-randomised comparison therefore the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias. |
| Lung function - Forced expiratory volume in one second, % predicted | McKenna et al (2004) | 8 | Direct | B | Forced expiratory volume in one second ($FEV_1$) is the maximum volume of air a patient can exhale in one second. It is expressed in litres or as percentage of predicted value (% predicted) based on age, size, sex and race. It is the most frequently used parameter to measure pulmonary function in emphysema patients.<br><br>In a non-randomised comparison, McKenna et al (2004) found a statistically significant difference in the percentage of patients with an improvement in $FEV_1$ % predicted (the cut-off point used to define improvement was not reported) in favour of open surgery (51% of VATS patients vs 60% of MS patients; p=0.05) at 12 months. However, no evidence of a difference was seen at 24 months (40% of VATS patients vs 47% of MS patients; p=0.12). Results for the randomised comparison were not reported.<br><br>These results suggest a greater proportion of open surgery patients showed improvements in $FEV_1$ in the short-term (up to 12 months) compared to VATS patients, but there was no evidence of a difference between the groups in the longer-term (up to 24 months). Absolute values were not reported so it was not possible to determine whether the differences seen at 12 months were clinically meaningful to patients.<br><br>These results should be treated with caution as although based on relatively large numbers (n=511) there may not be sufficient power to detect small differences of clinical significance. In addition, the results are based on a non-randomised comparison therefore the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias. |
| Exercise capacity - Maximum work, Watts | McKenna et al (2004) | 8 | Direct | B | This is a measure of integrated cardiopulmonary and physical performance. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. The maximum work load is the highest work level reached (measured in Watts) and maintained for a full minute. It is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks.<br><br>In a non-randomised comparison, McKenna et al (2004) found a statistically significant difference in the percentage of patients with an improvement in maximum work (defined as increase in maximum work of greater than 10 Watts from baseline) in favour of open surgery at 12 months (41% of VATS patients vs 46% of MS patients; p=0.05) and at 24 months (26% of VATS patients vs 35% of MS patients; p=0.03). Results for the randomised comparison were not reported.<br><br>The results suggest a greater improvement in exercise capacity with open surgery compared to VATS as measured by cycle ergometer maximum exercise capacity tests up to two years. Although the absolute values are not reported, the difference between the groups is likely to be clinically meaningful as to improve patients had to have an increase in maximum work of greater than 10 Watts from baseline, which the authors define as clinically significant.<br><br>These results should be treated with caution as although based on relatively large numbers (n=511), the results |

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| | | | | | 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. In addition, it was not possible to blind the patients to their allocated treatment so patients in the one of the groups may be more likely to try harder in the tests and hence bias the results. |
| Exercise capacity – Six-minute walk distance, feet | McKenna et al (2004) | 8 | Direct | B | The six-minute walk distance (6MWD) is defined as the distance that a patient can walk in six minutes, usually on a treadmill. Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. The distance that a patient can walk in six minutes is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks.<br><br>In a non-randomised comparison, McKenna et al (2004) found no significant difference in the percentage of patients with an improvement in 6MWD (the cut-off point used to define improvement was not reported) at 12 months (37% of VATS patients vs 44% of MS patients; p=0.09) and 24 months (25% of VATS patients vs 33% of MS patients; p=0.11). Results for the randomised comparison were not reported.<br><br>These results suggest that there is no difference in improvement in exercise capacity, as measured by the 6MWD, with VATS compared to MS for patients with severe emphysema.<br><br>These results should be treated with caution as although based on relatively large numbers (n=511) there may not be sufficient power to detect small differences of clinical significance. In addition, the results are based on a non-randomised comparison therefore the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias. In addition, it was not possible to blind the patients to their allocated treatment so patients in one of the groups may be more likely to try harder in the tests and hence bias the results. |
| QoL - Living independently | McKenna et al (2004) | 8 | Direct | B | The ability to live independently is an important component of QoL. This outcome was not defined by McKenna et al (2004), but it is likely to refer to the percentage of patients not hospitalised or living in a nursing or rehabilitation facility.<br><br>In the randomised comparison, McKenna et al (2004), reported there was a statistically significant difference in the percentage of patients living independently at 30 days after surgery in favour of VATS (87.3% of VATS patients vs 62.3% of MS patients, p=0.001). The difference at four months was statistically non-significant (90.1% of VATS patients vs 83.1% of MS patients, p=0.24). The baseline figures were not given.<br><br>The results suggest that VATS patients are more likely to live independently in the month after surgery compared to patients having open surgery, but this difference disappears by four months after surgery.<br><br>These results are based on a well conducted RCT with a moderate sample size (n=148) and overall provide good evidence that VATS patients are more likely to live independently within 30 days of surgery compared to open surgery patients. |
| QoL - St George's Respiratory Questionnaire | McKenna et al (2004) | 8 | Direct | B | The St George's Respiratory Questionnaire (SGRQ) is a 50-item questionnaire developed to measure QoL in patients with diseases of airways obstruction. It contains three sections investigating symptoms, activity, and impact of these limitations on mood state. |

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| | | | | | In a non-randomised comparison, McKenna et al (2004) found no statistically significant difference in the percentage of patients with an improvement in the SGRQ (defined as a decrease in SGRQ score of >8 units from baseline) at 12 months (55% of VATS patients vs 67% of MS patients; p=0.23) and 24 months (52% of VATS patients vs 53% of MS patients; p=0.73). Results for the randomised comparison were not reported.<br><br>The results suggest that there is no evidence of a difference in QoL as measured by SGRQ between VATS and open surgery in patients with severe emphysema up to two years.<br><br>These results should be treated with caution as although based on relatively large numbers (n=511) there may not be sufficient power to detect small differences of clinical significance. In addition, the results are based on a non-randomised comparison therefore the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias. In addition, it was not possible to blind the patients to their allocated treatment, so patients in one of the groups may be more likely to try harder in the tests and hence bias the results. |
| QoL - Quality of Wellbeing Scale | McKenna et al (2004) | 8 | Direct | B | The Quality of Wellbeing Scale consists of 71 items which measure overall health status and QoL over the previous three days in four areas: physical activities, social activities, mobility, and symptom/problem complexes.<br><br>In a non-randomised comparison, McKenna et al (2004) found no significant difference in the percentage of patients with an improvement in the Quality of Wellbeing Scale (the cut-off point used to define improvement was not reported) at 12 months (40% of VATS patients vs 44% of MS patients; p=0.45) and 24 months (36% of VATS patients vs 31% of MS patients; p=0.81). Results for the randomised comparison were not reported.<br><br>The results suggest that there is no evidence of a difference in QoL as measured by the Quality of Wellbeing Scale between VATS and open surgery in patients with severe emphysema up to two years.<br><br>These results should be treated with caution as although based on relatively large numbers (n=511) there may not be sufficient power to detect small differences of clinical significance. In addition, the results are based on a non-randomised comparison therefore the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias. In addition, it was not possible to blind the patients to their allocated treatment so patients in one of the groups may be more likely to try harder in the tests and hence bias the results. |
| Hospital utilisation - Operating time, minutes | McKenna et al (2004) | 8 | Direct | B | Operating times are an important outcome in terms of healthcare resources and also there is a greater risk of complications with longer times under general anaesthetic.<br><br>In a randomised comparison, McKenna et al (2004), found the mean operating time to be 8.8 minutes shorter for open surgery compared to VATS, but the difference was not statistically significant (p=0.30). No further details were given. The non-randomised comparison showed a statistically significant difference of 21.4 minutes shorter (p=0.001) for open surgery compared to VATS. The mean time was 126.7 minutes for VATS and 105.0 minutes for MS in the non-randomised comparison.<br><br>Overall, based on this trial, the evidence is unclear as to whether there is a real difference in operating times between the two groups.<br><br>The randomised comparison may lack the power to detect small differences and the non-randomised comparison |

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| | | | | | 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. |
| Hospital utilisation - Length of hospital stay, days | McKenna et al (2004) | 8 | Direct | B | Length of hospital stay after surgery is an important indicator of the length of recovery after LVRS and use of hospital resources. It is also important as it will impact on a patient's QoL.<br><br>In the randomised comparison of McKenna et al (2004), there was a statistically significant difference in the length of hospital stay of six days in favour of VATS (mean length was 13 days for VATS patients vs 19 days for MS patients; mean difference = 6 days; p=0.02).<br><br>The results suggest that VATS patients have a reduced hospital stay of six days less than open surgery patients. This is likely to be clinically meaningful to patients as it will impact on their QoL and to hospital utilisation and costs.<br><br>These results are based on a well conducted RCT with a moderate sample size (n=148). The trial was conducted in the USA so the results may not be applicable to the UK. However, overall these results provide good evidence that VATS patients have shorter hospital stays after surgery. |
| Hospital utilisation - Length of Intensive Care Unit stay, days | McKenna et al (2004) | 8 | Direct | B | Length of stay in an intensive care unit (ICU) for patients who survived at least 30 days after LVRS is an important outcome in terms of use of hospital resources and as an indication of complications associated with surgery.<br><br>McKenna et al (2004) reported the percentage of VATS and MS patients who stayed in ICU for 0-1 days (65.1% of VATS patients vs 43.1% of MS patients), 2 days (6.6% of VATS patients vs 15.3% of MS patients), 3-29 days (24.3% of VATS patients vs 36.2% of MS patients) and ≥30days (2% of VATS patients vs 2.3% of MS patients). A statistically significant difference in the distribution of days was seen between the two groups for this non-randomised comparison (p<0.001), but not for the randomised comparison (p=0.76).<br><br>Therefore, the evidence is unclear regarding differences in the length of stay in ICU after surgery between VATS and open surgery patients.<br><br>These results should be treated with caution as although the randomised comparison was based on a moderate number (n=148) there may not be sufficient power to detect small differences of clinical significance. In addition, some of the results are based on a non-randomised comparison therefore the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias. |
| Adverse events - Intraoperative complications | McKenna et al (2004) | 8 | Direct | B | Assessing complications arising during surgery is important as if serious and/or common they may outweigh the benefits associated with VATS.<br><br>McKenna et al (2004) reported that intraoperative complications included hypotension, arrhythmia, hypoxaemia, hypercapnia, cardiac arrest and uncontrolled air leak.<br><br>In the non-randomised comparison, McKenna et al (2004), found a statistically significant mean difference in the percentage of patients with intraoperative complications of 6.8% (13.8% of VATS group and 7.0% of MS group; p=0.02). However, the randomised comparison showed a non-significant difference (no figures reported). |

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| | | | | | Hypoxaemia was the only complication that was significantly different between the two groups with a higher rate seen in the VATS group (5.3% in VATS compared to 0.8% in MS; p=0.04) for the non-randomised comparison, but it was found to be non-significant in the randomised comparison (p=0.25).<br><br>Therefore, the evidence is unclear regarding any difference in intraoperative complications between the two groups.<br><br>These results should be treated with caution as although the randomised comparison was based on a moderate number (n=148) there may not be sufficient power to detect small differences of clinical significance. In addition, for the non-randomised comparison results the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias. |
| Adverse events - Postoperative complications | McKenna et al (2004) | 8 | Direct | B | Assessing complications arising after surgery is important as if serious and/or common they may outweigh the benefits associated with VATS.<br><br>McKenna et al (2004) reported that post-operative complications included arrhythmia, pneumonia, tracheostomy, failure of early extubation, reoperation for air leak and failure to wean from ventilation amongst others.<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>Looking at individual complications, in the randomised comparison a significantly greater percentage of patients with a failure to wean off ventilation in the MS groups compared to VATS (0% of VATS patients vs 7.8% of MS patients, p=0.03) was observed, but not in the non-randomised comparison. In addition, in the non-randomised comparison, a significantly greater percentage of patients with the need to reoperate for air leak in the VATS group compared to MS (5.9% of VATS group and 2.2% of MS group; p=0.05) was observed, but not in the non-randomised comparison.<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 MS was found in patients (65.8% in VATS vs 54.3% in MS; p=0.01). However, there was no difference between groups in the number of days with air leak (p=0.74). Air leak on seven or more days occurred in 46% of MS patients compared to 49% of VATS patients (p=0.48). When the analysis was restricted to randomised patients, there was no difference between groups in the presence of air leak at closure or in the number of days with air leak.<br><br>Therefore, there was very little evidence of a difference in postoperative complications between VATS and open surgery, with a reliable difference only observed for failure to wean off ventilation.<br><br>The results for individual complications should be treated with caution, as despite a non-significant result seen for postoperative complications overall between the two groups, many significance tests for individual postoperative complications for the randomised comparison and again for the non-randomised comparison were conducted, therefore it is possible these are false positive results due to multiple testing. Furthermore, although the |

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| | | | | | randomised comparisons were based on a moderate number (n=148) there may not be sufficient power to detect small differences of clinical significance. In addition, for the non-randomised comparison results the two groups may not be comparable. The VATS group had a greater proportion of homogeneous emphysema at baseline and there may be other unknown confounding factors that could introduce bias |
| Costs - Mean hospital and physician costs, $ | McKenna et al (2004) | 8 | Direct | B | In a time of finite resources, it is important to determine whether there are any differences in costs for the two types of surgery. McKenna et al (2004) compared hospital and physician costs associated with an admission for LVRS based on Medicare claims data. No further information was provided on included costs.<br><br>In the randomised comparison, McKenna et al (2004) analysed costs for patients with Medicare data available randomised to VATS (n=67) and to open surgery (n=45) by MS. They found no evidence of a difference in costs ($7,138 less for the VATS group compared with the MS group (95% CI on difference $5,900 to $20,177; p=0.28)) between the two groups for hospital and physician costs. Actual costs were not provided for each group for the randomised comparison, only differences in costs between the groups were provided.<br><br>McKenna et al (2004) also compared costs for all 489 patients with Medicare data available having LVRS (343 MS patients and 146 VATS patients) in a non-randomised comparison. The mean costs for LVRS and associated hospital stay was $30,350 (standard deviation (sd) = $37,219) for VATS and $38,557 (sd = $40,519) for MS). The mean hospital and physician costs for the LVRS admission was $8,207 significantly less for the VATS group compared with the MS group (95% CI on difference $917 to $16,035; p=0.03).<br><br>Therefore the evidence is unclear regarding any difference in costs of VATS compared to open surgery, with a randomised comparison finding no significant difference, while a lower quality non-randomised comparison with more patients found a significant difference.<br><br>These results should be treated with caution as there is a wide range of uncertainty around the cost estimates. In addition, the costs are from a US perspective and are over 10 years old so have limited applicability to the UK today. |
| Costs - Mean total costs during the 6 months after surgery, $ | McKenna et al (2004) | 8 | Direct | B | In a time of finite resources, it is important determine whether there are any differences in costs for the two types of surgery. McKenna et al (2004) compared total costs which included all medical and related non-medical costs incurred during the six months after LVRS and were based on Medicare claims data. No further details were provided.<br><br>In the randomised comparison, McKenna et al (2004) analysed costs for patients with Medicare data available randomised to VATS (n=67) and to open surgery (n=45) by MS. They found evidence of a significant difference in total costs of $6,500 less for the VATS group (95% CI on difference $4,295 to $8,705; p=0.001) compared to open surgery. Actual costs were not provided for each group for the randomised comparison, only differences in costs between the groups were provided.<br><br>McKenna et al (2004) also compared total costs for all 489 patients with Medicare data available having LVRS (343 MS patients and 146 VATS patients) in a non-randomised comparison. The mean total costs during the six months after surgery were $51,053 (sd=$4,502) for VATS and $61,481 (sd=$3,189) for open surgery. The difference in mean total costs during the six months after surgery were significantly less by $10,428 for the VATS group (95% CI on difference $9786 to $109,062; p=0.005) compared to open surgery. |

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| | | | | | These results suggest a lower cost is incurred during the six months after surgery for VATS compared to open surgery.<br><br>These results should be treated with caution as there is a wide range of uncertainty around the cost estimates. In addition, the costs are from a US perspective and are over 10 years old so have limited applicability to the UK today. |

## 9 Literature Search Terms

| **Search strategy** | |
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| **P – Patients / Population**<br>Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered? | People with symptomatic **pulmonary emphysema** with demonstrable **hyperinflation** persisting after pulmonary rehabilitation.<br><br>[Supporting information:<br>• Clinical markers might include the following: FEV1 20-40% predicted, RV:TLC> 60 (hyperinflation), DLCO >20% predicted, pCO2 <7KPa, no evidence of pulmonary hypertension, RV >180%.<br>• Subgroups with **heterogeneous emphysema** and with and without **collateral ventilation** should be considered.] |
| **I – Intervention**<br>Which intervention, treatment or approach should be used? | Video assisted thoracoscopic lung volume reduction surgery |
| **C – Comparison**<br>What is/are the main alternative/s to compare with the intervention being considered? | Maximal medical therapy<br>Lung volume reduction surgery using endobronchial valves<br>Open lung volume reduction surgery |
| **O – Outcomes**<br>What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use. | **Any including:**<br>**Clinical effectiveness**<br>**Cost effectiveness**<br><br>**Critical to decision-making:**<br>Improvement in health related quality of life: absolute reductions/improvements and percentage change mean difference (SF 36, SGRQ)<br>Improvement in respiratory physiology: absolute and percentage change mean difference (increase in FEV1 and reduction in RV,)<br>Survival rates at 30 days, 90 days, one year and five year<br><br>**Important to decision-making:**<br>Post-operative complications, including readmission with procedural complication<br>Reduction in readmission rate for COPD exacerbation or other COPD related admission<br>Improvement in MRC Dyspnoea scale<br>Improvement in exercise capacity: absolute increase and increase percentage mean difference in 6 min walk test or shuttle walk test |
| **Assumptions / limits applied to search**<br>Inclusion criteria: English language papers in peer reviewed journals from 2002 to date. Include case series where n>50<br>Exclusion criteria: limited case series n <50, case reports. Patients with coexisting malignancy, pulmonary fibrosis or pulmonary hypertension. | |

## 10 Search Strategy

Embase: search date 15th of January 2018

| # ▲ | Searches |
|---|---|
| 1 | *chronic obstructive lung disease/ or exp lung emphysema/ |
| 2 | ((sever* or serious* or advanced) adj5 (emphysema or copd or chronic obstructive pulmonary disease or chronic obstructive lung disease)).ti,ab. |
| 3 | (emphysema or copd or chronic obstructive pulmonary disease or chronic obstructive lung disease).ti. |
| 4 | 1 or 2 or 3 |
| 5 | ((lung or pulmonary) adj5 volume reduc*).ti,ab. |
| 6 | ((lung volume or pulmonary volume) adj5 reduc*).ti,ab. |
| 7 | lvr.ti,ab. |
| 8 | 5 or 6 or 7 |
| 9 | video assisted thoracoscopic surgery/ |
| 10 | ((video assist* adj2 (thoracic surg* or thorascop*)) or vats).ti,ab. |
| 11 | 9 or 10 |
| 12 | 4 and 8 and 11 |
| 13 | conference*.pt. |
| 14 | 12 not 13 |
| 15 | limit 14 to (english language and yr="2002 -Current") |

## 11 Evidence Selection

- Total number of publications reviewed: 19
- Total number of publications considered potentially relevant: 13
- Total number of publications selected for inclusion in this briefing: 4

## 12 References

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