LUNG VOLUME REDUCTION SURGERY (LVRS) FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) WITH UNDERLYING SEVERE EMPHYSEMA.

A West Midlands Development and Evaluation Committee Report

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About West Midlands Development and Evaluation Service

The West Midlands Development and Evaluation Service produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities. Each review takes 3-6 months and aims to give a timely and accurate analysis of the available evidence, generating an economic analysis (usually a cost-utility analysis) of the intervention accompanied by a statement of the quality of the evidence.

About InterDEC

West Midlands DEC is part of a wider collaboration with three units in other Regions (the Trent Working Group on Acute Purchasing, the Scottish Health Purchasing Information Centre and the Wessex Institute for Health Research and Development) to share the work on reviewing the effectiveness and cost-effectiveness of clinical interventions. This group, "InterDEC", shares work, avoids duplication and improves the peer reviewing and quality control of these reports.

Contributions of Authors

Jackie Young wrote the main report, liaising with researchers and experts to identify unpublished data and obtain views on both the protocol and the final report; reviewed the effectiveness data, independently assessing its quality and extracting data; undertook the modelling and economic evaluation and the review of the epidemiology and alternative treatments. Chris Hyde acted as main editor to the report but also assisted with all aspects of the report including the review of the effectiveness data, independently assessing its quality and extracting data, and the modelling and economic evaluation. Anne Fry-Smith undertook the searches for all data and acted as an additional editor to the final report. Lisa Gold provided advice and assistance on the economic analysis and modelling and read and commented on the full report.

West Midlands Development and Evaluation Committee Recommendation:

The recommendation for the use of LVRS in the management of people with COPD due to underlying severe emphysema was:

Borderline

With the strong recommendation that commissioners support recruitment to the ongoing trial in the UK.

Anticipated expiry date

- **This report was completed in April 1999**
- **The searches were completed in June 1998**
- **There are six multi-centre randomised controlled trials now known to be in progress, one of which is taking place in the UK. The results of these should provide the basis for a more precise and reliable estimate of the level of benefits associated with LVRS.**
- **If and when a more reliable estimate of the level of benefits becomes available the economic evaluation will have to be adjusted accordingly**
- **The UK based trial alone incorporates an economic analysis and appears to address many of the unanswered questions identified by this report *except* that on the longer term outcomes of LVRS**
- **Case series data which follows patients up beyond the two year period considered in this report continues to emerge and this should be reviewed as it becomes available.**

1 Summary

- **Description of proposed service**

Lung volume reduction surgery (LVRS) is a new surgical option for the treatment of severe, end-stage chronic obstructive pulmonary disease (COPD) due to underlying emphysema. Despite considerable uncertainty around the overall balance of benefits and risks, there is a growing demand for the procedure. It is currently not routinely funded by Health Authorities in the United Kingdom but it is proposed that all eligible patients who meet the selection criteria should be offered the surgery.

- **Epidemiology**

The prevalence of COPD due to underlying emphysema is likely to be around 7 per 1000 in men and 3 per 1000 in women. However, only a small subset of this population will have severe, end-stage COPD and meet the eligibility criteria for LVRS

- **Number and quality of studies and direction of evidence**

The most rigorous evidence on the effectiveness of LVRS came from case series. 75 potentially relevant studies were identified and 19 individual series met the methodological criteria for inclusion. Significant short-term benefits consistently occurred across a range of outcomes, which appear to continue into the longer term.

- **Summary of benefits**

LVRS mortality rates at 3-6 months ranged from 0-8%. Those of untreated patients range from 10-30% per annum. Percentage improvements from baseline for LVRS for key outcomes were as follows; FEV_1 - 39%; 6MWD - 32%; and dyspnoea - 47%. Tentatively, over a two year period, these benefits are equivalent to an average 0.45 additional QALYs per patient.

- **Costs**

Over two years, the average cost of LVRS is around £13,000 and that of medical management £9,000. Thus LVRS could result in average additional costs of around £4,000 per patient over medical management.

- **Cost/QALY**

The best guess estimate is an expected additional cost per QALY gained of around £9,000 [best case £7,000; worst case £24,000]

- **Limitations**

The research base for the effects and effectiveness of the intervention is potentially open to a high degree of bias. Although this is not likely to alter the impression that LVRS is effective, it does create uncertainty as to the true magnitude of effects. The tentativeness of the cost-utility estimates is further compounded by the absence of accurate data on costs and quality of life.

2 Introduction

Lung volume reduction surgery has recently emerged as a new surgical procedure for the treatment of severe, end-stage COPD due to underlying emphysema. Advocates claim that it represents a significant breakthrough in the management of a challenging group of patients. The procedure has received extensive lay and media coverage in the USA, where increasing demand from the general public and increasing enthusiasm among thoracic surgeons led to a situation in 1996 when the number of operations being performed was expanding in a rapid and uncontrolled way.[1] Subsequently, in 1997, Medicare refused to fund any further operations on the grounds that a robust research base on the effectiveness of the intervention did not exist.[1] At the moment the procedure is not routinely funded by Health Authorities in the United Kingdom. Although considerable uncertainty exists around the overall balance of benefits and risks, there is considerable interest in and demand for the procedure from both clinicians, and increasingly from patients themselves. The outcome of this report may help purchasers to decide whether, and how, to fund the intervention in the future.

3 Background

3.1. The conditions

3.1.1. COPD (chronic obstructive pulmonary disease)

COPD is a clinical condition characterised by the presence of progressive, largely irreversible airflow obstruction.[2] Onset is insidious, with a gradual increase in sputum production, cough and shortness of breath. Patients are usually diagnosed in their fifth decade when they present with a productive cough or an acute chest illness.[3] Acute exacerbations, consisting of increased cough, purulent sputum, wheezing and shortness of breath occur with increasing frequency as the disease progresses, particularly in the winter months.[4] Most often these exacerbations are managed by the primary care team but emergency admission to hospital is often necessary. By the sixth or seventh decade most patients will be short of breath on effort and their quality of life will be considerably affected. In the end-stages of the disease hypoxia and hypercapnia occur, many patients develop weight loss and eventually progress to cor pulmonale and death.[3] Table 1 indicates the range of severity of the condition and the resource implications of different stages, using the British Thoracic Society (BTS) classification for COPD. The condition is usually caused by underlying emphysema or chronic bronchitis, both of which largely occur as a result of prolonged tobacco smoking. When symptoms first become troublesome, patients will typically have been smoking at least 20 cigarettes a day, for around 20 years.[2]

Table 1. Classification and resource implications of COPD. (adapted from BTS Guidelines for the Management of COPD)[2]

	Clinical State	Lung Function Tests	Resource Implications
Mild	Smoker's cough, little or no breathlessness, no abnormal signs	FEV_1 60-70% of predicted, FEV_1/VC and other indices of expiratory flow mildly reduced	The majority of patients fall into this group. Probably pre-symptomatic in the community.
Moderate	Breathlessness ± wheeze on exertion, cough ± sputum, some abnormal signs	FEV_1 40-59% of predicted, often with increased FRC and reduced TLCO, some patients hypoxaemia but not hypercapnic	A minority of patients fall into this group. Probably known to the GP with intermittent complaints.
Severe	Breathlessness on any exertion, prominent wheeze and cough, clinical over-inflation usual, cyanosis, peripheral oedema and polycythaemia in some	FEV_1 < 40% predicted with marked over-inflation, TLCO variable but often low, hypoxaemic usual and hypercapnia in some	A minority of patients fall into this group. Likely to be known to hospital and the GP, with frequent problems and hospital admissions.

FEV_1 [Forced Expiratory Volume in 1 second] VC [Slow Vital Capacity] FRC [Functional Residual Capacity]
TLCO [Diffusing Capacity for Carbon Monoxide or Gas Transfer Factor]

3.1.2. Emphysema

Emphysema is a progressively destructive disease of the lungs, characterised by abnormal and permanent enlargement of the small air spaces, which is defined anatomically. Most patients with COPD will have underlying emphysema, chronic

bronchitis or both, and the majority of patients with emphysema will have COPD but this is not always the case.[3] Because it is defined anatomically, the clearest evidence of emphysema is obtained radiographically, through computerised tomography.[3] As the disease progresses the alveolar walls are gradually destroyed, resulting in the coalescence of individual alveoli into large spaces of varying size and distribution. These eventually reach a size at which they fill preferentially to the adjacent lung when they are referred to as bullae.[5] Bullae of less than 1cm in diameter are defined as blebs, and those greater than 1cm as bullae. Emphysema can be predominately *bullous*, when it is characterised by the presence of isolated, distinct bullae, some of which can become grossly enlarged when they are referred to as giant bullae. Alternatively, it can be predominately non-bullous, or *diffuse*, when it is characterised by the presence of multiple small bullae and blebs.[5] Diseased areas of lung are often *heterogeneously* spread throughout the lung affecting either upper versus lower, or central versus peripheral areas.[6] In the context of LVRS it is important to distinguish between the different types of emphysema as the operation is largely directed towards individuals with diffuse, heterogeneous disease. More specific diagnoses around the anatomical type of emphysema is again best obtained by computed tomography.[3]

The single most important cause of emphysema is smoking. Other possible contributing factors include cadmium, silica and coal, and atmospheric pollution, as well as socio-economic factors although the evidence for this is equivocal. Emphysema in non-smokers is associated with alpha-antitrypsin deficiency.[2]

3.2. The interventions

3.2.1. General management

There are very few treatment options for patients with end-stage COPD and their management represents a considerable challenge for respiratory physicians. Most available treatments are directed generally at COPD, and not specifically at COPD with predominant emphysema. The key elements of a typical package of care would included the following:

- inhaled or nebulised bronchodilators and steroids
- supplemental oxygen
- pulmonary rehabilitation
- smoking cessation advice and support
- early treatment of infection and management of acute exacerbations
- management of anxiety and depression
- home care and social support

Although the degree to which all these treatments are optimised in the majority of patients is unclear, typical candidates for LVRS will usually be receiving maximum medical therapy, including pulmonary rehabilitation, with little prospect of improvement.

3.2.2 Pulmonary rehabilitation

Pulmonary rehabilitation, is a relatively new intervention which is increasingly used in the treatment of COPD patients. It usually consists of a 6-8 week program of supervised physical and psycho-educational retraining. Its primary aim is to prevent deconditioning and enable patients to cope with their disease.[7] It is generally regarded as a critical factor in the care of patients undergoing LVRS. Patients will usually undergo intensive pulmonary rehabilitation pre-operatively to optimise physical and cardiopulmonary conditioning, exercise tolerance and pulmonary hygiene. These programmes are intensive usually consisting of 6 to 8 weeks of exercise 5 to 7 days a week. Postoperative pulmonary rehabilitation is resumed immediately after surgery and focuses on pulmonary hygiene and assessment of oxygen needs.[8]

3.2.3 Lung transplantation

When patients reach an appropriate stage in the disease they may be eligible for lung transplantation. This is an option only offered to those in the very late stages of the disease. It is a risky procedure with four year survival rates of between 40-50%, although patients with emphysema appear to do better than those with other diseases.[9] The operation carries a high risk of post-operative infection and many patients face life-long dependency on immunosuppression. In addition, only a small proportion of those eligible for the procedure are likely to receive it due to a shortage of suitable donors.[1]

3.2.4. LVRS

LVRS describes a variety of surgical procedures which remove areas of lung with the purpose of reducing lung volume and is thus sometimes referred to as reduction pneumoplasty or pnuemectomy.[10] However, the term is commonly reserved to refer to the resection of the most functionless areas of lung in cases of diffuse emphysema, to relieve the symptoms of advanced COPD. This procedure needs to be differentiated from the excision of areas of lung because they are diseased such as the removal of a tumour, or bullectomy, which involves the excision of large isolated bullae.[11]

Lung volume reduction surgery for diffuse emphysema, was first introduced by Dr. Otto Brantigan at the University of Maryland in the 1950's.[12,13] Although some success was demonstrated, further development was abandoned due largely to high mortality and morbidity rates associated with the procedure. In the 1990s, Brantigan's work has been revisited by Dr. Joel Cooper in St. Louis, who has achieved improved mortality and morbidity rates by using modern surgical developments to modify the original technique.[14,15]

The rationale for LVRS is to counter the cycle of airways obstruction and hyperinflation that occurs in emphysema. Destruction of elastic lung tissue impairs the normal outward pull which holds open the small airways, essentially reducing the volume of air expelled during expiration and trapping air in the peripheral airways. This leads to a sensation of breathlessness which causes the patient to work harder at

breathing, taking in much larger volumes than normal thus increasing the imbalance between inspiratory and expiratory volumes. Hyperinflation results, which compounds the problem by reducing the ability of the rib cage to expand, and causing flattening and tightening of the diaphragm, impairing the normal mechanism of breathing. Increasing shortness of breath occurs as the inspiratory muscles work harder but the patient experiences a sense of unrewarded inspiratory effort.[16]

Although the mechanism of LVRS is not fully understood, its aim is to counter these effects by restoring elastic recoil in the lungs, and mobility and function in the chest wall and diaphragm. This in turn, should reduce the sensation of breathlessness, and thus the work of breathing, helping to restore the balance between inspiration and expiration.[16]

A range of techniques and surgical approaches are currently available for LVRS. It can be performed as an open procedure using a variety of incisions, or as a closed procedure using video assisted thoracoscopy. Lung tissue can be excised using stapling, laser plication or both, and can be performed unilaterally or bilaterally. Suture lines can be reinforced to reduce post-operative air leaks.[10] The choice of technique depends on the surgical expertise and preference of the operator, but current consensus is that the best technique is bilateral stapling via a median sternotomy, with suture line reinforcement using bovine pericardium strips. This method is popular because most surgeons are comfortable with the approach and it has been shown to reduce post-operative problems with persistent air leaks.[5]

3.3 The outcomes of COPD (with underlying emphysema)

Untreated, patients would quickly decline with increasingly disabling shortness of breath, poor exercise tolerance, recurrent chest infections and eventually death. Most of the treatments currently available aim simply to improve patients' experience of health and well-being, as opposed to curing their condition, and many have associated adverse side effects. However, oxygen therapy is thought to be of some benefit in prolonging the life of some patients,[17] and pulmonary rehabilitation has been shown to bring about improvements in functional ability and quality of life, but is economically and practically difficult to maintain over long periods of time. [7,3] Researchers are currently investigating the possibility that adequate treatment of the anxiety and depression associated with COPD may also increase exercise tolerance and functional ability.[18]

LVRS is also, primarily, a form of symptom relief for patients with end-stage disease and it is a risky procedure. Immediate post-operative mortality appears to be around 3%.[19] The key clinical outcome measures are, therefore, those which assess quality of life in general, and others which may act as a proxy for quality of life such as exertional dyspnoea, exercise capacity and tolerance, and dependence on supplemental oxygen and steroids. These can be supplemented by physiological measures of lung function and mechanics.

The procedure is aimed at those patients who have reached a point where the potential benefits of the operation outweigh the risks, but in whom the disease has not progressed so far as to render them unfit for surgery. Eligibility is therefore assessed

using fairly tight criteria which select only those patients who have no hope of improvement with aggressive medical management, whose disease is most likely to respond to the procedure and who would not be considered a high risk for the surgery. These criteria are still evolving and vary between institutions. Generally, they are:

- severe, heterogeneous, diffuse emphysema
- disabling dyspnoea and poor quality of life despite maximal medical therapy
- markedly distended chests and flattened diaphragms, and other evidence of severe air trapping

NOT

- advanced age (>75) and significant co-morbidity
- dependence on steroids (> 10-15mg daily)
- raised arterial level of CO2
- smoking [5,1]

4 The problem

4.1. Epidemiology of COPD and COPD with underlying emphysema

COPD and emphysema are important causes of mortality and morbidity in the United Kingdom. In 1995 the age-standardised annual death rates for COPD were 50 per 100,000 in men and 24 per 100,000 in women. Over the last two decades a steady decline has been observed in male death rates although female rates have remained static.[20] Emphysema was the main cause of death in 6.4% of all male and 3.9% of all female deaths in 1992.[2] People with COPD form a major part of the workload in both the primary and secondary care sectors, accounting for around 680 hospital admissions, 9,600 inpatient days and 14,200 general practice consultations a year in an average health district of 250,000 people.[2] Mortality and morbidity rates rise steeply with age with most deaths occurring in elderly people, but about 4% of premature deaths in the 55 to 65 age group are attributable to COPD.[21]

Complete and reliable data on incidence and prevalence rates are not available, although it is known that the UK has among the highest rates in Europe.[22] Population surveys suggest that the UK prevalence of COPD, defined as impairment of ventilatory function in association with productive cough, is currently around 5 per 100 in middle aged men and 3 per 100 in middle aged women. Equivalent rates for chronic bronchitis, defined as persistent cough with phlegm production, are 17 per 100 in men and 6 per 100 in women.[22]

In the USA in 1995 it was estimated that around 14 million people suffered from COPD, and that approximately 1.65 (11%) million of these had underlying emphysema. Prevalence rates for people with a diagnosis of COPD, from population based studies, are around 4-6 per 100 in adult white males and 1-3 per 100 in adult white women.[3] Given that the condition is known to be more prevalent in the UK, these rates probably underestimate the true rates in the UK. Taking point estimates for COPD prevalence of 6 per 100 in men and 3 per 100 in women, and assuming that 11% of these people will have underlying emphysema, the prevalence of COPD due to underlying emphysema is likely to be around 7 per 1000 in men and 3 per 1000 in women.

In an average UK Health District of around 500,000 people, about 600 people will have COPD due to underlying emphysema. According to the British Thoracic Society classification only a minority of these will have severe, end-stage disease.[2] If this minority is assumed to be around 25%, then around 150 people will be potential candidates for the procedure. The equivalent figures for an average Primary Care Group of 100,000 or General Practice of 20,000 are 30 and 6 respectively. However, based on the eligibility criteria as they stand at present, less than 50% of these would be likely to be accepted for surgery.

Changes in the epidemiology of COPD are strongly related to changes in the prevalence of tobacco smoking, although a considerable time lag operates within this relationship. Gender differences and the overall decline in mortality and prevalence

rates observed over the last two decades are largely explained by differences in smoking patterns.[21,22]

4.2 Current service

There is a general lack of data on patterns of service delivery for people with COPD and the assessment of current service provision inevitably involved a degree of guesswork tempered by consultation with clinicians and patients. Most people are managed largely in the primary care setting. As the disease progresses more input from the secondary care sector is necessary. In patients with severe COPD treatment will probably be co-ordinated by a respiratory physician. It is likely that the level of care provided for patients who are severely affected will vary greatly at both the individual level and at that of the health district. This is particularly likely in relation to new services which are developing in an ad hoc way, such as pulmonary rehabilitation, and those which are of limited availability or are means tested such as community nursing services and social support. For example, in some areas patients who are unable to care for their own basic needs will receive help from the community nursing or social services, but in others the burden of care will be met solely by family and friends. When the latter is the case, the fact that most other services fall within the category of general medical care at the primary or secondary care level means that the true costs of caring for this group of patients are often hidden.

4.3 Proposed service

It is proposed that LVRS should be offered to all patients with severe COPD due to underlying emphysema who meet the eligibility criteria. In the West Midlands, the Regional Thoracic Surgery Unit is currently exploring the feasibility of providing such a service**.** From January 1996 to date they have operated on 17 patients and 17 are awaiting surgery.[23] The target capacity of a unit of this size is suggested as 50-100 procedures a year. Based on regional experience, the true demand for the procedure in the West Midlands region is unlikely to exceed 100 cases per year. However, current demand from patients and their General Practitioners is relatively low, but this may not remain true if the experience of the USA is repeated in the UK. Based on the available prevalence data, and the rigorous eligibility criteria for the procedure, this figure could potentially be as high as 5-600 cases a year.

In addition to the surgery itself, such a service may increase demand for additional related services. In particular, the importance of pulmonary rehabilitation in the pre and post operative periods suggests that a higher and more consistent level of provision will be required. In addition, it is likely that demand for a more specialised approach to the care of people with severe COPD will also increase.

4.4 The problem in summary

LVRS continues to be advocated as a viable option in the management of a group of people to whom limited options are available. Since it was refused funding in the USA due to a paucity of robust research, a steady trickle of research has continued, claiming ongoing improvements in techniques and outcomes and increased understanding of the mechanism of effect.

At the local level the problem is to decide whether a regional unit providing LVRS, using the currently preferred technique, to patients who have met the generally agreed inclusion criteria, should be supported by the continued commissioning of the procedure. The decision should take into account the potential that this will increase demand for other services such as pulmonary rehabilitation and specialist care. In addition, it is important to acknowledge that in the West Midlands this is probably a high profile issue because the regional thoracic surgery unit has a special interest in the surgery. While this will also be the case elsewhere, in some areas the real problem may be whether such a service should be set up at all.

5. Aims of the review

5.1 General

The remainder of this report is a health technology assessment, incorporating a systematic review, decision analysis and economic modelling, according to the general standards required for West Midlands DEC reports. The general aim is to inform a decision on the detailed problem described above.

5.2 Specific questions

The specific questions which this assessment proposes to answer on the basis of existing research and other data are:

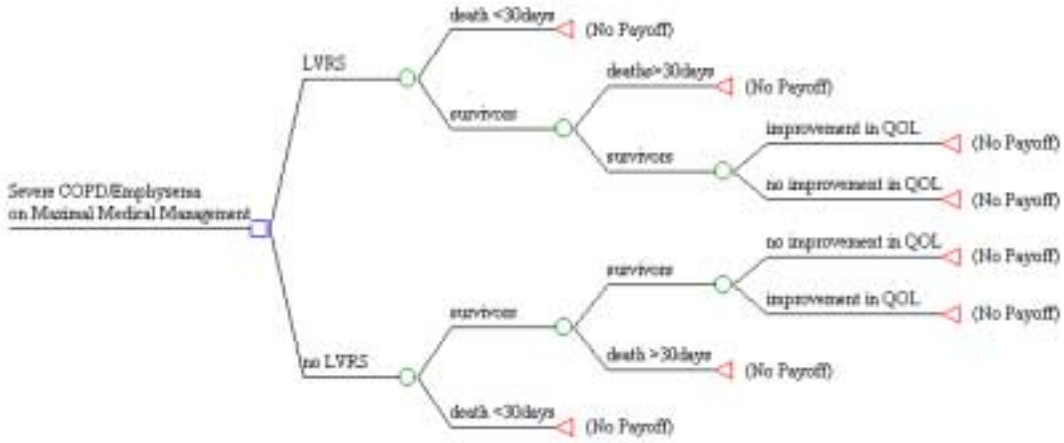
1. What are the effects of LVRS in patients with end-stage COPD due to underlying emphysema, particularly relative to maximum medical therapy including supplemental oxygen and pulmonary rehabilitation?
2. What is the overall effectiveness?
3. What is the cost-utility?

5.3 Decision tree

A pre-requisite for judging the overall effectiveness and cost-utility of LVRS is an explicit statement of the events and outcomes which appear to be of the greatest importance. These are expressed visually in the framework of the decision tree in figure 1, and form the basis of the overall judgement of effectiveness and cost-effectiveness. It is important to stress that a decision tree is a simplified model of reality which requires the selection of a restricted set of key factors. The selection of these factors inevitably involves implicit value judgements about which outcomes are of key importance and which are not. In addition, a compromise will often have to be made between those events for which reliable information is available, and those where it is not. For example; ideally, information about the effects of LVRS on quality of life (QOL) should allow a distinction between those patients whose condition actually improves, those whose condition remains the same and those whose condition actually gets worse. In reality, however, it was clear that the available studies would not contain outcome data at this level of sophistication, thus the outcomes chosen were simply "improvement" or "no improvement". In making this sort of compromise there is a strong possibility that subtle improvements in QOL,

or adverse effects beyond operative mortality, may be missed, thus over or underestimating the true impact of the intervention. Uncertainties of this nature are explored in the sensitivity analysis and the overall structure of the decision tree was validated through discussions with content experts and commissioners.

Figure 1. Decision tree for the main options and outcomes in the management of severe emphysema.



5.4 Existing reviews

Existing reviews on the topic do exist, [4,5,16,24,25,26,27,28,29,30,31,32,33] but the majority of these are narrative reviews which serve as useful sources of background reading, but are not systematic in their approach, or comprehensive in their coverage of the literature. One AHCPR health technology assessment does take a more systematic approach and attempts to summarise much of the published and unpublished data on the intervention. However, the coverage of the literature was largely confined to North America and as such was unlikely to be comprehensive.[24] The authors of this report concluded that the available data at the time did not allow a "logical and scientifically defensible conclusion regarding the risks and benefits of LVRS", although they felt there were indications towards some favourable short-term benefits. The most recent review to emerge is a report by a Canadian health technology assessment programme.[33] Again this is not systematic or comprehensive and makes no attempt to account for variations in the methodological quality of the studies it cites. It's authors also conclude that LVRS appears promising in the short-term for selected patients, but that the quality of the evidence is limited and the procedure should still be regarded as experimental.

6 Methods

6.1. Development of the protocol

The protocol for the report was developed using the literature identified through a formal ARIF[a] request which focused mainly on reviews of the effectiveness of LVRS. In addition to this, a body of primary research was obtained from a local clinician with an interest in the procedure. This research base was used to inform the background to the review, to formulate the question and to refine the final search strategy. The protocol was subjected to external scrutiny and appropriate amendments made.

6.2. Detailed search

A broad comprehensive search strategy was developed which was designed to identify *any* potentially relevant material on LVRS in COPD. The key elements of this strategy were as follows:

- Electronic searches of MEDLINE and EMBASE using terms such as "surgery", "emphysema" "pneumectomy" and "pneumoplasty" (Appendix I)
- Searches of the Cochrane Library Controlled Clinical Trials Register
- Contact with experts in the field to identify ongoing or unpublished research (Appendix II)
- Citation checking of all articles obtained

All sources were searched from 1975 onwards, as the first articles on the recent use of the operation emerged around this time. No language exclusion or other limits were applied, particularly in relation to study design. The search was amplified to capture articles containing cost data by running a specialised MEDLINE search (Appendix I), contacting organisations such as the Oxford Health Economics Research Centre, the Sheffield Health Economics Group, the Health Economics Research Group, the Centre for Health Economics and the Health Economics Research Unit, and searching additional sources such as DARE (NEED).

6.3. Making inclusion and exclusion decisions

All inclusion and exclusion decisions exhibited three key features:

- they were made independently of the detailed scrutiny of the results of the studies
- they were cross-checked by two reviewers (JY and CH)
- they were made using predetermined criteria laid out in a proforma (Appendix III)

The preliminary searches indicated that the majority of published studies on LVRS were likely to be case series, thus the inclusion criteria incorporated detail pertaining to the methodological quality of these anticipated studies, designed to focus on research designs above a particular level in the hierarchy of evidence. The basis for the methodological criteria was a checklist designed to assist with the critical appraisal of case series (Appendix IV). The main aim of this checklist was to assess

[a] ARIF (Aggressive Research Intelligence Facility) The University of Birmingham. - A unit which aims to advance the use of evidence in practice throughout the West Midlands region.

the potential for bias within the studies, considering specifically possible sources of selection, attrition and detection bias. Essentially, the exclusion of additional studies at this stage ensured that final estimates of effect and effectiveness were based only on the results of those primary studies which were of the highest possible internal validity.

Initially, the abstracts of all identified articles were scanned by one reviewer (JY), for relevance to the effects, effectiveness or cost-effectiveness of LVRS. When abstracts were not available the full article was obtained. For literature pertaining to the effects and effectiveness of the intervention the inclusion and exclusion were applied by one reviewer (JY) and cross-checked by the other (CH). Any discrepancies were resolved by discussion. Studies were also excluded if they had clearly originated from the same source as other included studies, and there was a suspicion that their analysis included some or all of the same patients. When several series emerged chronologically from the same source only the largest and most recent series was included. All studies which provided information on costs were obtained.

6.4. Validity assessment

As described above, for the review of the effects and effectiveness of LVRS the assessment of the internal validity, or methodological quality, of the studies was an implicit part of the inclusion and exclusion decisions. Additional detail on methodological quality was recorded and tabulated for each of the included studies. It was anticipated that the yield of studies on costs and costs-effectiveness would be small and that any relevant material would be utilised, but when appropriate, all studies were assessed using existing guidelines for the appraisal of economic studies.[34,35]

6.5. Data abstraction

Data was abstracted from the included studies by one reviewer (JY), using a predetermined form which was designed to collect both the data that might be required for the tables of included studies, and the cost utility analysis (Appendix V). RevMan 3.1 for Windows software was used to record this information and to generate the summary tables.

6.6. Review analysis

The tabulated characteristics and results of the included studies were qualitatively assessed, particularly in relation to possible sources of heterogeneity. The general design, quality and clinical heterogeneity of the included studies made a formal meta-analysis inappropriate but the tabulation process enabled the identification of a range of plausible values for the likely effect of LVRS on the key outcomes of interest. When necessary, the results of the individual studies were re-analysed, involving the re-calculation of certain data to facilitate comparison, such as the conversion of all six minute walking distances to metres, and the calculation of pre/post test differences when this was not done by the study authors. Data was summarised using additional statistics such as inter-quartile range, to give an indication of the general size and direction of effect.

6.7. Economic analysis and modelling

The cost-utility analysis was undertaken in collaboration with a health economist. according to the guidance laid out by the West Midlands DEC team. Costs were estimated using whatever information could be gleaned from the available research and validated by local clinical experts. Estimates of improvements in health gain were calculated primarily using one generic measure of quality of life, the EQ-5D.[36] DEC has traditionally used the IHQL[37] as the basis for the utility estimates, but in this instance the EQ-5D was selected as the measure of choice partly because it is more widely used in the NHS at present and has been calibrated against the UK population, and partly because it was possible to obtain slightly more reliable estimates from the available literature than for the IHQL. The effect on the economic analyses of using the IHQL is tested in the sensitivity analysis. Utilities were estimated using any existing research which utilised the EQ-5D or the IHQL, or other generic or disease specific quality of life measures, as well as information from the included studies. These cost and utility estimates were again validated through discussions with clinical experts. Cost-utility is estimated by calculating the benefits, disbenefits, costs and savings associated with LVRS, in relation to current best practice, using the decision model. Some aspects of the analysis were undertaken using the TreeAge, Data 3.0 software.

7 Results

7.1. Volume of relevant material for effects and effectiveness

Initially, 198 references were identified by the formal search. 123 were excluded on the basis of the information contained in the title or the abstract. 75 full text papers were obtained either because a decision could not be made using the available information, or because they were potentially relevant for inclusion. After application of the inclusion criteria 19 studies remained which were included in the final analysis. The main reasons for exclusion were; suspicion of duplication; measurement of inappropriate or irrelevant outcomes; the evaluation of interventions other than LVRS as it is defined in this review; inadequate duration of follow-up; and evidence that cases were identified and analysed retrospectively. Details of all included and excluded studies are contained in Appendix VI. It is important to note that a number of trials were also identified. However, all of these examined the effectiveness of different techniques and approaches for LVRS and not the effectiveness of the intervention versus an alternative, and as such were not suitable for inclusion. However, where possible the individual comparison groups from these trials were included as case series in their own right.

7.2. Volume of relevant material for costs

19 articles were identified by the searches for articles containing cost data but only 5 of these were obtained on the basis of the abstracts. The majority were excluded because they did not relate specifically to LVRS, or because they were editorials or commentaries. Two of those obtained were reviews. One of these was a general review of economic evaluation in respiratory disease[38] and another was a general narrative review of pulmonary rehabilitation.[39] Neither of these provided any helpful information on the costs of the intervention or it's alternatives. Two trials were identified which had incorporated economic analyses within their design, however one of these specifically compared the costs of the procedure with and without buttressing of the suture line using bovine pericardial strips[40] and the other looked at the costs and benefits of pulmonary rehabilitation in a before and after trial.[41] Although some useful information was contained within these trials all costs were given in US dollars and reflected the costs within the American healthcare system which may not be equivalent to the same costs in the NHS. Finally, one economic analysis was identified which evaluated LVRS, however this was based on a small case series and looked only at medical centre charges, professional fees and sponsor reimbursement again in the context of the American health care system, again limiting its relevance to the UK setting.[42] Where possible information obtained from these studies was used to cross validate cost estimates from other sources.

7.3. Analysis of effects

The detailed information abstracted from the 19 included studies is tabulated in Appendices VII and VIII. The key features of these tables are described below.

7.3.1. Characteristics of included studies

Intervention
Because the operative technique and approach used varied between studies, the majority of the results reflect those of the currently preferred technique, but this is not always the case. For example, in a number of the earlier studies laser is used to obliterate the areas of diseased lung and in a few of the more recent studies the procedure is conducted via video-assisted thoracoscopy.

Rehabilitation has been shown to have an effect on exercise capacity and quality of life in COPD patients, thus the estimate of effect may well be influenced by this.[7] The reporting of participation in pulmonary rehabilitation was inconsistent, and when it was reported the timing of base-line data collection in relation to pre-operative programmes was not clear, leading to considerable ambiguity overall about whether or not the effect of LVRS *and* pulmonary rehabilitation is being evaluated.

One additional factor which may have had a bearing on the results, for what is essentially an experimental technique, is the level of skill and experience of the operators. An estimate of this was obtained from information on the setting of the study and the duration of the programme. Generally, the studies took place in the context of large programmes in university hospitals or specialist medical centres, although on the few occasions when this was not the case the pattern of results was fairly consistent.

Populations examined
The populations examined also varied between the individual studies in terms of their selection criteria. Generally, these exhibited a high degree of selectivity however, in keeping with current practice as outlined in section 2.3, this is likely to be the way that LVRS is going to continue to be applied in the immediate future.

Outcomes
There was more consistency between the studies in the range of outcomes that were measured. All included studies collected data on some or all of the outcomes identified as important in section 2.3. The majority collected objective outcome data on both the physiological and the functional aspects of the procedure using standardised assessment tools, and mortality and morbidity data was generally provided. Shortness of breath was assessed by several studies but quality of life measures were used on only a few occasions. For all of the more subjective outcomes there was less homogeneity in terms of the measurement tools used.

Validity
Because all the included studies are case series and did not use parallel control groups, the entire research base for the intervention is highly prone to bias. In addition, none of the studies demonstrate that the assessment of outcomes was undertaken by independent observers, raising the potential for the introduction of detection bias into the results. This was less likely to be a problem when pre and post measurements were possible as in the case of most of the physiological measures, but more so when it was only possible to obtain a post-test measure as in the case of mortality.

More specifically, because the final group of included studies were selected partly on the basis of the validity assessment, there was a high degree of homogeneity between them in relation to their methodological quality. The majority were good-sized consecutive case series, which were conducted prospectively, with minimal losses to follow-up. For some studies, certain outcome data were not included in the final analysis, either because losses to follow-up were particularly high for those specific outcomes or because they were not measured in all the incident cohort. When this is the case this is made clear in the relevant table.

7.3.2. Results of included studies

Mortality

Early and late mortality rates could be calculated for most series and this data is presented in detail for 567 patients in table 2. The inter-quartile range (IQR) for early mortality (defined as hospital deaths or deaths occurring within 30 days of surgery) was 0-6%. The IQR for late mortality (defined as deaths occurring in the hospital or more than 30 days after surgery) at 3 to 6 months was 0-8%. Late mortality at 2 years was estimated as between 0 and 3%.

These rates compare favourably with those of the COPD population as a whole according to current published data.[b] For example, the one year mortality rate for a population with a starting FEV_1 of <0.75 litre has been estimated at 30%, and at 10% for a population with a starting FEV_1 <30% of predicted.[3] These rates increase rapidly with age. A patient aged >60 with an FEV_1 40-49% of predicted has a predicted mortality of around 25% at one year.[2]

[b] Current speculation is that patients with very low FEV_1 volumes may live considerably longer than predicted but at present no published evidence is available to support this. This is taken into account in the economic analysis by the conservative estimate of the probability of death over two years in untreated patients.

Table 2. Mortality data from included studies.

Study Reference (3-6 month follow-up)	Early Deaths (<30 days or hospital deaths)	Late Deaths (≥30 days or home deaths)	Overall Deaths
Argenziano	6/92 (6%)	8/86 (9%)	14/92 (15%)
Bagley	3/55 (5%)	3/52 (6%)	6/55 (11%)
Bousamra	3/45 (7%)	2/42 (5%)	5/45 (9%)
Criner	0/3 (0%)	0/3 (0%)	0/3 (0%)
Daniel	1/17 (6%)	0/16 (0%)	1/17 (6%)
Eugene[a]	1/44 (2%)	11/43 (25%)	12/44 (27%)
Eugene[b]	0/28 (0%)	3/28 (11%)	3/28 (11%)
Keller	0/25 (0%)	0/25 (0%)	0/25 (0%)
Kotloff[MS]	5/80 (6%)	6/75 (8%)	11/80(14%)
Kotloff[VATS]	1/40 (2%)	0/40 (0%)	1/40 (2%)
Little	N/A	N/A	3/55 (5%)
Miller	3/53 (6%)	2/50 (4%)	5/53 (9%)
Sciurbia	0/20 (0%)	0/20 (0%)	0/20 (0%)
Snell	1/20 (5%)	0/20 (0%)	1/20 (5%)
Stammerberger	0/42 (0%)	3/42 (7%)	3/42 (7%)
Zenati	0/35 (0%)	0/35 (0%)	0/35 (0%)
IQ Range	**0-6%**	**0-8%**	**0-11%**
(2 year follow-up)			
Cooper	*6/150 (4%)	*4/144 (3%)	10/150 (7%)
Cordova	0/25 (0%)	0/25 (0%)	0/25 (0%)

* deaths measured up to and after 90days VATS - video-assisted thoracic surgery MS - median sternotomy

FEV_1

Most studies collected data on a range of physiological outcomes. The FEV_1 (forced expiratory volume produced in one second) is an easily measured and fairly reliable test which is useful in determining the degree of airways obstruction. Because it has been shown to vary with gender, age and height, among other factors, it is often presented as a percentage of the value which might be predicted for a given individual, however, it has been suggested that this practice is flawed and in the UK alternative tests are increasing in popularity.[43] Until recently the FEV_1 has generally been regarded as a good indicator of impairment of the whole person and it forms the basis for the staging of COPD in both the USA and the UK.[2,3] Recently, however, several studies have demonstrated a poor correlation between physiological measures such as the FEV_1 and those which measure functional status and quality of life.[44,45] Nevertheless, it is still in common usage and was recorded by the majority of studies examined in the context of this review.

The results of the individual studies for FEV_1 and FEV_1 as a percentage of predicted are presented in table 3.

FEV_1 data was available for 925 patients. At baseline the FEV_1 was 0.64-0.73 litres (IQR). 3-6 months after LVRS this had risen to 0.91-1.07 litres (IQR), with a pre/post difference of 0.23-0.36 litres (IQR). Two studies presented data at 2 years follow-up; Cooper demonstrated a post-treatment FEV_1 of 1.25 litres and a pre/post test difference of 0.42 litres; and Cordova demonstrated a post-treatment FEV_1 of 0.91litres and a pre/post test difference of 0.22 litres.

FEV_1 as a percentage of predicted was presented for 806 patients. Baseline measurements were 24-28% (IQR). In the short-term these rose to 35-41% and the pre/post test difference was 9-13% (IQR). Only Cooper measured this in the longer-term demonstrating post-treatment results of 36% and 42%, and pre/post test differences of 12% and 15%, at 1 and 2 years respectively.

6 Minute Walking Distance

The 6 Minute Walk Test (6MWD) is an objective and reliable test which is used to assess the functional status of patients with COPD. It has been shown to be valid, safe, inexpensive and easy to apply and as a result is popular with clinicians. Statistically significant differences in 6MWD have been shown to correlate with significant changes in more subjective outcomes, such as shortness of breath and quality of life.[46]

The results of 486 patients for the 6MWD are presented in table 3. Ten studies collected data on this outcome. The unit of measurement varied across studies, so to facilitate comparison, all results were converted to metres. A typical 6MWD for a healthy individual walking along a street is around 700 metres and that of a person awaiting a hip replacement about 200metres.[46] The baseline distance covered by study participants was 241-290 metres (IQR). This rose to 306-434 metres post-treatment, with a pre/post difference of 32-96 metres (IQR). Only Cooper recorded this data in the longer-term, demonstrating a difference of 64 metres and 80 metres at 1 and 2 years respectively.

Table 3. Short and long-term results of all included studies for FEV_1, FEV_1 as a percentage of predicted, and 6 minute walking distance in metres.

Short term follow-up 3-6 months. (NB. Where studies give results for 3 and 6 months the 6 month results only are presented.)

Study (n)	FEV_1 (± standard deviation)			% predicted (± standard deviation)			6MWD (± standard deviation)		
	Pre	Post	Diff (P)	Pre	Post	Diff (P)	Pre	Post	Diff (P)
Argenziano (66)	0.52 ± 0.19	0.78 ± 0.38	0.26 #	22 ± 8	34 ± 14	12 #	176 ± 96	273 ± 96	96 #
*Bagley (55)	N/A	N/A	0.19 (0.0002)	N/A	N/A	N/A	N/A	N/A	32 (0.042)
Benditt (21)	1.12 #	1.12 #	0.00 #	24 #	28 #	4 #	N/A	N/A	N/A
*Bousamra (45)	0.68± 0.23	0.97 ± 0.38	0.29 (0.005)	26 ± 9	40 ± 15	14 (0.002)	N/A	N/A	N/A
*Cooper (101)	0.70 #	1.06 #	0.36 (<0.001)	25 #	38 #	13 #	338 #	402 #	64 (<0.001)
*Cordova (25) 3m	0.68 ± 0.19	0.93 ± 0.29	0.25 (<0.001)	27 ± 8	37 ± 12	10 #	257 ±113	338 ± 80	80 (0.001)
Criner (2)	0.41 ± 0.00	0.90 ± 0.36	0.49 #	38 ± 1	38 ± 2.80	0 #	N/A	N/A	N/A
Daniel (17)	0.73 #	1.02 #	0.29 (<0.0001)	25 #	36 #	11 #	N/A	N/A	N/A
Eugene [a] (44) 6m	0.41 ± 0.01	0.62 ± 0.03	0.21 #	15 #	23 #	8 #	N/A	N/A	N/A
Eugene [b] (25)	0.68 ± 0.05	0.91 ± 0.35	0.23 (<0.001)	N/A	N/A	N/A	N/A	N/A	N/A
*Keller (25)	0.80 ± 0.33	1.05 ± 0.41	0.25 (<0.001)	33 ± 8.40	35 ± 7.90	2 #	289 ± 96	322 ± 64	32 (0.01)
Kotloff [MS] (80)	0.73 ± 0.24	1.02 ± 0.40	0.29 #	27 #	38 #	11 #	N/A	N/A	N/A
Kotloff [VATS] (40)	0.73 ± 0.24	1.00 ± 0.37	0.27 #	25 #	36 #	11 #	N/A	N/A	N/A
*Little (28)	0.74 ± 0.07	0.85 ± 0.06	0.11 (0.009)	N/A	N/A	N/A	N/A	N/A	N/A
McKenna (166)	0.68 #	0.94 #	0.26 (<0.0001)	26 #	36 #	10 (<0.0001)	N/A	N/A	N/A
Miller (53)	0.56 #	1.10 #	0.54 #	24 #	52 #	28 #	241 #	482 #	241 #
Sciurbia (20)	0.87 ± 0.36	1.11 ± 0.45	0.24 (<0.001)	32 ± 11	41 ± 14	9 #	241 ± 80	273 ± 80	32 (0.05)
*Snell (20)	0.72 ± 0.19	1.07 ± 0.30	0.35 (<0.001)	28 ± 6	42 ± 11	14 (<0.001)	306 ± 129	434 ± 129	129 (<0.001)
Stammberger (42)	0.80 ± 0.24	1.18 ± 0.44	0.38 (<0.001)	29 ± 7	41 ± 13	12 #	241 ± 96[f]	338 ± 96[f]	96 (0.001)[f]
Zenati (35)	0.64 ± 0.22	0.97 ± 0.38	0.33 (<0.0001)	22 #	35 #	13 #	273 ± 80	306 ± 64	32 (<0.05)
IQ Range	**0.64-0.74**	**0.91-1.07**	**0.23-0.36**	**24-28**	**35-40**	**9-13**	**241-290**	**306-434**	**32-96**
Long term 1 years follow-up									
*Cooper (56)	0.69	1.00	0.31 #	24	36	12 #	354	418	64 #
*Cordova (13)	0.66 ± 0.17	0.90 ± 0.35	0.22 (<0.05)	N/A	N/A	N/A	N/A	N/A	N/A
18 months to 2 years follow-up									
*Cooper (20)	0.83	1.25	0.42 #	27	42	15 #	370	450	80 #
*Cordova (6)	0.69 ± 0.20	0.91 ± 0.37	0.22 (<0.12)	N/A	N/A	N/A	N/A	N/A	N/A

standard deviations/P value not given N/A - data not available * baseline data appears to have been obtained after pulmonary rehab in the majority of patients *f* 12MWD halved

Quality of life
Four series collected quality of life (QOL) data before and after the procedure (187 patients), but only three of these used specific measurement tools and none used the EQ-5D or the IHQL. Full details are contained in Appendix VIII.

Bagley used the Chronic Respiratory Disease Questionnaire (CRQ) developed by Guyatt and colleagues.[47] This is a widely accepted and validated measure of QOL for patients with chronic lung disease. It is specifically designed to detect changes in quality of life after an intervention. The test yields a score in each of four domains; dyspnoea, fatigue, emotional function and mastery. A significant change occurs for an individual patient when the dyspnoea score changes by ≥ 2.5, the fatigue score by ≥ 2.0, the emotional functioning score by ≥ 3.5, and the mastery score by ≥ 2.0.

Cooper used two well validated generic quality of life measures; the Nottingham Health Profile,[48] and the SF36,[49] The Nottingham Health Profile is a two part questionnaire which is designed to measure perceived health problems and how these problems affect an individual's usual activities. Part I measures subjective health
status in relation to such things as energy, pain, emotional reaction, sleep, social isolation and physical mobility, and Part II measures areas of task performance such as job and work, looking after the house, social life, home life, sex life, interests and hobbies, and holidays. The SF36 uses a similar technique to assess the impact on quality of life of disease and response to treatment.

Cordova used the Sickness Impact Profile,[50] which is a sensitive, behaviourally based measure of sickness related dysfunction composed of 136 items which are designed to reflect the patient's perception of his or her activities of daily living. SIP scores are inversely related to level of function and quality of life, thus the higher the score the poorer the functional ability and quality of life.

Full details of the QOL results as they were presented in the individual studies are presented in table 4. Although only limited data was presented in the studies, improvements in quality of life were observed across all studies and measurement tools.

Dyspnoea
Details of the results of the individual studies for changes in the subjective experience of dyspnoea are presented in Appendix VIII. Twelve studies measured dyspnoea before and after the intervention. A variety of measurement tools were used but only nine studies used validated, standardised tools.

The most commonly used tool was the Modified (American Thoracic Society) Medical Research Council of Great Britain scale (MMRC).[51] In this the patient grades their degree of dyspnoea from 0 to 4. The grade describes the activity that provokes dyspnoea thus the lower number correlates with less dyspnoea. Typically, 0 means breathlessness only with strenuous exercise and 4 means that the patient is unable to leave the house or is breathless when dressing. The MMRC scale results for 403 patients are presented in table 5.

Table 4. Results of quality of life data for included studies.

Study Reference (n)	Measurement Tool	Results
Bagley (55)	Chronic Respiratory Disease Questionnaire	Mean pre/post test difference: Fatigue - 3.16 (P 0.0001) Emotional function - 4.84 (P 0.0031) Mastery - 3.61 (P 0.0005)
Cooper (101)	SF36 Nottingham Health Profile	Compared with 1 year ago: 78% much better 20% somewhat better 1% about the same 1% somewhat worse 0% much worse Areas where statistically significant improvements occurred: Physical mobility Energy Vitality Non -statistically significant improvements were observed in most other areas.
Cordova (25)	Sickness Impact Profile	Mean scores: Pre Post P value Overall 18 7 <0.0002 Physical 13 4 <0.008 Psychosocial 11 4 <0.02
Daniel (17)	Non-validated patient based questionnaire	79% expressed a marked improvement 17% felt somewhat better 4% felt worse

Table 5. Individual study results for the MMRC dyspnoea scale.

Study (n)	pre-test score (± standard deviation)	post-test score (± standard deviation)	difference
Argenziano (66)	4.1(±0.8)	1.7(±1.3)	-2.4
Cooper (101)	2.8	1.2	-1.6
Eugene (44)	3.9	2.35	-1.55 (P<0.01)
McKenna (166)	2.9	1.9	-1.0 (P<0.0001)
Snell (20)	3.4(±0.5)	2.1(±0.8)	-1.3 (P<0.001)
Stammerberger (42)	3.5(±0.7)	1.6(±1.0)	-1.9

Bagley et.al. used the CRQ as described above, in which a significant change in the dyspnoea score is defined as a change equal to or greater than 2.5 points. The study recorded a mean improvement of 5.84 (P 0.0001).

The Borg[52] scale was used by two studies. This tool uses a subjective perspective to assess the extent of activity necessary to induce dyspnoea. The higher the score the greater the dyspnoea. In the Eugene[a] series the mean score decreased from 7.60 pre-operatively to 4.65 post-operatively. Zenati demonstrated a decrease from 3.71 to 2.40. The extreme difference in baseline is accounted for by the fact that the Eugene[a] series was one of those which included only very ill patients.

The Mahler Baseline Dyspnoea Index (BDI) and Transitional Dyspnoea Index (TDI) are used together to assess changes in the degree of dyspnoea experienced in patients with chronic respiratory disease.[53] The BDI measures the daily experience and the TDI measures changes in the degree of functional impairment after the intervention. Both indexes obtain measures for 3 categories; functional impairment; the magnitude of the task needed to invoke dyspnoea; and the magnitude of effort needed to invoke dyspnoea. The ratings for each category can be added to give the Baseline Focal Score (BFS) and the Transitional Focal Score (TFS). The BDI rates each category from 0 (severe) to 4 (unimpaired) giving a worst possible BFS of 0 and a best possible of 12. The TDI rates changes from 3 (major deterioration) to +3 (major improvement), giving a worst possible TFS of -9 and a best possible of +9. A score of 0 indicates no change. Three studies reported scores for the functional impairment component individually (Cooper, Zenati and Keller). The BDI scores for those were 0.83, 0.9 and 1.0 and the TDI scores were 2.2, 1.65 and 1.72. Keller reported an overall BFS of 3.36 and an overall TFS of 6.12, and Sciurbia an overall TFS of 5.1 ($P<0.001$).

Length of stay

Several series (668 patients) also provided information on length of stay, which gives a crude indication as to resource use associated with the procedure. Full details of this are presented in Appendix VIII. In those studies which reported it, IQR for length of stay was 13-18 days.

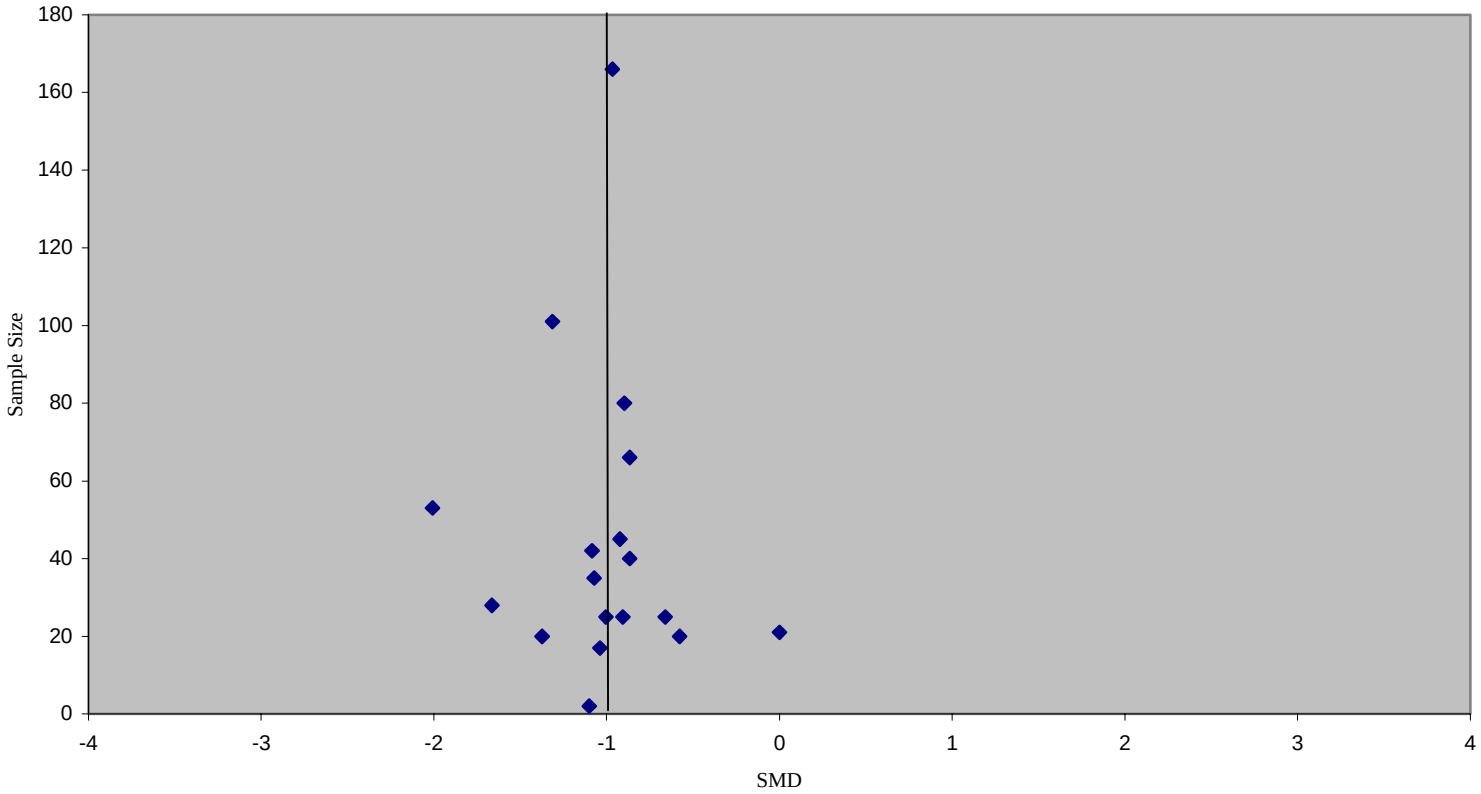
Supplemental oxygen

Finally, several studies (487 patients) also provided data on supplemental oxygen use before and after the procedure. This provides a crude indication of resource use, quality of life and functional ability. Details of this are also presented in Appendix VIII. In the short-term (3-6 months) the reduction in the percentage of patients requiring supplemental oxygen either continuously or on exertion was 16-42% (IQR). Cooper reports a reduction of 41% at one year and 52% at two years.

7.4. Assessing overall effectiveness

An overall judgement on the effectiveness of LVRS is hampered by the fact that none of the included studies directly measured the balance between the main benefits and risks of LVRS in terms of quality of life and functional ability, versus early death as a direct result of the operation, in the same population. An indication of the trade-off between these can be derived from section 6.3.2, but the clarity of this is obscured by the lack of true comparative data and the openness to bias of the estimates of effect for LVRS. This is compounded by the fact that for some of the important outcomes, such as quality of life, only limited information is available. It is also possible that the results of this review itself may have been prone to publication bias, however, it is difficult to assess the degree to which this might have occurred. The funnel plot in figure 2, which plots sample size against the standardised mean difference for FEV_1 in the included studies, acts as a crude visual check on the likelihood of missing studies.[54] It indicates that for this outcome there are no large gaps in the data set which might be suggestive of publication bias.

Figure 2. Funnel plot of 18*standardised mean differences (SMD) for FEV1 by sample size.



* Excludes one extreme outlier (Eugene a) which extended the x axis and hampered interpretation of the plot.

An important question remains as to whether the observed effect truly occurs as a result of LVRS alone. Because other interventions, particularly pulmonary rehabilitation,[7] have been shown to improve functional and health status for patients with end-stage COPD, combined with the fact that physiological benefits do not always equate to functional and quality of life changes,[55] it is impossible to be sure that the observed changes are due to the intervention of interest. For example, uncertainty around the timing of baseline data collection and inadequate reporting of the intervention raises the possibility that some of the effects demonstrated may incorporate those of pulmonary rehabilitation.

What can be established is that LVRS, with or without pulmonary rehabilitation, leads to subjective improvements in quality of life and shortness of breath. This is consistently demonstrated by the studies that examine this. The impact on subjective outcomes is supported by improvements in physiological and functional measures, such as FEV_1 and 6MWD. Improvements in these measures are also consistent across all the included studies which measure them. Mortality rates associated with the operation are consistent across individual studies, and compare favourably with those of untreated patients with COPD, who have high mortality rates even on maximum medical management. However, the possibility that the results of the individual studies or those of the review itself may be open to bias should not be underestimated. Even with those provisos, we would still judge that the benefits of LVRS demonstrated by the included studies are likely to outweigh the risks. This judgement is explored and tested further in the cost-utility analysis.

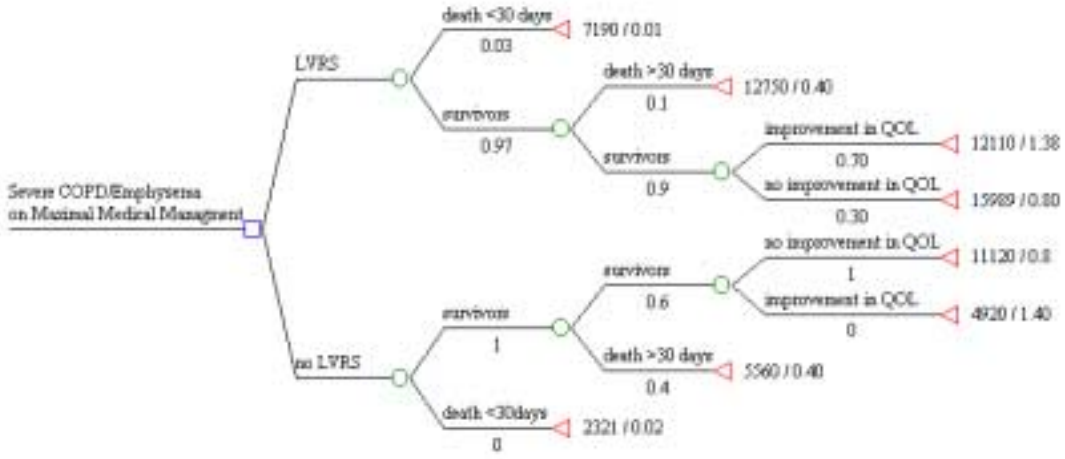
7.5. Cost utility analysis

Economic evaluation involves the assessment of the costs and consequences of a particular procedure compared to an existing alternative, of which a cost-utility analysis is only one of several types. Cost-utility analysis is the preferred eventual measure for DEC reports because it aims to present all relevant consequences in a single generic measure of outcome; the quality adjusted life year (QALY), which allows comparison across different interventions and conditions.

7.5.1. Decision tree

Before an assessment of cost-utility can be made, information is required on all the likely outcomes of the procedure and it's alternative, and the costs and utilities associated with these outcomes. Figure 3 outlines the decision tree introduced in section 4.3 including probabilities for all chance nodes, QALYs (based on the EQ-5D) and costs for all outcomes over 2 years.

Figure 3. Decision tree giving all probabilities, costs and utilities for the main options and outcomes.



The process through which these values were obtained is described in detail below and in the appendices to this report. It is important to note at the outset that the model takes the perspective of the NHS and that many costs incurred by other sectors are not taken into account such as local authority costs, and the considerable social costs of the condition to patients and their carers. Some of these are taken into account in the sensitivity analysis. In addition, the costs of the intervention are difficult to evaluate accurately as developmental costs and inefficiencies have not yet been eliminated. For example, these could fall as operator skill and experience rises, and the costs of materials and equipment are reduced in price.

Data on the effectiveness of the intervention is not available beyond 2 years follow-up. Although patients appear to continue to improve up to this point in time, it is not clear what happens to them after this. Current speculation is that, in most cases, physiological and functional improvements will plateau at around 2 years post-procedure and may be sustained for 1-2 years. Following this a decline in physiological measurements and functional ability is likely to recur at a rate equivalent to that experienced before the surgery. However, this is unlikely to have significant implications for the analysis as post-intervention annual costs over a given future time period would not exceed, and patient quality of life would not fall below, those experienced by patients on maximum medical management unless patients

experienced a deterioration in symptoms, or an increase in mortality, which was more rapid than that of the baseline population.

7.5.2. Probabilities

The probability estimates for the model were estimated from the general literature, where possible, and from the results of the included studies. Full details of how these were obtained are contained in Appendix IX.

Point estimates for early and late mortality post LVRS over 2 years were calculated from the included studies as **3%** and **10%** (annual 5%) respectively. An approximate mortality rate of **40%** (annual 20%) for the medical management arm was derived from studies of the natural history and prognosis of COPD.

No data on the results for individual patients or proportions of patients was available which would allow the calculation of the probability of objective improvement after the intervention. Estimates were therefore obtained from those studies which measured subjective improvement in some way. These results suggested that around 80% of people felt significantly better after the operation and only 2-4% experienced no improvement in symptoms. This should be viewed alongside more objective data on improvement such as that on supplemental oxygen requirements. Around 66% of those requiring oxygen either on exertion or continuously did not require it after the procedure. A conservative estimate of the probability of improvement after the intervention is therefore somewhere around **0.7**.

It should be stressed that considerable uncertainty exists around the relationship between these estimates and the actual results of the studies for the key outcomes. Subjective improvements in quality of life do not correlate well with physiological improvements in COPD, thus it is not necessarily the case that those patients who reported subjective improvements would also be those who demonstrated physiological improvements.[55] However, the outcomes identified at the outset as being clinically important in the context of LVRS for patients with severe COPD were those that examined subjective changes and in a sense the objective outcome data is supplementary to that.

The cumulative probabilities derived from the decision model for all outcomes are presented in table 6. Again full details of how these were derived are contained in Appendix IX.

Table 6. Cumulative probabilities for decision tree pathways.

Outcome	Probability Estimate	Cumulative Probability
LVRS/early death	0.03	0.03
LVRS/late death	0.1	0.097
LVRS/survive/improvement	0.70	0.611
LVRS/survive/no improvement	0.30	0.262
No LVRS/early death	0	0
No LVRS/late death	0.4	0.4
No LVRS/survive/improvement	0	0
No LVRS/survive/no improvement	1	0.6

7.5.3. Utilities

Full details of how utility values in terms of QALYs were assigned to the different outcomes are contained in Appendix X.

None of the evaluations of LVRS identified by the review measured health related quality of life using the EQ-5D, or other generic measures, that would facilitate the direct calculation of QALYs. The quality of life data in the included studies was of limited practical value largely due to the way the data was summarised and presented, and the fact that the measurement tools used by the studies did not lend themselves to translation into a more usable form. Utilities for the intervention were thus estimated using any useful information which could be extracted from the available literature, and these were subsequently validated by clinical experts. Uncertainties around the validity of these estimations are explored in the sensitivity analysis

The assessment of health related QOL is particularly important in the management of patients with COPD and a substantial body of literature exists around this. However, achieving a measure of QOL which accurately reflects the every day experience of living with the condition remains difficult. Generic QOL tools have been shown to be of limited value on their own, as they are insensitive to small but worthwhile clinical benefits.[55] Ideally, they should be supplemented by disease specific measures such as the St. George's Respiratory Disease Questionnaire (SGRQ), which have been shown to be more reliable, but which on their own do not facilitate ease of comparison with other diseases.[56]

It is also the case that QOL data for COPD patients is often difficult to interpret in relation to other outcome data. As mentioned above, improvements in QOL do not correlate well with improvements in physiological indicators, making it difficult to assess the impact on quality of life of changes in physiological outcomes when they are collected in isolation, as often occurs.[55] QOL changes alone have important clinical and economic implications which are often independent of similar physiological changes. This has been demonstrated by Osman and colleagues, who found a strong relationship between poor QOL and increased resource use in the NHS.[57]

The main source for the EQ-5D estimates was unpublished data from a small pilot study of the effectiveness of LVRS[58] which suggests that typical candidates for the operation will have a starting EQ-5D of around 0.37 and a post-operative EQ-5D of between 0.64 and 0.88. Other findings from this study were cross-checked against those of this review and these indicated that the two populations were similar both pre and post-operatively. Given the limitations of this pilot study and additional supporting information obtained from other relevant material (outlined in Appendix X), the point estimates for EQ-5D were taken as **0.40** pre-operatively and **0.70** post-operatively.

The EQ-5D uses a scale which ranges from 1 to 0, where 1 equates to full health and 0 to death. QALYs were calculated for all outcomes over 2 years by obtaining the product of the estimated quality of life scores and the duration of life. Thus the maximum QALYs over 2 years could be 2 and the minimum 0. The expected QALYs, as derived from the decision tree were calculated as the product of the QALY estimate and the cumulative probability for each outcome. These are presented in table 7 along with best and worst case scenarios where appropriate. Full details of these calculations are also provided in Appendix X.

Thus, using the EQ-5D, the total expected QALYs for LVRS are **1.09** (range 1.03-1.11), and the total expected QALYs for medical management are **0.64** (range 0.48-0.64). This represents a gain of **0.45** QALYs for LVRS.

Table 7. Expected QALYs for all decision tree outcomes using the EQ-5D.

Outcome	QALY estimate/ probability	Expected QALYs	Best Case	Worst Case
LVRS/early death	0.01/0.03	0.0003	n/a	0.0003
LVRS/late death	0.40/0.097	0.0388	0.06596	0.0291
LVRS/survive/improvement	1.38/0.611	0.84318	n/a	n/a
LVRS/survive/no improvement	0.80/0.262	0.2096	n/a	0.1572
Total expected QALYs		**1.09188**	**1.1104**	**1.02978**
no LVRS/early death	0.02/0	0*	n/a	n/a
no LVRS/late death	0.40/0.4	0.16	n/a	0.12
no LVRS/survive/improvement	1.40/0	0*	n/a	n/a
no LVRS/survive/no improvement	0.8/0.6	0.48	n/a	0.36
Total expected QALYs		**0.64**	**0.64**	**0.48**

7.5.4. Costs

None of the identified studies provided reliable data on the costs in the UK of the intervention, or of current best practice. All costs were estimated for two years using a variety of sources and were validated through consultation with local clinical experts from the primary and secondary care settings. Key sources included local provider and health authority data, relevant guidelines for the management of patients with COPD and expert opinion. Full details of how these were obtained are provided in Appendix XI.

Cost estimates were based on the following important assumptions;

- the costs of the medical management of patients for whom the intervention resulted in an improvement in symptoms would be reduced to take account of reductions in supplemental oxygen and steroid requirements
- all late deaths were assumed to occur on average half way through the 2 year period and early deaths half way through the 30 day period
- patients who did not improve or die were assumed to have one emergency admission per year excluding the year of surgery for patients undergoing LVRS
- late deaths or early deaths in the medical management group were assumed to cost the equivalent of an emergency admission as most would occur in the context of such an admission
- patients who died late were assumed not to experience an improvement in their condition
- patients undergoing LVRS would participate in two courses of pulmonary rehabilitation (pre and post procedure)
- *all* other patients would participate in one course of pulmonary rehabilitation per year
- patients who died early were assumed only to participate in one course of pulmonary rehabilitation and not to incur any additional costs associated with death

Table 8 outlines the costs for each outcome in the decision model with best and worst case estimates where appropriate. The expected cost for LVRS was estimated as **£13041** (range £12,965-£17,561). The nature of the condition and the eligibility criteria for the surgery means that patients who do not undergo LVRS will all be on maximal medical management, creating a situation where there is essentially no "no treatment" option. The expected total cost of managing a patient who did not undergo the procedure was estimated as **£8,896**. This represents an additional cost for LVRS to the NHS of **£4,145.**

Table 8. Expected costs for all decision tree outcomes.

Outcome	Cost estimate/ probability	Expected Costs	Best Case	Worst Case
LVRS/early death	£7,190/0.03	£216	n/a	n/a
LVRS/late death	£12,750/0.097	£1,237	£1,161	n/a
LVRS/survive/improvement	£12,110/0.611	£7,399	n/a	£11,919
LVRS/survive/no improvement	£15,989/0.262	£4,189	n/a	n/a
Total expected costs		**£13,041**	**£12,965**	**£17,561**
no LVRS/early death	£2,321/0	0	n/a	n/a
no LVRS/late death	£5,560/0.4	£2,224	n/a	n/a
no LVRS/survive/improvement	£4,920/0	0	n/a	n/a
no LVRS/survive/no improvement	£11,120/0.6	£6,672	n/a	n/a
Total expected costs		**£8,896**	**£8,896**	**£8,896**

7.5.5 Cost utility analysis

Thus, using the EQ-5D, the expected costs and benefits of LVRS can be estimated as £13,041 and 1.1 QALYs respectively. The expected costs and benefits of medical management over the same period can be estimated as £8,896 and 0.6 QALYs. This represents an additional cost per QALY gained of **£9,211**. Full details of these calculations are contained in Appendix XII.

7.5.6. Sensitivity analysis

Because it was not possible to derive a pooled numerical estimate of effect from the effectiveness data, the sensitivity analyses around the cost-utility estimate are illustrative rather than technical. The sensitivity of the model to variation in a number of key factors is explored. Primarily, this involves using the extremes of the ranges of costs and benefit estimates to generate best and worst case scenarios. More specifically, the impact of quantifying benefits using a different QOL measure is considered and the NHS perspective is breached in an attempt to capture the costs of dependency.

Effectiveness data and threshold sensitivity analysis
Because of the nature of the data and the considerable uncertainty around the much of the effectiveness data, it was difficult to identify key variables which could be tested in a one-way or even a multi-way sensitivity analysis. The approach taken was therefore to use the extremes of the individual ranges of the cost and benefit estimates to identify thresholds at which the intervention might cease to be cost-effective and to create a plausible range of overall cost-utility estimates within which the true value might lie.

Because the condition of patients on maximum medical management is unlikely to improve, LVRS could only be less effective if it were more harmful than "no treatment". Primarily, this implies that the combined early and late mortality rates for the intervention would have to exceed those of the untreated population. This situation could potentially occur if the probabilities in the model were based on the highest combined mortality rates for LVRS observed in the included studies (14%), and the lowest mortality rate estimated in the literature for Stage III COPD patients (10%).

An indication as to the range of possible estimates for the cost per QALY based on the EQ-5D can be gained by generating best and worst case scenarios arising from all the estimates of costs and QALYs. These are explored in table 9. The best case scenario takes the highest possible gain in QALYs, at the lowest possible additional cost and gives a cost per QALY of £6562, and the worst case scenario takes the lowest possible gain in QALYs at the highest possible cost giving a cost per QALY of £24,063.

It is important to note that the best and worst case estimates are two extremes which reflect the considerable uncertainties and difficulties involved in the estimation of the health gain associated with LVRS. Intuitively, it is difficult to envisage a situation where the considerable benefits experienced by patients undergoing this procedure did not render it the most cost-effective option, relative to medical management, for patients with severe COPD.

Table 9. Best and worst case scenarios for cost-utility of LVRS over medical management.

Cost/QALY estimate	Cost/QALY difference	Additional cost per QALY gained
Best case scenario		
Highest QALY for LVRS: 1.1	0.62	Costs of £6,562 per QALY
Lowest QALY for Medical Management: 0.48		
Lowest cost for LVRS: £12,965	£4,069	
Highest cost for Medical Management: £8,896		
Worst case scenario		
Lowest QALY for LVRS: 1.00	0.36	Costs of £24,063 per QALY
Highest QALY for Medical Management: 0.64		
Lowest cost for Medical Management: £8,898	£8663	
Highest cost for LVRS: £17,561		

IHQL

No literature was identified that facilitated the direct calculation of estimates of quality of life using the IHQL. These were obtained by modelling typical health states using descriptions of patient characteristics in the literature, consultation with clinical experts and informal interviews with, and observation of, patients. Full details of how utility values in terms of QALYs were assigned to the different outcomes based on the IHQL are contained in Appendix XIII. Using the IHQL classification a typical pre-operative patient was assigned a score of **0.65**, and a typical post-operative patient a score of **0.86.**

The QALYs for the IHQL are presented in table 10. The total expected QALYs for LVRS are 1.45(range 1.47-1.36), and the total expected QALYs for medical management are 1.04 (range 1.04-0.8). This represents a gain of 0.41 QALYs for LVRS. Thus, the expected costs and QALYs of LVRS over 2 years can be estimated as £13,041 and 1.4. The expected costs and QALYs of medical management over the same period can be estimated as £8,896 and 1.0. This represents an additional cost per QALY gained of **£10,362**, based on the IHQL, which is fairly close to the cost per QALY of £9,211 generated by the EQ-5D. Full details of all calculations are also contained in Appendix XIII.

Table 10. Expected QALYs for all Decision Tree Outcomes using the IHQL.

Outcome	QALY estimate/ probability	Expected QALYs	Best Case	Worst Case
LVRS/early death	0.03/0.03	0.0009	n/a	0.0006
LVRS/late death	0.65/0.097	0.06305	0.08245	0.0485
LVRS/survive/improvement	1.71/0.611	1.04481	n/a	n/a
LVRS/survive/no improvement	1.30/0.262	0.3406	n/a	0.262
Total expected QALYs		**1.44936**	**1.46876**	**1.36131**
no LVRS/early death	0.03/0	0*	n/a	n/a
no LVRS/late death	0.65/0.4	0.26	n/a	0.2
no LVRS/survive/improvement	1.71/0	0*	n/a	n/a
no LVRS/survive/no improvement	1.30/0.6	0.78	n/a	0.6
Total expected QALYs		**1.04**	**1.04**	**0.8**

Carer costs

As noted earlier, the NHS perspective does not capture many costs which might be incurred by other sectors such as, local authority costs, and the social costs for patients and their carers. The main benefits experienced by patients undergoing LVRS appear to relate to their quality of life and particularly to the degree to which they are able to cope with their own activities of daily living. Confining the analysis to an NHS perspective and not attempting to quantify the costs of dependency in some way may seriously underestimate the true value of LVRS, particularly in the context of recent developments in the NHS such as primary care groups and seamless budgets between health services and local authorities. For this reason the cost estimates were recalculated including a quantification of the cost of caring for an individual who is unable to cope with their own activities of daily living and the assumption that these costs are transformed into savings after the procedure in an individual whose condition improves.

The true cost of care is difficult to quantify and in this instance it was roughly estimated as the cost of an untrained carer for 1 hour per day, seven days per week, which is around £2,920. The degree to which these costs are realised will vary greatly throughout the country and it is recognised that in many real-life situations patients will not receive care of this nature with their needs being met by family or friends, or other sectors, at no cost at all to the public sector. In this case any benefits will be realised not as financial savings but possibly as reduced stress and improved QOL for the carer.

Table 11 summarises the costs for all outcomes including carer costs along with best and worst case scenarios where appropriate. The expected total cost of the procedure over two years including the costs of a carer was estimated as £14,857 and the costs of medical management as £13,568. Because it is assumed that these costs will only apply in people who do not improve, the overall costs of medical management are significantly increased when the model is manipulated in this way, and the difference between the two is smaller resulting in an additional cost for LVRS of just £1,289. This, as might be anticipated, is considerably less than that generated by the model when carer costs are not taken into account. Using the EQ-5D utility estimates, this represents an additional cost per additional QALY gained of just **£2,864**. Full details of all calculations are contained in Appendix XIII.

Table 11. Expected costs for all decision tree outcomes including carer costs.

Outcome	Cost estimate/ probability	Expected Costs including carer
LVRS/early death	£7,190/0.03	£216
LVRS/late death	£15,670/0.097	£1,520
LVRS/survive/improvement	£12,110/0.611	£7,399
LVRS/survive/no improvement	£21,839/0.262	£5,722
Total expected costs		**£14,857**
no LVRS/early death	£2,321/0	0
no LVRS/late death	£8,480/0.4	£3,392
no LVRS/survive/improvement	£4,920/0	0
no LVRS/survive/no improvement	£16,960/0.6	£10,176
Total expected costs		**£13,568**

7.6 Summary of results

7.6.1 Effects

The main observed effects of LVRS are outlined below:

- the pattern of results for most outcomes is fairly consistent across individual studies despite a significant degree of clinical heterogeneity
- significant short-term benefits occur across the range of outcomes, which appear to continue into the longer term
- physiological improvements in FEV_1 appear to be matched by functional improvements in 6MWD, and subjective improvements in dyspnoea and quality of life
- early mortality rates are low and late mortality rates compare favourably with those of the COPD population as a whole

An impression of the overall magnitude of effect can be obtained by examining the percentage improvements from baseline for the key outcomes. These are presented in table 12.

Table 12. Percentage improvement from baseline for key outcomes.

Outcome	% Improvement
FEV_1	39
6MWD	32
Dyspnoea (MMRC)	47

These effects should be viewed in the light of the following provisos:

- the entire research base for the intervention is prone to the high degree of bias which is inherent in study designs without parallel control groups.
- it is impossible to assess the degree to which detection bias may have occurred due to insufficient information on the assessment of outcome
- the review itself may have been prone to publication bias
- because the main benefits and risks were not measured directly in the same population and information on some important outcomes is limited, an overall judgement on effectiveness cannot be made
- there is insufficient information to be sure that the effects observed are directly due to LVRS and LVRS alone, and in particular that they do not incorporate the effects of pulmonary rehabilitation

7.6.2 Effectiveness

Based on the results demonstrated by the included studies we would judge that the benefits of LVRS are likely to outweigh the risks with the proviso that the results of the individual studies or those of the review itself may be open to bias which may have contributed to pattern of universality observed in the results.

7.6.3 Cost-utility

Given the considerable uncertainty and underlying assumptions around the cost-utility estimates, the expected additional cost per QALY gained for LVRS over medical management based on the EQ-5D is very tentatively around £9,000. Using the best and worst case scenarios generated from the most critical assumptions in the model, the lowest possible additional cost per QALY is around £7,000 and the highest possible additional cost per QALY gained is around £24,000. When the model is extended beyond the NHS perspective and carer costs are quantified the cost per QALY falls to around £3,000. The way in which the model has been populated is rooted in the assumption that the level of benefits identified from the evidence on the effects and effectiveness of LVRS is correct, which is by no means certain. If this should turn out to overestimate the true effects and effectiveness, the estimates of cost-utility would need to be re-examined.

8 Implications and conclusions of the review

Based on the results of this review, LVRS appears to be effective in the management of patients with severe end-stage emphysema. Even accounting for the fact that the observed evidence on its effectiveness is subject to several biases, it seems unlikely that LVRS is less effective than current best practice. This would require it to cause more harm than good or to have no effect at all. Given that LVRS has considerable resource implications the key question is thus:

What is the "quantity" of benefit offered by LVRS and is it worth the costs?

The cost-utility analysis was carried out to investigate this question further. The tentative estimates of cost-utility indicate that, provided the information on effects and effectiveness is accurate, it is likely that LVRS is cost-effective. However, we must make it clear that the relatively favourable cost-utility figures (£9,000 per additional QALY gained; best case £7,000; worst case £24,000) are contingent on the favourable estimates of effects and effectiveness, and there is genuine uncertainty about how reliable these are at this point in time. We would judge that the level of this uncertainty, compounded by the uncertainty around the cost and utility estimates, is such that it would be inappropriate to proceed as though this technology is of proven effectiveness and cost-effectiveness. Rather, it should be regarded as a new procedure which appears to have potential for improving the quantity and quality of life of a group for whom there are few other therapeutic options. Further, it seems that the procedure, although highly interventional, may not be as expensive as might first be expected, principally because the costs of medical management are so high.

It is also important to acknowledge that there are a whole set of issues around the effectiveness and cost-effectiveness of LVRS in the long-term management of end-stage emphysema that have not been addressed here, particularly given current speculation that untreated patients may survive longer than current published evidence suggests. We have been unable to incorporate potential benefits extending beyond two years into the model, nor to address the potential loss of benefits after two years which is still a possibility, raising related issues around the effectiveness and cost implications of repeat operations which could be significant.

Overall, the findings of this health technology assessment suggest that LVRS is a procedure where further rigorous research evidence on effectiveness is required before implementation. Amongst calls on R&D resources, LVRS should have a high priority, because if the favourable provisional estimates of effects, effectiveness and cost-utility are borne out, the procedure has the potential not only to be effective but also cost-effective. Superficially it appears that this priority has been recognised, with an RCT in the USA currently recruiting,[59] and one in the UK about to start.[60] However, it is not yet clear whether these will collect usable information which will improve current estimates of cost-utility, as well as those of effectiveness.

As regards general recommendations, it is tempting to believe that no further action is necessary or required by commissioners beyond recognising that they should not be

commissioning this procedure on a routine basis, but they should be aware that they will need to revisit this decision when new research becomes available. However, this is only true for areas where there is no existing interest or expertise in the procedure. This is not the case in the West Midlands where there is an active centre at Birmingham Heartlands Hospital, whose activity acted as the primary stimulus for this report. In this situation, and in the knowledge that this centre is already involved in the UK trial, we believe a more appropriate approach would be for commissioners to actively support and encourage accrual to the UK trial at the Heartlands centre. There may be some cost implications for commissioners but, based on this health technology assessment, we believe these to be justified, primarily because there is a reasonable chance that LVRS is a procedure which will become accepted as having a place in the management of end-stage emphysema on grounds of both effectiveness and cost-effectiveness, and secondly because supporting recruitment to the UK trial is a positive way of ensuring that the required information, confirming or refuting existing evidence of effectiveness, emerges as quickly as possible.

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