Lung Volume Reduction Surgery

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Assessment report

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee (MSAC) with the assistance of Dr Paul Fennessy, Ms Elizabeth Burrows, Ms Ornella Clavisi, Ms Alexandra Raulli, Dr Renea Johnson and Dr Elmer Villanueva (Centre for Clinical Effectiveness, Monash Institute of Health Services Research) and Mr Tony Harris and Ms Karen Yong (Health Economics Unit) of Monash University's Health Economics Unit. The report was endorsed by the Commonwealth Minister for Health and Aged Care on 28/04/2001.

Publication approval number 3124

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

Contents

Executive summary

The procedure

Lung volume reduction surgery (LVRS) is a palliative treatment for end-stage emphysema and chronic obstructive pulmonary disease (COPD). The surgery involves the removal of severely diseased, slowly ventilating and hyper-expanded lung tissue. This procedure allows for the better-conserved adjoining lung parenchyma to expand into the vacated space within the thorax and function more effectively. The operation can be accomplished by unilateral or bilateral thoracoscopy, thoracotomy or median sternotomy. The resection of hyper-inflated, non-functional lung reduces thoracic volume, improves chest wall and diaphragmatic mechanics and enhances ventilation of the remaining portions of lung.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. The medical literature on the technology is searched and the evidence is assessed and classified according to the National Health and Medical Research Council (NHMRC) four-point hierarchy of evidence[1]. A supporting committee with expertise in this area evaluates the evidence and provides advice to MSAC.

MSAC's assessment of lung volume reduction surgery

The results of a review of LVRS undertaken by the Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) were also incorporated in the assessment[2].

Clinical need

In Australia, COPD was the fourth leading cause of death among males and the sixth leading cause of death among females in 1998, resulting in 3,326 deaths for males and 2,026 deaths for females[3]. In 1996, 1.6 percent of the population was estimated to have COPD, a total of 296,590 people (177,100 males and 119,490 females)[3].

Safety

Mortality and morbidity data differ widely as LVRS encompasses many surgical techniques and surgeon experience varies between centres. The interquartile range (IQR) for early mortality (defined as hospital deaths or deaths occurring within 30 days of surgery) was zero to six percent, while the IQR for late mortality (defined as deaths occurring in the hospital or more than 30 days after surgery) at 3-6 months was zero to eight percent. Late mortality at two years was estimated as between zero and 3 percent[4].

Effectiveness

All published systematic reviews recommend waiting for results from the on-going randomised controlled trials which will better inform claims of clinical effectiveness. A limited amount of preliminary data from these trials has recently been published. Only six-month outcome data is currently available and does not, at this stage, confirm an advantage of LVRS over standard medical therapy with respect to mortality or lung function. LVRS does, however, appear to ease symptoms of chronic emphysema and COPD, and improve quality of life at this early stage. Until more comprehensive trial results are available, it is not possible to determine whether LVRS is clinically effective in the long term.

Cost effectiveness

It may be unwise to place great emphasis on the one and only study reporting cost data so far identified given the uncertainty surrounding the effectiveness of LVRS in reducing mortality and improving quality of life. The applicability of medical practice in the UK to the Australian setting[20] is also an issue that needs investigation. However, when better evidence becomes available on effectiveness and the cost of care in Australia, this study will provide a good framework for evaluation.

Recommendation

MSAC has recommended that on the strength of evidence relating to Lung Volume Reduction Surgery:

- public funding should not be supported for this procedure pending availability of overseas clinical trial data expected in 2003;
- surgeons performing lung volume reduction surgery are advised to seek approval in principle to continue performing the procedure from their hospital ethics committee or equivalent;
- patients undergoing this procedure should be appropriately informed of the risks of lung volume reduction surgery; and
- the Australian Health Ministers' Advisory Council be advised of this decision.

The Minister for Health and Aged Care accepted this recommendation on 28 April 2001.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the effectiveness of lung volume reduction surgery (LVRS). This is a procedure for the palliative treatment of end-stage emphysema and chronic obstructive pulmonary disease (COPD). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, taking into account other issues such as access and equity. MSAC uses an evidence-based approach for its assessment, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of references and membership are shown in Appendix A. MSAC is a multidisciplinary expert body with members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer affairs and health administration.

The Lung Volume Reduction Surgery (LVRS) Supporting Committee of MSAC (membership at Appendix B) has supervised a review of the use of LVRS for the treatment of chronic emphysema and COPD.

This report summarises the assessment of current evidence for LVRS for advanced emphysema and COPD.

Background

Lung volume reduction surgery for advanced emphysema and chronic obstructive pulmonary disease

The Procedure

Lung volume reduction surgery (LVRS) was introduced in the early 1950s as a palliative treatment for selected patients with advanced emphysema and end stage chronic obstructive pulmonary disease (COPD) suffering from progressive dyspnoea. The procedure is believed to improve pulmonary function and relieve symptoms. The mechanisms of LVRS are thought to be related to the restoration of compromised lung elastic recoil, correction of ventilation perfusion mismatch, improvement in efficacy of respiratory musculature and improvement of right ventricular filling.

Generally, a CT scan and a quantitative perfusion scan are required to identify the diseased lung tissue. The excision of lung parenchyma aims to reduce the volume of each lung by between 20 and 30 percent. The means of access to the lung can be by thoracotomy (for unilateral surgery), video assisted thoracoscopy (VATS, for unilateral or bilateral surgery), median sternotomy and clamshell incision (for bilateral surgery). It seems that bilateral reduction is the most preferred procedure. Median sternotomy has the advantage of providing the best exposure of the apical lobes without incision of the chest wall muscles, while VATS involves a smaller incision.

There are two common ways of achieving reduction in lung volume. One is by median sternotomy with surgical stapling of the periphery of both lungs (lung shaving). The second technique is performed unilaterally and reduction of lung volume is achieved with either laser ablation of lung tissue or surgical stapling or both. Surgical stapling using bovine pericardial strips to buttress the staples[5] has been frequently used in recent years.

One of the most common complications of LVRS is a prolonged air leak after surgery which may result in re-operation and longer hospital stays. An attempt to overcome this problem has been by the use of buttressing materials along the staple line, most commonly bovine pericardium, although collagen has also been suggested as a cheaper option.

An eight week pre-operative pulmonary rehabilitation program is required to maximise procedure success and minimise post-operative complications. Generally, one-day ICU stays and an average of 8-18 days of hospitalisation are expected after the operation. Post-operative pulmonary rehabilitation is absolutely critical to recovery.

Intended purpose

LVRS is indicated as a second line of treatment for patients with end-stage emphysema and COPD who have failed conservative medical treatment. LVRS has been considered as an alternative to lung transplantation. In addition, LVRS may be offered to patients who otherwise may not have been considered candidates for lung transplantation.

It is suggested that LVRS should be limited to patients who are proven refractory to optimal medical treatment and with predominantly upper-lobe emphysema, severe hyperinflation and an FEV_1 <40 percent predicted.

Clinical need/burden of disease

COPD is a term used to describe a combination of several different but related diseases. COPD is a progressive and disabling disorder characterised by diminished breathing capacity of the lungs. Chronic bronchitis and emphysema are the two prominent COPD diseases[3].

In Australia, COPD was the fourth leading cause of death among males and the sixth leading cause of death among females in 1998, resulting in 3,326 deaths for males and 2,026 deaths for females[3]. The mortality rate for males decreased from a peak of 75 per 100,000 in 1982 to a low of 38 per 100,000 in 1998. Female mortality rate increased marginally from 11 per 100,000 in 1979 to 17 per 100,000 in 1998[3]. Reduction in the male mortality rate is believed to reflect the decline in smoking rates for males, while the increased female mortality rate may be suggestive of the delayed effects resulting from an increasing number of female smokers[3].

The incidence of COPD in Australia for 1996 was 20,162. When this was stratified by gender, males had a higher incidence (12,124) of COPD than females (8,038). In 1996, 1.6 percent of the population was estimated to have COPD, a total of 296,590 people (177,100 males and 119,490 females)[6].

Table 1 lists the rates and frequencies for bronchitis/emphysema, with males having higher rates than females for all states in Australia. The condition severely affects patient quality of life as the impaired respiratory function and chronic disabling dyspnoea significantly limits a patient's basic daily activity and requires supportive care from families and/or health care systems. The three-year survival for COPD is about 60 percent[7].

Table 1 Frequency and rates of bronchitis/emphysema (ICN 490-492) in Australia

	Number			Crude Rate†			Direct Rate‡	
	Male	Female	Total	Male	Female	Total	Female	Total
ACT	33	29	62	0.4	0.3	0.4	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)
NSW	2994	2167	5161	35.8	25.5	30.6	24.2 (23.2, 25.2)	31.8 (30.9, 32.7)
NT	26	16	42	0.3	0.2	0.2	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)
QLD	1841	1245	3086	22.0	14.7	18.3	13.1 (12.4, 13.8)	17.7 (17.1, 18.3)
SA	869	659	1528	10.4	7.8	9.1	7.7 (7.1, 8.3)	10.1 (9.6, 10.6)
TAS	-	-	-	-	-	- -	-	-
VIC	1600	1257	2857	19.1	14.8	17.0	13.7 (12.9, 14.4)	17.3 (16.6, 17.9)
WA	859	712	1571	10.3	8.4	9.3	6.9 (6.4, 7.4)	8.4 (7.9, 8.8)

† per 100,000

‡ per 100,000 (Age Std)

- no available data

COPD was the third leading cause of the burden of disease in 1996 with COPD contributing 3.7 percent of the total disease adjusted life years (DALYs). The DALY is a summary measure of population health that combines information on mortality and non-fatal outcomes. It uses time as a common currency and is a measure of the years of healthy life lost due to illness or injury – one DALY is one lost year of healthy life.

In 1998 the burden of disease for COPD in Australia was higher for males (55,866,000 DALYs) than females (37,521,000 DALYs)[3]. The burden due to COPD increases with age peaking for males between the ages of 55 and 74 years for males and 75 years and over for females. Among those aged 65 years and over, COPD ranks as the fourth leading cause of burden for both males (30,348,000 DALYs) and females (21,838,000 DALYs), accounting for 5.8 percent and 4.0 percent, respectively, of the total burden[8].

In 1997-98, there were almost 40,000 hospital separations with the principal diagnosis of COPD involving an average length of stay of 5.3 days. Hospitalisations for COPD occur principally among the elderly. Hospital separation rates for COPD were higher for males than for females. Male hospital separations rates increased sharply from 140 per 100,000 in the 50-54 years age group to a peak of 4,300 per 100,000 in the age group 85 years and over. The increase in female rates with age was not pronounced, rising from 170 per 100,000 in the 50-54 years age group to a peak of 1,450 per 100,000 in those aged 80-84 years[3].

According to the third LVRS Activity Survey conducted in August 1998, 16 centres in Australia had performed 262 cases. Twelve units are currently performing LVRS in Australia with 400 patients (correspondence with Mr Julian Smith, 19 February 2001).

Existing procedures and Comparators

No surgical technique currently exists that parallels LVRS. The appropriate comparator for LVRS has usually been standard clinical management, ie. best supportive care, although it appears that pulmonary rehabilitation is now the preferred option. There is also discussion as to whether lung transplantation should be considered. A general description of each individual comparator was adapted from the recently published University of Birmingham systematic review[4].

Standard clinical management

Very few treatment options are available for patients with end-stage COPD. In the majority of cases, most available options are directed towards patients with COPD. There are no treatment options that are specifically tailored for patients with COPD with predominant emphysema. Standard clinical management for end-stage COPD can include:

- 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; and
- home care and social support.

The manner in which these treatment options are optimised by the majority of patients with COPD is yet to be resolved, although candidates for LVRS will generally receive maximum medical therapy including pulmonary rehabilitation.

Pulmonary rehabilitation

Pulmonary rehabilitation is a relatively new treatment option for patients with COPD. The primary aim of this medical intervention is to prevent deconditioning and help patients cope with their disease. This type of treatment will usually consist of six to eight weeks of exercise for five to seven days a week plus psycho-educational retraining. For patients undergoing LVRS, pulmonary rehabilitation is considered a crucial pre-operative practice. Patients will usually undergo intensive pulmonary rehabilitation for optimising physical and cardiopulmonary conditioning, exercise tolerance and pulmonary hygiene prior to surgery. Pulmonary rehabilitation is also undertaken post-operatively following LVRS. However, post-operative treatment focuses more on pulmonary hygiene and assessment of oxygen needs.

Lung transplantation

Lung transplantation can be an option for patients with late stage COPD. This type of operation carries a number of risks such as post-operative infection and life-long dependency on immunosuppression. This procedure has a four-year survival rate of between 40 and 50 percent for most patients, except those with emphysema who appear

to fare better than those with other diseases. This procedure, however, is subject to a shortage of suitable lung donors which means that only a small proportion of those patients eligible for lung transplantation is likely to receive this treatment.

Marketing status of the device / technology

This procedure is relatively new and conducted only at twelve tertiary institutions across Australia.

Current reimbursement arrangement

LVRS is currently claimed under the Medicare Benefits Schedule (MBS) using the item numbers 38456 (intrathoracic operation), 38424 (thoracotomy) and 38440 (wedge resection of the lung).

Approach to assessment

In undertaking its assessment, MSAC reviewed the literature available on LVRS and convened a Supporting Committee to evaluate the evidence of the procedure and provide expert advice. This review follows methods outlined in the Cochrane Collaboration Handbook[10].

Review of literature

The medical literature was searched to:

- identify high level evidence, including randomised controlled trials, that had been published since the release of the University of Birmingham Systematic 1999 review;
- evaluate any identified high level evidence that had been published subsequent to the release of the University of Birmingham Systematic 1999 review;
- determine the status of randomised controlled trials currently underway; and
- evaluate the cost-effectiveness of LVRS based on published data (if it existed).

In 1998 ASERNIP-S conducted a review to assess the literature regarding the procedure of LVRS in patients with emphysema and make recommendations on the safety and efficacy of the technique. Their review evaluated the scientific literature up to September 1998.

A literature search for the period 1998 to April 2000 inclusive was conducted for this report. Table 2 lists the electronic databases accessed for this search.

Table 2 Electronic databases (including edition) used in the review

Database	Period Covered
Best Evidence (OVID)	**1998 to 2000**
Cochrane Library including:	Issue 1, 2000
• the Cochrane Databases of Systematic Reviews	
• the Database of Abstracts of Reviews of Effectiveness	
• the Cochrane Controlled Trials Register	
HealthStar	1998 to April 2000
Medline (OVID & PubMed)	1998 to April 2000
SumSearch	
BiomedNet	

Search strategy

The following search strategy was employed to retrieve articles focusing on LVRS for COPD and emphysema. No language restrictions were applied to the search.

Table 3 Search terms used to identify citations foc using on LVRS for COPD and emphysema

Search terms used to identify citations for COPD and Emphysema	Search terms used to identify citations for LVRS
Emphysema	Pneumonectomy
Lung disease$†	Pneumectomy
Airway obstruction	Pneumoplasty
Pulmonary emphysema	Pneumonoplasty
Chronic obstructive pulmonary disease	Lung surgery
COPD	Thoracotomy
	Surgical stapling
	Laser surgery
	Lung$ volume$ reduc$ surg$†
	LVRS

* Terms were searched as text words. A medical subject heading (MeSH) term was conducted if allowed by the databases

† Represents wildcard

As well as those databases listed above, the Internet was searched for references to randomised controlled trials on LVRS. . Relevant sites included: the National Coordinating Centre for Health Technology Assessment[11], International Society of Technology Assessment in Health Care[12], International Network of Agencies for Health Technology Assessment[13] (and 28 member organisations, see Appendix C), British Columbia Office of Health Technology Assessment (Canada)[14], Center for Medical Technology Assessment (Sweden)[15], Minnesota health technology assessment[16], the National Heart, Lung and Blood Institute[17], the National Research Register[18], the Canadian Medical Association[19] and the American Thoracic Society[20].

If randomised controlled trials were identified but not yet completed, the authors or coordinators of each trial were individually contacted by email or fax. Each author/coordinator was asked to: a) clarify the details of each trial, and b) provide a trial update.

Inclusion and exclusion criteria

The following *a priori* criteria were developed to identify relevant literature:

Population

Inclusion: Patients diagnosed with diffuse severe emphysema with significant functional limitation despite maximum medical therapy.

Exclusion: Patients with large isolated emphysematous bullae in the presence of normal underlying compressed lung.

Intervention

Inclusion LVRS (reduction pneumoplasty or pneumectomy/pneumonectomy) defined as multiple lung resection and/or plications of diseased lung tissue to reduce lung volume.

Exclusion: The excision of localised giant bullae.

Outcomes

Inclusion: All outcomes that address clinical and physiological factors attributable to LVRS.

Exclusion: Undetermined at this stage.

Methodology

Inclusion: Individual comparative studies and systematic reviews of studies that compare the outcomes of patients who undergo LVRS with a group of control patients who do not have this type of surgery. Studies that compare various techniques and approaches of the procedures will also be included.

Exclusion: Case series and non-systematic reviews of LVRS.

An initial assessment of abstracts for the selected citations allowed for the exclusion of articles that did not meet the selection criteria. Ambiguous or uncertain citations proceeded to the next stage. Two independent reviewers examined each citation for inclusion.

Discrepancies in selection were discussed and resolved through consensus. From an initial search of 211 articles, 187 were rejected, leaving 24 articles to be assessed in full text form. Of these, the majority were English language articles (n=21). With regards to their research methodology, eight were randomised controlled trials, nine were non-randomised comparative studies with concurrent controls and seven articles were of uncertain study design. Full text articles from these citations were retrieved and assessed. A final decision to reject or accept articles was based on a thorough reading of the complete article. Only the studies that successfully passed this process are discussed in this report.

Expert advice

A supporting committee with expertise in cardiothoracic surgery, vascular surgery, thoracic medicine and consumer issues was convened to assess the evidence of the procedure. In selecting members for supporting committees, MSAC's practice is to approach the relevant colleges, specialist societies and associations, and consumer bodies for nominees. The supporting committee membership is shown at Appendix B.

Results of assessment

Is it safe?

Safety data on mortality and morbidity differ widely since LVRS encompasses many surgical techniques and surgeon experience differs between centres performing this procedure. The complications resulting from LVRS include those that arise from respiratory surgery as well as those from non-respiratory surgery as patients eligible for LVRS are often debilitated and suffer from a comorbidity. The most common complication is persistent air leak that is specific to LVRS. Other complications include pneumonia, sepsis, myocardial infarction, stroke, respiratory failure, bleeding, phrenic nerve paralysis, wound infection, thrombophlebitis, intestinal perforation, empyema, deep venous thrombosis/pulmonary embolism, ventilator dependence, re-operation, oxygen dependence, re-intubation, arrhythmia, colitis, sternal dehiscence and mediastinitis. [2, 4, 21, 22]

Table 4 was extracted from the results of the systematic review by the University of Birmingham[4]. The authors calculated early and late mortality rates for LVRS. The interquartile range (IQR) for early mortality (defined as hospital deaths or deaths occurring within 30 days of surgery) was 0-6 percent, while the IQR for late mortality (defined as deaths occurring in the hospital or more than 30 days after surgery) at 3-6 months was zero to 8 percent. Late mortality at two years was estimated as between zero and 3 percent[4].

Table 4 Mortality data from included studies in the University of Birmingham Systematic Review[4]

Study Reference (2-6 month follow-up)	Early Deaths (<30 days or hospital deaths)	Late Deaths (³ 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%)
Cooper	*6/150 (4%)	*4/144 (3%)	10/150 (7%)
Cordova	0/25 (0%)	0/25 (0%)	0/25 (0%)
Criner	0/3 (0%)	0/3 (0%)	0/3 (0%)
Daniel	1/17 (6%)	0/16 (0%)	1/17 (6%)
Eugene	1/44 (2%)	11/43 (25%)	12/44 (27%)
Eugene	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%)

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

In the systematic review by ASERNIP-S[2], the authors found that respiratory failure was responsible for most of the early deaths. Prolonged air leak is the most common complication, averaging about 45 percent in most series. Re-operation in the more severe cases has been necessary in about four percent of cases. Pneumonia has occurred with a frequency of about 10 percent and re-operation for pleural space problems, including bleeding, was necessary in four percent of cases. Other commonly reported complications of low incidence include phrenic nerve paralysis, tracheostomy or re-intubation for respiratory failure, wound infection, thrombophlebitis, myocardial infarction, intestinal perforation and empyema[22].

Three controlled trials have been published subsequent to the publication of the systematic reviews by the University of Birmingham and ASERNIP-S. The mortality rate in LVRS patients in these studies ranged from six percent to 21 percent after varying follow-up periods. Geddes et al 2000[27] reported that of 24 patients randomised to LVRS, five died (21%) compared to three (12%) in the medical group after a follow-up of 12 months. Operative mortality (in-hospital deaths after surgery) occurred in four patients (17%) and was due to respiratory failure; the fifth patient died 287 days after surgery. No data on complications were presented.

In a RCT by Criner, Cordova *et al*[26], mortality among patients who underwent LVRS was nine percent (three of 32 patients) compared to three percent (one of 37 patients) in patients on medical therapy after a follow-up of three months. Licker, de Perrot *et al* [28], in a non-randomised comparative study, reported a mortality rate of six percent (one of 17 patients) in patients undergoing LVRS compared to 23 percent (three of 13 patients) in patients undergoing lung transplantation after a follow-up period ranging from six to 24 months. Complications among patients with LVRS in this study included re-operation (two patients) and pulmonary infection (one patient).

Is it effective?

This review assessed the effectiveness of LVRS following critical appraisal of systematic reviews and randomised controlled trials examining this procedure.

Critical appraisal of published systematic reviews

This critical appraisal makes use of a modification of the checklist recommended by the Quality of Reporting of Meta-Analyses (QUOROM) group[23]. Five systematic reviews have been identified and assessed:

- University of Birmingham systematic review[4];
- ASERNIP-S systematic review[2];
- Alberta Heritage Foundation for Medical Research systematic review[21];
- Minnesota Health Technology Advisory Committee systematic review[24]; and
- Agency for Health Care Policy and Research systematic review[25].

Appraisal was conducted by two independent assessors with expertise in general medicine, basic science, epidemiology, and biostatistics. Disagreements were resolved by consensus. Descriptors were identified in both documents and are reported as "**+**" if present; "**-**" if absent; and "NA" if not applicable. The results are presented in Table 6.

Summary

All identified reviews have been fully evaluated. Although of varying quality, all came to similar conclusions:

- LVRS is considered investigational;
- no scientifically defensible claims are possible given the current state of evidence; and
- results of on-going randomised controlled trials will better inform claims of clinical effectiveness.

Critical appraisal of controlled trials

Twelve trials were identified that purported to be controlled trials comparing LVRS with standard medical therapy or pulmonary rehabilitation. After reviewing the published data and contacting the authors or coordinators of those trials identified but still being conducted, only seven controlled trials were found that have been completed or are currently underway (the other five trials were either case series or did not meet selection criteria).

Published controlled trials of LVRS

Only two recently published randomised controlled trials (Criner, Cordova *et al*[26]; Geddes et al 2000[27]) and one controlled trial (Licker, de Perrot *et al*[28]) were identified. Criner, Cordova *et al*[26] was excluded because it did not specifically compare patients receiving LVRS with those receiving standard medical treatment or pulmonary rehabilitation.

Table 5 outlines the characteristics of those published controlled studies included in this review. The Geddes et al study is a randomised controlled trial (RCT) of 48 patients with severe emphysema: 24 intervention patients randomised to LVRS and 24 control patients randomised to medical treatment[29]. The second study, Licker, de Perrot *et al*, is a comparative study also in patients with severe emphysema.[28] This study compared patients undergoing LVRS (n=17) with patients undergoing lung transplantation (LT; n=14). Pre- versus post-surgery lung function assessments were made after five to six months follow-up, but only peri-operative assessments were compared between the two treatment arms (see Table 10).

Table 5 Descriptive characteristics of included studies evaluating the effectiveness of LVRS.*

First Author and Year of Publication	NHMRC Level of Evidence	Study Design	Location	Dates of Enrol-ment	Characteristics of Study Population		
Geddes et al 2000[27]	II	Randomised controlled trial	UK	April 1996 to Feb 1999	I=24 C=24	I=62 (56-67)[a] C=60 (53-69)[a]	I=7:17 C=18:6
Licker et al 1998[28]	III-3	Comparative study with historical controls	Switzerland	I=1996 C=1993	I=17 C=14	I=62 (7)[b] C=51 (4)[b]	I=7:10 C=8:5

* Abbreviations: I = intervention group; C = comparison group; M = male; F = female

[a] Median (interquartile range); [b]Mean (standard deviation)

Table 6 Quality of published systematic reviews

Heading	Descriptor	ASERNIP-S[2]	Young[19]	AHFMR[20]	AHCPR[21]	HTAC[22]
Title	**Identify the report as a systematic review**	+	-	-	-	-
Abstract	Use of a structured format	No Abstract Available	+	+	-	No Abstract Available
	Explicit description of clinical question		+	-	+	
	Description of databases and other information sources		-	-	-	
	Description of selection criteria		-	-	-	
	Description of methods for validity assessment		-	-	-	
	Description of methods for data abstraction		-	-	-	
	Description of study characteristics		+	-	-	
	Description of quantitative data synthesis		-	-	-	
	Description of characteristics of included and excluded studies		-	-	-	
	Description of quantitative findings		+	-	+	
	Description of qualitative findings		+	-	+	
	Description of results of subgroup analysis		+	NA	NA	
Introduction	Explicit description of clinical problem	+	+	+	+	+
	Explicit description of biological rationale for intervention	+	+	+	+	+
	Explicit description of rationale for review	+	+	-	+	+

Table 6 cont. Quality of published systematic reviews

Heading	Descriptor	ASERNIP-S[2]	Young[19]	AHFMR[20]	AHCPR[21]	HTAC[22]
Methods	Detailed description of info. sources	+	+	+	-	-
	Detailed description of restrictions on searching	+	+	-	-	-
	Description of inclusion and exclusion criteria	+	+	-	-	-
	Description of criteria and process used for validity assessment	+	+	-	-	-
	Description of processes used for data abstraction	-	+	-	-	-
	Description of study characteristics included	+	+	+	+	-
	Description of methods of assessment of clinical heterogeneity	-	+	-	-	-
	Description of principal measures of effect	-	-	-	-	-
	Description of methods of combining results	NA	NA	NA	NA	NA
	Description of methods used to handle missing data	-	-	-	-	-
	Description of methods of assessment of statistical heterogeneity	NA	NA	NA	NA	NA
	Description of rationale for *a priori* sensitivity testing and subgroup analysis	NA	NA	NA	NA	NA
	Description of methods to assess publication bias	-	+	-	-	-
Results	Description: profile of trial flow	-	+	-	-	-
	Presentation of descriptive data for each trial	+	+	+	-	-
	Report of agreement on the selection of studies	-	+	-	-	-
	Report of agreement on validity assessment	-	-	-	-	-
	Presentation of simple summary results	-	+	+	-	-
	Presentation of data needed to calculate effect sizes and confidence intervals	-	+	+	-	-
Discussion	Summarisation of key findings	+	+	+	+	+
	Discussion of clinical inferences based on internal and external validity	+	+	+	+	+
	Interpretation of the results in the light of the totality of available evidence	+	+	+	+	+
	Description of potential biases in the review process	-	+	+	-	-
	Suggestions for future research agenda	+	+	-	+	+

Study quality

The randomisation of patients in the RCT[27] was conducted by an independent institute (the Clinical Trials Unit, Institute of Cancer Research, England) and is judged to be satisfactory, although specific details of their methods are not provided. The comparative study[28] with historical controls retrospectively assessed LVRS and lung transplantation (LT) in selected patients. Lung transplant data were extracted from 1993 onwards while LVRS data were collected from 1996 forward. Time, in addition to the procedures, may have had an impact on differences in patients' outcomes. Also, LVRS and LT patients were not matched for confounding factors which might have resulted in significant differences between the groups for age and some aspects of lung function at baseline. Adjustment for potential confounders that could potentially affect the validity of these results was not performed by the authors. Table 7 outlines the methodological quality of these studies.

Table 7 Methodological quality of included studies evaluating the effectiveness of LVRS.*

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Geddes et al 2000[27]	RCT	Yes	Unclear	At 3 months: I=21%;C=4% At 6 months: I=21%; C=4% At 12 months: I=46%,C=21%s
Licker et al 1998[28]	Comparative study with historical controls	No	No	No losses

*Abbreviations: = RCT = randomised controlled trial, I = intervention group, C = comparison group;

Patient criteria

In the RCT[27], 48 study patients were recruited from 174 people referred by specialist pulmonary physicians for consideration as candidates for LVRS. Reasons for patient exclusion were: low results on lung function/walking distance test (n=78), refusal to take part in the study (n=32), other lung disease (n=8), continued smoking (n=5) and geographic or other reasons (n=3).

In the non-randomised comparative study, no details of the source from which patients were initially chosen are presented. As a result, the extent to which the results of these patients can be generalised to other patient populations is unknown. In addition, the inclusion and exclusion criteria were different between the treatment arms which is an indication that the patient populations were different.

Table 8 provides the patient inclusion and exclusion criteria for each of the reviewed studies.

Table 8 Patient criteria of included studies evaluating the effectiveness of LVRS.*

First Author and Year of Publication	Patient Criteria
Geddes et al 2000[27]	Inclusion: severe emphysema as shown on computed tomography, age <75 years, FEV_1 >500ml, use of oxygen for <18 hours/day, corticosteroid dose <10 mg/day, partial pressure of arterial carbon dioxide <45 mmHg. Exclusion: patients with asthma, previous thoracic surgery or other serious medical conditions. ***Exclusion criteria were changed (after the deaths of 5 of 15 enrolled patients) to also exclude patients with carbon monoxide gas transfer <30% of predicted value or shuttle-walking distance of less than 150 metres.
Licker et al 1998[28]	LT inclusion: respiratory insufficiency ($VEMS_1$,25%, DL_{CO} <20%), resting hypoxemia, unable to perform minor activities. LVRS inclusion: age <75, emphysema, dyspnea resistant to medical treatments, severely restricted in performing daily activities, stopped smoking, maximum of =15 mg/day corticotherapy, measures of pulmonary lung function: FEV_1=35%, residual volume >150%, emphysema diagnosed on CT-scan, scintigraphy, consent to participate in the respiratory rehabilitation program, acceptance of risk. LVRS exclusion: chronic hypercapnia ($PaCO_2$ >7kPa), DL_{CO}<20%, pulmonary artery hypertension (average PAP>35mmHg), significant co-morbidity (coronary pathology, cardiac, renal or hepatic insufficiency), major involvement of air routes, previous thoracic surgery

* Abbreviations: LVRS = lung volume reduction surgery, LT = lung transplantation, FEV_a = forced expiratory volume in one second

Interventions examined

The two studies described in detail the treatment regimens to which patients were exposed. In the RCT both groups of patients underwent medical treatment and six weeks of outpatient rehabilitation after which they were reassessed for suitability and randomly assigned to either LVRS or continued medical treatment. It is unclear, however, what type of continued medical treatment was offered to patients not assigned to LVRS and thus the potential exists for LVRS to appear to be more effective if the type of medical treatment was not optimal. Table 9 outlines the treatment protocols of the two included studies.

Table 9 Therapeutic protocols used in intervention and comparison groups of included studies evaluating the effectiveness of LVRS.*

First Author and Year of Publication	Intervention Group	Comparison Group
Geddes et al 2000[27]	n=24[t]: LVRS - bilateral lung resection through median sternotomy or thoracoscopy	n=24: Medical treatment - no specific details, individualised to patients' requirements
Licker et al 1998[28]	n=17: LVRS through thoracoscopy	n=14; LT - unilateral by thoracotomy, or bilateral by sternothoracotomy.

* Abbreviations: LVRS = lung volume reduction surgery, LT = lung transplantation, n = sample size

t 24 randomised but one patient withdrew after randomisation

Review of published clinical experience

LVRS compared to medical therapy

One randomised controlled trial compared LVRS to medical therapy. Improvement or deterioration from baseline in forced expiratory volume in one second (FEV_1), shuttle-walking distance and scores on the 36 item Short Form Questionnaire (SF-36) were measured at three, six and 12 months post-surgery or post-randomisation in patients continuing on medical therapy. However, adequate follow-up (>80%) was not achieved. The12 months follow-up results included data from only 54 percent of patients in the LVRS arm and 79 percent in the medical arm. Outcome data describing changes from baseline were presented graphically so it was not possible to tabulate all the results here.

Thus, the following results are limited to only selected outcome data that were reported numerically. Additional results are presented in Table 10.

FEV_1: At six months follow-up, and compared to the control arm, patients who received LVRS had significantly improved FEV_1 median scores (-80 ml versus +70 ml, p=0.02). By 12 months, however, this improvement had not been maintained and values were no longer significantly different from those in the control arm. Median FEV_1 values declined throughout the 12 month period in control patients.

Shuttle-walking distance: At six months follow-up, compared to controls, patients who received LVRS had significantly improved shuttle-walking distances (-20 metres versus +50 metres, p=0.02). By 12 months the improvement had declined. However, it remained significantly higher than for patients on medical therapy, whose distances decreased throughout the follow-up period.

36-Item Short-form Questionnaire (SF-36) scores: At six months follow-up, compared to controls, patients who received LVRS had higher SF-36 scores (-12 versus +22, p=0.003). This improvement continued to be maintained at 12 months follow-up. The SF-36 scores of control patients steadily declined over the 12 month period.

Five of 19 (26%) surviving patients showed no benefit from LVRS. In addition, mortality was higher in the LVRS group (n=5 versus n=3) and, while the difference was not significant, the study did not have sufficient power to detect a 10 percent difference.

LVRS compared to lung transplantation

One non-randomised comparative study compared LVRS to lung transplantation[30]. The authors state that, at six months follow-up, there was a significantly greater improvement in FEV_1 in patients who had received LT than in patients who received LVRS (200% increase versus 63%). Since outcome data was only reported as a comparison to baseline within *and not between* treatment arms, it was not possible to compare the effectiveness of LVRS to lung transplantation.

LVRS was more effective than LT only in terms of post-operative outcomes. The study reported significantly greater improvements in patients who had undergone LVRS compared to LT with regard to: requiring mechanical ventilation (one patient versus 12 patients, p<0.05); days in the intensive care unit (median =5, range 2-11 versus median=12, range 6-19, p<0.05); and days in hospital (median=37 days, range 25-60 versus median=19 days, range 11-40, p<0.05). However, patients who received LVRS required more days of thoracic drainage than those in the LT group (median=4, range 1-8 versus median=11, range 5-43)[30]. Complications would appear to be more frequent in LT patients, although these results were not statistically assessed. These and additional results are presented in Table 10.

Australian data on the effectiveness of LVRS

Two Australian-based studies have published results of LVRS performed in 70 patients with severe emphysema: Porter, Ruffin *et al* [31] (sample size = 50) and Snell, Solin & Chin[32] (sample size = 20). Both studies compared lung function and exercise performance before and after LVRS in a series of patients and concluded that improvements resulted from LVRS. However, the lack of a control group of patients, in addition to not being randomised, significantly limits the validity of the findings of these studies. Since there exists more rigorous evidence from controlled studies of Geddes et al 2000 and Licker,

de Perrot *et al*, both of which corroborate the results of the Australian studies, evaluation of the effectiveness of LVRS is confined to these trials[31, 32].

Long-term effectiveness of LVRS

The ASERNIP-S review reports long-term effectiveness at 12 and 24 months based on the results of the study by Meyers, Yusen *et al*[33]. In this study, comparison groups were comprised of a control group of 22 patients suitable for, but denied, LVRS due to a change in Medicare coverage, and a group of 65 patients who underwent LVRS. Physiological criteria of the two groups were stated to be well-matched. At 12 months, 100 percent of control patients and 78 percent of patients who underwent LVRS provided follow-up data. At 24 months, 77 percent of control patients and 69 percent of LVRS patients provided follow-up data. FEV_1 was significantly higher in LVRS patients than in the control group at both follow-up assessments. Survival of patients with and without LVRS was compared at one, two and three years. The survival for non-LVRS patients was 100 percent at 12 months. This study was not included in the University of Birmingham review where long-term effectiveness was based on results of case series only.

Six months of follow-up is the longest time period for which 100 percent of enrolled LVRS and control patients have outcome measures reported in the three trials (Geddes et al 2000[27], Criner, Cordova *et al* [26], & Licker, de Perrot *et al* [28]) published subsequent to the reviews by ASERNIP-S and the University of Birmingham. In the RCT reported by Geddes et al, baseline measures of lung function and performance were compared with outcomes at three, six and 12 months. At 12 months, outcomes were compared for 54 percent (13 of 24 patients) of LVRS patients and 79 percent (19 of 24 patients) of medical patients. Compared to medical patients, LVRS patients had significantly greater changes from baseline in SF-36 scores. However, there were no significant differences in median changes in shuttle-walking difference and FEV_1. Failure to detect a difference may be due to an inadequate sample size at 12 months. Since the proportion of patients who achieved a 30 percent difference in FEV_1 (the amount set as the benchmark for the trial) is not provided, this can not be tested. Similarly, the lack of data on proportions of patients who had important levels of improvements in shuttle-walking distance and SF-36 scores also limits the inferences about expected long-term effectiveness. Changes in shuttle-walking distance and FEV_1 among LVRS patients declined over the follow-up period, while SF-36 scores remained relatively constant after six months. The authors state that "the rate of decline in lung function after randomization was similar in the two groups, with a yearly decrease of 100 ml in FEV_1. This result suggests that surgery produced a one-time benefit but did not modify the subsequent natural history of the disease".

Criner, Cordova *et al* [26] report the results of an RCT but compared outcomes for LVRS and medical patients at three months on a pre-post basis only with no between-group comparisons. Thus, this study does not provide comparative results of effectiveness between alternative treatments. In the controlled trial of Licker, de Perrot *et al* [28], at six months the degree of improvement in FEV_1 was significantly greater in LT patients than in LVRS patients (200% increase versus 63%). Although authors stated that patients were followed for 24 months, no additional data on outcome measures of effectiveness were presented.

Randomised controlled trials of LVRS currently underway

Authors or coordinators of randomised controlled trials identified by the searching protocol (refer Approach to Assessment) were emailed or faxed and asked to clarify whether their trials were underway and to provide recent data if possible. Nine trials purported to be randomised controlled trials that are currently recruiting or following patients randomised to either LVRS or standard medical treatment. Four trials were subsequently excluded because the clarification provided reflected four case series and not randomised controlled trials. Not all authors/coordinators responded to our request for clarification and recent data. The most recent data are provided in Table 11.

The reader should be aware that these randomised controlled trials cannot be evaluated since data are neither available nor published. A number of caveats exist concerning these on-going randomised controlled trials:

- The NETT trial[34] (USA) has reduced its target number of patients from 4,700 (based on the numbers that the investigators thought would be referred to the NETT trial) to 2,500 (based on statistical power);

- No confirmatory feedback has been received from two of the trials (OBEST[35] and VOLREM[36]), although all information identified supports the trial design as randomised controlled trials,

- The OBEST trial[35] is being conducted by a Health Maintenance Organization in the USA (BlueCross/BlueShield). No information is expected to be made available from this trial;

- The VOLREM trial[36] is a multi-centre randomised controlled trial. The coordinator, Professor Löfdahl at the University of Lund, is soon expected to publish preliminary data (personal correspondence from a colleague of Professor Löfdahl); and

- There is some inconsistency in the surgical methodology between the different trials.

Summary of clinical experience from on-going randomised controlled trials

These trials are large, properly designed and appear to be methodologically rigorous. However, no data have yet been released from these trials. Results are expected to become available within the next two years.

Table 10 Critical appraisal of the published controlled trials

First Author, Date	Location	Patient Population Inclusion & Exclusion Criteria	Age	Sex ratio (M:F)	n	Intervention	Comparison
Geddes et al 2000[27]	USA	Inclusion: severe emphysema as shown on computed tomography, age <75 years, FEVs >500ml, use of oxygen for <18 hours/day, corticosteroid dose <10 mg/day, partial pressure of arterial carbon dioxide <45 mmHg. Exclusion: patients with asthma, previous thoracic surgery or other serious medical conditions. Exclusion criteria were changed (after the deaths of 5 of 15 enrolled patients) to exclude patients with carbon monoxide gas transfer <30% predicted value or shuttle-walking distance of < 150 metres.	LVRS, median (interquartile range): 62 (56-67) Medical, median (interquartile range): 60 (53-69)	All: 35:13 LVRS: 17:7 Medical: 18:6	n=48 LVRS:24 (including 1 patient who refused surgery) LVRS: 24	LVRS- bilateral, through median sternotomy or by thoracoscopy.	Continued medical treatment: not clearly described, individualised to patient requirements
Licker et al 1998[28]	Switzerland	Lung Transplantation (LT) inclusion: respiratory insufficiency ($VEMS_1$,25%, DL_{CO} <20%), resting hypoxemia, unable to perform minor activities. LVRS inclusion: age <75, emphysema, dyspnea resistant to medical treatments, severely restricted in performing daily activities, stopped smoking, maximum of =15 mg/day corticotherapy, measures of pulmonary lung function: FEV_1 =35%, residual volume >150%, emphysema diagnosed on CT-scan, scintigraphy, consent to participate in the respiratory rehabilitation program, acceptance of risk. LVRS exclusion: chronic hypercapnia ($PaCO_2$ >7kPa), DL_{CO}<20%, pulmonary artery hypertension (average PAP>35mmHg), significant co-morbidity (coronary pathology, cardiac, renal or hepatic insufficiency), major involvement of air routes, previous thoracic surgery	*LVRS* mean (SD): 62 (7) *LT* mean (SD): 51 (4)	All: 15:15 LVRS: 7:10 LT: 8:5	n=30 LVRS: 17 LT: 14	LVRS (thoracotomy)	Lung transplantation (unilateral by thoracotomy, *or* bilateral by sternothoracotomy

First Author Date	Quality					Results
	Concealment of allocation	Random -isation	Inclusion of randomised participants	Masking	Loss to Follow-up	Outcomes
Geddes et al 2000[27]	Unclear	Yes	Yes	No	At 3 months: LVRS: 21% Medical: 4% At 6 months: LVRS: 21% Medical: 4% At 12 months: LVRS: 46% Medical: 21%	At 3 months: *FEV_1 median change from baseline: LVRS vs medical*: graphed data only - increased from baseline vs decreased since baseline, p=0.02 *Shuttle-walking distance, median change from baseline: LVRS vs medical*: graphed data only – increased from baseline vs decreased from baseline, p=0.10 *Short form 36 scores, median change from baseline: LVRS vs medical*: graphed data only - increased from baseline vs decreased from baseline, p=0.18 At 6 months: *FEV_1 median change from baseline: LVRS vs medical*: increased by 70 ml vs decreased by 80 ml, p=0.02, Shuttle-walking distance, median change from baseline: LVRS vs medical: increased by 50 metres vs decreased by 20 metres, p=0.02. Short form 36 scores, median change from baseline: LVRS vs medical: increased by 22 points versus decreased by 12 points, p=0.003. At 12 months: *FEV_1 median change from baseline: LVRS vs medical*: graphed data only-increased from baseline vs decreased from baseline, p=0.07 *Shuttle-walking distance, median change from baseline: LVRS vs medical*: graphed data only-increased from baseline vs decreased from baseline, p=0.05. *Short form 36 scores, median change from baseline: LVRS vs medical*: graphed data only- increased from baseline vs decrease from baseline, p=0.01 Hospital stay: days: LVRS vs medical, mean (range): 19 days (8-64) vs 0. <u>Complications:</u> LVRS vs medical, n (%): 5 (21) vs 3 (12), p>0.05

First Author Date	Quality					Results
	Concealment of allocation	Random-isation	Inclusion of randomised participants	Masking	Loss to Follow-up	Outcomes
Licker et al 1998[28]	No	No	Not applicable	No	None	Lung function and capacity: no comparison data between LVRS and LT were reported. Only pre-post (at 5-6 months post-operative) data were provided. Post-operative outcomes (LVRS vs LT): Mechanical ventilation (n pts): 1 vs 12, p<0.05 Days thoracic drainage: Median (min-max): 11 (5-43) vs 4 (1-8) Days ICU or recovery: median (min-max): 5 (2-11) vs 12 (6-19), p<0.05 Days in hospital: median (min-max): 19 (11-40) vs 37 (25-60) P<0.05 Complications: Re-operation: 2 vs 3; Lung infection: 1 vs 5; Rejection: n/a vs 4 (3 deaths)

Table 11 Update of identified multi-centre, randomised controlled trials currently underway examining the effectiveness of LVRS for emphysema or COPD compared with standard medical therapy

Trial	Start	Finish	Target Number of Patients	Patients Screened	Patients Randomised	LVRS Methodology	Control Group	Outcomes	Date of Latest Update
NETT[34] (USA)	1998	2004	2500	2136	624	2 arms: Bilateral VATS & median sternotomy	Standard medical therapy	Not yet available	11/1/2000
CLVR[37] (Canada)	1997	?	350	350	45	1 arm: Bilateral median sternotomy	Standard medical therapy	Not yet available	10/2/2000
OBEST[35] (USA)	?	3 years	220	?	?	1 arm: Bilateral VATS or median sternotomy	Standard medical therapy	?	1999
Lomas et al.[38] (UK)	1999	2002/3	120	?	2	?	Standard medical therapy	Not yet available	28/1/2000
VOLREM[36] (Sweden)	?	?	?	?	?	?	?	?	15/2/2000

What are the economic considerations?

Review of the literature

Nineteen studies were initially identified as containing cost data for LVRS. On the basis of information published in the abstracts, only four of these were retrieved. In addition, the University of Birmingham review modelled the cost-effectiveness of LVRS[39]. An assessment of this modelled cost-utility analysis and other cost studies has been undertaken. As part of that assessment, an attempt to assess the usefulness of converting the UK modelled cost effectiveness analysis was made to provide an estimate of the potential cost-effectiveness of LVRS in the Australian context.

Summary

The study by Young, Fry-Smith *et al*[39] is a decision analytic cost-utility analysis of LVRS compared to standard medical management. Over a model duration of two years, the average cost of LVRS in the UK was found to be £13,041 and that of medical management £8,896. Thus, they estimated that LVRS could result in average additional costs of £4,145 per patient over medical management. The estimated additional cost per QALY (using the EQ-5D [40]to measure utility) was £9,211.

Mortality

In the UK modelled cost effectiveness analysis, 97 percent of LVRS patients (3% early mortality rate) remain in the model beyond 30 days and faced a risk of late mortality of 10 percent over two years (annual mortality of 5%). All patients on medical management were assumed to face a risk of late mortality of 40 percent over two years (annual 20%), derived from studies of the natural history and prognosis of COPD. The probability of early death for patients not undergoing LVRS was assumed to be zero. The clinical evidence reviewed above does not support these assumptions. Rather it is more reasonable to state that, at this stage, it is not possible to determine whether LVRS has any long-term impact on survival.

Although differences in quality-adjusted life years (QALYs) depend on these mortality rates, the cost per QALY from the UK model was found to increase as the late mortality rate for patients not undergoing LVRS increases, ie increasing the late mortality rate for patients on medical management resulted in less QALYs (higher incremental QALYs compared to LVRS), but also resulted in lower costs for patients on medical management as fewer patients survive for an additional year and incur less costs, eg medical management and pulmonary rehabilitation (hence higher incremental costs compared to LVRS). The effect on costs outweighed the effect on QALYs resulting in higher costs per QALY as the mortality rate for patients on medical management increased.

Improvement in Quality of Life (QoL)

The University of Birmingham review discussed a number of observational studies that collected quality of life data before and after the procedure, potentially suitable for inclusion in a cost utility analysis, but only three of these used specific measurement tools and none used a utility measure. All studies have limitations, are uncontrolled and therefore only offer fair levels of evidence.[7, 38, 41-43]

None of the evaluations of LVRS identified in the review measured health-related quality of life using a generic measure that would allow the direct calculation of QALYs. Utilities for LVRS were estimated in the Birmingham evaluation. The main source for the QoL values was unpublished data from a small pilot study of the effectiveness of LVRS that collected QoL data using the EQ-5D instrument.[21] The results suggested that typical candidates for the operation have a starting EQ-5D of around 0.37 and a post-operative EQ-5D of between 0.64 and 0.88. Given the limitations of this pilot study and additional supporting information obtained from other relevant material, the point estimates for EQ-5D were taken by the UK model as 0.40 pre-operatively and 0.70 post-operatively. Patients who became worse, either post-operatively or through general deterioration, were assigned a utility score of 0.30. Given the way in which these values were established, there must be considerable doubt about the validity of the utility values for the health states in the analysis.

Index of Health-related Quality of Life (IHQL)

The Birmingham study performed a sensitivity analysis using estimates of QoL from another instrument (the IHQL[44]). The estimates of QoL 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. The three dimensional classification, based on knowledge about patients before and after LVRS and obtained from descriptions in the literature and informal discussion with and observation of individual cases, were used to estimate the IHQL. The key source was a review of LVRS which described patients who, pre-operatively, were dependent on others for all activities of daily living, the majority of whom required continuous supplemental oxygen[45].

The information within the included studies for dyspnoea was used as indicators for improvements in QoL after the intervention. The information suggested that, post-operatively, the majority of patients would be able to handle their own activities of daily living, get out and about more easily and even undertake light jobs around the house and garden. Hence, the UK model used a disability dimension score of six pre-operation and four post-operation. A pre-operative population was described in the study as being unable to shower or bathe, get dressed alone or leave the house without great difficulty[46]. A patient in a similar pre-operative state described troublesome pain and stiffness in his limbs and chest[23]. One year post-operatively he was able to perform all his own activities of daily living. Hence, the Birmingham modelled analysis used a discomfort (physical) dimension score of 3 pre-operation and 2 post-operation. The relationship between anxiety and depression and COPD is well-documented[45]. The model used a distress (emotional) dimension score of 3 pre-operation and 2 post-operation.

Using the IHQL three dimensional classification, scores for typical health states for 'baseline', 'improved', and 'deteriorated' patients were estimated to be 0.648, 0.861, and 0.498, respectively. Hence, in sensitivity analysis using the IHQL classification, the UK model assigned a typical pre-operative patient a score of 0.65, a typical post-operative patient a score of 0.86 and a patient who deteriorated a score of 0.50.

The total expected QALYs for LVRS were 1.45, while the total expected QALYs for medical management are 1.04. This represents a gain of 0.41 QALYs for LVRS. This meant that the additional cost per QALY gained of £10,362 based on the IHQL was fairly close to the cost per QALY of £9,211 generated by the EQ-5D. Hence, this

sensitivity analysis based on the IHQL shows the cost per QALY is relatively insensitive to changes in utility values for each of the health states.

The natural history of COPD is such that all patients not undergoing LVRS will continue to decline making the probability of improvement zero. Estimates for the probabilities of improvement in quality of life for LVRS patients were obtained from studies that measured subjective improvement in some way and from objective data on supplemental oxygen use. Of the LVRS patients surviving, 70 percent were assumed to have an improvement in quality of life. This is based on 80 percent of people feeling significantly better after the operation, from those studies that measured subjective improvement in some way. Around 66 percent of those requiring oxygen, either on exertion or continuously, did not require it after LVRS[28]. The figure of 70 percent is therefore not well validated and is subject to considerable uncertainty. It is unclear whether the Birmingham modelled cost effectiveness study performed a sensitivity analysis around this estimate of 70 percent; for this report their model was reproduced and this parameter was varied. The results are shown in Table 12.

Table 12 Cost per QALY versus probability of improvement in QoL for LVRS patients

Probability of improvement in QoL – LVRS patients	Cost per QALY (£)
0	£65,149 / QALY
0.6	£11,208 / QALY
0.8	£ 7,612 / QALY
1	£ 5,214 / QALY

Table 12 suggests that the incremental cost per QALY is very sensitive to the probability of a (substantial) improvement in the quality of life after the procedure. Even a potentially large improvement in quality of life comes at a high cost per QALY if there is less than a 60 percent chance of that improvement.

Costs

The costs used in the Birmingham cost-utility analysis were estimated using information from available research and validated by local clinical experts. Key sources included local provider and health authority data, relevant guidelines for the management of patients with COPD and expert opinion.

The main cost components used in the cost-utility analysis were:

- cost of the intervention (ie LVRS);
- costs of medical management including drug costs and oxygen requirements;
- costs of emergency admission; and
- costs of pulmonary rehabilitation.

Conversion into Australian dollars

The question is: What would the resources used in the UK for the procedure cost in Australian dollars if performed in Australia (assuming the same physical resources were used)? This is not straightforward since it depends on the relative value of health resources compared to other commodities purchased in each country. As one means of

conversion, the relative proportion of total health expenditure as a proportion of GDP (gross domestic product) was used to approximate the cost components in terms of relative cost in Australia, and was then converted into Australian dollars at purchasing power parity (PPP). This is in principle more accurate than a straight financial exchange rate. The converted costs are presented in Table 13. Although Australian data are available for some of the individual cost components in the UK model, Australian costs of the larger cost components, such as LVRS, oxygen use and pulmonary rehabilitation, have not been collected. As a result, a common conversion factor was consistently applied to all costs.

Total health expenditure as a proportion of GDP in Australia is 8.6 percent[45]. Health expenditure as a proportion of GDP in the UK is 6.9 percent. Hence, an estimate of the relative health costs for Australia:UK is 8.6:6.9 (relative index of 1.25 is used to convert UK health costs to costs in Australia). In other words if Australian resource intensity were used in the UK it would cost 1.25 times more.

The PPP for GDP for Australia:UK is 1.31:0.664[46]. Hence, the UK health costs are multiplied by 1.97 to convert into Australian dollars. Therefore, to convert the costs in the UK model to Australian dollars, the costs are multiplied: 1.25 x 1.97 = 2.46. This approach assumes a constant relationship between health care expenditure and GDP, and may be an overestimate as the OECD health PPP for 1996 suggests a factor of 2.1. On the other hand the financial exchange rate at the beginning of 2001 was closer to 2.7.

Table 13: Individual unit costs converted into Australian dollars by multiplying by a conversion factor of 2.46

Intervention		
Lung Volume Reduction Surgery	total per case	$15,246
District nurse	daily visit for 2 weeks	$ 1,205
Total intervention costs		$16,450
Pulmonary Rehabilitation Costs	per 8 week course	$ 1,229
Emergency Admission (at 1 per year)		
GP visit	1 @ $73.77	$74
Ambulance transfer	1 @ $400.81	$401
A/E attendance	1 @ $437.70	$438
Inpatient days	10 @ $479.50	$ 4,795
Total emergency admission costs		**$ 5,707**
Maximum Medical Management (all over 1 year)		
Drug Costs		
Ventolin inhaler	2 per month @ $5.66	$ 136
Atrovent inhaler	2 per month @ $10.35	$ 248
Phyllocontin Continus	2 per month @ $8.09	$ 194
Becloforte inhaler	2 per month @ $56.80	$1,363
Serevent inhaler	2 per month @ $70.33	$1,688
Total Drug Costs		**$3,629**
Other medical management costs (all over 1 year)		
Oxygen concentrator	15 hours per day	$ 1,967
GP visits	1 per month @ $73.77 each	885
Outpatient appointment	2 per year @ $127.87 each	$ 256
Total maximum medical management costs		**$6,738**

Relevance of UK modelled costs to Australia

The cost of LVRS in Australia is uncertain. Generally, one-day ICU stays and an average of 8-18 days of hospitalisation are expected after the operation (estimated to cost around $4,000). Hence, converting the cost of LVRS in the UK to Australian dollars ($15,246 in Table 13) may result in an overestimate of the costs of LVRS. Young, Fry-Smith & Hyde[39] did not provide a breakdown of cost components for the estimated £6,200 cost for LVRS, so it is difficult to cost out the individual components of LVRS to estimate an Australian cost for the LVRS procedure.

Emergency admission

Patients who did not improve or who died were assumed to have had one emergency admission per year, excluding the year of surgery for LVRS patients. Patients who died late were assumed not to have experienced an improvement in their condition. The cost of an emergency admission in Australia may be reasonably approximated to $5,707 (Table 13). The cost of a GP visit in UK converted into Australian dollars is an overestimate of the actual cost of a GP visit in Australia (estimated to be around three times less). The cost of ambulance transfer in UK converted into Australian dollars is also expected to be an overestimate. The cost of the inpatient care (10 days) is the largest cost component of an emergency admission. The cost per inpatient day in UK converted into Australian dollars appears reasonable. Hence, the total costs of an emergency admission in UK, converted into Australian dollars ($5,707), may be a reasonable approximation, if not a slight overestimate, of the total cost.

Medical Management

The total maximum medical management costs can be converted into $6,738. It is uncertain how comparable the drug costs in the UK are to actual Australian costs. The costs of Ventolin and Atrovent inhalers in UK converted into Australian dollars appear to be underestimated (compared to the costs of Ventolin nebules and Atrovent on the PBS), while the costs of Becloforte and Serevent inhalers in UK converted into Australian dollars appear to be overestimated (compared to the costs of Becloforte and Serevent on the PBS). The total drug costs as part of maximum medical management, calculated to be $3,629, may be a reasonable approximation to actual Australian costs. The UK group[20] estimated the costs of reduced medical management for patients for whom the intervention resulted in an improvement in symptoms as the costs of maximum medical management minus 50 percent use of steroids and supplemental oxygen, which converts to $4,820 (multiplying the cost by 2.46 to convert into Australian dollars). It is uncertain how comparable the costs of pulmonary rehabilitation and oxygen used in the analysis by the UK group are to actual Australian costs.

Other Cost Studies

The cost studies identified found costs for LVRS around US$20,000 in the United States. At the University of Washington, Seattle, the median charge for LVRS was US$26,669 (range, US$20,032 to US$75,561), of which 73 percent (US$19,592) was for medical centre services and 27 percent (US$6,373) was for physician services. This is based on 23 patients undergoing LVRS at an institution in the United States with a median length of stay of eight days[47]. A study by Elpern in the USA, found that hospital costs per case ranged from US$11,712 to US$121,829, with mean costs of US$30,976 and median costs of US$19,771 based on 52 patients receiving bilateral LVRS at a medical centre with a median hospital stay of 10 days[48]. The average Medicare reimbursement per LVRS procedure was US$31,398 for Medicare enrollees from 1994 to 1996[49], and the average

total hospital costs and charges were US$27,178 for video-assisted thoracoscopy (VATS) and US$37,299 for sternotomy. These data are based on 42 patients with severe emphysema undergoing LVRS (19 via sternotomy and 23 via thoracoscopy) from 1995 to 1997 at one institution by a single surgeon.[50]

These costs of around US$20,000 - $30,000 could be compared to the estimated intervention cost of $16,450 in Table 13. It is unclear whether medical centre charges or hospital charges identified in the US studies include pulmonary rehabilitation costs and other costs for medical management and emergency admission, but it appears that the hospital charges in these studies do not include costs other than intervention costs (ie comparable to the total LVRS intervention costs consisting of LVRS and district nursing costs in Table 13).

The question is what would the resources used in the US for the procedure cost in Australian dollars if performed in Australia (assuming that the same physical resources were used). This is not straightforward since it depends on the relative value of health resources in each country compared to other commodities purchased in each country. Australia's total health expenditure as a proportion of GDP is 8.6 percent.. The US' health expenditure as a proportion of GDP is 13.6 percent. Hence, a crude estimate of the relative cost of health care (adjusted for the general cost of living) for Australia:US is 8.6:13.6 (relative index of 0.63 is used to convert US health costs to costs in Australia). The PPP for GDP for Australia:US is 1.31[51]. US health costs are multiplied by 1.31 to convert into the cost facing the Australian community in terms of its purchasing power. Therefore, to convert Australian costs to US dollars, the costs are divided by (0.63 X 1.31 = 0.83) or multiplied by 1.21 (this is close to the OECD health PPP index for 1996 of 0.86). LVRS intervention costs in Table 13 (A$16,450) are converted into US$19,858, which is close to the lower end of the range of US$20,000 identified from the LVRS US cost studies in the literature,[47, 48] but lower than the upper end of the range of around US$30,000 from the other US cost studies.[49, 50]

Results of preliminary Australian cost-utility analysis

A preliminary Australian cost per QALY can be estimated by converting the UK costs in Table 13 to Australian dollars. The expected cost for LVRS is $32,066 (total intervention costs of $16,725 represent half of these total costs). The expected total cost of managing a patient who did not undergo LVRS is estimated at $21,878. This represents an additional cost for LVRS of $10,188. If the assumption of a significant gain in both quality of life as measured by the EQ-5D and survival is accepted, the incremental cost per extra QALY would be $22,640. However as noted above while there is some preliminary evidence of an improvement in the quality of life associated with LVRS compared to medical management there is no high quality evidence of a gain in survival. Moreover the evidence on the extent and value of the quality of life improvement is not of a high quality.

Conclusions

Safety

Safety data on mortality and morbidity differ widely as LVRS encompasses many surgical techniques and surgeon experience differs between centres. The interquartile range (IQR) for early mortality (defined as hospital deaths or deaths occurring within 30 days of surgery) was zero to six percent, while the IQR for late mortality (defined as deaths occurring in the hospital or more than 30 days after surgery) at 3-6 months was zero to eight percent. Late mortality at two years was estimated as between zero and three percent[4].

Effectiveness

All published systematic reviews recommend waiting for results from on-going randomised controlled trials that will better inform claims of clinical effectiveness.

Preliminary data from the randomised controlled trials is only beginning to be published now. Twelve months of outcome data is currently available on only 19 LVRS patients in the study by Geddes et al 2000[27] and at this stage does not confirm a sustained advantage of LVRS over standard medical therapy with respect to mortality or lung function. LVRS does, however, appear to improve quality of life.

At this point there is no RCT evidence to determine whether LVRS is clinically effective in the longer term. The recently published study by Geddes, although small, shows a downward trend in most patients' outcomes at 12 months.

Cost-effectiveness

There has been one published modelled cost effectiveness analysis of LVRS.[23] That study appears to have made a reasonable assessment of costs for LVRS and medical management in the UK which, if converted into Australian dollars, results in costs of $16,450 for the initial intervention. The cost is consistent with the magnitude of relative costs reported in US studies and is therefore likely to be a reasonable guide to the order of magnitude cost in Australia.

Based on a series of assumption on effectiveness, the UK study calculated an additional cost per QALY equivalent to $22,640. The estimated cost per QALY is dependent on the mortality rates, probability of improvement in QoL and utility values assumed in the UK study. Uncertainty exists around utility values (derived from unpublished data from a small pilot study) and the proportion of LVRS patients with an improvement in quality of life (derived from those studies which measured subjective improvement in some way and objective data on supplemental oxygen use).

It is questionable whether great emphasis can be placed on just one study given the uncertainty surrounding the effectiveness of LVRS in reducing mortality and improving quality of life and the applicability of medical practice in the UK to the Australian setting. However, when better evidence is available on effectiveness and the cost of care in Australia, the study will provide a framework for evaluation.

At this point in time, it is only possible to say that LVRS is likely to be an expensive procedure with a cost that could be in excess of $15,000 per patient. There is some evidence of an improvement in quality of life associated with the procedure compared to medical management but the evidence on any survival gain is weak. Therefore the information available does not allow us to calculate the likely cost effectiveness of LVRS.

Recommendations

MSAC recommended that on the strength of evidence relating to Lung Volume Reduction Surgery:

- public funding should not be supported for this procedure pending availability of overseas clinical trial data, which is expected in 2003;
- surgeons performing lung volume reduction surgery are advised to seek approval in principle to continue performing the procedure from their hospital ethics committee or equivalent;
- patients undergoing this procedure should be appropriately informed of the risks of lung volume reduction surgery; and
- the Australian Health Ministers' Advisory Council be advised of this decision.

The Minister for Health and Aged Care accepted this recommendation on 28 April 2001

Appendix A MSAC terms of reference and membership

The terms of reference of the Medical Services Advisory Committee are to advise the Commonwealth Minister for Health and Aged Care on:

- the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness; and
- references related either to new and/or existing medical technologies and procedures.

It also undertakes health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and reports its findings to the AHMAC.

The membership of the Medical Services Advisory Committee comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise**
Professor David Weedon (Chair)	Pathology
Ms Hilda Bastian	Consumer health issues
Dr Ross Blair	Vascular surgery (New Zealand)
Mr Stephen Blamey	General surgery
Dr Paul Hemming	General practice
Dr Terri Jackson	Health economics
Professor Brendon Kearney	Health administration and planning
Assoc. Professor Richard King	Internal medicine
Dr Michael Kitchener	Nuclear medicine
Professor Peter Phelan	Paediatrics
Dr David Robinson	Plastic surgery
Mr Alan Keith	Assistant Secretary of the Diagnostics and Technology Branch of the Commonwealth Department of Health and Aged Care
Professor John Simes	Clinical epidemiology and clinical trials
Dr Bryant Stokes	Neurological surgery, representing the Australian Health Ministers' Advisory Council (from1/1/99)

Appendix B Supporting committee

Supporting committee for MSAC application 1011
Lung volume reduction surgery for advanced emphysema

Dr Ross Blair (Chair) MbChB, RACS Vascular surgeon Director of Vacular Surgery Waikato Hospital, New Zealand	Member of MSAC
Dr Peter Adkins MBBS FRACGP General practitioner Birkdale, Queensland	Nominated by the Royal Australian College of General Practitioners
Dr Allan Glanville MBBS FRACP MD Respiratory physician Health and Lung Transplant Unit St Vincent's Hospital, Sydney	Co-opted member
Professor Guy Maddern MD MBBS PhD FRACS MS Abdominal surgeon Department of Surgery Queen Elizabeth II Hospital Adelaide	ASERNIP-S representative
Mr David Martin	Consumer representative
Professor Dick Ruffin BSc MBBS MRACP FRACP MD Respiratory medicine Queen Elizabeth II Hospital, Adelaide	Nominated by the Royal Australian College of Physicians and Thoracic Society of Australia & New Zealand
Mr Julian Smith MBBS MS FRACS FRACS (Card) Cardiothoracic surgeon Department of Cardiothroacic Surgery The Alfred Hospital, Melbourne	Nominated by the Royal Australian College of Surgeons

Appendix C Member organisations of INAHTA, the International Network of Agencies for Health Technology Assessment

AETS	Agencia de Evaluacion de Tecnologias Sanitarias	Spain
AETSA	Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia	Spain
AHFMR	Alberta Heritage Foundation for Medical Research	Canada
AHRQ	Agency for Healthcare Research and Quality	USA
ANAES	L'Agence Nationale d'Accreditation et d'Evaluation en Sante	France
ASERNIP/S	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical	Australia
CAHTA	Catalan Agency for Health Technology Assessment	Spain
CCOHTA	Canadian Coordinating Office for Health Technology Assessment	Canada
CEDIT	Comite d´ evaluation et de Diffusion des Innovations Technologiques	France
CETS	Conseil d'Evaluation des technologies de la sante	Canada
CVZ	College voor Zorgverzekeringen	Netherlands
DIHTA	Danish Institute for Health Technology Assessment	Denmark
DIMDI	German Institute for Medical Documentation and Information	Germany
DSI	Danish Institute for Health Services Research and Development	Denmark
ETESA	Unidad De Technologias de Salud	Chile
FINOHTA	Finnish Office for Health Care Technology Assessment	Finland
GR	Gezondheidsraad	Netherlands
UKHSC	UK Horizon Scanning Center	UK
ICTAHC	Israel Center for Technology Assessment in Health Care	Israel
INHEM	Instituto Higiene y Epidemiologia	Cuba
ITA	HTA-unit of the Institute of Technology Assessment	Austria
MSAC	Medical Services Advisory Committee	Australia
NCCHTA	UK National Coordinating Centre for Health Technology Assessment	UK
NHSCRD	NHS Centre for Reviews and Dissemination	UK
NZHTA	New Zealand Health Technology Assessment	New Zealand
OSTEBA	Basque Office for Health Technology Assessment Health Department	Spain

SBU	Swedish Council on Technology Assessment in Health Care	Sweden
MTS/SFOSS	Medical Technology Section, Swiss Federal Office of Social Security	Switzerland
SMM	Norwegian Centre for Health Technology Assessment	Norway
SSC/TA	Swiss Science Council/Technology Assessment	Switzerland
TNO	TNO Prevention and Health	Netherlands
VATAP	Veterans Affairs Technology Assessment Program	USA

Abbreviations

COPD	Chronic obstructive pulmonary disease
LVRS	Lung volume reduction surgery
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council

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