NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of insertion of endobronchial nitinol coils to improve lung function in emphysema

Emphysema is a progressive lung condition in which the small air sacs (alveoli) inside the lungs break down, resulting in abnormally large air spaces. These large spaces can compress surrounding airways and restrict the flow of air to healthy parts of the lung, making it difficult to breathe. Insertion of endobronchial nitinol coils aims to improve lung function by reducing the size of the diseased areas in the lungs, allowing air to reach healthy areas.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in April 2014 and updated in August 2014

Procedure name

- Insertion of endobronchial nitinol coils to improve lung function in emphysema

Specialist societies

- British Thoracic Society
- Society of Cardiothoracic Surgeons of Great Britain and Ireland
- British Lung Foundation

Description

Indications and current treatment

Emphysema is a chronic lung disease, which is usually related to smoking but may also be inherited. It is one of a group of diseases referred to as chronic obstructive pulmonary disease (COPD). Common symptoms of emphysema are dyspnoea, coughing, fatigue and weight loss.

Current treatment options include pulmonary rehabilitation (advice on smoking cessation, patient and carer education, exercise training and breathing retraining) and use of inhaled or oral bronchodilators and glucocorticoids. Some patients benefit from oxygen treatment. In advanced disease, lung volume reduction surgery (thoracoscopic or open), insertion of one-way endobronchial valves or lung transplantation may be needed.

What the procedure involves

Insertion of endobronchial nitinol coils (ENCs) is intended to be a minimally invasive alternative to lung volume reduction surgery. The procedure aims to reduce the volume of diseased areas of the lungs. This minimises airflow to the least functional diseased lung segments, allowing air to flow to healthier parts of the lungs, with the aim of improving gas exchange and, as a result, lung function. The procedure is intended to improve lung function in patients with upper or lower lobe heterogeneous emphysema, as well as in patients with multiple emphysematous lobes with focal tissue defects.

ENCs can be inserted with the patient under general anaesthesia or sedation. The bronchial tree of the diseased area of the lung is visualised by bronchoscopy and a low-stiffness guidewire is advanced through the bronchoscope under fluoroscopic guidance. A catheter is then passed over the guidewire. The guidewire is removed and a straightened coil is introduced through the catheter. The catheter is withdrawn while the coil is held in place using a grasper. When released, the straightened coil springs back to a predetermined shape, pulling on the surrounding diseased tissue and reducing lung volume. Typically, 5 to 15 coils are inserted in each treated lobe and each lung is treated in separate procedures. The coils are intended to remain in place permanently.

Outcome measures

St George’s Respiratory Questionnaire

The St George’s Respiratory Questionnaire (SGRQ) is designed to measure health impairment in patients with respiratory disease. Three component scores are calculated for the SGRQ:

- Symptoms – concerned with the effect of respiratory symptoms, their frequency and severity.
- Activity – concerned with activities that cause or are limited by breathlessness.
- Impacts – covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease.

A total score is also calculated, which summarises the impact of the disease on overall health status. Scores are expressed as a percentage of overall impairment, in which 100 represents the worst and 0 indicates the best possible health status.

Modified Medical Research Council dyspnoea scale

The Modified Medical Research Council (mMRC) dyspnoea scale is a simple 5-point grading system that is widely used to assess a patient's shortness of breath. Scores range from 0 to 4 with lower scores indicating decreasing breathlessness.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to the insertion of endobronchial nitinol coils to improve lung function in emphysema. Searches were conducted of the following databases, covering the period from their commencement to 26 August 2014: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with emphysema.
Intervention/test	Endobronchial nitinol coils.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 208 patients from 1 randomised controlled trial and 6 case series.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on insertion of endobronchial nitinol coils to improve lung function in emphysema

Study 1 Shah PL (2013)

Details

Study type	**Multicentre randomised controlled trial**
Country	United Kingdom
Recruitment period	2010-11
Study population and number	Patients with various types of emphysema **n=47 (23 endobronchial nitinol coils [ENCs] versus 24 usual care)**
Age and sex	Age: ENC group, 62 years; usual care group, 65.3 years Sex: ENC group, 52% male; usual care group, 70% male
Patient selection criteria	Inclusion criteria: patients >35 years with CT confirmation of unilateral, bilateral, homogeneous or heterogeneous emphysema were included. All patients had a post-bronchodilator FEV_1 ≤45% predicted, a total lung capacity >100% predicted, mMRC dyspnoea score ≥2 and had stopped smoking for a minimum of 8 weeks before enrolment. Exclusion criteria: patients with a change in FEV_1 ≥20% post-bronchodilator, a single-breath diffusing capacity for carbon monoxide <20% predicted, a history of recurrent clinically significant respiratory infection, an uncontrolled pulmonary hypertension (defined by right ventricular pressure >50 mm Hg or evidenced by echocardiogram), clinically significant bronchiectasis, giant bullae greater than a third of lung volume, who were unable to walk >140 m in 6 minutes or who were taking >20 mg prednisone (or similar steroid) daily were excluded.
Technique	ENC group: 86% (38/44) of procedures were performed under local anaesthesia with a combination of topical lidocaine, intravenous midazolam and fentanyl. The remaining procedures were performed under general anaesthesia at the patient's request. A bronchoscope was used to insert up to 10 ENCs into the selected lobe under fluoroscopic guidance. Patients received 2 ENC treatments. Usual care group: no further details were provided in the article; however, authors were contacted to determine the type(s) of treatment administered to patients. Usual care included inhalers, bronchodilators, inhaled steroids and pulmonary rehabilitation.
Follow-up	**3 months after last treatment**
Conflict of interest/source of funding	The trial was funded by the manufacturer. Authors state: "The sponsor designed the trial with the corresponding author and facilitated monitoring of safety and independent audit, collection, and storage of data".

Analysis

Follow-up issues: 1 patient in the ENC group and 1 patient in the usual care group were lost to follow-up at 90–day follow-up; however, all patients were included in each group for the intention-to-treat analysis.

Study design issues: a computer-generated sequence (block randomisation) was used to allocate patients to treatment groups after completion of all baseline investigations. Bronchoscopists and patients were aware of group allocations; however, all follow-up assessments were performed by research nurses and physiologists who were blinded to group allocations.

Study population issues: Authors state that baseline St George's Respiratory Questionnaire (SGRQ) and mMRC dyspnoea scores (no values reported) were higher in the ENC group; no p values were reported. Baseline 6–minute walk test distances were higher in the usual care group. The study was powered at 84% to detect at least a 4–point reduction in SGRQ scores with a minimum of 22 patients included in each group.

Other issues: no details were provided about the type of treatment administered to patients in the usual care group. Three procedures necessitated hospital stays of 2 days and 1 procedure necessitated a hospital stay of 3 days.

- SGRQ scores range from 0 to 100 with lower scores indicating better quality of life.
- mMRC dyspnoea scores range from 0 to 4 with lower scores indicating decreasing breathlessness.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **47 (23 ENC versus 24 usual care)**

Change in outcome measures from baseline

	Baseline values (mean)		Mean change at 3–month follow-up (95% CI)		
	ENC	Usual care	ENC	Usual care	p value
SGRQ scores	65.17	53.12	-8.11 (-13.83 to -2.39)	0.25 (-5.58 to 6.07)	0.04
TLC (L)	7.97	8.02	-0.24 (-0.38 to -0.10)	-0.13 (-0.27 to 0.01)	0.22
RV (L)	5.12	4.94	-0.51 (-0.73 to -0.30)	-0.20 (-0.42 to 0.02)	0.03
FEV_1 (L) *	0.72	0.78	14.19 (6.84 to 21.55)	3.57 (-4.02 to 11.17)	0.03
6–minute walk tests (m)	293.74	346.22	51.15 (27.65 to 74.66)	-12.39 (-36.61 to 11.83)	<0.001
mMRC dyspnoea scores	NR	NR	-0.24 (-0.57 to 0.09)	-0.09 (-0.44 to 0.26)	0.5

NR - not reported

*** Baseline FEV_1 values were reported in litres, changes were reported as percentages**

Proportion of patients who showed improvements in outcome measures

	% (n/N)		
	ENC	Usual care	P value
≥4-point improvement in SGRQ scores	65 (15/23)	22 (5/23)	0.01
≥8-point improvement in SGRQ scores	57 (13/23)	17 (4/23)	0.01
≥0.35 L reduction in RV	57 (13/23)	17 (4/23)	0.01
≥26 m improvement in 6-minute walk test	74 (17/23)	17 (4/23)	<0.001
≥10% improvement in FEV_1	57 (13/23)	26 (6/23)	0.07

Safety

Proportion of adverse events at 1–month follow-up

	% (n/N)	
	ENC (n=44 procedures)	Usual care (n=23)
Device removal	0	0
Exacerbation	5 (2/44)	4 (1/23)
Haemoptysis	0	0
Lower respiratory tract infection	5 (2/44)	0
Pneumothorax	5 (2/44)	0
Respiratory failure	0	0

Proportion of adverse events at 3-month follow-up

	% (n/N)	
	ENC (n=44 procedures)	Usual care (n=23)
Device removal	0	0
Exacerbation	7 (3/44)	9 (2/23)
Haemoptysis	0	0
Lower respiratory tract infection	0	4 (1/23)
Pneumothorax	0	0
Respiratory failure	0	0

Abbreviations used: CI, confidence interval; ENC, endobronchial nitinol coils; FEV_1, forced expiratory volume in 1 second; mMRC, modified Medical Research Council; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

Study 2 Deslee G (2014)

Details

Study type	**Case series**
Country	Multicentre (France, Germany and Netherlands)
Recruitment period	2009–11
Study population and number	**Patients with bilateral heterogeneous emphysema** **n=60**
Age and sex	Mean age: 60.9 years Sex: 55% male
Patient selection criteria	Inclusion criteria: patients aged ≥35 years with CT confirmation of bilateral, homogeneous or heterogeneous emphysema were included. All patients had a post-bronchodilator FEV_1≤45% predicted, a total lung capacity >100% predicted, a residual volume >175% predicted, mMRC dyspnoea score ≥2, and had stopped smoking for a minimum of 8 weeks before enrolment. Exclusion criteria: patients with a change in FEV_1 ≥20% post-bronchodilator, a single-breath diffusing capacity for carbon monoxide <20% predicted, a history of recurrent clinically significant respiratory infection, an uncontrolled pulmonary hypertension (defined by right ventricular pressure >50 mm Hg or evidenced by echocardiogram), clinically significant bronchiectasis, giant bullae greater than a third of lung volume, who were unable to walk >140 metres in 6 minutes, or who were taking >20 mg prednisone (or similar steroid) daily were excluded.
Technique	All procedures were done under general anaesthesia. Coils were inserted under fluoroscopic guidance with the objective of achieving equal subsegmental distribution throughout 1 target lobe. The contralateral lung was treated 1 month after the initial procedure.
Follow-up	**12 months**
Conflict of interest/source of funding	The trial was funded by the manufacturer. The manufacturer designed the trial with the corresponding author and facilitated monitoring of safety and independent audit, collection, and storage of data.

Analysis

Follow-up issues: 2 patients were lost to follow-up at 6-month follow-up. After the 6–month follow-up, 24 patients were withdrawn because the respective centre's ethics committee declined to extend the assessment period by another 6 months. As such, 34 patients were available for assessment at 12–month follow-up.

Study design issues: Patients were recruited from 11 treatment centres.

Study population issues: Potential overlap with other studies included in table 2 (Hartman 2014, Slebos 2012 and Herth 2010). 55 patients were treated bilaterally in 2 sequential procedures whereas 5 patients had ENC treatment in 1 lung.

Other issues:

- SGRQ scores range from 0 to 100 with lower scores indicating better quality of life.
- mMRC dyspnoea scores range from 0 to 4 with lower scores indicating decreasing breathlessness.
- Authors did not specify the difference between serious and non-serious COPD exacerbations.
- Authors did not specifically state the numerators and denominators when they reported the proportion of patients who showed improvements in outcome measures.
- Adverse event incidence rates were calculated by the IP team.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **58 at 6 months and 34 at 12 months**

Change in outcome measures from baseline

	Baseline values	Mean change at 6 months (mean±SD) *	Mean change at 12–month follow-up (mean±SD) *
SGRQ scores	61.5	-12.1±12.9	-11.1±13.3
RV (L)	5.29	-0.65±0.90	-0.71±0.81
FEV_1 (L)	0.83	0.11±0.20	0.11±0.30
FVC (L)	2.49	0.20±0.53	0.28±0.45
6-minute walk tests (m)	316	29.7±74.1	51.4±76.1
mMRC dyspnoea scores	3.0	-0.6±1.2	-0.7±0.8

* Significant improvements from baseline values were reported at all follow-up assessments (p values<0.05)

- No significant differences in FEV_1, RV, SGRQ and 6-minute walk test values were observed between patients with heterogeneous emphysema and patients with homogeneous emphysema, at 12 month follow-up.

Proportion of patients who showed improvements in outcome measures

	%	
	6 months	12 months
≥4 point improvement in SGRQ scores	74.1	65.6
≥8 point improvement in SGRQ scores	61.1	53.1
≥0.35 L reduction in RV	64.8	57.6
≥26 m improvement in 6-minute walk test	52.8	60.0
≥12% improvement in FEV_1	48	40.6

Note that the authors only reported percentages: numerators and denominators were not specified.

Safety

Proportion of with adverse events (out of all patients)

	% (n/N)		
	Within 1 month	Between 1 month and 6 months	Between 6 month and 12 months
Serious adverse events			
COPD exacerbation	12.1 (7/58)	17.2 (10/58)	8.8 (3/34)
Pneumonia	8.6 (5/58)	5.2 (3/58)	17.6 (6/34)
Haemoptysis	1.7 (1/58)	0	0
Pneumothorax	6.9 (4/58)	3.4 (2/58)	2.9 (1/34)
Non-serious adverse events			
COPD exacerbation	12.1 (7/58)	25.9 (15/58)	44.1 (15/34)
Pneumonia	5.2 (3/58)	5.2 (3/58)	8.8 (3/34)
Mild haemoptysis (<5ml)	60.3 (35/58)	5.2 (3/58)	5.9 (2/34)
Cough	3.4 (2/58)	5.2 (3/58)	0
Transient chest pain	34.5 (20/58)	10.3 (6/58)	8.8 (3/34)

Note that the authors did not specify the difference between serious and non-serious COPD exacerbations.

Abbreviations used: COPD, chronic obstructive pulmonary disease CI, confidence interval; ENC, endobronchial nitinol coils; FEV_1, forced expiratory volume in 1 second; mMRC, modified Medical Research Council; RV, residual volume; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

Study 3 Hartman JE (2014)

Details

Study type	**Case series**
Country	Netherlands
Recruitment period	2009–10
Study population and number	**Patients with severe emphysema** **n=38**
Age and sex	Mean age: 59.2 years Sex: 26% male
Patient selection criteria	No selection criteria were specifically reported in the study manuscript, though authors referred to a supplement. It is assumed that the selection criteria from previous studies by the same study group were used. Inclusion criteria: patients aged ≥35 years with CT confirmation of bilateral, homogeneous or heterogeneous emphysema were included. All patients had a post-bronchodilator FEV_1≤45% predicted, a total lung capacity >100% predicted, a residual volume >175% predicted, mMRC dyspnoea score ≥2, and had stopped smoking for a minimum of 8 weeks before enrolment. Exclusion criteria: patients with a change in FEV_1 ≥20% post-bronchodilator, a single-breath diffusing capacity for carbon monoxide <20% predicted, a history of recurrent clinically significant respiratory infection, an uncontrolled pulmonary hypertension (defined by right ventricular pressure >50 mm Hg or evidenced by echocardiogram), clinically significant bronchiectasis, giant bullae greater than a third of lung volume, who were unable to walk >140 metres in 6 minutes, or who were taking >20 mg prednisone (or similar steroid) daily were excluded.
Technique	All procedures were done under general anaesthesia. Coils were bronchoscopically placed, under fluoroscopic guidance, in 2 sequential procedures.
Follow-up	**3 years**
Conflict of interest/source of funding	Two co-authors received financial support and/or travel grants from the manufacturer. Furthermore, the manufacturer funded the original pilot studies (Deslee 2014 and Slebos 2012) from which patients were recruited.

Analysis

Follow-up issues: Three patients were lost to follow-up at 1–year follow-up. At 2 years, 8 more patients were excluded from analysis due to death, loss to follow-up or because they received another lung volume reduction treatment (27 patients were analysed). At 3 years, 5 more patients were excluded from analysis due to death, loss to follow-up or because they received another lung volume reduction treatment (22 patients were analysed).

Study design issues: Potential for selection bias: participants volunteered to receive annual follow-up visits.

Study population issues: Potential overlap with other studies included in table 2: authors state that patients were recruited from 2 previous studies (Deslee 2014 and Slebos 2012). 92% (35/38) of patients had heterogeneous emphysema.

Other issues:

- SGRQ scores range from 0 to 100 with lower scores indicating better quality of life.
- mMRC dyspnoea scores range from 0 to 4 with lower scores indicating decreasing breathlessness.
- Authors stated that no median changes were observed in mMRC scores at 1 and 2–year follow-up but reported p values of 0.007 in both instances.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **35 at 1 year, 27 at 2 years and 22 at 3 years**

Change in outcome measures from baseline

	Baseline	Median change at 1-year follow-up (range)	Median change at 2-year follow-up (range)	Median change at 3-year follow-up (range)
SGRQ scores	63.2	-4.2 * (-44 to 13.1)	-8.0 * (-39.9 to 20.4)	-7.2 (-29.6 to 21.2)
RV (%)	228	-21.0 * (-91 to 32)	-10.0 * (-83 to 43)	-2 (-89 to 57)
FEV_1 (%)	27	1 (-6 to 20)	-1.0 (-9 to 17)	0 (-14 to 19)
FVC (%)	81.5	3 * (-12 to 44)	1.0 (-25 to 44)	6 (-18 to 38)
6-minute walk tests (m)	326	31.0 (-110 to 185)	-12.0 (-140 to 238)	-31.5 (-120 to 177)
mMRC dyspnoea scores	3	0 * (-3 to 2)	0 * (-3 to 1)	-0.5 * (-3 to 1)

* Significant changes from baseline values were reported (p values<0.05).

- Authors stated that no mean changes were observed in mMRC scores at 1 and 2–year follow-up but reported p values of 0.007 in both instances.

Decline in FEV_1

The mean rate of decline in FEV_1 during study participation was 0.036 litres per year compared against a pre-treatment rate of 0.082 litres per year (p=0.018). The mean rate of decline after in FEV_1 after more than 6 months of follow-up was 0.06 (p value for comparison against baseline was 0.45).

Proportion of patients who showed improvements in outcome measures

	% (n/N)		
	1 year	2 years	3 years
≥4-point improvement in SGRQ scores	51 (18/35)	63 (17/27)	59 (13/22)
≥0.4 L reduction in RV	40 (14/35)	30 (8/27)	19 (4/20)
≥26 m improvement in 6-minute walk test	57 (20/35)	27 (7/26)	40 (8/21)
≥10% improvement in FEV_1	31 (11/35)	33 (9/27)	38 (8/20)
≥100 ml improvement in FEV_1	23 (8/35)	19 (5/27)	33 (7/20)

Safety

Proportion of with adverse events (out of all patients)

	% (n/N)		
	Between Baseline and 1-year	Between 1 year and 2–year follow-up	Between 2-year and 3–year follow-up
Death [a]	3 (1/35)	11 (3/27) [c]	9 (2/22) [c]
Pneumothorax	6 (2/35)	0	0
Pneumonia	46 (16/35)	7 (2/27)	5 (1/22)
Hospitalisation due to COPD exacerbation	51 (18/35)	37 (10/27)	36 (8/22)
Haemoptysis [b]	74 (26/35)	0	5 (1/22)

[a] Deaths were not related to the procedure

[b] Very mild haemoptysis was reported immediately after the procedure in 74% (26/35) of patients. Only 1 patient experienced spontaneous haemoptysis between 2-year and 3-year follow-up.

[c] Authors used an incorrect denominator (n=35); as a result percentages were recalculated be the IP team.

- Segmental atelectasis was reported in 8% (3/35) of patients. Timing of occurrence was not reported.

Abbreviations used: COPD, chronic obstructive pulmonary disease;FEV_1, forced expiratory volume in 1 second; mMRC, modified Medical Research Council; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

Study 4 Kontogianni K (2014)

Details

Study type	**Case series**
Country	Germany
Recruitment period	2011–13
Study population and number	**Patients with severe heterogeneous emphysema** **n=26**
Age and sex	Mean age: 66 years Sex: 50% male
Patient selection criteria	Inclusion criteria: patients with severe unilateral heterogeneous emphysema and bilaterally incomplete interlobar fissures (defects >10%) were included. All patients had a post-bronchodilator FEV_1 <45% predicted, a total lung capacity >100% predicted, and a residual volume >200% predicted. Exclusion criteria: patients with alpha-1 antitrypsin deficiency, giant bullae, bronchiectasis or an active infection were excluded. Patients who had an unstable cardiological status or who were active smokers were also excluded.
Technique	All procedures were done under general anaesthesia. Under fluoroscopic guidance, a total of 10 coils were inserted into the subsegmental bronchi of the lobe most affected by emphysema. All patients had intravenous antibiotic prophylaxis.
Follow-up	**6 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: 1 patient missed 3–month follow-up but was available for assessment at 6–month follow-up. 3 patients were lost to follow-up at 6–month follow-up.

Study design issues: The primary end point was an improvement in FEV_1 at 6 months.

Study population issues: None identified

Other issues:

- SGRQ scores range from 0 to 100 with lower scores indicating better quality of life.
- mMRC dyspnoea scores range from 0 to 4 with lower scores indicating decreasing breathlessness.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **26; however, numbers varied at each follow-up assessment**

Change in outcome measures from baseline

	Baseline values	3 months (mean±SD)	6 months (mean±SD)	ANOVA p value
SGRQ scores	65±12	58±13	59±13	<0.001
FEV_1 (L)	0.67±0.17	0.78±0.25	0.73±0.21	<0.001
RV (L)	6.17±1.6	5.57±1.65	5.75±1.28	0.005
TLC (L)	8.16±1.72	7.93±1.65	8.05±1.56	NS
RV/TLC (%)	75±8	69±10	72±9	0.001
6-minute walk test (m)	216±107	262±97	262±112	0.001
mMRC score	3.0±1.1	2.6±1.2	2.4±1.3	NS

NS – Not significant

CT analysis of emphysema volume at 3-month follow-up

- Emphysema volume was 2.79 litres at baseline and 2.80 litres at 3–month follow-up (not significant)

Proportion of patients who showed improvements in outcome measures

	% (n/N)	
	3 months	6 months
≥4-point improvement in SGRQ scores	46 (11/24)	NR
≥26 m improvement in 6-minute walk test	NR	69 (16/23)
≥12% improvement in FEV_1	66 (14/25)	43 (9/21)

NR – Not reported

Safety

Proportion of with adverse events (out of all patients)

Adverse event	% (n/N)
COPD exacerbation *	23.1 (6/26)
Light haemorrhage	23.1 (6/26)
Pneumothorax	7.7 (2/26)

* COPD exacerbations were treated by antibiotic therapy

Abbreviations used: ANOVA, Analysis of variance; COPD, chronic obstructive pulmonary disease; ENC, endobronchial nitinol coils; FEV_1, forced expiratory volume in 1 second; mMRC, modified Medical Research Council; NR, not reported; NS, Not significant; RV, residual volume; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

Study 5 Slebos DJ (2012)

Details

Study type	**Case series**
Country	Multicentre (Netherlands and Germany)
Recruitment period	2009–10
Study population and number	**Patients with heterogeneous emphysema** **n=16**
Age and sex	Mean age: 57 years Sex: 25% male
Patient selection criteria	Inclusion criteria: patients with heterogeneous emphysema with an FEV_1 <45% predicted, a total lung capacity >100% predicted, and mMRC dyspnoea score >1 were included. All patients had stopped smoking for a minimum of 8 weeks before enrolment. Exclusion criteria: patients with a change in FEV_1 ≥20% post-bronchodilator, a single-breath diffusing capacity for carbon monoxide <20% predicted, right ventricular pressure >50 mmHg, >3 hospitalisations due to exacerbations of COPD in the previous 12 months, clinically significant bronchiectasis, previous lung surgery, a giant bulla (greater than a third of lung volume) or >75% destruction of the upper lobes were excluded. Patients who were unable to walk >140 m in 6 minutes were also excluded.
Technique	All procedures were performed under general anaesthesia. A bronchoscope was used to insert 5 to 12 ENCs into the selected lobe under fluoroscopic guidance. Patients received 1 or 2 treatments.
Follow-up	**Up to 6 months after last treatment**
Conflict of interest/source of funding	The study was sponsored by the manufacturer. Authors state that the sponsors had no role in the design of the study, the collection and analysis of data, or in the preparation of the manuscript.

Analysis

Follow-up issues: the number of patients analysed at each follow-up assessment varied.

Study design issues: none identified.

Study population issues: Potential overlap with other studies included in table 2 (Deslee 2014 and Herth 2010). 12 patients were treated bilaterally in 2 sequential procedures and 4 patients received ENC treatment in 1 lung.

Other issues: Authors did not clearly specify the time span between the first and second treatments.

- SGRQ scores range from 0 to 100 with lower scores indicating better quality of life.
- mMRC dyspnoea scores range from 0 to 4 with lower scores indicating decreasing breathlessness.
- Adverse event incidence rates were calculated by the IP team by deducing numerators and denominators: authors reported adverse event as integers; however, it was noted that a total of 28 procedures were performed in the study population.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **16; however, numbers varied at each follow-up assessment**

Change in clinical outcomes from baseline

Outcome measure	Baseline value	Change at 1 month after 1st treatment (Mean±SD)	Change at 1 month after 2nd treatment (Mean±SD)	Change at 3 months after 2nd treatment (Mean±SD)	Change at 6 months after 2nd treatment (Mean±SD)	Change at 6 months after final treatment (Mean±SD)
Number of patients analysed	16	16	12	12	12	14
FVC (% predicted)	83.1±14.4	11.5±13.6	17.0±14.9	10.7±11.9	13.3±13.2	13.4±12.9
FEV_1 (% predicted)	28.7±7.1	10.3±13.1	22.6±21.7	19.9±20.0	17.3±19.4	14.9±17.0
RV (% predicted)	225±43	-9.5±6.5	-12.4±9.0	11.1±9.9	-10.6±9.59	-11.4±9.0
RV/TLC (% predicted)	60.5±6.4	-6.7±4.8	-8.2±7.1	-6.6±6.7	-8.1±5.2	-8.0±5.5
6-minute walk test (m)	338±112	35.4±30.6	69.8±64.2	62.2±76.6	80.5±78.8	84.4±73.4
SGRQ scores	64±9	-14.2±11.6	-12.2±13.5	-12.6±10.8	-15.8±12.2	-14.9±12.1

- Significant changes in all outcome measures were observed at all follow-up assessments (p values <0.05).
- No migration of coils observed in any patients at 1, 3 or 6-month follow-up.

Proportion of patients who showed improvements in outcome measures

	% (n/N)
≥12% improvement in FEV_1	64.3 (9/14)
≥10% improvement in RV	64.3 (9/14)
≥48 m improvement in 6-minute walk test	64.3 (9/14)
≥25 m improvement in 6-minute walk test	85.7 (12/14)
≥4-point improvement in SGRQ scores	78.6 (11/14)

Safety

Respiratory adverse events (out of 28 procedures)

Adverse event	Adverse events within 1 month of 1st or 2nd treatment % (n/N)	Adverse events 1- 6 months after completed treatment % (n/N)
COPD exacerbation	21.4 (6/28)	50 (14/28)
Pneumonia	7.14 (2/28)	10.7 (3/28)
Pneumothorax	3.6 (1/28)	0
Slight haemoptysis	75 (21/28)	0
Chest pain	14.3 (4/28)	7.14 (2/28)
Influenza	7.14 (2/28)	3.6 (1/28)
Cough	7.14 (2/28)	7.14 (2/28)
Pulmonary embolism (non-treated lung)	0	3.6 (1/28)

Adverse events related to anaesthesia (out of 28 procedures)

Adverse event	% (n/N)
Paroxysmal atrial fibrillation	3.6 (1/28)
Phlebitis	3.6 (1/28)
Headache	7.14 (2/28)
Hoarseness	10.7 (3/28)
Bronchospasm	3.6 (1/28)

Abbreviations used: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council; RV, residual volume; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

Study 6 Herth FJF (2010)

Details

Study type	**Case series**
Country	Multicentre (Netherlands and Germany)
Recruitment period	2008–09
Study population and number	Patients with heterogeneous and homogeneous emphysema n=**11**
Age and sex	Mean age: 62.5 years Sex: 27.3% male
Patient selection criteria	Inclusion criteria: patients ≥35 years with CT confirmation of unilateral, bilateral, homogeneous or heterogeneous emphysema were included. All patients had a post-bronchodilator FEV_1 ≤45% predicted, a total lung capacity >100% predicted, mMRC dyspnoea score ≥2 and had stopped smoking for a minimum of 8 weeks before enrolment. Exclusion criteria: patients with a change in FEV_1 ≥20% post-bronchodilator, a single-breath diffusing capacity for carbon monoxide <20% predicted, a history of recurrent clinically significant respiratory infection, an uncontrolled pulmonary hypertension (defined by right ventricular pressure >50 mmHg or evidenced by echocardiogram), clinically significant bronchiectasis, giant bullae greater than a third of lung volume, who were unable to walk >140 m in 6 minutes or who were taking >20 mg prednisone (or similar steroid) daily were excluded.
Technique	All procedures were performed under general anaesthesia. A bronchoscope was used to insert 3 to 6 ENCs into the selected lobe under fluoroscopic guidance. 10 patients received a second treatment; implants for second treatments were placed in the contralateral lung in 6 patients and in the same lung as the first treatment in 4 patients.
Follow-up	**Up to 11 months: patients were followed-up for 3 months after an initial treatment and 3 months after a second treatment (if necessary). The time period between initial treatment and second treatment was 1 to 5 months.**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: 10 out of 11 patients received a second treatment; however, all patients were included in the analyses.

Study design issues: The time period between initial treatment and second treatment was 1 to 5 months. No p values were reported. Authors state that the study was neither designed nor powered to evaluate a statistical significance between groups.

Study population issues: Potential overlap with other studies included in table 2 (Deslee 2014 and Slebos 2012). There were 8 patients who had homogeneous emphysema, whereas 3 patients had heterogeneous emphysema.

Other issues:

- SGRQ scores range from 0 to 100 with lower scores indicating better quality of life.
- mMRC dyspnoea scores range from 0 to 4 with lower scores indicating decreasing breathlessness.
- Adverse event incidence rates were calculated by the IP team by deducing numerators and denominators: authors reported adverse event as integers; however, it was noted that 21 procedures were performed in the study population.
- Authors stated the incidence rates of dyspnoea and ‘shortness of breath’; however, they did not specify the difference between the 2.

Key efficacy and safety findings

Efficacy

Number of patients analysed:**11**

Change in clinical outcomes from baseline

Outcome measure	Baseline value	Change at 1 month after 1st treatment (Mean±SD)	Change at 3 months after 1st treatment (Mean±SD)	Change at 1 month after 2nd treatment (Mean±SD)	Change at 3 months after 2nd treatment (Mean±SD)
FEV_1	% predicted				
Overall	32.81±9.05	6.5±3.9	3.3±3.2	-1.3±3.2	-5.0±2.9
Heterogeneous	NR	12.6±9.9	9.6±2.5	3.9±5.3	-0.9±4.0
Homogeneous	NR	4.2±4	0.2±4.2	-3.5±3.8	-6.8±3.8
FVC	% predicted				
Overall	69.2±14.3	1.6±6.5	9.5±5.7	1.3±7.6	-1.5±6
Heterogeneous	NR	19.7±19.6	18.7±10.6	25.5±7.7	9.6±11.3
Homogeneous	NR	-5.2±4.2	4.9±6.5	-9.1±7.5	-6.3±6.8
RV	% predicted				
Overall	230.9±47.0	2.2±0.1	-1.5±4.3	11.8±9.2	3.3±4.6
Heterogeneous	NR	-9.5±10.8	-9.1±8.8	-13.1±7.8	-8.6±7.2
Homogeneous	NR	6.6±3.4	2.3±4.6	22.5±10.5	9.2±4.4
RV/TLC	% predicted				
Overall	167.3±20.3	2.2±3.0	-1.3±2.1	5.8±4.3	1.8±2.4
Heterogeneous	NR	-6.7±6.5	-6.3±3.6	-7.9±4.4	-3.4±3.1
Homogeneous	NR	6.0±2.2	0.9±2.3	12.7±3.3	4.9±2.7
6–minute walk test	Metres	*			
Overall	268±78	2.5±7.5	10.8±8.8	2.9±7.9	5.6±8.5
Heterogeneous	NR	18.4±16.4	32.3±11.9	35.5±1.4	31.9±12.3
Homogeneous	NR	-3.5±7.9	0.1±9.5	-11.1±5.2	-7.6±6.4
SGRQ scores	Points				
Overall	68.4±13.59	-4.7±3.0	-7.8±3.7	-5.4±4.2	-6.1±4.4
Heterogeneous	NR	-6.4±2.5	-14.1±2.8	-19.6±3.8	-12.2±11.8
Homogeneous	NR	-4.1±4.1	-4.6±5.1	0.7±4.0	-3.4±4.2
mMRC scores	Points				
Overall	3.4±0.8	-0.5±0.2	-0.5±0.3	-0.6±0.3	-0.2±0.4
Heterogeneous	NR	-0.3±0.3	-0.7±0.3	-1.7±0.3	-1.0±0.6
Homogeneous	NR	-0.5±0.3	-0.4±0.4	-0.1±0.3	0.2±0.5

*** Changes in 6-minute walk test distances were reported as percentages**

Safety

Adverse events that authors deemed related to the procedure/device (out of 21 procedures):

Adverse event	% (n/N)
Dyspnoea	47.6 (10/21)
Coughing	23.8 (5/21)
COPD exacerbations	14.3 (3/21)
Shortness of breath	9.5 (2/21)
Chest pain	4.8 (1/21)

Adverse events that authors deemed <u>unrelated</u> to the procedure/device (out of 21 procedures):

Adverse event	% (n/N)
Intermittent tachycardia	4.8 (1/21)
Hoarseness	4.8 (1/21)
Abdominal pain	4.8 (1/21)
Headache	4.8 (1/21)
Chest pain	4.8 (1/21)
Rhinitis	4.8 (1/21)
Influenza	4.8 (1/21)
Pneumonia	4.8 (1/21)
Vertebral fracture	4.8 (1/21)
Infective exacerbation	9.5 (2/21)
Dizziness	9.5 (2/21)

Abbreviations used: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council; NR, not reported; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

Study 7 Klooster K (2014)

Details

Study type	**Case series**
Country	Netherlands
Recruitment period	2011–12
Study population and number	**Patients with homogeneous emphysema** **n=10**
Age and sex	Mean age: 54 years Sex: 10% male
Patient selection criteria	Inclusion criteria: patients >35 years with CT confirmation of homogeneous emphysema were included. All patients had a post-bronchodilator FEV1 ≤45% predicted, a post-bronchodilator FVC ≤90% predicted, a total lung capacity >120% predicted, residual volume >225% predicted, mMRC dyspnoea score >1 and had stopped smoking for a minimum of 6 months before enrolment. Exclusion criteria: patients with a single-breath diffusing capacity for carbon monoxide <20% predicted, a history of recurrent clinically significant respiratory infection, an uncontrolled pulmonary hypertension (defined by right ventricular pressure >50 mmHg), clinically significant bronchiectasis, giant bullae greater than a third of lung volume, who were unable to walk >140 m in 6 minutes or who were taking >20 mg prednisone (or similar steroid) daily were excluded.
Technique	All procedures were performed under general anaesthesia. A bronchoscope was used to insert up to 12 ENCs into the selected lobe under fluoroscopic guidance. During the first procedure ENCs were placed into the right upper lobe. Two months later, ENCs were inserted into the left upper lobe. Patients were given a prophylactic 5-day course of prednisolone (25 mg once a day) starting 2 days before the procedure and a 5-day course of azithromycin (250 mg once a day) starting on the day of the procedure.
Follow-up	**6 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: no patients were lost to follow-up.

Study design issues: none identified.

Study population issues: none identified.

Other issues:

- SGRQ scores range from 0 to 100 with lower scores indicating better quality of life.
- mMRC dyspnoea scores range from 0 to 4 with lower scores indicating decreasing breathlessness.
- Clinical COPD questionnaire scores range from 0 to 6 with lower scores decreasing COPD severity.
- Adverse event incidence rates were calculated by the IP team by deducing numerators and denominators: authors reported adverse event as integers; however, it was noted that a total of 20 procedures were performed in 10 patients.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **10**

Clinical outcomes

Outcome measure	Baseline (median)	6 months (median)	p value
FEV_1 (L)	0.58	0.69	0.102
FVC (L)	2.17	2.55	0.047
Intra-thoracic gas volume (L)	6.02	5.84	0.009
RV (L)	5.04	4.44	0.007
RV (% predicted)	253	231	0.007
TLC (L)	7.48	7.36	0.037
RV/TLC (%)	68	60	0.005
Airway resistance (kPa.sec/L)	0.82	0.62	0.009
Airway resistance at 5 hertz minus proximal resistance at 20 hertz (kPa/L/sec)	0.28	0.27	0.043
6–minute walk test (m)	289	350	0.005
SGRQ symptom score	63	36	0.017
SGRQ activity score	89	79	0.018
SGRQ impact score	44	32	0.074
Total SGRQ score	63	48	0.028
Clinical COPD questionnaire scores	3.0	2.3	0.007
mMRC scores	2.5	2.0	0.16
CT Volume for right upper lobe (ml)	1514	1399	0.053
CT Volume for left upper lobe (ml)	1685	1547	0.037
CT Volume for treated lobes (ml)	3204	2941	0.037
CT Volume for untreated lobes (ml)	3496	3489	0.646

Proportion of patients who showed improvements in outcome measures

	% (n/N)
≥0.43L in RV	70 (7/10)
≥26 m improvement in 6–minute walk test	70 (7/10)
≥48 m improvement in 6–minute walk test	50 (5/10)
≥4 point improvement in SGRQ scores	70 (7/10)
≥8 point improvement in SGRQ scores	70 (7/10)
≥0.4 point improvement in clinical COPD questionnaire scores	80 (8/10)

Safety

Adverse events within 1 month of 1st or 2nd treatment (n=20 procedures)

Outcome measure	% (n/N)
Pneumothorax	5 (1/20)
COPD exacerbation requiring hospitalisation	0
COPD exacerbation	15 (3/20)
Slight haemoptysis (<5 ml)	25 (5/20)
Chest discomfort (non-cardiac)	30 (6/20)
Dyspnoea	0
Bronchitis	5 (1/20)
Hypertension	0
Hypermenorrhoea	0

Adverse events within 6 months of 1st treatment (n=10 patients)

Outcome measure	up to 6 months after 1st treatment % (n/N)
Pneumothorax	0
COPD exacerbation requiring hospitalisation	20 (2/10)
COPD exacerbation	50 (5/10)
Slight haemoptysis (<5 ml)	0
Chest discomfort (non-cardiac)	0
Dyspnoea	10 (1/10)
Bronchitis	0
Hypertension	10 (1/10)
Hypermenorrhoea	10 (1/10)

Abbreviations used: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume; FVC, forced vital capacity; mMRC, modified Medical Research Council; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

Efficacy

St George's Respiratory Questionnaire (SGRQ) scores

A randomised controlled trial of 47 patients compared patients with emphysema treated by ENCs (n=24) against patients who had usual care (n=23; treatment included inhalers, bronchodilators, inhaled steroids and pulmonary rehabilitation). Mean baseline SGRQ scores (scores range from 0 to 100 with lower scores indicating better quality of life) decreased by 8.11 points (from 65.17) in the ENC group and increased by 0.25 points (from 53.12) in the usual care group at 3–month follow-up (p value between groups=0.04). In the same study, SGRQ scores improved by more than 8 points in 57% (13/23) of patients in the ENC group and 17% (4/23) of patients in the usual care group at 3–month follow-up (p=0.01)[1].

In a case series 60 patients, mean SGRQ scores decreased by 11.1 points (from 61.5) at 12-month follow-up (p<0.05). In the same study, SGRQ scores improved by more than 4 points in 66% of patients at 12–month follow-up. No numerators or denominators were reported[2].

In a case series of 38 patients, median SGRQ scores decreased by 4.2 points (from 63.2) at 1–year follow-up (p<0.05). At 2–year follow-up, median SGRQ scores decreased from baseline by 8.0 points (p<0.05). At 3–year follow-up, median SGRQ scores decreased from baseline by 7.2 points (not significant)[3].

In a case series of 16 patients, SGRQ scores improved by more than 4 points in 79% (11/14) of patients at 6-month follow-up[5].

Forced expiratory volume in 1 second (FEV_1)

In the randomised controlled trial of 47 patients with emphysema treated by ENCs or usual care, mean baseline forced expiratory volumes in 1 second (FEV_1) were 0.72 litres and 0.78 litres respectively. At 3–month follow-up, FEV_1 increased by 14.19% and 3.57% respectively (p value between groups=0.03). An improvement of at least 10% in FEV_1 was observed in 57% (13/23) of patients in the ENC group and 26% (6/23) of patients in the usual care group (not significant)[1].

In a case series of 26 patients, mean FEV_1 values improved from 0.67 litres to 0.73 litres at 6–month follow-up (p<0.001)[4].

Total lung capacity (TLC)

In the randomised controlled trial of 47 patients with emphysema treated by ENCs or usual care, mean baseline TLC values decreased by 0.24 litres (from 7.97 litres) and 0.13 litres (from 8.02 litres) respectively at 3–month follow-up (p value between groups not significant)[1].

In the case series of 26 patients, TLC values decreased from 8.16 litres to 8.05 litres at 6–month follow-up (not significant)[4].

In a case series of 10 patients, TLC values decreased from 7.48 litres to 7.36 litres at 6–month follow-up (p=0.005)[7].

6–minute walk test distance

In the randomised controlled trial of 47 patients with emphysema treated by ENCs or usual care, mean distances walked in 6 minutes increased by 51.15 metres (from 293.74 metres) in the ENC group and decreased by 12.39 metres (from 346.22 metres) in the usual care group at 3–month follow-up (p value between groups<0.001). In the same study, 6–minute walk test distances improved by at least 26 metres in 74% (17/23) of patients in the ENC group and in 17% (4/23) of patients in the usual care group (p<0.001)[1].

In the case series of 60 patients, mean distances walked in 6 minutes increased by 51.4 metres (from 316 metres) at 12–month follow-up (p<0.05)[2].

In the case series of 38 patients, median distances walked in 6 minutes increased by 31.0 metres (from 326 metres) at 1–year follow-up (not significant). At 2-year follow-up, median distances walked in 6 minutes decreased from baseline by 12.0 metres (not significant) At 3–year follow-up, median distances walked in 6 minutes decreased from baseline by 31.5 metres (not significant)[3].

In the case series of 16 patients, the mean distance walked in 6 minutes increased by 35.4 metres (from 338 metres), 1 month after an initial ENC treatment, and by 69.8 metres 1 month after a second ENC treatment (p values <0.05). The mean distance walked in 6 minutes increased from baseline by 84.4 metres 6 months after a final ENC treatment (p<0.05)[5].

Modified Medical Research Council (mMRC) dyspnoea scale

In the randomised controlled trial of 47 patients with emphysema treated by ENCs or usual care, mean mMRC dyspnoea scores (scores range from 0 to 4 with lower scores indicating decreasing breathlessness) decreased by 0.24 points and 0.09 points respectively, at 3-month follow-up (p value between groups not significant). Baseline values were not reported[1].

In the case series of 38 patients, median mMRC scores decreased by 0.5 points (from 3.0) at 3-year follow-up (p<0.05)[3].

In a case series of 10 patients, median mMRC dyspnoea scale scores decreased from 2.5 to 2.0 at 6–month follow-up (p value not significant)[7].

Clinical COPD questionnaire

In the case series of 10 patients, median clinical COPD questionnaire scores (scores range from 0 to 6 with lower scores indicating decreasing COPD severity) decreased from 3.0 to 2.3 at 6–month follow-up (p value not significant)[7].

Safety

Pneumothorax

Pneumothorax was reported after 5% (2/44) of ENC procedures and in no patients who had usual care at 1–month follow-up in the randomised controlled trial of 47 patients with emphysema treated by ENCs or usual care[1].

Pneumothorax was reported in 3.4% (3/58) of patients, between 1 and 6 months after treatment, in the case series of 60 patients[2].

Pneumothorax was reported after 4% (1/28) of ENC procedures, within 1 month of first or second treatment, in the case series of 16 patients[5].

Exacerbations of chronic obstructive pulmonary disease (COPD)

Exacerbations of COPD were reported in the randomised controlled trial of 47 patients after 5% (2/44) of ENC procedures and in 4% (1/23) of patients who had usual care, at 1–month follow-up. At 3–month follow-up, exacerbations of COPD were reported after 7% (3/44) of ENC procedures and in 9% (2/23) of patients who had usual care[1].

Serious exacerbations of COPD were reported in 17.2% (10/58) of patients, between 1 and 6 months after treatment, in the case series of 60 patients[2].

Exacerbations of COPD were reported after 21% (6/28) of ENC procedures, within 1 month of first or second treatment, in the case series of 16 patients. In the same study, COPD exacerbation was reported after 50% (14/28) of ENC procedures between 1 and 6 months after treatment[5].

Chest pain or discomfort

Chest pain was reported after 14% (4/28) of ENC procedures, within 1 month of first or second treatment, in the case series of 16 patients. In the same study, chest pain was reported after 7% (2/28) of ENC procedures between 1 and 6 months after treatment[5].

Transient chest pain was reported in 8.6% (3/35) of patients, between 6 and 12 months after treatment, in the case series of 60 patients[2].

Chest discomfort (non-cardiac) was reported after 30% (6/20) of ENC procedures, within 1 month of first or second treatment, in the case series of 10 patients[7].

Respiratory tract infections

Lower respiratory tract infections was reported in the randomised controlled trial of 47 patients after 5% (2/44) of ENC procedures and in no patients who had usual care, at 1-month follow-up. At 3-month follow-up, lower respiratory tract infections were reported after 0% of ENC procedures and in 4% (1/23) of patients who had usual care[1].

Pneumonia was reported after 7% (2/28) of ENC procedures, within 1 month of first or second treatment, in the case series of 16 patients. In the same study, pneumonia was reported after 11% (3/28) of ENC procedures between 1 and 6 months after treatment[5].

Influenza was reported after 7% (2/28) of ENC procedures, within 1 month of first or second treatment, in the case series of 16 patients. In the same study, influenza was reported after 4% (1/28) of ENC procedures between 1 and 6 months after treatment[5].

Bronchitis was reported after 5% (1/20) of ENC procedures, within 1 month of first or second treatment, in the case series of 10 patients[7].

Haemoptysis

Slight haemoptysis (<5 ml) was reported after 75% (21/28) of ENC procedures, within 1 month of first or second treatment, in the case series of 16 patients[5].

Slight haemoptysis was reported after 25% (5/20) of ENC procedures, within 1 month of first or second treatment, in the case series of 10 patients[7].

Other adverse events

Paroxysmal atrial fibrillation was reported after 4% (1/28) of ENC procedures in the case series of 16 patients (time of occurrence not reported). The authors described this as anaesthesia-related. In the same study, headache, hoarseness and bronchospasm were reported after 7% (2/28), 11% (3/28) and 4% (1/28) of procedures respectively. These adverse events were also described as anaesthesia-related[5].

Dyspnoea was reported after 48% (10/21) of ENC procedures in a case series of 11 patients (time of occurrence not reported)[6].

Hypertension was reported in 1 patient, up to 6 months after a first ENC treatment, in the case series of 10 patients[7].

Coughing was reported after 24% (5/21) of ENC procedures in the case series of 11 patients (time of occurrence not reported)[6].

Pulmonary embolism, in the non-treated lung, was reported after 4% (1/28) of ENC procedures between 1 and 6 months after treatment in the case series of 16 patients. No further details were provided[5].

Validity and generalisability of the studies

- There was only 1 comparative study available that compared the efficacy of ENCs to that of 'usual care', including inhalers, bronchodilators, inhaled steroids and pulmonary rehabilitation[1].
- The manufacturer funded 3 of the 7 studies in this overview [1, 2, 5].
- All studies used similar inclusion and exclusion criterion and outcome measures.
- Only 1 study specifically investigated the safety and efficacy of ENCs for treating heterogeneous emphysema[4].
- Only 1 study specifically investigated the safety and efficacy of ENCs for treating homogeneous emphysema[6].

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Lung volume reduction surgery for advanced emphysema. NICE interventional procedure guidance 114 (2005). Available from http://www.nice.org.uk/guidance/IPG114
- Insertion of endobronchial valves for lung volume reduction in emphysema. NICE interventional procedure guidance 465 (2013). Available from http://www.nice.org.uk/guidance/IPG465

Technology appraisals

- Roflumilast for the management of severe chronic obstructive pulmonary disease. NICE technology appraisal guidance 244 (2012). Available from http://www.nice.org.uk/guidance/TA244

Clinical guidelines

- Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). NICE clinical guideline 101 (2010). Available from http://www.nice.org.uk/guidance/CG101
- Depression in adults with a chronic physical health problem: treatment and management. NICE clinical guideline 91 (2009). Available from http://www.nice.org.uk/guidance/CG91

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr Andrew Medford, Dr Nicholas Hopkinson, Dr Neal Navani, Dr Pallav Shah (British Thoracic Society)

- Three specialist advisers have never performed the procedure, whereas 1 specialist adviser performs the procedure regularly.
- Three specialist advisers described the procedure as novel and of uncertain safety and efficacy. The other specialist adviser described the insertion of endobronchial coils as a new class of procedure.
- All specialist advisers stated that fewer than 10% of specialists are engaged in this area of work.
- Comparator treatments include lung volume reduction surgery, lung volume reduction with airway valves, and supportive care (including smoking cessation, pulmonary rehabilitation, as well as, oral or inhaled medications).
- Specialist advisers did not highlight any additional adverse events reported in the literature.

- Specialist advisers listed bleeding, infection and pneumothorax as anecdotal adverse events.
- Specialist advisers highlighted haemorrhage, coil migration, pneumomediastinum, respiratory failure and erosion of coils into major vessels as theoretical adverse events.
- Specialist advisers listed key efficacy outcomes as reduction in the frequency of COPD exacerbations, as well as improvements in exercise capacity (for example, 6-minute walk test), lung function (for example, forced expiratory volume in 1 second, forced vital capacity and residual volume) and quality of life (for example, St George's Respiratory Questionnaire).
- Specialist advisers stated that uncertainties surrounding the efficacy of the procedure include the long-term effects on lung function, exacerbations and quality of life beyond 2 years. One specialist adviser stated that the safety and efficacy of the procedure in patients with coexisting bronchiectasis or patients taking anticoagulants is currently unknown. Another specialist adviser highlighted that current trials lacked adequate blinding and used quality of life as a primary end point; this may be inappropriate because of a potentially high placebo effect.
- Two specialist advisers considered the procedure to have a major impact on the NHS; another believed the procedure would have moderate impact, whereas the fourth specialist adviser considered the procedure to have a minor impact on the NHS.

Patient commentators' opinions

NICE's Public Involvement Programme sent 5 questionnaires to 2 NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 2 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Issues for consideration by IPAC

Ongoing trials:

NCT01608490: Lung volume reduction coil treatment in patients with emphysema (RENEW); study type, multicentre randomised controlled study; location, USA; estimated enrolment, 315; estimated completion date, September 2014.

NCT01822795: A safety and feasibility study of re-treating patients with severe emphysema with the RePneu LVRC system (RECOIL); study type, multicentre randomised controlled study; location, France; estimated enrolment, 100; estimated completion date, June 2015.

NCT02012673: A safety and feasibility study of re-treating patients with severe emphysema with the RePneu LVRC system (RECOIL); study type, case series; location, Netherlands; estimated enrolment, 12; estimated completion date, January 2018.

NCT02059057: LVRC IDE crossover study (cross over from IDE trial CLN0009) (CROSSOVER); study type, randomised controlled study; location, USA; estimated enrolment, 150; estimated completion date, December 2019 (primary outcome measure – December 2015).

NCT01806636: post-market observational, prospective, multicenter registry using the PneumRx Inc. lung volume reduction coil (LVRC) system; study type, case series; location, Germany; estimated enrolment, 1000; estimated completion date, September 2019.

References

1. Shah PL, Zoumot Z, Singh S, Bicknell SR, Ross ET, Quiring J, Hopkinson NS, Kemp SV (2013). Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial. The Lancet Respiratory Medicine:1 (3): 233-240
2. Deslee G, Klooster K, Hetzel M, Stanzel F, Kessler R, Marquette CH, Witt C, Blaas S, Gesierich W, Herth FJ, Hetzel J, van Rikxoort EM, Slebos D. (2014) Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial. Thorax. doi: 10.1136/thoraxjnl-2014-205221
3. Hartman JE, Klooster K, Gortzak K, Ten Hacken NH, Slebos DJ. (2014) Long-term follow-up after bronchoscopic lung volume reduction treatment with coils in patients with severe emphysema. Respirology. [Epub ahead of print] doi: 10.1111/resp.12435.
4. Kontogianni K, Gerovasili V, Gompelmann D, Schuhmann M, Heussel CP, Herth FJ, Eberhardt R. (2014) Effectiveness of endobronchial coil treatment for lung volume reduction in patients with severe heterogeneous emphysema and bilateral incomplete fissures: a six-month follow-up. Respiration. 2014;88(1):52-60.
5. Slebos DJ, Klooster K, Ernst A, Herth FJ, Kerstjens HAM (2012) Bronchoscopic Lung Volume Reduction Coil treatment of patients with severe heterogeneous emphysema. Chest:142 (3): 574-582
6. Herth FJ, Eberhard R, Gompelmann D, Slebos DJ, Ernst A. (2010) Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study. Therapeutic Advances in Respiratory Disease: 4 (4): 225-31
7. K. Klooster, N. ten Hacken, I. Franz, H. Kerstjens, E.M. van Rikxoort and D.J. Slebos (2014) Lung Volume Reduction Coil Treatment in Chronic Obstructive Pulmonary Disease Patients with Homogeneous Emphysema: A Prospective Feasibility Trial. Respiration; 88 (2): 116-25.

Appendix A: Additional papers on Insertion of endobronchial nitinol coils to improve lung function in emphysema.

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Iftikhar, IH, McGuire FR, Musani AI (2014) Efficacy of bronchoscopic lung volume reduction: A meta-analysis. International Journal of COPD. 9: 481-491	Systematic review n = Not reported FU = Not reported	Studies that assessed the efficacy of one-way valves, sealants (BioLVR), lung volume reduction coils, airway bypass stents, and bronchial thermal vapour ablation, were included. Primary outcomes included mean changes in the lung function tests, 6-minute walk test distances and St. George's Respiratory Questionnaire (SGRQ) scores. Only 6-minute walk distance and SGRQ data were analysed from 2 lung volume reduction coil studies; analysis revealed a pooled mean change of 84.4 metres (95% CI: 48.43 to 120.36; P<0.001) and −10.79 points (95% CI: −17.66 to −3.92; p<0.01) respectively.	Poor reporting of outcome measures. Authors pooled the results from studies that assessed various methods of lung volume reduction (including surgery, coils and valves). The only useful results available pool data from 2 small case series that are already included in table 2.

Appendix B: Related NICE guidance for insertion of endobronchial nitinol coils to improve lung function in emphysema

Guidance	Recommendations
Interventional procedures	**Lung volume reduction surgery for advanced emphysema. NICE interventional procedures guidance 114 (2005).** 1.1 Current evidence on the safety and efficacy of lung volume reduction surgery for advanced emphysema appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Clinicians wishing to use lung volume reduction surgery for advanced emphysema should ensure that patients are fully informed about the risks of the procedure and the likelihood of deterioration in the longer term. Use of the Institute's information for the public is recommended. 1.3 Patient selection is important because mortality is increased in patients with the most seriously compromised lung function. The Institute has issued a clinical guideline on chronic obstructive pulmonary disease. 1.4 The procedure should be undertaken by a multidisciplinary team that includes a respiratory physician, specialists in pulmonary rehabilitation and a thoracic surgeon. **Insertion of endobronchial valves for lung volume reduction in emphysema. NICE interventional procedure guidance 465 (2013).** 1.1 Current evidence on the efficacy of insertion of endobronchial valves for lung volume reduction in emphysema shows some clinical and quality-of-life benefits. However, this evidence includes data from patients who have and those who have not had assessment of collateral ventilation, which specialists now advise as fundamental to selection for treatment. Evidence of safety in the short term is adequate but the evidence of safety in the longer term is inadequate in quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

	1.2 Clinicians wishing to undertake insertion of endobronchial valves for lung volume reduction in emphysema should take the following actions. • Inform the clinical governance leads in their NHS trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. • Audit and review clinical outcomes of all patients having insertion of endobronchial valves for lung volume reduction in emphysema (see section 7.1). 1.3 Patient selection should be done by a multidisciplinary team experienced in the management of emphysema including a chest physician, a chest radiologist and a thoracic surgeon. 1.4 This procedure should only be carried out by clinicians with specific training and expertise in interventional bronchoscopy (including provision of sedation), who should perform their initial procedures with an experienced mentor. 1.5 NICE encourages further research into insertion of endobronchial valves for lung volume reduction in emphysema. Research should take the form of studies that allow comparison of the procedure with the natural history of the disease and other treatment options including surgery. The studies should define the criteria and techniques used for patient selection. Outcome measures should include lung function, dyspnoea score, exercise tolerance, quality of life and long-term safety.
Technology appraisals	**Roflumilast for the management of severe chronic obstructive pulmonary disease. NICE technology appraisal guidance 244 (2012).** 1.1 Roflumilast is recommended only in the context of research as part of a clinical trial for adults with severe chronic obstructive pulmonary disease (COPD) (for the purposes of this guidance defined as forced expiratory volume in 1 second [FEV1] post-bronchodilator less than 50% predicted) associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment. 1.2 Such research should be designed to generate robust evidence about the benefits of roflumilast as an add-on to long-acting muscarinic antagonists (LAMA) plus long-acting beta2 agonists (LABA) plus inhaled corticosteroids (ICS), or LAMA plus LABA for people who are intolerant to ICS.

	1.3 People receiving roflumilast should have the option to continue treatment until they and their clinicians consider it appropriate to stop.
Clinical guidelines	**Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). NICE clinical guideline 101 (2010).** **Depression in adults with a chronic physical health problem: treatment and management. NICE clinical guideline 91 (2009).**

Appendix C: Literature search for insertion of endobronchial nitinol coils to improve lung function in emphysema

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	26/08/2014	Issue 8 of 12, August 2014
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	26/08/2014	Issue 3 of 4, July 2014
HTA database (Cochrane Library)	26/08/2014	Issue 3 of 4, July 2014
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	26/08/2014	Issue 7 of 12, July 2014
MEDLINE (Ovid)	26/08/2014	1946 to August Week 2 2014
MEDLINE In-Process (Ovid)	26/08/2014	August 25, 2014
EMBASE (Ovid)	26/08/2014	1974 to 2014 week 34
CINAHL (NLH Search 2.0)		n/a
PubMed		n/a
JournalTOCS		n/a

Trial sources searched on 16/04/2014

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov

Websites searched on 16/04/2014

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference websites
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 exp Emphysema/ (10744)

2 Pulmonary disease, chronic obstructive/ (22038)

3 Lung diseases, obstructive/ (17960)

4 Emphysem*.ti,ab. (19136)

5 (COPD or COAD or COLD).ti,ab. (96181)

6 pulmonary emphysema/ (13475)

7 hyperinflat*.ti,ab. (2255)

8 (Chronic adj4 Obstructi* adj4 (pulmonary or airway* or airflow* or Lung* or respirat*)).ti,ab. (30439)

9 (Endobronchial adj4 (nitinol or coil* or valve* or spring* or spiral*)).ti,ab. (112)

10 (Bronchoscop* adj4 lung* adj4 volume adj4 reduction*).ti,ab. (80)

11 (Lung adj4 volume adj4 reduction adj4 coil*).ti,ab. (5)

12 (LVR or LVRC or LVR-coil or LVRcoil or LVR coil).ti,ab. (267)

13 11 or 12 (269)

14 ((Flex* adj4 spiral) or ((Spring or flex*) adj4 coil*) or (elastic adj4 recoil*)).ti,ab. (1755)

15 or/1-8 (149098)

16 9 or 10 or 13 or 14 (2182)

17 15 and 16 (414)

18 animals/ not humans/ (3834114)

19 17 not 18 (367)