

**Imperial College  
London**

Royal Brompton & Harefield   
NHS Foundation Trust

# Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (The BeLieVeR-HIFi trial)

Version 2 3-6-13

MAIN SPONSOR: Imperial College London

FUNDERS: Efficacy and mechanism evaluation program of MRC and NIHR

STUDY COORDINATION CENTRE: Imperial College, Royal Brompton Campus

REC reference: 11/LO/1608

InfoEd reference: P38601

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## Funder

"This project was awarded by the Efficacy and Mechanism Evaluation (EME) Programme\* and is funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership".

\*The EME Programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales and the HSC R&D Division, Public Health Agency in Northern Ireland. It is managed by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) based at the University of Southampton.

This protocol describes the Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.

Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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## GLOSSARY OF ABBREVIATIONS

BLVR	Bronchoscopic lung volume reduction
CAT	COPD assessment test
EELV	End expiratory lung volume
FEV <sub>1</sub>	Forced expiratory volume in one second
FFM	Fat free mass
FVC	Forced vital capacity
IC	Inspiratory capacity
ITGV	Interthoracic gas volume
LVRS	Lung volume reduction surgery
MRC	Medical Research Council
PFT's	Pulmonary function tests
RV	Residual volume
SGRQc	St George's Respiratory Questionnaire for COPD
TLC	Total Lung capacity
TLco	Transfer factor for carbon monoxide

## KEYWORDS

Bronchoscopic lung volume reduction, emphysema, collateral ventilation, exercise

## STUDY SUMMARY

**TITLE** Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures

**DESIGN** A randomised controlled trial comparing bronchoscopic lung volume reduction using Zephyr endobronchial valves in patients with heterogeneous emphysema and intact interlobar fissures.

**AIMS** The aim of this study is to establish whether an approach treating only the subgroup of patients with intact fissures and the most heterogeneous pattern of disease will lead to a large and consistent benefit in lung function and exercise capacity.

**OUTCOME MEASURES** Measured at 90 days post procedure

Primary

- FEV<sub>1</sub>

Secondary

- Endurance time on cycle ergometer

- 6 minute walk distance

- RV, ITGV, TLC

- Health status – SGRQc, CAT, EQ-5D

- Lobar lung volumes on CT scan

**POPULATION** Adult patients with heterogeneous emphysema

**ELIGIBILITY** *Inclusion criteria-*

- 1) Adult patients with stable severe COPD (GOLD stage III or IV with FEV<sub>1</sub><50%pred).
- 2) MRC dyspnoea score between 3 and 5,
- 3) Total lung capacity (TLC)>100%predicted, residual volume (RV)>150%pred
- 4) Six minute walk distance of <450m.
- 5) Patients will be on optimum medical therapy including inhaled corticosteroids and long acting beta 2 agonist and anticholinergic agents unless they are intolerant or decline to use them.
- 6) CT thorax must demonstrate heterogeneous emphysema with a defined target lobe with lung destruction and intact adjacent interlobar fissures. Scans will be reviewed by 2 radiologists independently and a third will adjudicate on any disagreements. Radiologists will have to agree that the worst affected lobe of the lung has an emphysema score of  $\geq 2$  (according to the NETT study scoring system), that it is at least 1 point higher than ipsilateral lobes and that it has intact fissures visible on at least one projection.

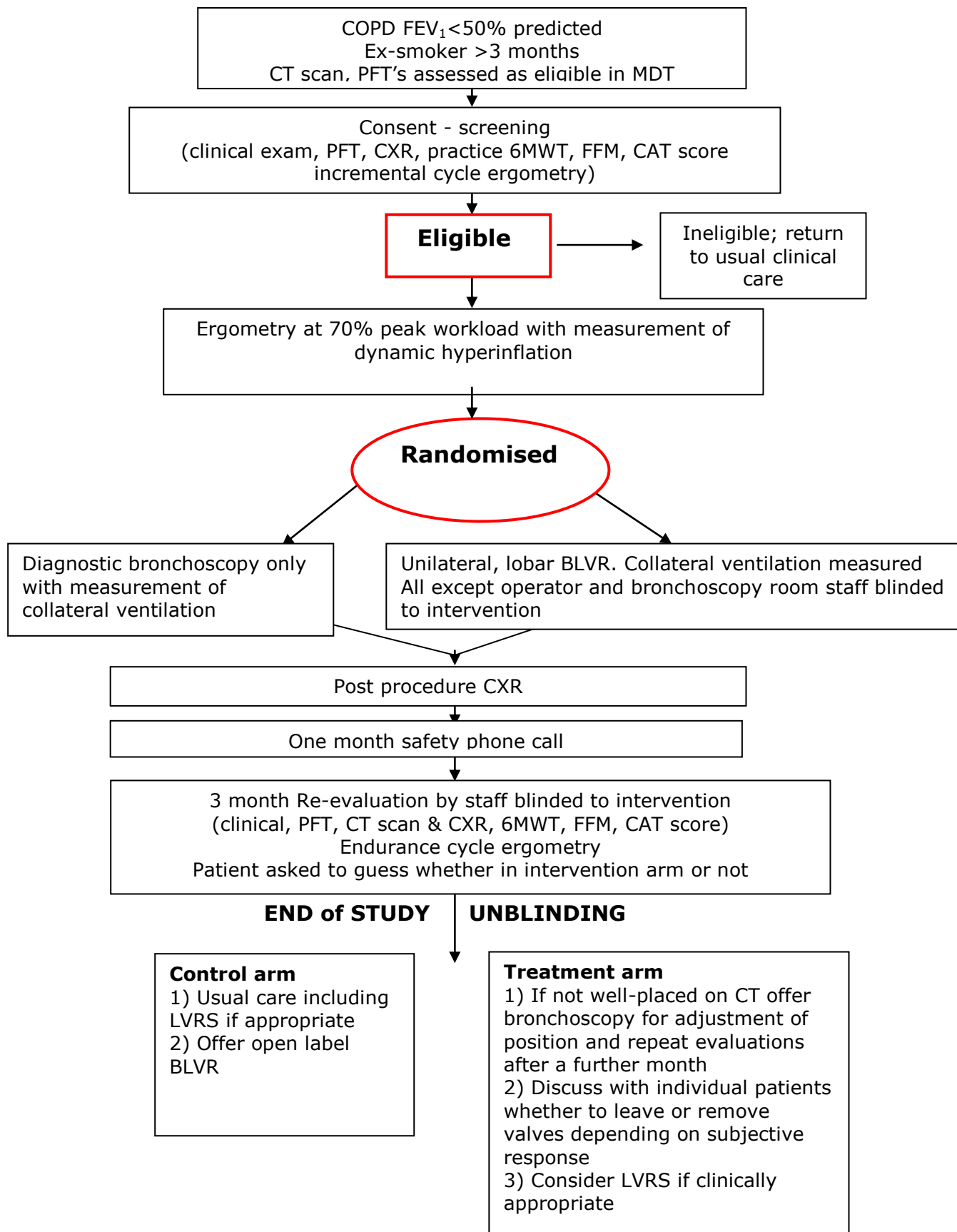
*Exclusion criteria-*

- 1) Significant co morbidity which limits their exercise capacity or prognosis,
- 2) Significant daily sputum production
- 3) Hypoxia (i.e. PO<sub>2</sub>≤6.5Pa).

**TREATMENT** Placement of endobronchial valves

**DURATION** 90 days

## REFERENCE DIAGRAM



# 1. INTRODUCTION

## 1.1 BACKGROUND

Despite optimal pharmacological therapy and pulmonary rehabilitation, patients with chronic obstructive pulmonary disease (COPD) remain significantly disabled. Emphysema, the destruction of lung parenchyma, is an important feature of the disease. Loss of lung elastic recoil leads to airflow obstruction, gas trapping and increased operating lung volumes. Where the condition is heterogeneous, the worst affected areas of lung expand disproportionately, restricting the ventilation of relatively more healthy areas. Lung volume reduction surgery (LVRS), resecting the worst areas of lung, has been clearly shown to improve outcomes in selected patient groups[1-3]. The surgical intervention is however, associated with significant morbidity and an early mortality rate of about 5%.[1, 2] There is therefore considerable interest in developing novel treatment approaches that can reduce lung volumes and gas trapping, either more safely than LVRS, or else in patients for whom LVRS is not an option [4].

One such approach is bronchoscopic lung volume reduction (BLVR), the placement of endobronchial valves using a fiberoptic bronchoscope, to allow air to leave but not enter emphysematous areas of the lung, causing them to collapse. In heterogeneous disease this allows the relatively healthier lung to function better. Initial pilot work by our group[5, 6] and others has been encouraging.[7-12] We demonstrated that valve placement could reduce dynamic hyperinflation with improved exercise capacity associated with improvements in inspiratory capacity and gas transfer.[5] Moreover, follow up of our original cohort has shown that all patients in whom radiological atelectasis had occurred (n=5) were alive 6 years post- procedure whereas 8 of the 14 without radiological atelectasis had died (Figure 1) [13]. This offers the possibility that BLVR may like LVRS offer a survival advantage where effective in appropriately selected patients.

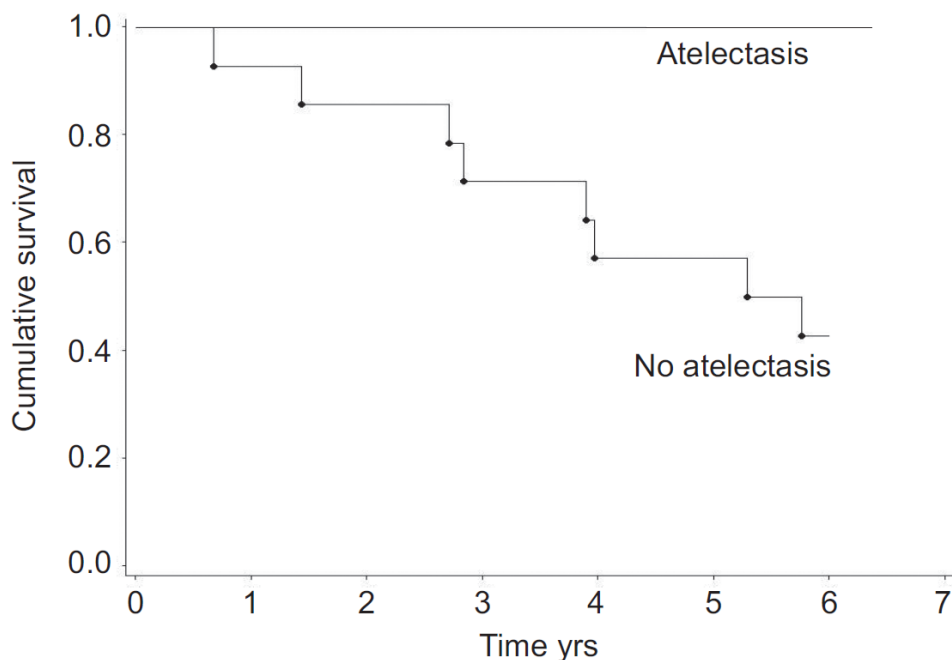
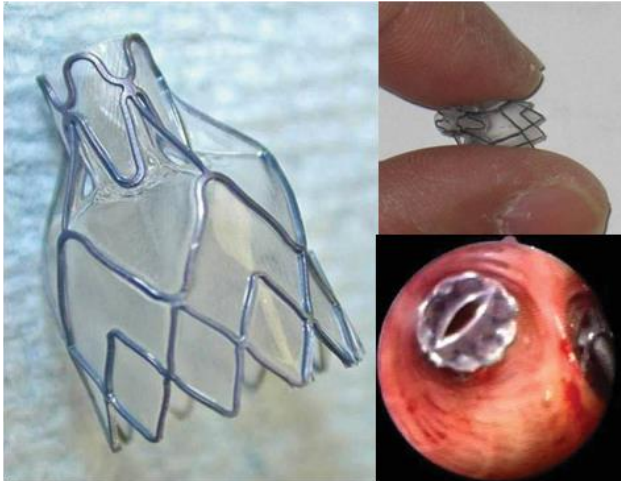


Figure 1 Atelectasis following BLVR was associated with improved survival ( $p=0.026$ ) [13].

A 'lobar' approach has generally been adopted, with valves placed in order to occlude all the segmental airways of the target lobe. This should lead to lobar atelectasis. The major problem with this approach is collateral ventilation. If the interlobar fissures have been damaged, air may enter the target lobe via the adjacent lobe preventing atelectasis. Improvement in lung function may occur in the absence of radiological volume reduction, perhaps by the diversion of airflow to healthier lung, but

benefits are greatest where atelectasis occurs.[5] However because of the destruction of lung parenchyma in COPD collateral ventilation may occur between lobes where the interlobar fissures are no longer intact. Results of a large randomised controlled trial of BLVR, the VENT study were recently published[14]. 321 patients with heterogeneous emphysema were randomly assigned to receive either unilateral lobar occlusion with Zephyr endobronchial valves or standard medical care. This confirmed that the treatment was effective but the overall benefits were modest with a 6.85% difference in FEV<sub>1</sub> between treatment and control groups at 6 months follow and a 5.7% difference in 6 minute walk distance. This occurred at the expense of a modest increase in acute exacerbations.



*Figure 2  
The Zephyr endobronchial valve*

After prolonged discussion the FDA did not approve the use of these valves in emphysema because the overall group benefits were too small. However, a subgroup of “lobar exclusion” patients was identified in whom pre-procedure CT showed that the interlobar fissures appeared intact and post procedure CT confirmed that valves were satisfactorily placed (i.e. there was no airway proximal to where they were sited). Post hoc analysis of this subgroup, where the target lobe had been effectively isolated, revealed improvements of a similar order of magnitude to those that have been observed following LVRS – with a median 21% increase in FEV<sub>1</sub>. By contrast, the group without intact fissures had only 2% change in FEV<sub>1</sub> at six months. Heterogeneity of response is therefore to be expected and a proper assessment of the usefulness of BLVR will require the identification of a responder subgroup phenotype.

Another feature was that although there was heterogeneity in the CT scans of people enrolled in the trial (as an entry criteria), in many this represented a difference in lung density due to either microscopic emphysema or airways disease rather than a more macroscopic “lung destruction” pattern. The latter appears to be more responsive to BLVR and it appears that a number of patients included in the VENT trial may not be the most responsive to BLVR. In fact patients with the greatest heterogeneity on CT benefited the most from BLVR in the VENT study

An endobronchial catheter-based device (Chartis® System, Pulmonx, Inc., Palo Alto, Calif., USA) has been developed for estimating collateral resistance. This may prove useful for target lobe selection. The Chartis system consists of a balloon occlusion catheter with a flow sensor. At bronchoscopy the catheter is inserted into the target lobe and the occlusion balloon inflated. The aim is to completely occlude the target lobe. The balloon occludes the airway, enabling no direct flow of inspired air into the lung compartment. The Chartis console displays expiratory air flow (orange), pressure (blue), and resistance (green) measurements. The balloon is occluded for up to 5 minutes. If flow stops then it is assumed there is no collateral ventilation. However if there is still active flow then collateral ventilation is present.[15]

A number of alternative approaches to the Zephyr valve which we propose to use in the current study are available or are under investigation to achieve volume reduction in patients with emphysema and are reviewed briefly here –



*Lung volume reduction surgery* Novel techniques need to be considered in the context of lung volume reduction surgery (LVRS). This involves resection of the worst affected area of emphysematous lung. Lung volumes improve because bullous areas, which expand at the expense of more healthy lung, have been resected and because the remaining relatively healthier lung has greater elastic recoil allowing it to empty more effectively [16]. The best evidence around the indications for this treatment come from the National Emphysema Treatment Trial (NETT) [2]. This multicenter trial randomized more than 1200 patients to LVRS or usual care. An early finding was the identification of a high risk group ( $FEV_1 < 20\%$  predicted with either a homogeneous pattern of disease or transfer factor of the lung for carbon monoxide (TLco)  $< 20\%$  predicted). Subsequent enrolment from this patient group was stopped. Analysis was based on *a priori* categories of exercise capacity and pattern of emphysema. At 24-months a survival benefit was apparent in surgical patients with a low exercise capacity and upper-lobe predominant emphysema. Excluding the high risk group, procedural (90 day) mortality was 5.5% in the NETT trial, with serious morbidity after LVRS observed in 59% of patients (persistent air leak (33%), respiratory failure (22%), pneumonia (18%), cardiac arrhythmias (24%))[2]. A subsequent report from the NETT trial demonstrated that the beneficial effects LVRS were sustained[17], with increased survival in the LVRS group at a median 4.3 years of follow-up (0.11 deaths per person/year in the LVRS group versus 0.13 in the medical group (RR=0.85;  $p < 0.02$ )). Patients with upper lobe predominant emphysema and low baseline exercise capacity had the largest benefit with  $> 70\%$  still alive at 5 years compared with  $< 50\%$  of those treated medically (RR=0.57,  $P < 0.01$ ). This group also had improvements in exercise capacity ( $P < 0.001$ ) and quality of life ( $P < 0.001$ ). The cost of LVRS was \$140,000 per quality adjusted life year (QALY) gained at 5 years, and projected to be \$54,000 per QALY gained at 10 years[18]. National and international guidelines now recommend that LVRS be considered in patients with upper lobe predominant disease and low exercise capacity.[19, 20] The prior single centre study performed at the Brompton yielded similar results [1, 21]

*Spiration Valve:* Spiration Incorporated (Redmond, WA) have developed an umbrella shaped device which when expanded allows air and secretions to leave but not enter the occluded lobar segment. A central proximal rod can be grasped to collapse the umbrella and allow it to be removed. In a multicenter pilot trial of 91 patients with severe heterogeneous emphysema, a mean of 6.7 valves were inserted per patient resulting in nine pneumothoraces and one fatality. Although quality of life improved in this unblinded study lung function did not improve.[22] This may be because a non-lobar approach (for example only targeting 2 out of 3 right upper lobe segmental bronchi was adopted). A double blind, multicentre, randomised controlled trial with this device has completed recruitment but results have not yet been published. A non-lobar approach has again been used and our results locally (we were a centre in this trial) have suggested little benefit initially. Interestingly we did see a better response when the procedure was “completed” after the end of the study period (i.e. occluding the remaining segmental bronchus to achieve lobar occlusion).

*Polymeric lung volume reduction (PLVR)* (Aeris Therapeutics, Inc; Woburn, MA) involves deployment of a biodegradable gel into subsegmental bronchi bronchoscopically. The solution, which contains aminated polyvinyl alcohol and glutaraldehyde creates a hydrogel foam when delivered to the distal airways. As gas within the foam (which fills damaged alveoli) is absorbed, the foam which is now adherent to the alveolar tissue collapses and as it does so reduces lung volume and hyperinflation. An open-label multi-centre exploratory phase 2 clinical study with PLVR hydrogel administered to 8 subsegmental sites in 25 patients with upper lobe emphysema showed improvements in lung function and functional parameters which persisted at 6 months[23]. The safety profile was acceptable in this study however the Medicines and Healthcare Products Regulatory Agency (MHRA) has objected to the use of the AeriSeal system in the United Kingdom on the grounds of patient safety, owing to the presence of potentially toxic glutaraldehyde in the gel, and 2 deaths in preliminary studies.

*Bronchoscopic thermal vapour ablation (“steam”)* - The bronchoscopic thermal vapour ablation (BTVA) system (Uptake Medical, Seattle, Wash., USA) delivers heated water vapour bronchoscopically, via a dedicated catheter, into the targeted emphysematous lung segments. The delivered heat causes acute tissue injury which is followed by scarring and fibrosis, leading to lung volume reduction. In a pilot safety and feasibility study, Herth *et al.* unilaterally treated 20 patients with heterogeneous

emphysema[24]. Two patients developed pneumonia with a prolonged hospital stay, but all patients had physiological benefits at 30 days. Longer term follow up data is not yet available.

*Bronchoscopic instillation of autologous blood for volume reduction* - The use of autologous blood and fibrinogen to trigger a scarring response and achieve volume reduction could avoid the need for expensive devices and expensive and potentially toxic agents. Pilot work in Japan has shown promise[25], and further trials are underway.

*RePneu Coil® lung volume reduction* - The RePneu® coil (PneumRx Inc., Mountain View, Calif., USA) is an implantable coil-like device composed of Nitinol, a super-elastic memory shape alloy. The implant is delivered bronchoscopically under fluoroscopic guidance into the targeted airways and when its sheath is removed recoils to its original shape preventing expansion of lung tissue. It may also act as a tensioning stent preventing larger airway collapse. Two pilot trials of 11 and 22 patients showed that the coil insertions are safe and observed that patients with predominantly heterogeneous disease appeared to show substantial improvements in physiological and clinical outcomes[26]. A multicentre feasibility randomised controlled trial in heterogeneous emphysema is now underway. Safety data after >1350 coils have been implanted in 164 patients has shown no deaths, no device migration or expectoration, 6 pneumothoraces (resolved quickly with intercostal chest drain insertion) and 9 pneumonias in 8 patients (which did not require prolonged hospital stay).

*Airway Bypass Stents* - Exhale® Airway Bypass drug eluting stents (Broncus Inc; Mountain View, CA) are placed bronchoscopically through cartilaginous airways into emphysematous lung parenchyma (Figure 3). Computerised tomography mapping is used to target the areas with the most severe emphysema and a Doppler probe to avoid airway wall blood vessels. Initial pilot data in patients with homogenous emphysema showed encouraging persistent benefits in physiological and functional parameters at 6 months [27]. However, a double-blind multicenter pivotal trial, which has been published in abstract form, has been disappointing. Significant reductions in lung volumes were seen immediately post procedure but these did not persist. This appears to be because of a loss of stent patency. Although the concept of transbronchial airway bypass has been proven, the problem of stent occlusion will need to be addressed before it can be of value for patients.

*Percutaneous transpleural airway bypass ('spiracles')* An alternative to the transbronchial approach to airway bypass is to create a transpleural pneumonostomy. This is similar to an intrabullous drainage procedure (the Brompton/Monaldi technique[28]) but with a permanent track being fashioned to allow a pathway for air to escape. The Portaero Pneumostoma System (Portaero Inc., CA) creates a pneumonostomy channel through a minimally-invasive transthoracic surgical approach in a procedure that takes approximately 1 hour to complete. The patient is required to change the Portaero tube daily to maintain patency. This has now been trialled in 6 patients with encouraging results[29]. In the 4 patients who retained the bypass tube for 3 months or more, there was a 23% increase in FEV<sub>1</sub>. The technique has been refined and further trials are underway.

Airway bypass techniques depend on collateral ventilation to be effective and are therefore likely to be most effective in patients with homogenous disease and are not relevant to the population targeted in the present application.

## **1.2 RATIONALE FOR CURRENT STUDY**

This proposal involves the prospective, independent validation of use of a medical device; the Zephyr endobronchial valve (Pulmonx), through a double blind randomised controlled trial. The population are patients with severe or very severe COPD (GOLD stage III and IV) with a heterogeneous pattern of emphysema and intact interlobar fissures. The intervention is the placement of endobronchial valves to achieve lobar occlusion. The comparator will be a control group who will have a bronchoscopy and "sham" valve placement. Outcomes will be improvement in lung function and exercise capacity three months post procedure. Health-related quality of life will also be assessed.

The project fits the EME remit because there is some initial evidence that endobronchial valves are effective, but to date it has not been shown that a population of responders can be identified prospectively to give evidence for effect size. Inconsistency of response, likely due to collateral ventilation between lobes where the interlobar fissures are incomplete is a major problem in refining the use of this therapy. We aim to demonstrate this under ideal conditions – conducting the trial at a highly experienced centre, recruiting patients selected carefully but in a transparent and reproducible way. Confirming the effect on lung function and exercise capacity is an essential step before proceeding to larger studies looking at endpoints such as quality of life, survival and health economics.

Although a positive outcome of the trial could lead to more widespread use of bronchoscopically deployed valves, which would be of interest to device manufacturers, a potential strength of our non-commercial study is that we will define a narrow subset of patients that experience substantial benefit, whereas commercial trials will tend to try to identify as wide a population as possible. Use of valves in patients with emphysema outside the criteria defined in this trial would need to be justified by subsequent studies.

## **2. STUDY OBJECTIVES**

Studies have to date demonstrated modest overall group benefits with the placement of endobronchial valves in COPD. We hypothesise that it is possible to identify a group of COPD patients prospectively with heterogeneous emphysema and intact interlobar fissures in whom lobar occlusion can be achieved and hence lung volume reduction, both to a significant degree and consistently. The study will therefore address the following questions, with outcomes assessed at 3 months post procedure.

- 1 Does endobronchial valve placement in this subgroup of COPD patients lead to a significant improvement in airflow obstruction ( $FEV_1$ ) compared to controls?
- 2 Will endobronchial valve placement in this group lead to significant improvement in lung volumes; residual volume (RV), total lung capacity (TLC), functional residual capacity (FRC) measured by body plethysmography compared to controls?
- 3 Will endobronchial valve placement in this group lead to significant improvement in exercise capacity (endurance time at 70% of maximum workload) and dynamic hyperinflation measured during endurance cycle ergometry as isotime end expiratory lung volume?
- 4 Will endobronchial valve placement lead to an improvement in walking distance assessed using the 6 minute walk test.
- 5 Will endobronchial valve placement in this group lead to significant improvement in health related quality of life?
- 6 Will the benefit seen in this group be of a magnitude likely to be sufficient to justify the cost of the procedure and complications that occur?

## **3. STUDY DESIGN**

We propose a double-blind, randomised, controlled trial to investigate the effect of bronchoscopic lung volume reduction (BLVR) with endobronchial valves in patients with severe (GOLD III and IV) heterogeneous emphysema and intact interlobar fissures. 50 patients will be studied. A sham bronchoscopy will be performed to maintain blinding. Outcomes will be assessed 90 days after treatment.

Allocation will be 1:1 treatment:control, determined by block randomisation (n=4) and managed by the Imperial College Clinical Trials Unit.

We have successfully recruited to the EASE multicentre trial of bronchoscopically placed airway bypasses for patients with homogeneous emphysema (fastest global recruitment site) which required sham bronchoscopy and blinded physiological assessment so are confident that this research design will be feasible. Patients will be identified through our own clinics and our extensive network of referring clinicians. To augment this we will write to Respiratory Physicians in South East England to

inform them of the trial and also publicise it through the British Thoracic Society Meetings and Newsletter.

### 3.1 STUDY OUTCOME MEASURES

*Lung function* The primary endpoint will be the percentage change in post-bronchodilator FEV<sub>1</sub> measured 90 days post procedure. This has been selected as the primary endpoint as it is the measure most usually accepted by regulatory authorities. These and other lung function measures will be measured in the lung function department of Royal Brompton Hospital according to international guidelines and with rigorous quality assurance in place. Plethysmographic lung volumes (TLC, RV, FRC) will also be measured. It is expected that improvement in lung function in patients with BLVR will be accompanied by reductions in lung volumes and possibly increases in transfer factor. These will be measured to understand response patterns better. A weakness of trial of volume reduction technologies to date has been the lack of overlap in outcome measures. Our assessment of patient response will therefore be comprehensive. All lung function tests will be performed with the patients taking their usual regular medication and 30 minutes after salbutamol 200mcg via MDI and volumatic spacer to standardise conditions.

*Exercise* Secondary endpoints will be change in endurance time on cycle ergometry at 70% baseline peak workload with a metabolic measurement cart to allow measurement of dynamic hyperinflation. The endurance exercise tests will be performed immediately after the lung function testing. Patients will perform inspiratory capacity (IC) manoeuvres each minute through the test. The IC value is subtracted from TLC to calculate end expiratory lung volume (EELV). Changes in EELV at isotime will be compared.[5] Isotime refers to the last 30 second period completed in the shorter of the two exercise tests. Patients will perform an initial incremental test with 5-10 watt increments to establish the workload for the endurance test. This will be performed on a separate day from the first endurance cycle or with at least a two hour gap to ensure recovery.

A 6 minute walk test will also be performed at last one hour after the cycle test to allow time to recover according to ATS guidelines. Patients will have practised this on a previous occasion to reduce learning effects. The 6MWT has been chosen as this walking test is in the process of becoming accredited as an outcome measure by the FDA.

*CT scanning* Changes in CT lung volume (total and lobar) will also be assessed as explanatory variables for improvement in exercise capacity and lung function.

*Health status* The COPD assessment (CAT) score will be used to evaluate quality of life – this symptom score has been shown to be responsive both to exacerbations and to pulmonary rehabilitation.[30, 31] The SGRQ will be used alongside this as well as the EQ-5D to allow QALY's to be estimated.

## 4. PARTICIPANT ENTRY

### 4.1 PRE-RANDOMISATION EVALUATIONS

Clinical history, pulmonary function tests, HRCT thorax will be reviewed in the Advanced COPD multidisciplinary meeting. Pharmacological treatment should have been optimised.

### 4.2 INCLUSION CRITERIA

- 1) Adult patients with stable severe COPD (GOLD stage III or IV with FEV<sub>1</sub><50%pred).
- 2) MRC dyspnoea score between 3 and 5,
- 3) Total lung capacity (TLC)>100%predicted, residual volume (RV)>150%pred
- 4) Six minute walk distance of <450m.
- 5) Patients will be on optimum medical therapy including inhaled corticosteroids and long acting beta 2 agonist and anti-cholinergic agents unless they are intolerant or decline to use them.
- 6) CT thorax must demonstrate heterogeneous emphysema with a defined target lobe with lung destruction and intact adjacent interlobar fissures. Scans will be reviewed by 2 radiologists

independently and a third will adjudicate on any disagreements. Radiologists will have to agree that the worst affected lobe of the lung has an emphysema score of  $\geq 2$  (according to the NETT study scoring system), that it is at least 1 point higher than ipsilateral lobes and that it has intact fissures visible on at least one projection.

#### **4.3 EXCLUSION CRITERIA**

- 4) Significant co morbidity which limits their exercise capacity or prognosis,
- 5) Significant daily sputum production
- 6) Hypoxia (i.e.  $PO_2 \leq 6.5Pa$ ).

#### **4.4 WITHDRAWAL CRITERIA**

Participants may withdraw from the study at any time. This will not affect their clinical care. Their data will be kept unless they specify otherwise.

### **5. RANDOMISATION AND ENROLMENT PROCEDURE**

#### **5.1 RANDOMISATION OR REGISTRATION PRACTICALITIES**

Consenting patients will receive a randomisation number – treatment allocation will be by sealed envelope opened in the bronchoscopy suite once the patient is sedated.

#### **5.2 UNBLINDING**

If necessary unblinding can be carried out by contacting the bronchoscopist (Dr Shah) who will be aware of treatment allocation but not otherwise involved in assessments or follow up.

### **6. TREATMENTS**

#### **6.1 TREATMENT ARMS**

Patients in the active treatment arm would have Zephyr (Pulmonx, California) valves (Figure 2) placed bronchoscopically to occlude all segmental bronchi of the target lobe. The one way valves are placed via a delivery system passed through the working channel of a standard bronchoscope. They are silicone mounted on a nitinol frame and allow air and secretions to leave the target lobe. Procedures will be performed with sedation and local anaesthetic and would take less than 30 minutes. The control group will have a similar bronchoscopy but without valve placement to blind them to treatment allocation. The use of sham bronchoscopy has been acceptable to patients, regulators and ethics committees in previous studies in this field and has been performed safely.

During the procedure (in both control and active treatment patients) collateral ventilation will be measured using a pressure catheter system to see how this relates to CT fissure integrity. We have not used this as one of our selection criteria as we are testing a CT based prediction system but the additional data from the measurement of collateral ventilation may be of use in further developing targeting strategy

Patients will stay for 4 hours post procedure and have a chest x-ray performed before they go home to exclude pneumothorax; the x-ray will be reviewed by the treating physician (Dr Shah).

## 7. ADVERSE EVENTS

### 7.1 DEFINITIONS

**Adverse Event (AE):** any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

**Serious Adverse Event (SAE) or Serious Adverse Reaction:** any untoward medical occurrence or effect that at any dose

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

### 7.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures.

#### 7.2.1 Non serious AEs

All such events, whether expected or not, should be recorded.

#### 7.2.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs. All SAEs should be reported to the London Bentham Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

**Contact details for reporting SAEs and SUSARs**  
**Fax: 020 73497778 attention Dr NS Hopkinson**  
**Please send SAE forms to: Dr NS Hopkinson, Royal Brompton Hospital, Fulham Rd, London SW3 6NP**  
**Tel: 020 73518029 (Mon to Fri 09.00 – 17.00)**

## 8. ASSESSMENT AND FOLLOW-UP

In patients with a suitable HRCT appearance and lung function parameters during clinical evaluation who consent to participate in the study, the following baseline investigations will be performed. Prior to the procedure, patients will perform spirometry, gas transfer measurement, plethysmographic lung volumes, arterialised capillary earlobe blood gases and a six minute walk test. An incremental exercise test on a cycle ergometer followed by an endurance cycle at 70% of maximum workload.

A one month phone call to assess safety will be made.

At three months, patients will undergo repeat cycle ergometry, full pulmonary function tests, 6MWT and CAT score. Investigators (blind to treatment allocation) will have the option to extend this by a further month if the patient is having an exacerbation or has had a pneumothorax or other acute complication likely to acutely influence performance on the tests.

CT scan will be repeated both to review lobar changes in lung volume and to assess valve placement. From this point the conduct of the trial will need to be pragmatic as blinding would be difficult to maintain whilst reproducing a rational clinical approach to the possible outcomes of the intervention in any individual.

Post trial management – all patients will be reviewed in the multidisciplinary meeting

1) If valves are not adequately placed (i.e. there is an airway proximal to the valve or a valve has been coughed up) patients will be offered the opportunity to have them re-sited to produce occlusion. If they choose this option then assessments would be carried out again one month after the repeat procedure to establish whether lobar occlusion has been successful.

2) If patients wish, the valves can be removed following discussion of the response with their physician.

3) Where clinically appropriate patients may wish to proceed to LVRS.

4) Patients in the control arm may wish to proceed to valve placement. This will be carried out in an open label fashion but 3 month post procedure data on exercise capacity, lung function and QOL will be collected as per standard practice.

The main safety analysis will be occurrence of adverse events in the first 3 months. This will focus on exacerbation, hospital admission, pneumothorax or valve expectoration.

Safety data will be collected systematically for at least 5 years. Following the end of the study most patients will remain under clinical follow in the Advanced COPD clinic. Late complications will be identified in this way. In addition they will receive a prompt card to contact the study team if they have a complication (particularly exacerbation, hospital admission, pneumothorax or valve expectoration). All cases will be considered annually through the MDT meeting and follow up phone calls will be made for 5 years post procedure to those not under routine clinical follow up.

An un-blinded safety monitoring committee will be established.

### 8.1 LOSS TO FOLLOW-UP

Where patients are lost to follow up, vital status will be assessed at annually through the ONS.

## 9. STATISTICS AND DATA ANALYSIS

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period. This has been based on the results of the VENT study. In the subgroup where complete lobar occlusion was achieved (n=37) there was a 20.6% improvement in

FEV<sub>1</sub> at 6 months with an SD of 25.1 (Online supplement S7)[14]. In the VENT control group FEV<sub>1</sub> fell by 2.5% SD 2.5. We consider an absolute difference in response between the two arms of 15% to be clinically significant. For 90% power and a significance level of 0.05 we would need to study 21 subjects in each arm assuming that the mean change in FEV<sub>1</sub> from baseline in the control group was 0 (SD 2.5) and the mean change in the group receiving BLVR was 15% (SD 25). To allow for 20% drop out we plan to recruit 50 patients in total.

Improvements in other lung volumes and exercise capacity and quality of life are non-independent of change in FEV<sub>1</sub> but will be assessed to help characterise the pattern of response.

In the combined dataset from the VENT studies (both European and North American data provided by Pulmonx) the lobar exclusion sub group (n=61) had lung volume changes as follows 6 months post procedure; total lung capacity (TLC) fell from 7.45(1.31)L to 7.19(1.36) a mean change of 0.26L (3.1%); functional residual capacity (FRC) fell from 5.65(1.18) to 5.19(1.27) a mean change of 0.47 L (8.2%); residual volume fell from 4.69(1.1)L to 4.15(1.28) a mean change of 0.54L (11.5%). By contrast in the control arm (n=161) the relative changes for TLC/FRC/RV were 0mls, -50mls and -30mls. The sample size proposed is adequate to identify changes of these magnitudes as well.

The study will be performed at a single centre by an experienced operator, but recruitment will be facilitated through a network of collaborators and referring hospitals across the London area so the sample size proposed is feasible.

Statistical analysis will be carried out by Mr Winston Banya of CTEU and the NIHR Biomedical Research Unit of Royal Brompton and Harefield NHS Foundation Trust and Imperial College. He is an experienced statistician who has previously worked on the HYVET study.[32] The Primary comparison will use an unpaired t test to compare mean responses between groups for changes in FEV<sub>1</sub>, cycle endurance time and lung volumes to establish whether there is a significant effect of the intervention. Analysis will be on an intention to treat basis. A single end of study assessment will be planned.

## **10. MONITORING**

### **10.1 RISK ASSESSMENT**

Experience to date shows that bronchoscopy can be safely carried out in this group of COPD patients (experience in the VENT and EASE trials). Valve placement is associated with a risk of pneumothorax, so post procedure CXR will be performed.

### **10.2 MONITORING AT LOCAL SITE**

The study will be monitored by the Chief Investigator but may be audited by the Imperial College Joint research Office.

## **11. REGULATORY ISSUES**

### **11.1 CTA**

As the Zephyr valves are being used for their CE marked indication MHRA approval is not necessary.

### **11.2 ETHICS APPROVAL**

The Study Coordination Centre has obtained approval from the London Bentham Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Study Coordination Centre will require a copy of the SSA approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

### **11.3 CONSENT**

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent



should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

#### **11.4 CONFIDENTIALITY**

Participants' identification data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

#### **11.5 INDEMNITY**

Imperial College holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

#### **11.6 SPONSOR**

Imperial College London will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

#### **11.7 FUNDING**

Efficacy and mechanism evaluation program of MRC and NIHR are funding this study.

#### **11.8 AUDITS AND INSPECTIONS**

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

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## APPENDIX 1. LIST OF EXPECTED ADVERSE EVENTS

<b>Side effect</b>
<b>Bronchoscopy:</b>
Cough
Acute exacerbation
Haemoptysis
<b>Valve placement:</b>
Pneumothorax
Valve expectoration
Acute exacerbation

## APPENDIX 2. SUMMARY OF INVESTIGATIONS, TREATMENT AND ASSESSMENTS

	Pre-assessment	Screening tests	Bronchoscopy visit	One month safety phone call	Visit 4 90 days Trial ends	Annual Safety phone call/ clinic visit for 5 years
Clinical history	X	X			X	X
CT scan	X				X	
<sup>1</sup> PFT's	X	X			X	
Discussed in MDT	X					
Informed consent		X				
CXR		X	X <sup>2</sup>		X	
ECG		X			X	
MRC dyspnoea score	X	X			X	
FFM		X			X	
Incremental exercise test		X				
6MWT		X			X	
Endurance cycle ergometry at 70%		X			X	
Randomised			X			
Collateral Ventilation measured			X			
CAT score		X			X	
SGRQc		X			X	
EQ-5D		X			X	

<sup>1</sup> Spirometry, gas transfer, plethysmographic lung volumes, capillary blood gases. <sup>2</sup>post procedure