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# Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (The BeLieVeR-HiFi trial): study design and rationale

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2014-205127>).

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Received 10 January 2014

Revised 12 February 2014

Accepted 3 March 2014

Published Online First

24 March 2014

**ABSTRACT**

Although lung volume reduction surgery improves survival in selected patients with emphysema, there has been ongoing interest in developing and evaluating bronchoscopic approaches to try to reduce lung volumes with less morbidity and mortality. The placement of endobronchial valves is one such technique, and although some patients have had a significant improvement, responses have been inconsistent because collateral ventilation prevents lobar atelectasis. We describe the protocol of a trial (ISRCTN04761234) aimed to show that a responder phenotype, patients with heterogeneous emphysema and intact interlobar fissures on CT scanning, can be identified prospectively, leading to a consistent benefit in clinical practice.

**BACKGROUND**

Despite optimal pharmacological therapy and pulmonary rehabilitation, patients with 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) to resect these areas has been clearly shown to improve outcomes in selected patient groups.<sup>1</sup> However, this surgical intervention is associated with significant morbidity and an early mortality rate of about 5% was reported in the NETT trial, though this is likely to be lower in current practice.<sup>2</sup> 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.

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 by diverting air to more perfused areas and recruiting prior 'compressed' alveoli. Initial pilot work by our group and others was encouraging, demonstrating that valve placement could reduce dynamic hyperinflation,

improving exercise capacity in association with improvements in inspiratory capacity and gas transfer.<sup>3</sup> Moreover, follow-up of an early cohort showed 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.<sup>4</sup> This raised the possibility that BLVR may, like LVRS, offer a survival advantage in appropriately selected patients.

The large multicentre prospective study (Endobronchial Valve for Emphysema Palliation Trial (VENT)) aimed to determine the effectiveness of unilateral endobronchial valves compared to standard medical treatment with coprimary endpoint of forced expiratory volume in 1 s (FEV<sub>1</sub>) and 6 min walk distance (6MWD) at 6 months.<sup>5</sup> Over an 18-month period, 321 patients were randomised (2:1) to either unilateral lobar valves (n=220) or standard medical care (n=101). The protocol did not blind the patients or assessors to the allocation of treatment, and no sham procedures were carried out and, therefore, a degree of placebo effect cannot be ruled out. The study achieved statistically but not clinically significant improvements in primary endpoints; a 6.85% difference in FEV<sub>1</sub> and 5.7% difference in 6MWD between treatment and control groups at 6 months. As the effect size overall was small, it was considered insufficient for approval by the US Food and Drug Administration. However, a posthoc analysis identified a subgroup of responders: patients with high heterogeneity and intact interlobar fissures. At 12-month follow-up, 17.9% improvement was seen in FEV<sub>1</sub> if fissures were intact compared to 2.8% if fissures were incomplete. Additionally, patients with the greatest degree of heterogeneity on computerised tomography (CT) had significantly greater improvement in FEV<sub>1</sub> and 6MWD.

These results confirmed the concept of 'lobar exclusion' where benefit from endobronchial valve placement is greatest when air is prevented from entering the target lobe by occlusion of anatomical airways and by the absence of abnormal collateral ventilation through pathological gaps in interlobar fissures.

Based on these data and evidence for a survival benefit where radiological atelectasis occurred, we obtained funding from the UK National Institute for Health Research (NIHR) efficacy and



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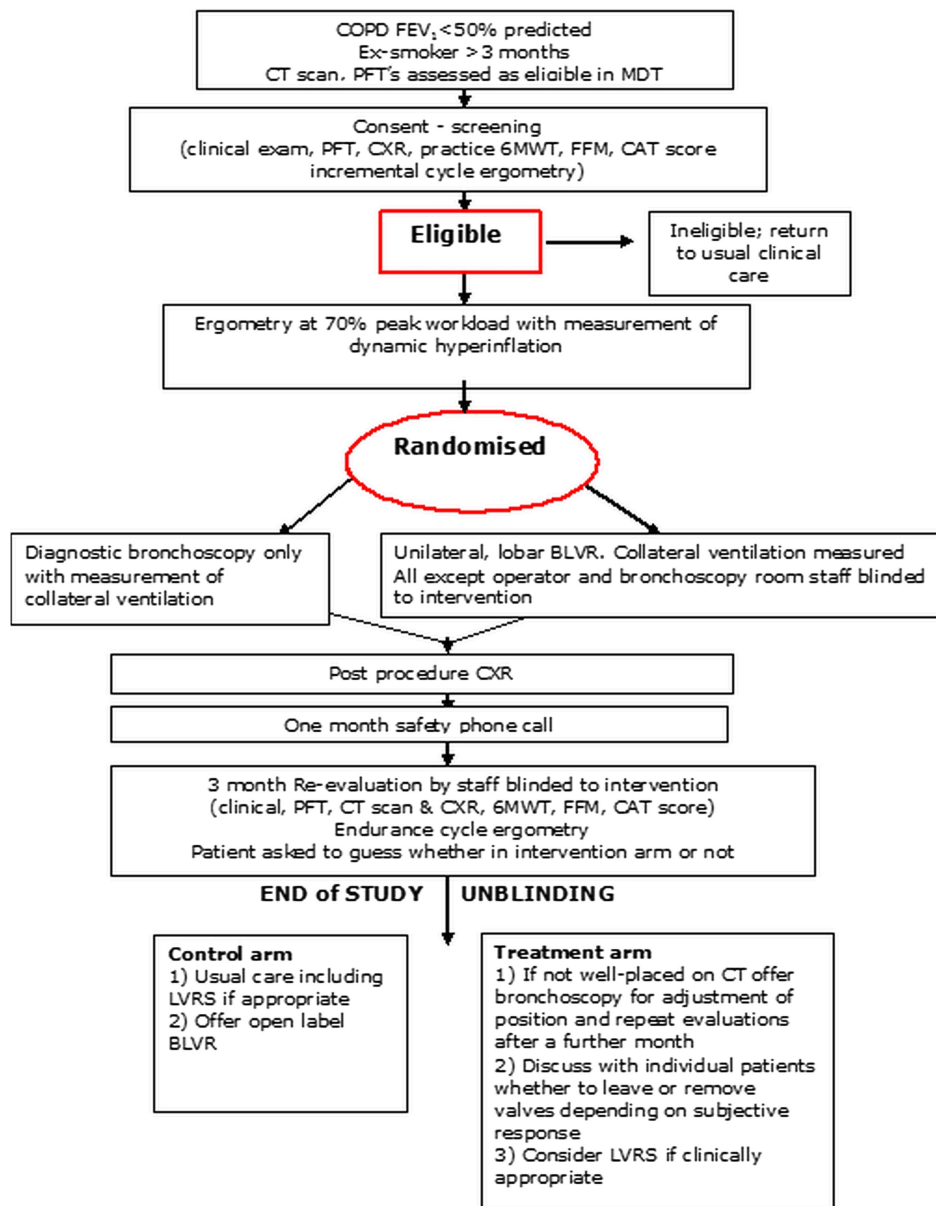


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**To cite:** Davey C, Zoumot Z, Jordan S, et al. *Thorax* 2015;**70**:288–290.



**Figure 1** Flow diagram for the BeLieVeR-HiFi study.



mechanisms evaluation (EME) scheme to conduct a randomised, double-blind placebo-controlled trial of endobronchial valve placement in patients with COPD, the BeLieVeR-HiFi study (BLVR for patients with high heterogeneity and intact fissures). This is the first implantable device study to have been funded by the EME programme.

### STUDY DESIGN

The BeLieVeR-HiFi study aims to prospectively select stable, severe (GOLD III or IV) COPD patients with hyperinflation (TLC > 100% and RV > 150%) with a limited exercise capacity 6MWD < 450 m despite optimal medical therapy (figure 1). The full protocol is available as an online supplement. Patients will be identified through a COPD multidisciplinary team meeting including chest physicians, surgeons and radiologists. CT thorax must demonstrate heterogeneous emphysema with a defined target lobe with lung destruction and intact adjacent interlobar fissures. Scans will be reviewed by two 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 > 2 (according to the NETT study scoring system),<sup>1</sup> that it is at least 1 point higher than ipsilateral lobes and that it has > 90% intact fissures visible on at least one projection. Exclusion criteria will be (1) significant comorbidity which limits exercise capacity or prognosis, (2) significant daily sputum production, (3) Hypoxia (ie, PaO<sub>2</sub> < 6.5 kPa breathing air). Lower limits for lung function were not otherwise formally defined, but patients were excluded if they were considered clinically to be too limited or frail to undergo bronchoscopy or to tolerate a pneumothorax.

Study participants will be randomised either to undergo unilateral lobar endobronchial valve placement aiming to achieve lobar atelectasis, or in the control group, to bronchoscopy and 'sham' valve placement. Although target lobe selection will be based on CT appearances alone, measurements of collateral ventilation using the Chartis system will also be made.<sup>3</sup> This bronchoscopic system uses a balloon to occlude the target airway. If continuing flow is identified, this is taken to indicate collateral ventilation 'CV positive'. Although associated with the occurrence of atelectasis in case series, it is not possible to

obtain meaningful measurements in a significant proportion of patients.

### OUTCOME MEASURES

The primary endpoint will be the percentage change in post-bronchodilator FEV<sub>1</sub> measured 90 days postprocedure. This has been selected as the primary endpoint as it is the measure most usually accepted by regulatory authorities. Plethysmographic lung volumes and carbon monoxide transfer factor 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. Other outcomes will include health-related quality of life (COPD assessment test (CAT) score and the EQ5D), as well as change in endurance time on cycle ergometry at 70% baseline peak work-load exercise capacity.

Outcomes will be assessed at 90 days after treatment by trial staff blind to treatment allocation. The purpose of the study is to assess whether the 'responder' phenotype can be identified prospectively. After 90 days, the trial ends and patients will be offered a range of options on a clinical basis including, as appropriate, LVRS or open-label valves in control subjects who were CV negative. We included LVRS as a treatment option as there is a considerable overlap between candidates for BLVR and LVRS, and the latter has a strong evidence base including for improved survival.<sup>1</sup> Additionally, a pragmatic approach in the future is likely to involve using BLVR as a way to avoid or delay the need for LVRS.

A key issue will be around safety. The main safety analysis will be the occurrence of adverse events in the first 3 months, in particular exacerbations, hospital admissions and pneumothorax. However, longer-term safety data will be collected for at least 5 years. In trials of BLVR, to date, the reported rate of pneumothorax has been about 1%. However, as patient selection improves and with it the frequency with which lobar atelectasis increases, pneumothoraces will also occur more often, as this

complication is driven by changes in lung volumes. Patients selected for BLVR must not have such severe disease that they would be unlikely to survive a pneumothorax if it occurs, and this challenges the idea that BLVR is necessarily an option for patients whose COPD is too severe for LVRS to be considered.

**Acknowledgements** The study is funded by the NIHR efficacy and mechanisms evaluation programme and supported by the NIHR Biomedical Research Unit at Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London. The endobronchial valves are being provided free of charge by the manufacturers PulmonX Ltd. PulmonX have had no input into the trial design, data analysis or presentation. PS and NSH have been investigators in trials of endobronchial valves, coils and airway bypasses.

**Contributors** NSH, MIP, SJ, DHC, ZZ, PLS and CD are all investigators in the study described. NSH and CD prepared the first draft of this paper which all authors subsequently contributed to and approved. NSH is the guarantor.

**Funding** NIHR efficacy and mechanisms evaluation programme (grant no: EME - Project: 10/90/10).

**Competing interests** PS and NSH have been investigators in trials of endobronchial valves, coils and airway bypasses.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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