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Early View

Original research article

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Lung volume reduction surgery vs endobronchial valves: a randomised controlled trial

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Summary: Word count: 249**/**250 max

Background: Lung volume reduction surgery (LVRS) and bronchoscopic lung volume reduction (BLVR) with endobronchial valves (EBVs) can improve outcomes in appropriately selected patients with emphysema. However, no direct comparison data exist to inform clinical decision-making in people who appear suitable for both procedures. Our aim was to investigate whether LVRS produces superior health outcomes when compared to BLVR at 12 months.

Methods: this multi-centre, single-blind parallel-group trial randomised patients from five UK hospitals, who were suitable for a targeted lung volume reduction procedure, to either LVRS or BLVR, and compared outcomes at one year using the i-BODE score. This composite disease severity measure includes body mass index, airflow obstruction, dyspnoea and exercise capacity (incremental shuttle walk test). The researchers responsible for collecting outcomes were masked to treatment allocation. All outcomes were assessed in the intention-to-treat population.

Findings: 88 participants (48% female, mean(SD) age 64.6(7.7), FEV_1%predicted 31.0(7.9) were recruited at five specialist centres across the UK and randomised to either LVRS(n=41) or BLVR(n=47). At 12 months follow up, the complete i-BODE was available in 49 participants (21 LVRS/ 28 BLVR). Neither improvement in the i-BODE score (LVRS: -1.10 (1.44), BLVR: -0.82 (1.61) p=0.54) nor in its individual components differed between groups. Both treatments produced similar improvements in gas trapping; RV% predicted (LVRS -36.1 (-54.1, -10), BLVR: -30.1 (-53.7, -9) p=0.81). There was one death in each treatment arm.

Interpretation: Our findings do not support the hypothesis that LVRS is a substantially superior treatment to BLVR in individuals who are suitable for both treatments.

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Keywords: COPD; Emphysema; Lung Volume Reduction; Surgery; Endobronchial valve

Take home message: In this first randomised study to compare lung volume reduction surgery and endobronchial valve placement in people who are suitable for both treatments, surgery did not produce substantially superior outcomes at one-year post procedure.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common and often disabling condition which is now the third largest cause of death worldwide(1). Breathlessness, exercise limitation and mortality in COPD are all associated with increased lung volumes occurring due to airflow obstruction and increased lung compliance. COPD is progressive and despite optimum care including smoking cessation, pharmacotherapy and pulmonary rehabilitation, many patients remain breathless and limited in everyday activities(2, 3). Surgical and bronchoscopic approaches to lung volume reduction are available which can bring substantial benefits in appropriately selected individuals, though both are also associated with some risk(4). Lung volume reduction surgery (LVRS) involves removing the worst affected area of emphysematous lung, allowing the remaining healthier and less compliant lung to function more effectively, with the respiratory muscles working at less of a mechanical disadvantage(5). LVRS has been shown to improve survival, exercise capacity and quality of life in appropriately selected patients with heterogeneous emphysema and poor exercise capacity (5-9)and is recommended in national and international guidelines for the management of COPD(10, 11). However, uptake has been limited, due in part to exaggerated concerns about surgical morbidity and mortality(9, 12). In modern clinical practice, morbidity and mortality from the procedure are substantially lower(9, 13) than was the case in trials conducted around the turn of the century(5). Common complications that may be associated with LVRS include prolonged air leak, infection and need for revision of procedure.

An alternative LVR approach is endobronchial placement of valves to the airways supplying the most emphysematous lobe causing it to deflate. This form of bronchoscopic lung volume reduction (BLVR) can produce lobar atelectasis and is intended to achieve similar benefits to LVRS but with less morbidity (14-18). It is only effective in the absence of interlobar collateral ventilation (CV)(17, 19). If this is present, air can enter the target lobe from an adjacent lobe and atelectasis does not

occur. In patients with a heterogeneous pattern of emphysema and no collateral ventilation, valve placement produces significant improvements in lung function, exercise capacity and health status(4, 14, 15, 17). There is also evidence to suggest that EBVs may benefit those with a homogenous pattern of emphysema(16). The most important complication post-BLVR is pneumothorax, which occurs in up to 30% of cases (20) and can on occasion be fatal. Acute exacerbation-like events are also common, while valve expectoration or misplacement, can necessitate additional procedures (21, 22).

People with heterogeneous emphysema and an absence of collateral ventilation may therefore benefit from either BLVR or LVRS, but there are no direct comparison data on the relative value of the two procedures to guide clinical decision-making. The aim of our study was to determine whether LVRS produces a health benefit at 1 year that is sufficiently greater(23) than BLVR to be likely to influence choice of procedure.

METHODS

Study design and participants

The CELEB study was a multicentre, randomised controlled, parallel group superiority trial in which patients with COPD who were considered by a lung volume reduction multidisciplinary team (MDT) meeting to be suitable candidates for both forms of targeted lung reduction therapy, and who did not have CV on Chartis assessment (PulmonX, Redwood, USA), were randomised to either BLVR or unilateral LVRS (Figure S1, online supplement).

Ethical approval was obtained from Fulham Research Ethics Committee, London, UK (REC reference: 16/LO/0286). The trial protocol has been published previously(24).

The trial was registered prospectively; ISRCTN19684749. A trial steering committee with an independent chair met quarterly to review progress, conduct, safety and consistency of trial processes and decision making at each centre throughout the course of the trial.

Participants were recruited at five UK hospital sites which had an established MDT meeting dedicated to identifying suitable candidates for LVR; the Royal Brompton Hospital (London, UK) Glenfield Hospital (Leicester, UK) St Bartholomew's Hospital (London, UK) Northern General Hospital (Sheffield, UK) and Golden Jubilee National Hospital (Glasgow, Scotland).
Eligibility criteria: (i) significant airflow obstruction (FEV_1< 60% predicted), hyperinflation (total lung capacity >100% predicted, residual volume (RV) >170% predicted)(25), considered to have heterogeneous emphysema based on CT and lung perfusion, and with an absence of collateral ventilation (>90% interlobar fissures on CT and negative Chartis assessment).
Exclusion criteria: (i) smoked in previous 3 months(25) pulmonary fibrosis or other major comorbidity that could affect survival or mean that LVR procedures were unlikely to be effective. (iii) hypoxaemia PaO_2 <7.0kPa. (For complete inclusion/exclusion criteria, see appendix 1, online supplement)
All participants were assumed to be medically optimised and required to have undergone a course of Pulmonary Rehabilitation (PR) within the 12 months preceding trial enrolment. The clinical MDT then decided on whether a patient was suitable for both interventions and if there was equipoise between the two options. It was only after this point in the normal clinical process that a trial screening visit was arranged, and written informed consent was obtained.

Randomisation and masking

Randomisation to treatment arm occurred only after the MDT and once participants had undergone a fibreoptic bronchoscopy to allow for assessment of the presence of CV using the Chartis system. People who were CV positive exited the study as valves would not be effective, so there was no longer equipoise (Online supplement Figure S1). Randomisation was completed by a trial co-ordinator at each individual centre, on a 1:1 basis using a computer-generated random sequence from SealedEnvelope.com that used centre and i-BODE score (>7/≤7) for stratification. Blinding of trial participants and trial co-ordinator was not possible due to the nature of the interventions, but primary outcome data were collected by an assessor with no knowledge of participant procedure and participants were asked to not reveal their treatment allocation.

Procedures

LVRS, to remove the most emphysematous part of the target lung, was carried out by a thoracic surgeon under general anaesthetic (GA), primarily using either unilateral video assisted thoracoscopic surgery (VATS) or unilateral robot assisted surgery (RATS). Where required, an open thoracotomy was performed at the discretion of the surgeon. As per usual clinical practice, participants initially went to the high dependency unit postoperatively and were transferred to ward-based care as soon as deemed medically stable, for further postoperative management, prior to discharge.

BLVR, placing Zephyr endobronchial valves (PulmonX) to occlude the target lobe, was performed via bronchoscopy by an operator experienced in placing endobronchial valves, either under conscious sedation or GA, as necessary. A chest X-ray was performed 1 hour after procedure and participants were required to spend a minimum of three nights post procedure as an inpatient in case a pneumothorax was to occur. Further details about procedures has been published previously(24) and a summary can be accessed via online data supplement (appendix 2). Participants were

followed up at 3 and 12 months post procedure. Trial outcomes were assessed and recorded at baseline, and three and 12 months after intervention (figure S1).

Outcomes

The primary outcome for the trial was the between intervention group difference in i-BODE score from baseline to 12 months post procedure. This composite measure of disease severity is made up of the incremental shuttle walk test (ISWT), BMI, airflow obstruction (FEV_1% predicted) and the MRC dyspnoea score, and has been related to prognosis in a number of settings (26). A score is assigned based on these four criteria, with the highest possible score being ten and lowest, zero. Higher scores are associated with increased mortality. Secondary outcomes were as follows; health related quality of life (CAT score); patient experience of physical activity (McRoberts MoveMonitor) assessed using the clinic visit PROactive Physical Activity in COPD (c-PPAC) score which has domains of amount and difficulty(27); change in residual volume (RV% predicted); and change in fat free mass index (FFMI). Procedure related morbidity data was also compared including length of hospital stay, days with intercostal drainage, days spent in Intensive Care and need for further intervention including pneumothorax and other complications.

Statistical analysis

Sample size calculation was based on a study comparing change in BODE score three months post LVRS between survivors and non-survivors at 5 years(23). We took the difference between these groups (1.5 points) to be sufficiently important to influence clinical decision making. For practical purposes we have taken the BODE and the i-BODE score to be equivalent(26). Based on a standard deviation of 1.8 for change in i-BODE score and taking a 5% significance level and 90% statistical

power, we would require 34 participants in each arm, and allowing for a 10% dropout rate, a recruitment target of 76 participants.

Change in outcome measures between groups were analysed using independent t-tests where normally distributed, otherwise the Wilcoxon rank-sum (Mann-Whitney) test was used. Treatment effect was reported as difference between means with the associated 95% confidence interval or the Hodges-Lehman estimate with its associated 95% confidence intervals. All analyses were performed according to a predefined statistical analysis plan(24), based on an intention-to-treat (28) principle. A sensitivity analysis, where missing data were imputed under a missing at random assumption, was performed, imputing data on all variables with missing data. These values were replaced using Multiple Imputation by Chained Equations, including the 3 month iBODE score components. For each variable 10 imputed datasets were created and Rubin's rule was used to obtain an overall estimate (29). Data were analysed by a healthcare statistician (WB) using STATA 6.1 software.

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Between 16th September 2016 and 22nd July 2019, 163 patients were assessed for their eligibility to be enrolled in the trial. Of 149 patients who were screened and thought on the basis of their CT scan to be CV negative 38 (26%) were CV positive on Chartis assessment and 9(6%) had a low flow or indeterminate Chartis. 88 eligible participants were randomly assigned to either LVRS (n=41) or

BLVR(n=47) (Figure 1). Of the randomised participants, 46(52%) were male, mean(±SD) age 64.6±7.7, FEV_1%predicted 31.0±7.9, RV %predicted 240.1 ±39.0, 48±27pack/year smoking history and median exacerbation rate 2 (range 1-3)/year. 87(98.9%) described their ethnicity as white and 1(1.1%) Middle Eastern. Groups were well matched in terms of lung function parameters, exercise capacity, health related quality of life (HRQoL) and i-BODE score (Table 1). Among participants who were initially thought to be eligible for the study at the MDT meeting but later excluded after full screening, the most common reason for exclusion (n = 47 (77.0%)) was the presence of CV at Chartis assessment or an indeterminate CV measurement (Figure 1).

80 participants received treatment (34 LVRS / 46 BLVR). Six randomised to LVRS, and one randomised to the BLVR group decided against having the procedure post-randomisation and therefore exited the trial prior to treatment. One trial participant randomised to LVRS died before surgery was performed. These participants were not included in the ITT analysis. Follow up of patients was interrupted due to the COVID-19 pandemic. Some in-person research visits were missed as they were not possible or considered unsafe in this vulnerable patient group. Where able, outcomes were collected over the phone. The COVID 19 pandemic also meant that access to some trial data were delayed, because research staff had been redeployed. Survival data at 12 months were available for all participants. Outcome data were available for 71 participants at three months (32 LVRS/ 39 BLVR) and 63 at 12 months (26 LVRS/ 37 BLVR). Complete primary end point data (all i-BODE items at 12 months) were available for 49 participants (21 LVRS / 28 BLVR) (Figure 1)- and in each of the composites as follows; BMI: (22 LVRS/35 BLVR), FEV_1% predicted: (24 LVRS/ 33 BLVR), MRC dyspnoea score: (26 LVRS/ 36 BLVR), ISWT: (22 LVRS/ 32 BLVR)

At 12 months post procedure both intervention groups showed an improvement in i-BODE score (LVRS: -1.10 (1.44), BLVR: -0.82 (1.61)) with no significant difference between the two groups (treatment effect: -0.27 (-0.62 to 1.17) p=0.54) (figure 2). Likewise, there was no difference reported in each of the four individual component measures that make up the i-BODE, between the two groups (table 2 and figure 3). A post-hoc analysis showed that responder rates (using a fall of 1 point in i-BODE index, as the score only allows whole number changes) at 12 months post procedure were comparable between the two groups (48.8% in the LVRS group and 46.8% in the BLVR group (X^2= 0.34, p=0.85)). Responder rates for components of the i-BODE index, and for secondary outcomes are presented in the online supplement (Figures 4,5,6).

Both the LVRS and BLVR groups showed improvements in all secondary outcomes; RV% predicted (LVRS; -36.1 (-54.1, -10), BLVR: -30.1 (-53.7, -9) p=0.81) physical activity experience (total c-PPAC measuring amount and difficulty) (LVRS: +18.3(17.3), BLVR: +16.1(16.9) and HRQoL (CAT) (LVRS : -7(-11, -1), BLVR: -1(-3, 2) . The only statistically significant between group change in secondary outcomes was change in CAT score, which favoured those in the LVRS group; (Treatment effect (95%CI) -6(2 to 9), p=0.005) (Table 2 and online supplement figures S2, S3 and S4).

There were no differences at baseline between those with and without complete data at 12 months (online supplement Table S1). This supported the data missing at random assumption, allowing a sensitivity analysis using multiple imputation, to derive data on missing items needed to calculate the composite iBODE score. This showed similar results (i-BODE; LVRS: -0.74 (1.62), BLVR: -0.89 (1.43), treatment effect -0.15 (-0.89 to 0.53) (p= 0.66)), while the CAT score showed a smaller

difference between the two treatment arms at 12 months (LVRS:-3.60 (7.30), BLVR – 0.04 (7.58), treatment effect 3.56 (0.18 to 6.93) (online supplement tables S2,3,4,5). Of the study participants who had complete RV follow up data, 4 (14.8%) in the BLVR group had an RV% predicted that achieved the MCID (6.1%) at three months post procedure but no longer showed this benefit at 12 months. In the LVRS group this occurred in only (5.3%) patient (Figure 6).

Median length of stay for the initial procedure was 9 (IQR 16.5) days in the LVRS group and 3 days (IQR 2) in the BLVR group (p= 0.006). There were two deaths during the 12 months follow up period. One occurred in the BLVR arm 44 days after valve insertion, due to complications related to the procedure and one in the LVRS arm at 5 months post intervention due to a non-infective acute exacerbation of COPD which was not thought to be related. At 12 months follow up there were 29 respiratory related SAE's in 17 participants undergoing LVRS (50.0%) versus 35 in 18 participants receiving BLVR (39.1%) (p=0.262, Fisher's exact test).

The most common complication was subcutaneous emphysema (29.3%) in the LVRS group and pneumothorax (30.4%) in the BLVR group. Of those who had a pneumothorax, 9 (81.8%) occurred whilst still an inpatient post procedure, median(IQR) time to onset 2(30) days and drain was removed after a median(IQR) 10(12) days. The median (IQR) number of days with a chest drain post LVRS was 8.0(11.0). 26(59.1%) of BLVR patients achieved complete lobar atelectasis and a further 10 (21.7%) partial atelectasis. 8 (17.0%) BLVR recipients required at least one further bronchoscopy or procedure following initial intervention, and 4(8.5%) crossed over to LVRS, within the 12 months follow up period. In the LVRS arm, 2(4.9%) required a further bronchoscopy or

procedure and one (2.4%) crossed over to BLVR. Safety outcomes are presented in table 3. Further procedure related details can be found in the online supplement (appendix 3).

DISCUSSION

The CELEB trial is the first randomised controlled trial to compare the effects of LVRS with BLVR. We found that surgery was not substantially superior to bronchoscopic treatment in patients with intact fissures and that both were similarly safe. Both approaches produced a clinically meaningful reduction in hyperinflation and similar improvements, assessed using either the i-BODE composite index or its individual components, were seen in both treatment arms at one-year post procedure. The initial length of hospital stay was longer following LVRS, but the BLVR group were more likely to have undergone a further intervention. There were also no significant differences found between the two groups in other secondary outcome measures (FFMI and physical activity experience and steps per day), with the exception of the CAT score which favoured LVRS at 12 months.

The use of a composite measure is considered a more meaningful way to evaluate prognosis and response to disease modifying interventions, than FEV_1 alone (31) and indeed, due to the significantly heterogenous clinical phenotypes of COPD, combinations of several indices have better prognostic capability than any one outcome in isolation(32). The i-BODE index was selected as our primary outcome, as differences in the BODE score at 3 months following LVRS have previously been shown to be associated with long term survival(23) and it has also been shown to improve following BLVR (15, 33). However, we do acknowledge the difficulties associated with using a measure that transforms continuous outcomes into categories, specifically that the likelihood of an individual making a meaningful change is determined by how close to a threshold they were for a baseline measurement, and therefore may not represent the actual magnitude of change an

individual has made. Although the study hypothesis was based on a "substantial" benefit favouring surgery, defined as a 1.5 point mean difference between groups, a difference of one point has been shown to be a significant predictor of prognosis when assessing COPD interventions(34, 35). A post hoc responder analysis also found no difference between the proportions in each trial arm achieving this level (one point) of benefit.

The greater the reduction in lung volume following LVR intervention, the greater the improvement in other outcomes such as lung function, exercise capacity and quality of life (4). In terms of intervention efficacy, both LVRS and BLVR produced similar improvements in RV%, with both exceeding the minimum clinically important difference (MCID), defined as a 6.1% fall from baseline(36), by a clear margin.

The improvement in gas trapping observed in both study arms was accompanied by improvements in participants' experience of physical activity (PA) assessed using the c-PPAC score of two to three times the established MCID of 6 points; amount (LVRS: 18.3; BLVR: 15.3) and difficulty (LVRS: 17.2; BLVR: 12.0)(37). The c-PPAC score, a combination of activity monitor data and subjective questionnaire is considered a better method of measuring PA than a subjective or objective measure in isolation (38) The magnitude of change seen in this outcome following LVR treatment would represent an important difference in a population who are greatly limited in everyday activities(39).

Safety outcomes were similar, with no statistical differences in adverse events between the two groups. There was no perioperative (30-day) mortality in either group and a single death in each arm by 12 months. This rate is not more than would be expected without intervention in patients

with this severity of disease, and indeed a low mortality rate is expected given the survival benefit associated with effective LVR in people with COPD(40). The most common complication in the BLVR arm (pneumothorax) occurred in 30.4% post BLVR, which is consistent with other studies (41, 42) and occurred at a median 2 days post procedure which supports clinical practice of post procedural in-patient observation, to allow this complication to be dealt with safely if it occurs (43). Subcutaneous emphysema following LVRS, which can be distressing when severe(44), was the most common peri-operative complication (35.3%) in the surgical arm. Unfortunately, the severity of this was not documented so it is unclear whether this should be considered a significant adverse event or accepted as an anticipated complication.

Although LVRS required a longer initial hospital stay, it was associated with fewer subsequent procedures and more participants crossed over (LVRS; 1 (2.4%), BLVR; 4 (8.5%) in the BLVR group. In addition, the CAT score at 12 months favoured LVRS with a benefit exceeding the accepted MCID of 2 points, based on previous pulmonary rehabilitation and bronchodilator studies (45, 46). This could reflect the need for fewer repeat procedures and the occurrence of numerically fewer exacerbations in the LVRS arm. As an isolated secondary endpoint this must be interpreted with some caution, in particular as the use of a health status outcome in an unblinded trial can be subject to bias based on participants' knowledge and expectations about the intervention. Furthermore, the sensitivity analysis using multiple imputations revealed a smaller difference between groups at 12 months, that was no longer statistically significant. Of note, the CAT score was included in the mixed-effects model used during data analysis.

We acknowledge a number of limitations and methodological issues with the present study. First, the findings relate to a very specific COPD phenotype, namely people who were considered to be suitable for both interventions, and cannot therefore be extrapolated to all people being considered for LVR. Some individuals have a non-anatomical pattern of emphysema where surgery may be more effective. Others may have comorbidities such as pulmonary hypertension that could preclude LVRS but where valve treatment could be considered. Second, although this first head-to-head study did not demonstrate that LVRS was substantially more effective than BLVR to an extent that would change existing clinical equipoise, that does not necessarily mean that they are equivalent and further larger trials will need to address this. Third, due in large part to the logistical difficulties conducting clinical visits during the COVID-19 pandemic, although we had complete data for survival, there were missing data for some endpoints. The sensitivity analysis using a pre-specified multiple imputation approach to missing data, supports the headline findings of the study however (Table S5). We recognise that it may have been prudent to plan for a greater than 10% drop out rate in our study design, given the known difficulties with participant cross-over in interventional RCT's investigating surgical procedures, such as ours(47, 48). These studies do however, compare surgical intervention with no intervention and therefore must be considered in this context. Of note, the SD for change in iBODE score that we observed (1.44) was lower than that used in our sample size calculation. Re-calculating this post hoc, using that standard deviation, to exclude a 1.5 point difference between the two groups at a 90% power level and a significance level of 5% would require 20 patients in each treatment arm, suggesting that our trial was in fact adequately powered. Fourth, an unavoidable limitation in our trial was the lack of double blinding, as it was not possible to conceal treatment allocation from participants. We are aware that blinding of research staff collecting key outcomes would not completely address this bias and the use of a blinding questionnaire to address the magnitude of this confounding may have been appropriate

(49). A further potential source of bias may be considered in the lack of consistency in post discharge care. For example, although all patients were required to undergo a course of PR prior to enrolment on the trial, participation in post intervention rehabilitation was not obligatory or documented. Given the well documented effect PR can have on many outcomes (50), including those investigated in this trial (FEV1, CAT, physical activity) the influence this may have had must be recognised. However, our study reflects differences in routine care pathways. A standardised pathway that necessitates post intervention PR may maximise patient outcomes from these interventions. Fifth, although the i-BODE index has not been formally validated within an LVR cohort, several studies have suggested that it may be of value in assessing patients post LVRS (51, 52). Finally, several participants withdrew from the trial following randomisation to LVRS during the interval between a surgery date being arranged. It is possible that more participants dropped out following randomisation to LVRS because they preferred to undergo what they believed to be a less invasive procedure, which may have introduced some bias into the findings. The topic of patient preference and satisfaction around undergoing an endoscopic versus a surgical procedure should be explored further. Our results are important for clinicians educating patients on these important procedures and in guiding informed decision making. Future research is called for to support these findings and a larger trial is already underway (NCT04537182). An economic evaluation of the CELEB trial data will increase understanding of the comparative value of the two approaches.(24)

Conclusion

The results of this study do not support the hypothesis that LVRS is a substantially superior treatment compared to BLVR, in terms of health outcomes achieved one-year post procedure. These broadly similar results at 12 months, were obtained with a longer length of stay initially for

LVRS but with less need for subsequent interventions than was the case with valve placement. The findings should help the LVR MDT to frame treatment options for patients and guide discussions around shared decision making, in individuals with severe COPD who are suitable for both LVRS and BLVR.

CONTRIBUTORS

NSH wrote the study protocol and obtained ethics approval and authorisation. SB, SVK, PLS, DW, SJ, WB and MCS were involved in trial design and revisions of the final protocol. SB, AL, LL, KH, EB and JB carried out all research visits and randomisation. PLS, RB, SJ, SVK, AGBK, KL, SR, ST, DW carried out the trial procedures and management of the patients involved in the trial. JM acted as trial committee chair. SB and AL provided trial oversight and SB wrote the first draft of the manuscript. NSH, SB an WB have directly accessed and verified the data report. WB carried out the statistical analysis and production of graphs for manuscript. All authors contributed to study design, study conduct, interpretation and revising the manuscript. All authors have agreed on the final manuscript and accept final responsibility to submit for publication.

DECLARATION OF INTERESTS

PLS and DW have received payment from PulmonX for educational lectures. NG has received grants to institution from GSK and Genentech and grants for lectures and travel from AZ and Chiesi. RL is a member of the British Thoracic Society COPD Specialist Advisory group, a member of South Yorkshire Clinical Senate and a member of South Yorkshire and Bassetlaw Respiratory Clinical Network

DATA SHARING

Fully anonymised data will be provided upon reasonable request to the corresponding author.

Figure 1; Trial profile

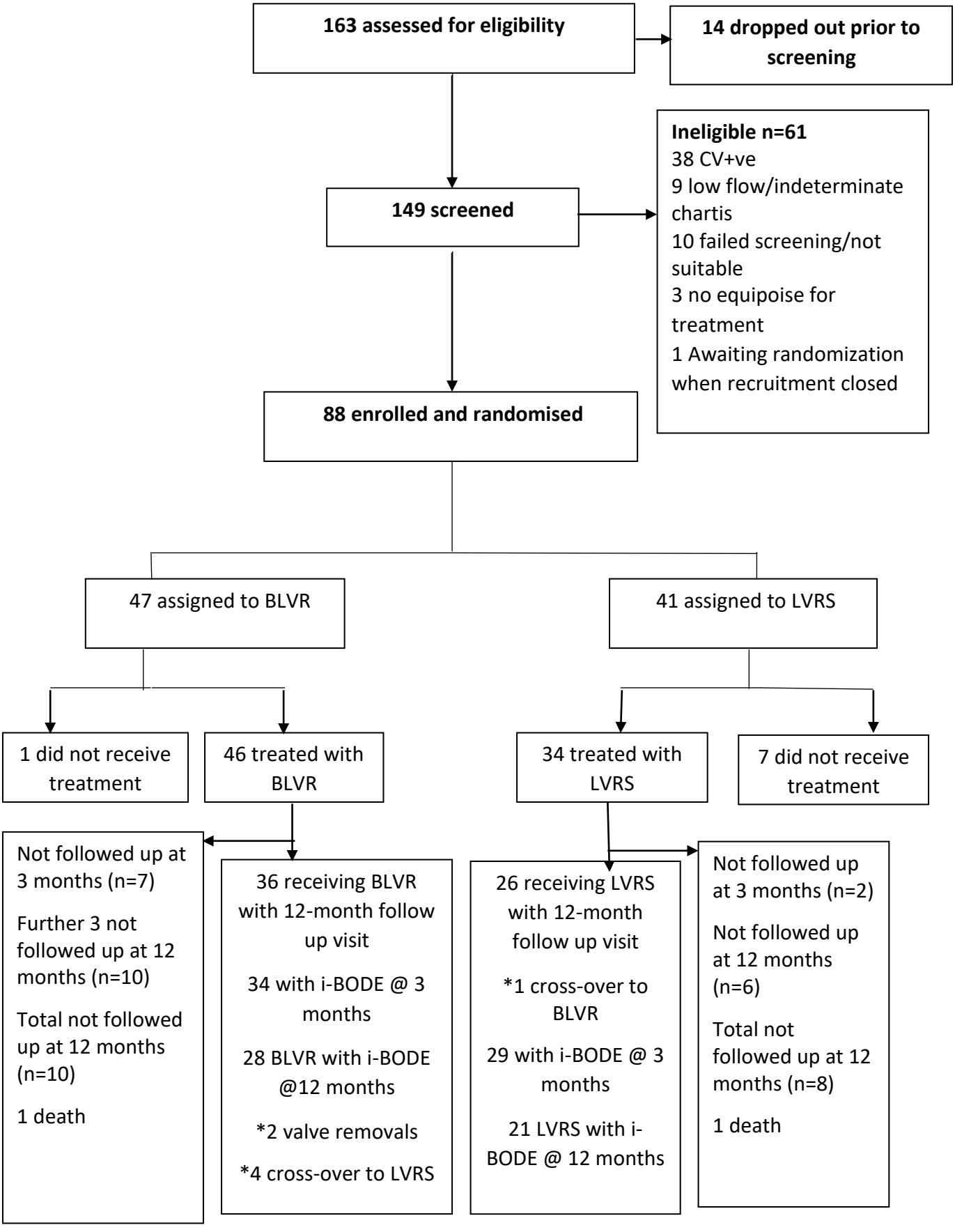
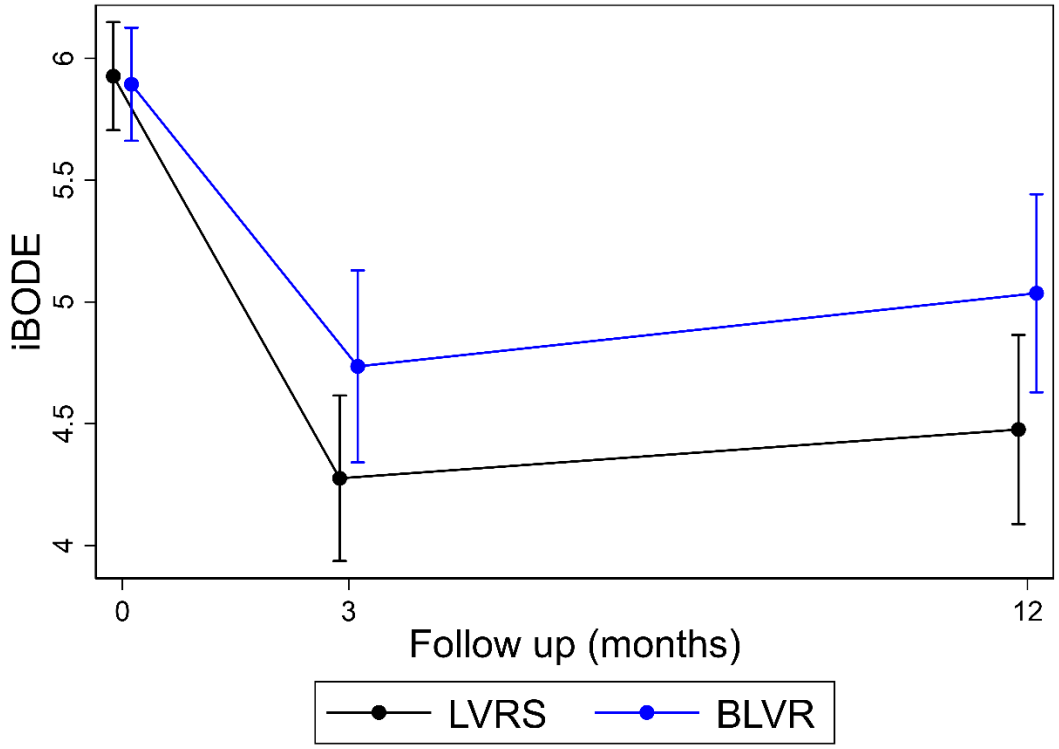


Figure 2. Effect of lung volume reduction interventions on i-BODE score



Legend to figure 2: Data presented are mean (SD) for baseline, 3 months and 12 months post procedure and are based on all available data in the intention-to-treat population. LVRS: Lung volume reduction surgery; BLVR: Bronchoscopic lung volume reduction. i-BODE: composite health status measure made up of B=BMI; O=Obstruction (FEV_1%predicted); D= Dyspnea (MRC score); E=Exercise capacity (ISWT). Between group difference at 12 months: p=0.54.

Figure 3: Effect of lung volume reduction procedures on i-BODE score component measures

Figure 3a: BMI

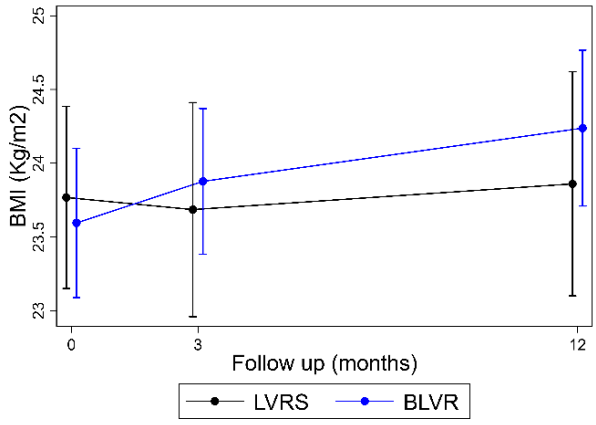


Figure 3b: FEV_1 %predicted

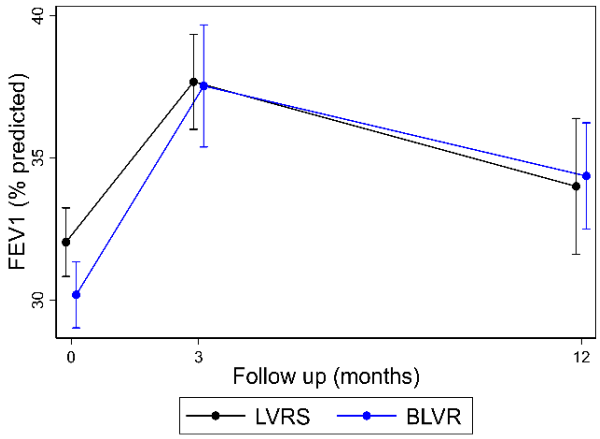


Figure 3c: MRC Dyspnoea

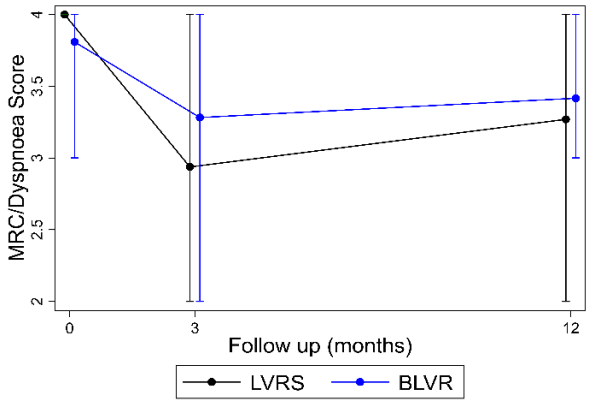
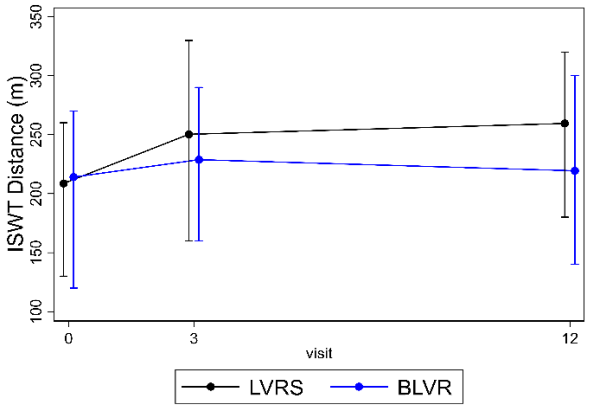
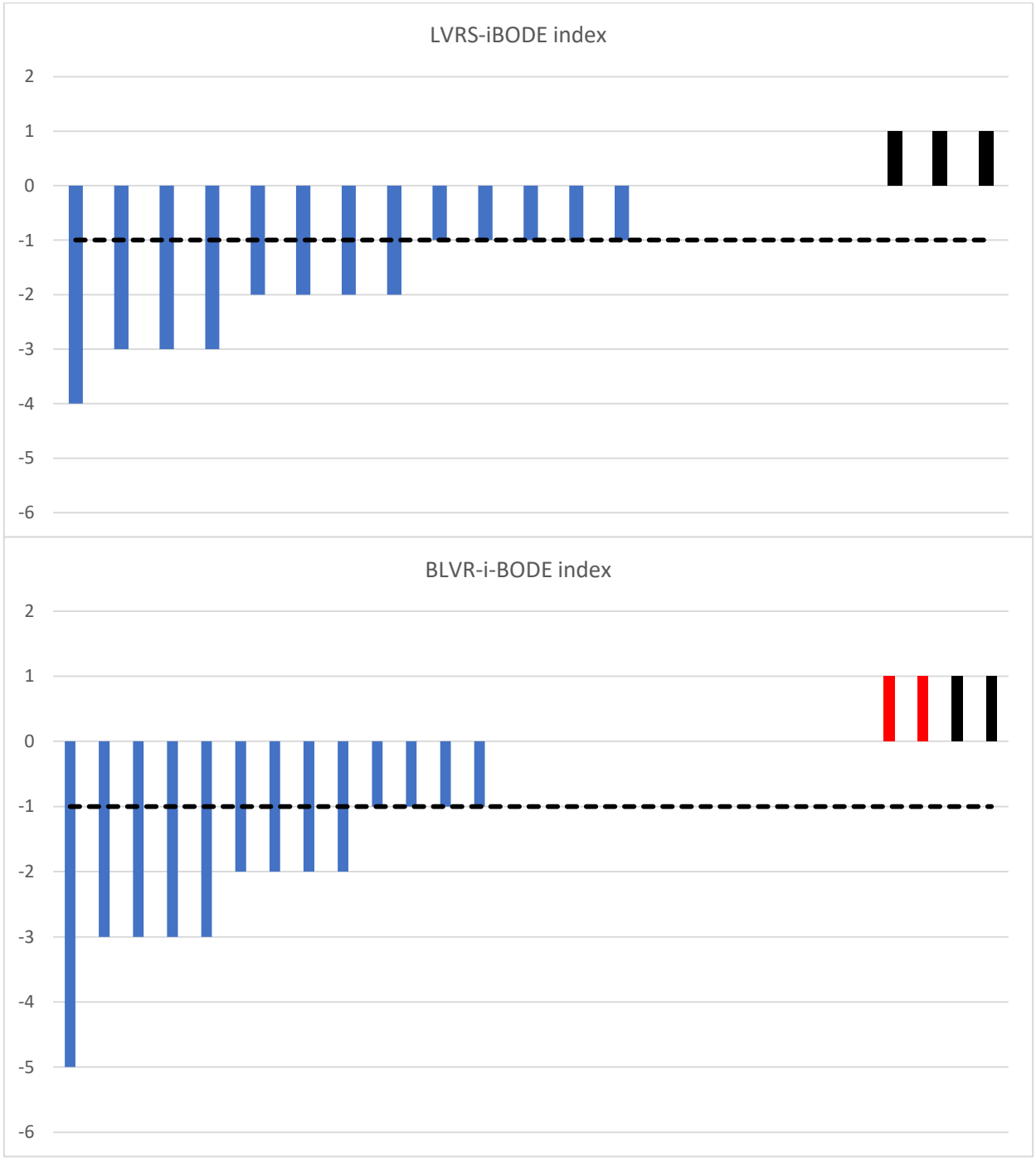


Figure 3d: ISWT (m)



Legend to figure 3: Data presented are mean (SD) or median (IQR) for baseline, 3 months and 12 months post procedure and are based on all available data in the intention-to-treat population. LVRS: Lung volume reduction surgery; BLVR: Bronchoscopic lung volume reduction; BMI: Body mass index; FEV_1: Forced expiratory volume in 1 second; MRC: Medical research council; ISWT: Incremental shuttle walk test. Between group difference at 12 months; figure 3a p=0.16; figure 3b p=0.11; figure 3c p=0.19; figure 3d p=0.09.

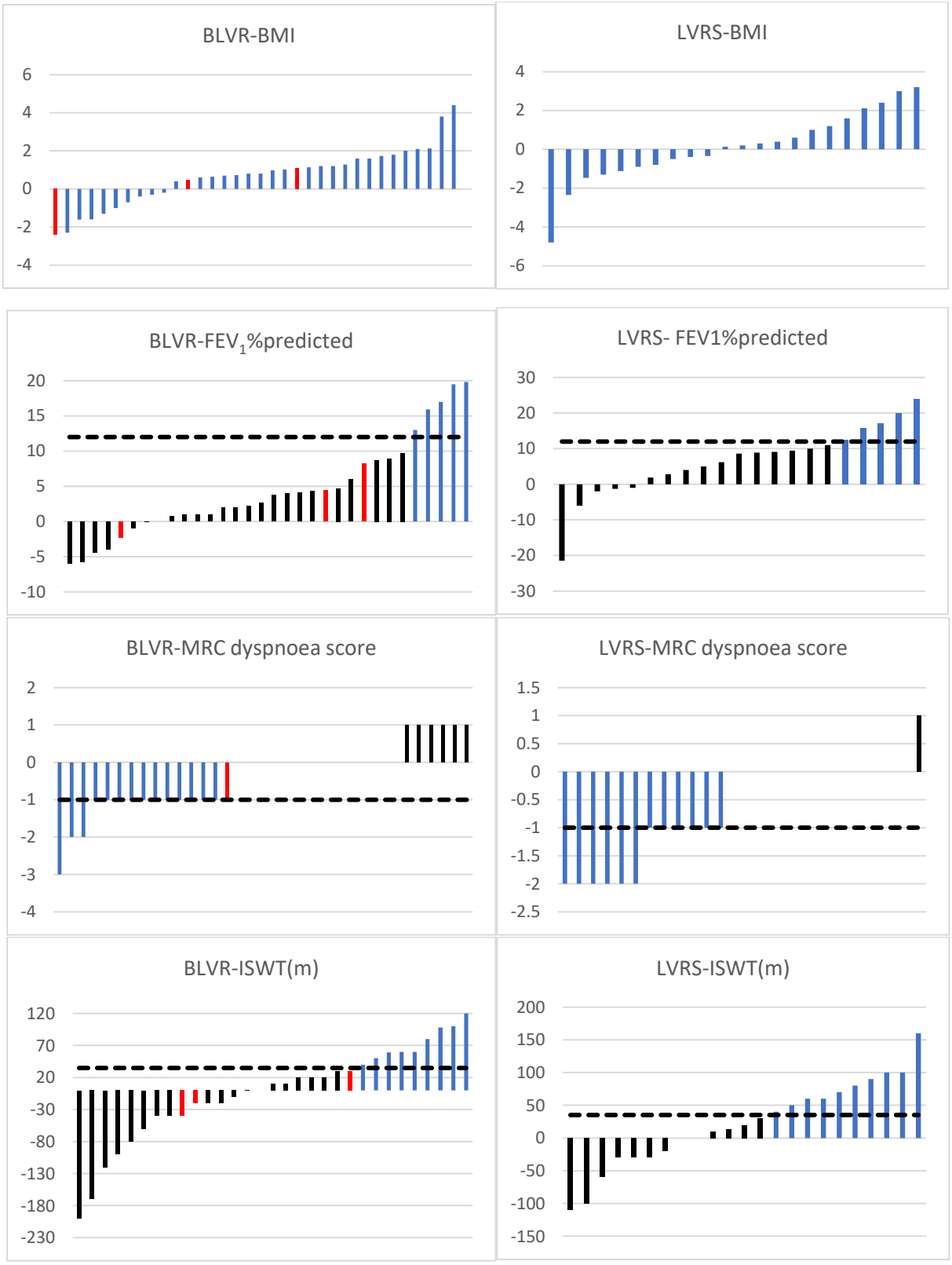
Figure 4: Responders based on Minimal Clinically Important Difference for the i-BODE index (complete case analysis)



Legend to Figure 4: Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for the iBODE index: -1 points; Black bars represent subjects who did not meet the MCID. Dotted line represents the MCID. Red bars represent those patients that either crossed over or had valves removed, where data was collected.

Figure 5: Responders based on Minimal Clinically Important Difference- i-BODE index components

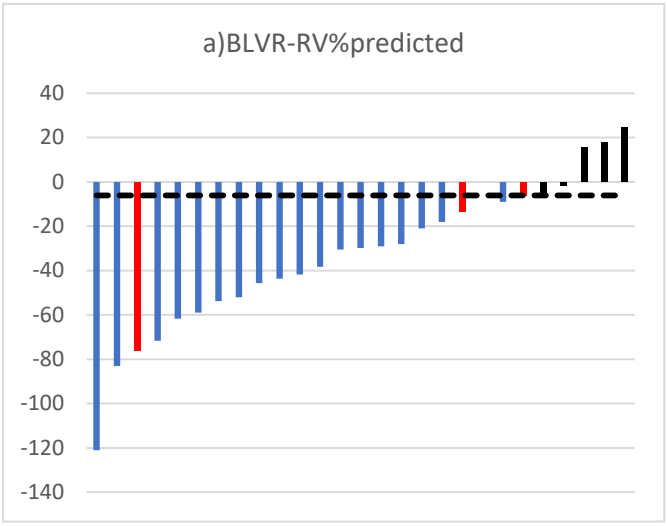
(complete case analysis)

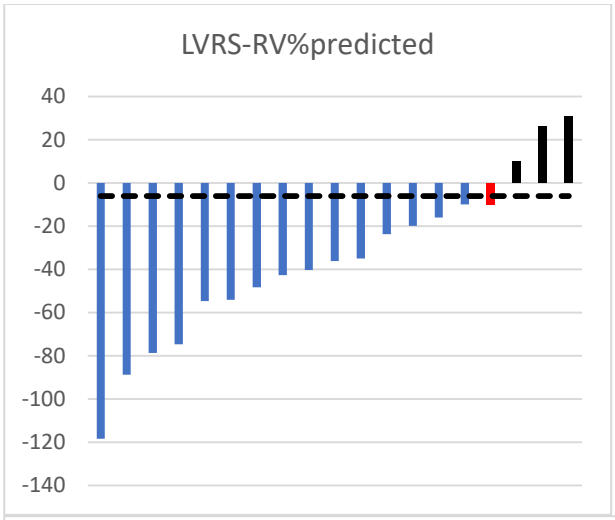


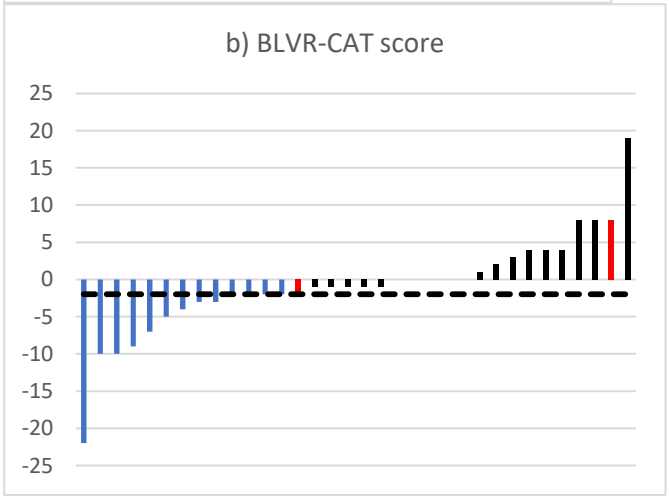
Legend to Figure 5: Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for the specific outcome; a) BMI: no established MID; b) FEV_1%predicted: 12%; c) MRC dyspnoea score: -1 points; d) ISWT: Black bars represent subjects who did not meet the MCID. Dotted line represents the MCID. Red bars represent those patients that either crossed over or had valves removed, where data was collected.

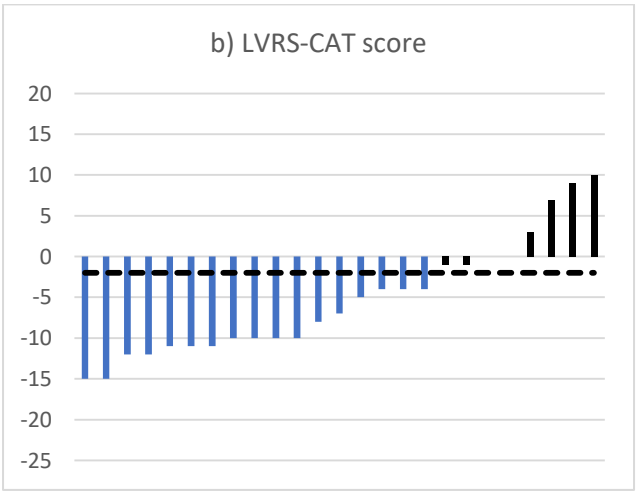
Figure 6: Responders based on Minimal Clinically Important Difference- Important secondary outcomes

(complete case analysis)









Legend to Figure 6: Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for a) RV%predicted (-6.1%) b) CAT

score (-2 points) Black bars represent subjects who did not meet the MCID. Dotted line represents the MCID. Red bars represent those patients that either crossed over or had valves removed, where data was collected.

Table 1: Baseline characteristics of whole cohort and by treatment allocation

	All (n=88)	LVRS (n=41)	BLVR (n=47)
Age (years)	64.6 (7.7)	65.2 (7.9)	64.0 (7.6)
Gender: Female, n (%)	42 (47.7)	22 (53.7)	20 (42.6)
Male, n (%)	44 (52.3)	19 (46.3)	27 (57.4)
Ethnicity: White, n (%)	87 (98.9)	40 (97.6)	47 (100.0)
Ethnicity: Middle Eastern, n (%)	1 (1.1)	1 (2.4)	0 (0.0)
Exacerbations*	2 (1, 3)	1.5 (1, 2.5)	3 (1, 4)
A&E Attendances*	0 (0, 1)	0 (0, 0)	0 (0, 1)
Hospital admissions*	0 (0, 0)	0 (0, 0)	0 (0, 1)
Hospital days*,	0 (0, 0)	0 (0, 0)	0 (0, 1)
LTOT use, n (%)	1 (1.1)	0 (0.0)	1 (2.1)
Ambulatory oxygen use, n (%)	8 (9.1)	5 (12.2)	4 (8.5)
i-BODE index score	5.9 (1.5)	5.9 (1.4)	5.9 (1.6)
BMI (kg/m$^{2)}$	23.7 (3.7)	23.8 (3.9)	23.6 (3.5)
$FEV_{1,}$ %predicted	31.0 (7.9)	32.0 (7.7)	30.2 (8.0)
MRC dyspnoea score	4 (3, 4)	4 (4, 4)	4 (3, 4)
ISWT (m)	210 (125, 265)	200 (130, 260)	210 (120, 270)
Other Lung function parameters			
FEV_1(l)	0.80 (0.22)	0.81 (0.21)	0.80 (0.22)
FVC (l)	2.82 (0.81)	2.80 (0.70)	2.84 (0.90)
FVC, %predicted	86.1 (19.0)	88.2 (20.0)	84.3 (18.1)
FEV_1/FVC ratio	28.03 (24.08, 35)	28.02 (25.5, 32)	29.0 (23.89, 35.4)
TLC (l)	8.08 (1.83)	7.91 (1.87)	8.20 (1.81)
TLC, %predicted	142.0 (14.1)	142.4 (13.8)	141.7 (14.5)
RV (l)	5.3 (1.2)	5.2 (1.3)	5.4 (1.1)
RV, %predicted	240.1 (39.0)	236.9 (39.3)	242.9 (39.0)
RV_TLC ratio	64.0 (30)	63.9 (5.6)	64.0 (7.0)
FRC (l)	6.3 (1.4)	6.1 (1.5)	6.4 (1.3)
FRC, % predicted	195.5 (182, 211.5)	197.5 (182.4, 209.1)	194.5 (178.9, 214.6)
TLco, %predicted	35.8 (10.0)	35.9 (10.6)	35.7 (9.5)
Kco, %predicted	46.7 (13.9)	46.4 (14.4)	47.1 (13.5)
Other Secondary outcomes			
FFMI (kg.m^2)	30.9 (5.7)	30.9 (6.2)	30.9 (5.3)

CAT score	23.1 (6.4)	23.9 (6.6)	22.5 (6.1)
c-PPAC amount	28.4 (12.7)	27.5 (11.1)	29.2 (14.4)
c-PPAC difficulty	50.4 (12.8)	53.8 (11.5)	47.6 (13.4)
c-PPAC total	44.8 (12.8)	47.1 (13.4)	42.8 (12.1)
Steps per day	2551 (1463, 3812)	2809 (1455, 5398)	2292 (1471, 3450)

Data are presented as n (%) , mean(SD) or median (IQR). LVRS=lung volume reduction surgery. BLVR= bronchoscopic lung volume reduction. LTOT= long term oxygen therapy. BMI= body mass index. FEV_1= forced expiratory volume in 1 sec. FVC= forced vital capacity. TLC= total lung capacity. RV= residual volume. FRC= functional residual capacity. TLco= carbon monoxide transfer factor. Kco= carbon monoxide transfer coefficient.MRC= Medical Research Council. ISWT= incremental shuttle walk test. CAT= chronic obstructive pulmonary disease (COPD) assessment test score. i-BODE= composite health status measure made up of B=BMI; O=Obstruction (FEV_1%predicted); D= Dyspnoea (MRC score); E=Exercise capacity (ISWT).* Self-reported in preceding year.

Table 2: Primary and secondary outcomes: change from baseline to 12 months follow up

	–Change from baseline		Treatment Effect (95% CI)	p
	LVRS	BVLR		
i-BODE score	21: -1.10 (1.44)	28: -0.82 (1.61)	0.27 (-0.62 to 1.17)	0.54
BMI (kg/m^2)	22: 0.10 (1.83)	35: 0.74 (1.57)	0.64 (-0.27 to 1.56)	0.16
FEV$_1$%predicted	24: 1.1 (9.1)	33: 4.5 (6.8)	3.4 (-0.8 to 7.6)	0.11
MRC dyspnoea score	26: -0.65 (0.89)	36: -0.33 (0.97)	-0.32 (-0.80 to 0.16)	0.19
ISWT (m)	22: 27.9 (60.7)	32: -4.8 (73.8)	-32.7 (-71.0 to 5.5)	0.09
RV % predicted	19: -36.1 (-54.6, -10)	27: -30.1 (-53.7, -9)	2.7 (-25.4 to 19.1)	0.81
CAT score	25: -7 (-11, -1)	34: -1 (-3, 3)	-6 (2 to 9)	0.005
FFMI (kg/m^2)	19: -0.79 (-3.67, 1.44)	28: 0.46 (-1.84, 1.89)	0.98 (-1.25 to 3.20)	0.39
C-PPAC Amount	18.0 (19.7)	15.3 (14.5)	-2.7 (-24.6 to 19.2)	0.79
C-PPAC Difficulty	17.2 (14.4)	12.0 (17.9)	-5.2 (-17.1 to 6.7)	0.38
C-PPAC Total	18.3 (17.3)	16.1 (16.9)	-2.2 (-15.8 to 11.4)	0.74
Steps per day	-478.5 (-1166, 1102)	543 (-226, 1332)	-847.5 (-2857, to 8726)	0.31

Data are presented as number of participants data collected for, followed by mean (SD) or median (IQR) change from baseline to 12 months follow up. Treatment effects are for BLVR vs LVRS. i-BODE= composite health status measure made up of B=BMI; O=Obstruction (FEV$_1$%predicted); D= Dyspnoea (MRC score); E=Exercise capacity (ISWT; incremental shuttle walk test). FFMI: Fat free mass index; RV= Residual Volume; CAT: COPD assessment test; RV: Residual Volume; C-PPAC: Clinical visit-PROactive Physical Activity in COPD.

Table 3: Safety outcomes

	LVRS (n=34)				BLVR (n=46)			
	Subjects <30 days	Subjects 1 – 12 months	Events <30 days	Events 1-12 months	Subjects <30 days	Subjects 1 – 12 months	Events <30 days	Events 1-12 months
Any haemoptysis	1 (2.9)	0	1	0	2(4.3)	2(4.3)	2	2(4.3)
Massive haemoptysis	0	0	0	0	0	0	0	0
Mortality	0	1 (2.9)	0	1(2.9)	1 (2.2)	0	1	0
AECOPD requiring hospitalisation	2(5.9)	1(2.9)	2	1(2.9)	2 (4.3)	7 (15.2)	2	7(15.2)
AECOPD requiring NIV	0	0	0	0	1 (2.2)	0	1	0
AECOPD requiring ITU stay	0	0	0	0	0	0	0	0
AECOPD treated at home	8 (23.5)	3 (8.8)	10	3(8.8)	9 (19.6)	6(13.0)	19	6(13.0)
Pneumonia	0	1 (2.9)	0	1(2.9)	2 (4.3)	1 (2.2)	2	2 (4.3)
Pneumothorax	n/a	n/a	n/a	n/a	14(30.4)	1	14	1 (2.2)
Post-surgical air leak	4 (11)	0	5	0	-	-	-	-
Respiratory failure	1 (2.9)	0	1	0	0	0	0	0
Subcutaneous emphysema	12(35.3)	0	12	0	1 (2.2)	0	1	0
Valve migration	-	-	-	-	2 (4.3)	0	2	0
Valve removal	-	-	-	-	2 (4.3)	1 (2.2)	2	1
Other repeat procedure	2 (4.3)	0	2	0	5 (10.9)	0	5	0
Prolonged stay post procedure	11 (32.4)	n/a	n/a	n/a	13 (28.3)	n/a	n/a	n/a

Legend to table 3: Data are presented as n(%). AECOPD: Acute exacerbation of chronic obstructive pulmonary diseases; LVRS: Lung volume reduction surgery; BLVR: bronchoscopic lung volume reduction. NIV: Non-invasive ventilation; ITU:

Intensive care unit. Serious adverse events (SAE's) were events leading to death, hospitalisation, or prolongation of existing hospitalisation, persistent or significant disability/incapacity or to serious deterioration in health that resulted in a life-threatening illness or injury, a permanent impairment of a body structure or body function. Prolonged length of stay defined as >10 days in LVRS and >4 days in BLVR.

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Online Data Supplement

Comparative Effectiveness of Lung Volume Reduction Surgery for Emphysema and Bronchoscopic lung volume reduction with valve placement: a randomised controlled trial.

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Appendix

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Table S1: Comparing baseline characteristics of participants with and without primary outcome at 12 months follow up.

	Full i-BODE collected (n=49)	Full i-BODE not collected (n=39)	P value
Age (years)	64.4 (7.2)	64.8 (8.5)	0.82
Gender (M/F)	24/27	22/15	0.26
Exacerbations*,	2.3 (1.7)	2.8 (3.0)	0.34
A&E Attendances*,	0.4 (0.8)	0.4 (0.8)	0.31
Hospital admissions*,	0.4 (1.0)	0.4 (0.8)	0.40
Hospital days*,	1.7 (4.3)	1.9 (4.6)	0.42
i-BODE index score	5.8 (1.6)	6.1 (1.4)	0.29
BMI ($kg/m^{2)}$	23.6 (3.5)	23.4 (3.9)	0.60
$FEV_{1,}$ %predicted	31.2 (7.9)	30.9 (7.9)	0.88
MRC dyspnoea score	3.9 (0.7)	3.9 (0.8)	0.95
ISWT (m)	229.(120)	187 (90.0)	0.06
Other Lung function parameters			
FEV_1(l)	0.78 (0.20)	0.83 (0.23)	0.36
FVC, %predicted	89.1 (19.3)	82.1 (18.0)	0.09
TLC, %predicted	142.3 (13.4)	140.9 (15.7)	0.65
RV, %predicted	237.6 (36.8)	242.6 (41.8)	0.57
RV/TLC ratio	63.7 (5.9)	64.5 (7.1)	0.56
TLco, %predicted	35.6 (10.9)	36.1 (8.6)	0.80
Kco, %predicted	46.7 (14.1)	46.7 (13.7)	0.99
FFMI ($kg.m^2$)	30.8 (6.1)	31.0 (5.0)	0.93
CAT score	22.9 (6.6)	23.4 (6.1)	0.69

Data are presented as n (%) mean (SD) or median (IQR). i-BODE= composite health status measure made up of B=BMI; O=Obstruction (FEV_1%predicted); D= Dyspnoea (MRC score); E=Exercise capacity (ISWT).
BMI= body mass index. FEV_1= forced expiratory volume in 1 sec. MRC= Medical Research Council. ISWT= incremental shuttle walk test. FVC= forced vital capacity. TLC= total lung capacity. RV= residual volume. TLco= carbon monoxide transfer factor. Kco= carbon monoxide transfer coefficient. CAT= chronic obstructive pulmonary disease (COPD) assessment test score. FFMI= fat free mass index. * Self-reported in preceding year.

Table S2: 3 Months Follow up – based on all available data

Variable	All subjects (n=80)		LVRS (n=34)		BLVR (n=46)		p
	Missing	Statistic	Missing	Statistic	Missing	Statistic	
No. of Exacerbations	8	1 (0, 1)	3	0 (0, 1)	5	1 (0, 1)	0.15
A&E Attendances	8	0 (0, 0)	3	0 (0, 0)	5	0 (0, 0)	0.70
Hospital admissions	9	0 (0, 0)	4	0 (0, 0)	5	0 (0, 0.5)	0.19
Hospital days	27	0 (0, 0)	7	0 (0, 0)	20	0 (0, 0)	0.79
i-BODE score	17	4.5 (2.1)	6	4.3 (1.8)	11	4.7 (2.3)	0.39
BMI	10	23.8 (3.5)	7	23.7 (4.1)	3	23.9 (3.0)	0.82
MRC dyspnoea score	9	3.1 (1.0)	3	2.9 (1.0)	6	3.3 (1.1)	0.17
ISWT (M)	10	220 (160, 310)	3	205 (160, 330)	7	220 (160, 290)	0.81
FVC %	17	94.3 (20.5)	6	91.0 (18.9)	11	97.1 (21.7)	0.24
FEV_1/FVC	20	31.2 (8.3)	7	32.3 (9.2)	13	30.2 (7.5)	0.32
TLC (L)	24	7.4 (1.5)	10	7.2 (1.5)	14	7.6 (1.5)	0.31
TLC %	24	127.9 (13.9)	10	125.5 (14.5)	14	129.8 (13.2)	0.25
RV	24	4.3 (1.1)	10	4.2 (0.9)	14	4.3 (1.3)	0.63
RV %	24	188.8 (46.0)	10	185.3 (48.5)	14	191.6 (44.4)	0.61
RV%TLC	24	56.9 (8.8)	10	57.7 (8.3)	14	56.2 (9.2)	0.53
FRC	33	5.6 (1.3)	12	5.3 (1.2)	21	5.8 (1.4)	0.19
FRC %	33	174.5 (25.8)	12	172.1 (26.3)	21	176.7 (25.6)	0.54
TLCo	27	38.9 (12.9)	12	37.3 (11.1)	15	40.1 (14.1)	0.44
Kco	28	46.8 (12.8)	12	45.8 (12.8)	16	47.7 (12.9)	0.61
PaO_2	41	9.8 (1.4)	18	10.3 (1.6)	23	9.4 (1.2)	0.06
$PaCO_2$	41	4.82 (0.55)	18	4.78 (0.58)	23	4.85 (0.54)	0.69
CAT score	9	18.3 (8.4)	3	16.0 (8.2)	6	20.2 (8.2)	0.034
FFMI	14	30.6 (6.1)	5	31.0 (6.1)	9	30.2 (6.1)	0.63

Data are presented as mean(SD) or median (IQR). LVRS=lung volume reduction surgery. BLVR= bronchoscopic lung volume reduction surgery. BMI= body mass index. FEV_1= forced expiratory volume in 1 sec. MRC= Medical Research Council. ISWT= incremental shuttle walk test FVC= forced vital capacity. TLC= total lung capacity. RV= residual volume. FRC= functional residual capacity. TLco= carbon monoxide transfer factor. Kco= carbon monoxide transfer coefficient. PaO_2= arterial partial pressure of oxygen. $PaCO_2$=arterial partial pressure of carbon dioxide. CAT= chronic obstructive pulmonary disease (COPD) assessment test score. *Self-reported in preceding year.

Table S3: 12 Month Follow up –based on all available data

Variable	All subjects (n=80)		LVRS (n=34)		BLVR (n=46)		p
	Missing	Statistic	Missing	Statistic	Missing	Statistic	
AECOPD*	16	1 (0, 2)	7	1 (0, 2)	9	1 (0, 2)	0.97
A&E Attendance*	17	0 (0, 0)	7	0 (0, 0)	10	0 (0, 0)	0.44
Hospital admissions*	15	0 (0, 0)	6	0 (0, 0)	9	0 (0, 0)	0.92
Hospital days*	16	0 (0, 0)	6	0 (0, 0)	10	9 (0, 0)	0.43
iBODE score	31	4.8 (2.0)	13	4.5 (1.8)	17	5.0 (2.2)	0.38
BMI (kg/m^2)	21	24.1 (3.3)	11	23.9 (3.6)	10	24.2 (3.1)	0.68
FEV1 %	22	34.2 (11.0)	10	34.0 (11.7)	12	34.4 (10.7)	0.91
MRC dyspnoea score	17	3.35 (0.98)	8	3.27 (0.96)	9	3.42 (1.00)	0.61
ISWT (m)	25	235 (160, 310)	12	265 (180, 320)	13	210 (150, 310)	0.57
FVC (l)	22	2.96 (0.99)	10	2.84 (0.93)	12	3.04 (1.01)	0.44
FVC %	22	92.3 (28.0)	10	90.0 (30.5)	12	94.0 (26.4)	0.61
FEV_1/FVC	22	30.0 (6.5)	10	31.4 (6.3)	12	29.0 (6.5)	0.17
TLC (l)	32	7.5 (1.5)	14	7.4 (1.7)	18	7.6 (1.4)	0.63
TLC %	33	133.4 (16.3)	15	132.1 (16.7)	18	134.2 (16.2)	0.55
RV (l)	32	4.48 (1.15)	14	4.48 (1.39)	18	4.49 (0.96)	0.98
RV %	33	201.4(43.9)	15	199.6(48.4)	18	202.7(41.5)	0.81
RV%TLC	32	59.6 (9.6)	14	60.5 (11.2)	18	59.0 (8.3)	0.59
FRC (l)	36	5.7 (1.3)	15	5.6 (1.5)	21	5.8 (1.2)	0.57
FRC %	37	182.1(28.9)	16	181.2(32.6)	21	182.8(26.6)	0.86
TLco	37	38.4 (10.1)	18	37.8 (12.0)	19	37.3 (11.5)	0.77
Kco	36	49.0 (14.8)	18	48.9 (14.7)	18	49.1 (15.2)	0.97
PaO_2	44	9.7 (1.4)	23	10.3 (1.5)	21	9.4 (1.4)	0.08
$PaCO_2$	44	4.96 (0.56)	23	4.78 (0.61)	21	5.05 (0.53)	0.19
CAT	20	20.2 (8.1)	9	18.3 (8.0)	11	21.7 (7.9)	0.10
FFMI	29	30.5 (6.3)	13	28.9 (5.5)	16	31.7 (6.6)	0.12

Data are presented as mean(SD) or median (IQR). LVRS=lung volume reduction surgery. BLVR= bronchoscopic lung volume reduction surgery. BMI= body mass index. FEV_1= forced expiratory volume in 1 sec. MRC= Medical Research Council. ISWT= incremental shuttle walk test FVC= forced vital capacity. TLC= total lung capacity. RV= residual volume. FRC= functional residual capacity. TLco= carbon monoxide transfer factor. Kco= carbon monoxide transfer coefficient. PaO_2= arterial partial pressure of oxygen. $PaCO_2$=arterial partial pressure of carbon dioxide. CAT= chronic obstructive pulmonary disease (COPD) assessment test score. * Self-reported in preceding year.

Table S4: Imputed Data Analysis for Primary and secondary outcome variables

Baseline	**LVRS (n=41)**	**BLVR (n=47)**	**P**
i-BODE index score	5.9 (1.4)	5.9 (1.4)	0.92
BMI (kg/m^2)	23.6 (4.0)	23.6 (3.5)	0.83
FEV_1%predicted	32.0 (7.7)	30.2 (8.0)	0.27
MRC dyspnoea score	4 (4,4)	4 (3,4)	0.32
ISWT (m)	200 (130, 260)	210 (120, 270)	0.79
FEV1	0.81 (0.21)	0.80 (0.22)	0.82
RV % predicted	236.7 (38.8)	242.4 (38.7)	0.50
CAT	23.9 (6.6)	22.5 (6.1)	0.31
FFMI	31.0 (6.0)	30.8 (5.2)	0.89
3 Months			
Variable	**LVRS (n=34)**	**BLVR (n=46)**	**P**
i-BODE index score	4.4 (2.1)	4.9 (2.3)	0.38
BMI (kg/m^2)	23.4 (4.1)	24.1 (3.6)	0.45
FEV_1%predicted	37.7 (9.4)	37.1 (12.3)	0.82
MRC dyspnoea score	3 (2,4)	4 (2,4)	0.12
ISWT (m)	190 (11, 332)	220 (160, 290)	0.85
RV % predicted	190.7 (44.0)	195.8 (49.8)	0.63
CAT score	16 (8, 23)	21 (14, 27)	0.028
FFMI (kg/m^2)	31.0 (5.8)	31.2 (6.4)	0.89
12 Months			
Variable	**LVRS (n=34)**	**BLVR (n=46)**	**P**
i-BODE score	5.1 (21.)	5.0 (21.)	0.94
BMI (kg/m^2)	23.9 (4.0)	24.1 (3.4)	0.82
FEV_1%predicted	33.7 (10.8)	33.1 (11.6)	0.81
MRC dyspnoea score	3.5 (3,4)	3 (3,4)	0.80
ISWT (m)	212 (165, 310)	208 (157, 296)	0.76
RV % predicted	195.6 (62.6)	106.3 (46.2)	0.38
CAT score	20.5 (9.1)	22.4 (8.4)	0.36
FFMI (kg/m^2)	30.1 (6.3)	31.4 (6.5)	0.38

Data are presented as mean(SD) or median (IQR). LVRS=lung volume reduction surgery. BLVR= bronchoscopic lung volume reduction surgery. BMI= body mass index. FEV_1= forced expiratory volume in 1 sec. MRC= Medical Research Council. ISWT= incremental shuttle walk test FVC= forced vital capacity. TLC= total lung capacity. RV= residual volume. FRC= functional residual capacity. TLco= carbon monoxide transfer factor. Kco= carbon monoxide transfer coefficient. PaO_2= arterial partial pressure of oxygen. $PaCO_2$=arterial partial pressure of carbon dioxide. CAT= chronic obstructive pulmonary disease (COPD) assessment test score.

* Self-reported in precluding year.

Table S5: Primary and secondary outcomes: Change from Baseline to 12 months- complete case analysis and imputed data

Complete-Case Analysis

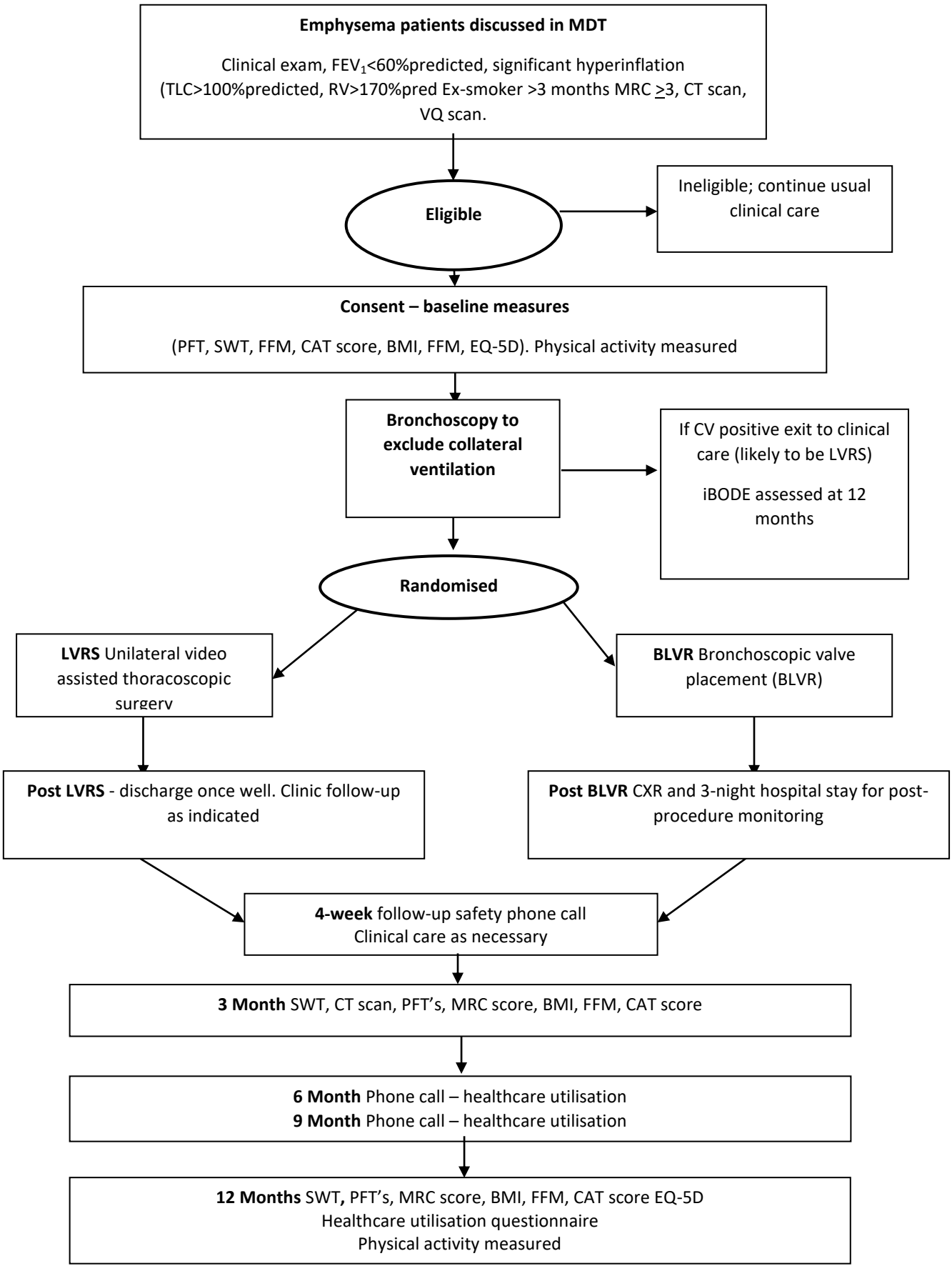
	Difference: 12 months - Baseline		Treatment Effect (95% CI)	p
	LVRS	BLVR		
i-BODE index score	21: -1.10 (1.44)	28: -0.82 (1.61)	0.27 (-0.62 to 1.17)	0.54
BMI (kg/m^2)	22: 0.10 (1.83)	35: 0.74 (1.57)	0.64 (-0.27 to 1.56)	0.16
FEV1 %predicted	24: 1.1 (9.1)	33: 4.5 (6.8)	3.4 (-0.8 to 7.6)	0.11
MRC dyspnoea score	26: -0.65 (0.89)	36: -0.33 (0.97)	-0.32 (-0.80 to 0.16)	0.19
ISWT (m)	22: 27.9 (60.7)	32: -4.8 (73.8)	-32.7 (-71.0 to 5.5)	0.09
FFMI (kg/m^2)	19: -0.79 (-3.67, 1.44)	28: 0.46 (-1.84, 1.89)	0.98 (-1.25 to 3.20)	0.39
RV % predicted	19: -36.1 (-54.6, -10)	26: -30.1 (-53.7, -9)	-2.7 (-25.4 to 19.1)	0.81
CAT score	25: -7 (-11, -1)	34: -1 (-3, 3)	6 (2 to 9)	0.005

Imputed data

Variable	Difference: 12 months - Baseline		Treatment effect (95%CI)	P
	LVRS	BLVR		
i-BODE score index	-0.74 (1.62)	-0.89 (1.43)	-0.15 (-0.84 to 0.53)	0.66
BMI (kg/m^2)	0.07 (1.74)	0.64 (1.48)	0.57 (-0.15 to 1.29)	0.12
MRC dysponea score	-0.50 (1.02)	-0.40 (0.89)	0.1 (-0.33 to 0.53)	0.64
FEV1 %PRED	1.3 (8.5)	2.8 (8.0)	1.5 (-2.3 to 5.2)	0.44
ISWT (m)	21.6 (67.1)	9.2 (74.7)	-12.4 (-30.5 to 1.5)	0.45
FFMI (kg/m^2)	-0.34 (-2.49, 1.43)	0.51 (-2.95, 3.17)	0.81 (-0.95 to 2.81)	0.38
RV % predicted	-32.47 (-55.66, -10)	-29.10 (-59, -9.67)	-0.38 (-17.60 to 17.96)	0.99
CAT score	-3.60 (7.30)	-0.04 (7.58)	3.56 (0.18 to 6.93)	0.04

Data are presented as mean(SD) or median (IQR). LVRS=lung volume reduction surgery. BLVR= bronchoscopic lung volume reduction surgery. BMI= body mass index. FEV_1= forced expiratory volume in 1 sec. MRC= Medical Research Council. ISWT= incremental shuttle walk test FVC= forced vital capacity. TLC= total lung capacity. RV= residual volume. FRC= functional residual capacity. TLco= carbon monoxide transfer factor. Kco= carbon monoxide transfer coefficient. PaO_2= arterial partial pressure of oxygen. $PaCO_2$=arterial partial pressure of carbon dioxide. CAT= chronic obstructive pulmonary disease (COPD) assessment test score. * Self-reported in preceding year.

Figure S1: Schematic outline of the trial design.



Legend to Figure S1: BLVR, bronchoscopic lung volume reduction; BMI, body mass index; CAT, COPD Assessment Test; CV, collateral ventilation; CXR, chest X-ray; FFM, fat-free mass; iBODE, a composite score including BMI, airflow obstruction, dyspnoea and exercise capacity (incremental shuttle walk test); LVRS, lung volume reduction surgery; MDT, multidisciplinary team; MRC, Medical Research Council; PFT, pulmonary function tests, RV, residual volume; SWT, shuttle walk test; TLC, total lung capacity; VQ lung ventilation/perfusion scan

Figure S2: Mean change in secondary outcome measures at 3 months and 12 months post procedure in the LVRS group compared with the BLVR group.

Figure S2a: RV% predicted

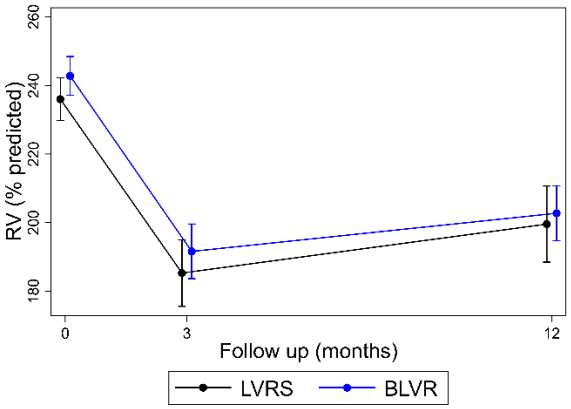


Figure S2b: CAT score

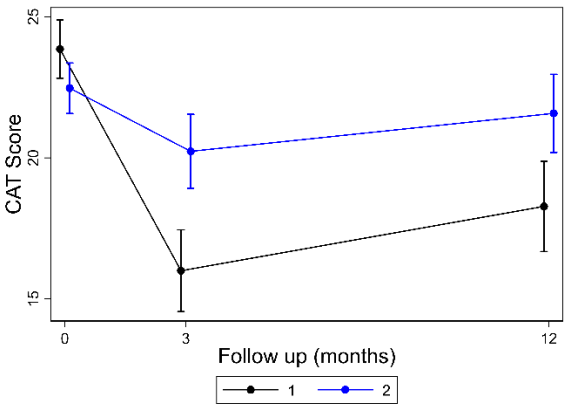


Figure S2c: FFMI

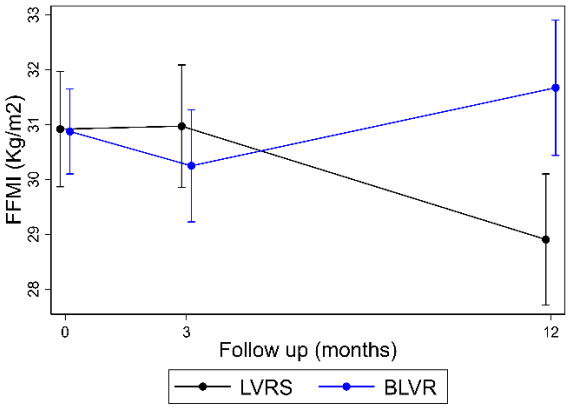
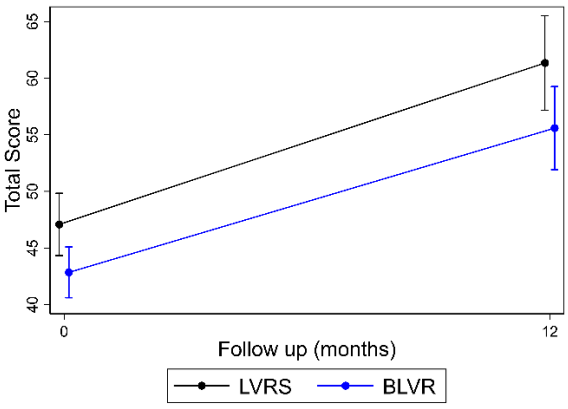
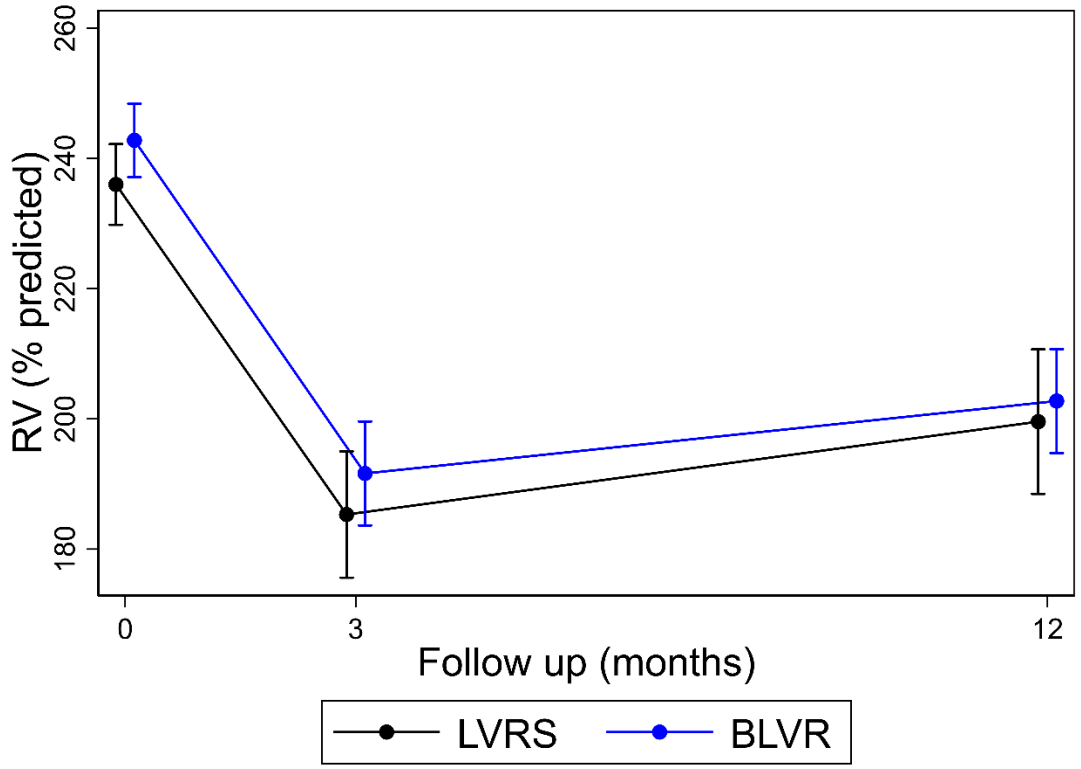


Figure S2d: Total C-PACC score



Legend to figure S2: Data presented are mean (SD) for baseline, 3 months and 12 months post procedure. LVRS: Lung volume reduction surgery; BLVR: Bronchoscopic lung volume reduction. RV: Residual Volume; CAT score: chronic obstructive pulmonary disease (COPD) assessment test score; FFMI; Fat free mass index; C-PACC score: Clinical visit-PROactive Physical Activity in COPD. Figure S2a p=0.81; Figure S2b p=0.005; Figure S2c p=0.39; Figure S2d p=0.74.

Figure S3: Effect of lung volume reduction interventions on Residual Volume (%predicted)



Legend to figure S3: Data presented are mean (SD) for baseline, 3 months and 12 months post procedure. Lung volume reduction surgery; BLVR: Bronchoscopic lung volume reduction. RV: Residual Volume. Between group difference at 12 months; p=0.81

Figure S4: Change in Physical activity outcomes at 3 months and 12 months post procedure in the LVRS group compared with the BLVR group.

Figure S3a: C-PPAC Amount score

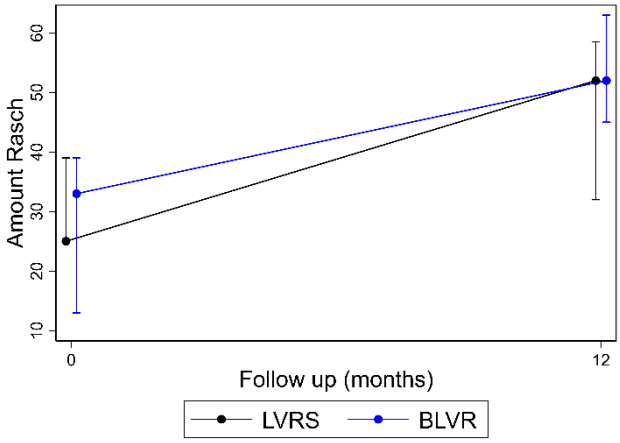


Figure S3b: C-PPAC Difficulty score

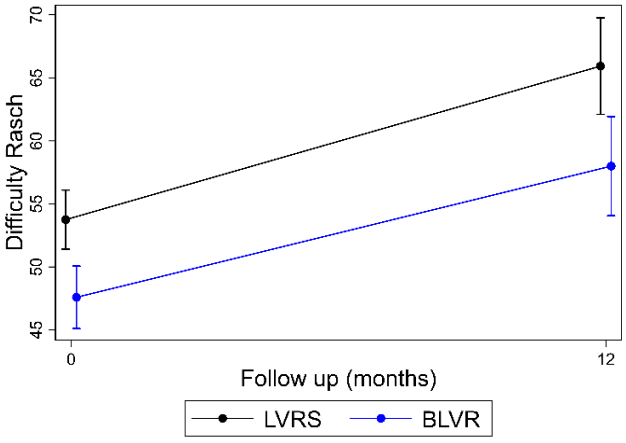


Figure S3d: C-PPAC Total score

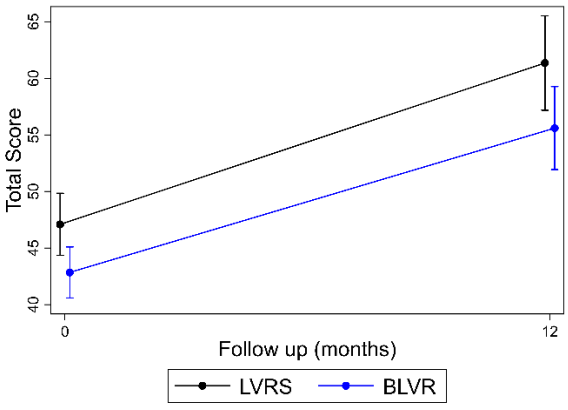
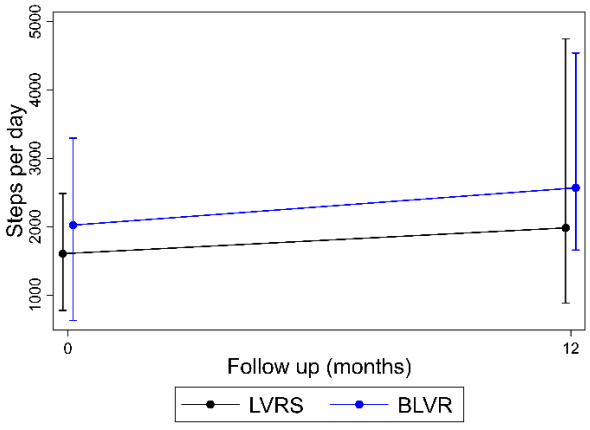
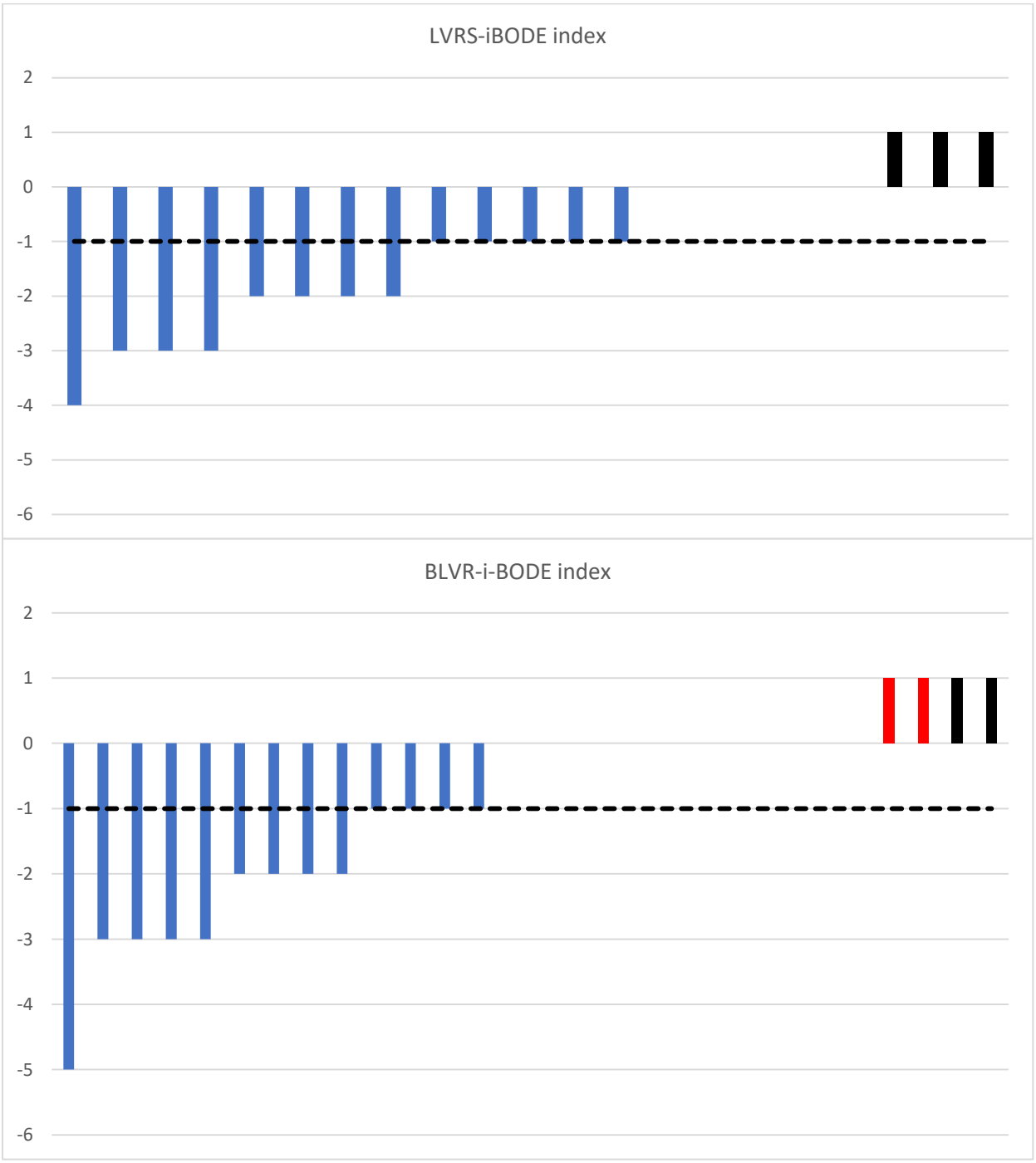


Figure S3c: Steps per day



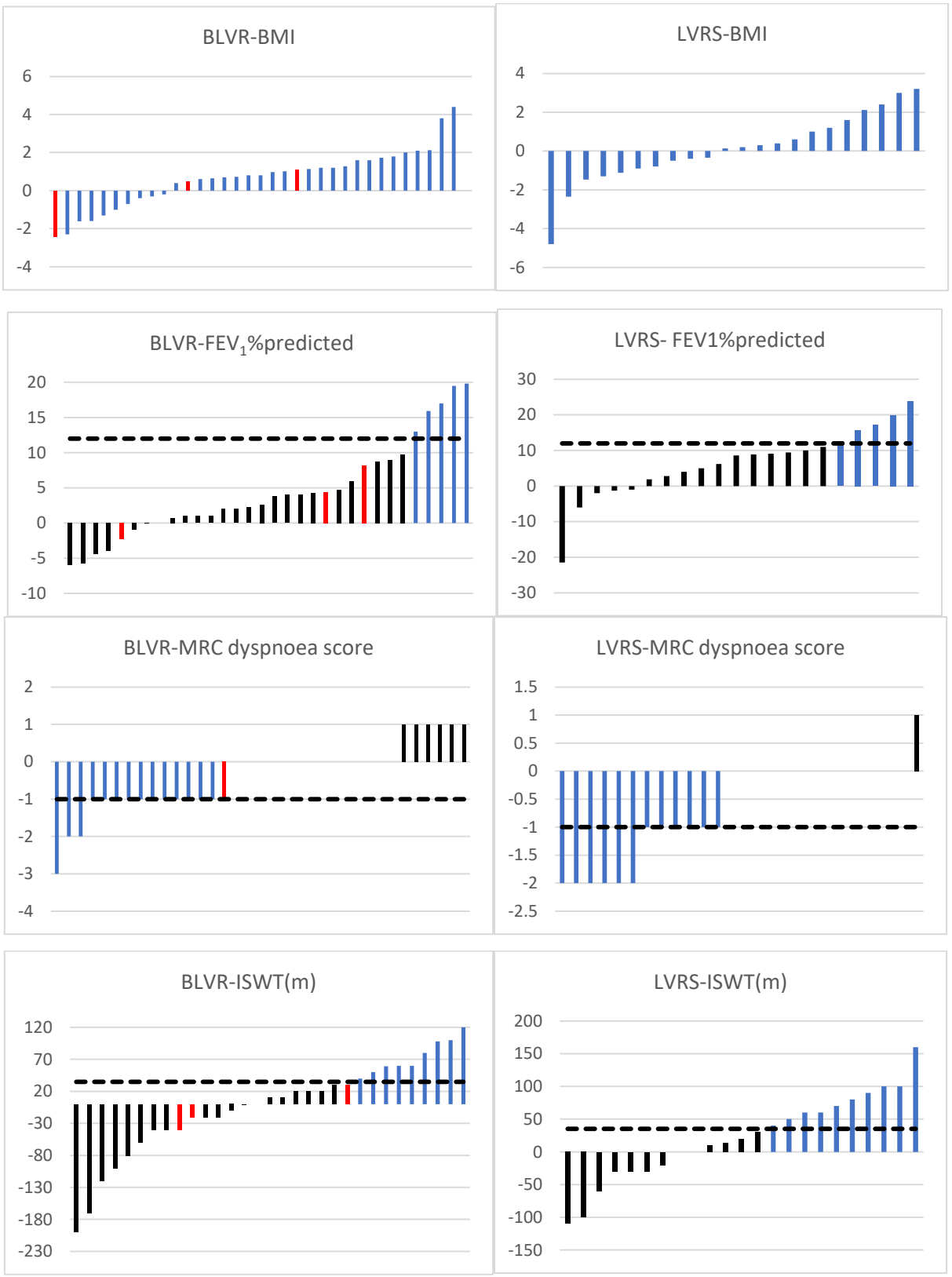
Legend to figure S3: Data presented are mean (SD) for baseline, 3 months and 12 months post procedure. LVRS: Lung volume reduction surgery; BLVR: Bronchoscopic lung volume reduction; compared with the BLVR group. C-PACC score: Clinical visit-PROactive Physical Activity in COPD. Figure S3a p=0.79; Figure S3b p=0.38; Figure S3c p=0.74; Figure S3d p=0.39

Figure S5: Responders based on Minimal Clinically Important Difference for the i-BODE index (complete case analysis)



Legend to Figure S5: Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for the iBODE index: -1 points; Black bars represent subjects who did not meet the MCID. Dotted line represents the MCID. Red bars represent those patients that either crossed over or had valves removed, where data was collected.

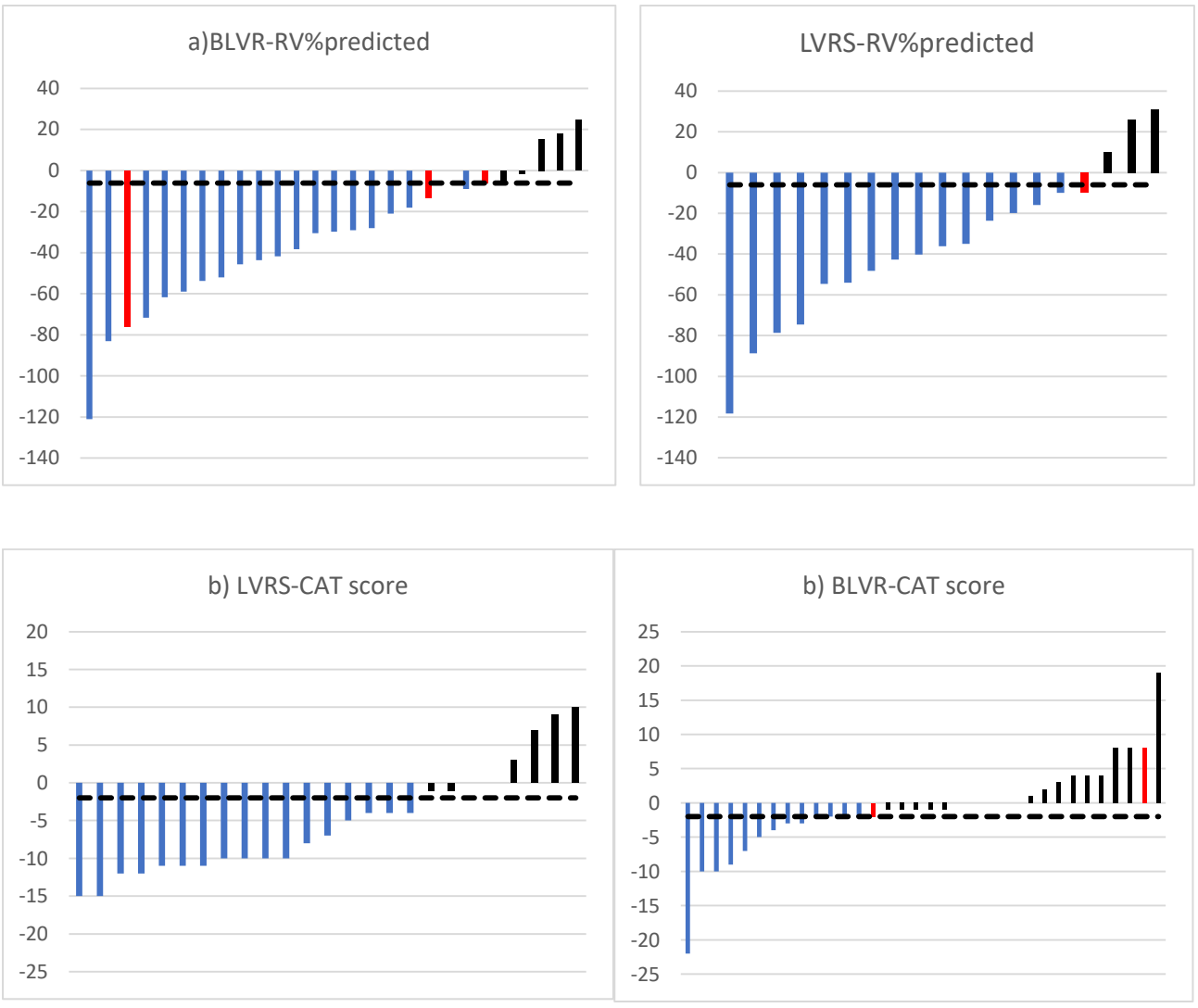
Figure S6: Responders based on Minimal Clinically Important Difference- i-BODE index components (complete case analysis)



Legend to Figure S6: Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for the specific outcome; a) BMI: no established MID; b) FEV_1%predicted: 12%; c) MRC dyspnoea score: -1 points; d) ISWT: Black bars represent subjects who did not meet the MCID. Dotted line represents the MCID. Red bars represent those patients that either crossed over or had valves removed, where data was collected.

Figure S7: Responders based on Minimal Clinically Important Difference- Important secondary outcomes

(complete case analysis)



Legend to Figure S7: Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for a) RV%predicted (-6.1%) b) CAT score (-2 points) Black bars represent subjects who did not meet the MCID. Dotted line represents the MCID. Red bars represent those patients that either crossed over or had valves removed, where data was collected.

Appendix 1

CELEB trial eligibility criteria

Eligibility criteria:	***Inclusion criteria:*** ▪ adults with COPD ▪ FEV_1 <60% ▪ TLC>100% ▪ RV>170% ▪ assessed at MDT to have intact interlobar fissures and heterogeneous emphysema and a candidate for LVRS or BLVR based on thoracic CT and lung perfusion, lung function and functional performance data.
	Exclusion criteria: ▪ smoking within 3 months ▪ CT scan shows interlobar fissures are not intact ▪ major comorbidity limiting survival ▪ significant pulmonary fibrosis ▪ FEV_1 and TLco <20% ▪ PaO_2 < 7.0kPa ▪ $PaCO_2$ > 7kPa ▪ Collateral ventilation assessed by Chartis^{TM} system.

Appendix 2

Chartis procedure

The Chartis™ Pulmonary Assessment System (PulmonX, Redwoood) consists of a single-patient-use catheter with a compliant balloon component at the distal tip, which upon inflation blocks the airway. Air can then flow out from the target compartment into the environment only through the Chartis catheter's central lumen. By connecting to a Chartis console, airway flow and pressure can be displayed. Airway resistance can be calculated and Collateral ventilation (CV) in isolated lung compartments can be measured (1)

Appendix 3

Treatment Details

A median of 4 valves (range 2-7) per subject were placed in the 46 BLVR subjects. Treatment distributions were as follows; 17 (37%) Left upper lobe, 9 (19.7%) left lower lobe, 11 (23.9%) right upper lobe, 4 (8.7%) right lower lobe. 4 (8.7%) right upper and middle lobe combined and 1 (2.2%) right middle and lower lobe combined. In the LVRS arm 19 participants received right sided LVRS, and 15 left sided LVRS. 30 participants received video-assisted thorascopic surgery (VATS) whilst 2 received robot-assisted thorascopic surgery (RATS) and 2 underwent a thoracotomy. All participants in the LVRS arm underwent unilateral procedures.

Appendix 4;

Individual participant details: Repeat procedures, cross-overs and valve removals

In the LVRS arm one participant went back to theatre for EBV insertion due to a prolonged air leak (cross-over) and one participant had a redo thoracotomy and wash out of haemothorax.

There were seven repeat procedures in the BLVR group requiring the participant to undergo a further bronchoscopy; 4 related to pneumothoraces with two requiring surgical chest drains and 2 undergoing blood pleurodesis. Two participants had valves removed and one participant had valves removed and re-placed before undergoing a LVRS (cross-over). Three further participants in the BLVR arm crossed over into the LVRS arm due to no symptomatic benefit.

References

1. Herth FJ, Eberhardt R, Gompelmann D, Ficker JH, Wagner M, Ek L, et al. Radiological and clinical outcomes of using Chartis™ to plan endobronchial valve treatment. European Respiratory Journal. 2013;41(2):302-8.