Lung Volume Reduction Procedures in Chronic Obstructive Pulmonary Disease – Outcomes and Access

Submitted for the degree of Doctor of Philosophy

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Declaration of originality

I declare that the work presented in this thesis is my own, unless otherwise clearly stated or adequately referenced. This is the first time this work has been submitted for assessment as part of a higher degree. Publications arising from this thesis are cited and permission to report data from these publications has been sought from the publishing journal.

Statement of contribution

Chapter 3 was developed by myself, Professor Nicholas Hopkinson (NSH), Professor Mick Steiner (MS) and Professor Jenni Quint (JQ). MS and JQ provided the data from the National Asthma and COPD Audit and guidance for its interpretation. Data analysis and presentation was completed by myself with assistance from Dr Adam Lewis (AL) and oversight from Winston Banya (WB). Chapter four was devised by NSH who wrote the study protocol and obtained ethics approval and authorisation. I was then involved in developing the trial design along with Dr Sam Kemp (SK), Professor Pallav Shah (PSH), Mr David Waller (DW), Mr Simon Jordan (SJ), Mr Winston Banya (WB) and MS. I carried out all research visits, data collection and randomisation for patients at RBH and led the data management and coordination of all other recruiting sites. To ensure adequate blinding, collection of the i-BODE index data was carried out by clinical research staff and lung function data was collected by specialist Physiologists in the lung function department at respective centres; Royal Brompton Hospital, Glenfield Hospital, Golden Jubilee Hospital, Northern General Hospital, and St Bartholomew's Hospital. Trial LVR procedures and clinical management of the patients involved in the trial were both carried out by thoracic surgeons and interventional bronchoscopists at each centre. I set up a trial steering committee and organised quarterly meetings where I acted as the secretary. Professor John Moxham acted as trial committee chair. I provided trial oversight including putting together and submitting amendments, and this duty as well as data collection was taken on by Dr Adam Lewis during the period I was on maternity leave. WB developed the statistical analysis plan for the CELEB trial and carried out the primary analysis and imputation, guided by regular discussion and feedback between myself and him. The initial production of the before and after line graphs were by WB and edited by myself. I carried out the sensitivity analysis and produced the waterfall plots.

The literature review and meta-analysis that is described in chapter five was part of a larger scoping review conducted by the Mobilise-d research team. This team, including myself, carried out the initial scope of the literature and identified the included studies. I then completed an updated search to ensure any newly published records were included. Ashley Polhemus and Laura Delgado Ortiz led on the organisation of the main review and provided key guidance in the early stages of my work. This included devising Figures 5.1, Table 5.2, and Appendix 3, that I then adapted for my work. The statistical meta-analysis for this chapter was carried out by myself with substantial guidance from Costas Kallis (CK). Data extraction and grading of the studies was carried out by myself, Parris Williams and Saeed Alghamdi.

Chapter six was designed by myself and NSH, and support was provided from Athma+LungUK with setting up the trial. The UKLVR registry database was designed and set up by myself and NSH in partnership with Westcliffe Solutions who hosted the web-based platform in line with information governance and GDPR. All centres involved in the study that are recognised in chapter six were responsible for the collection and inputting of data in the registry as well as consenting of patients. At RBH the consent process was completed by myself or AL and data collection was mainly completed by myself or Ashraf Hussain. I provided data trial oversight at all centres. This involved working with each centre's research and development departments for study set up and providing training of research staff involved in data collection and ongoing support. I completed the data analysis for this trial with support from CK.

The idea for chapter seven was developed by myself and NSH and was developed as part of a Kings Health Partnership (KHP) Transformation Programme. The survey was developed by myself with input from NSH and I set up and sent out the survey via SurveyMonkey. Focus groups were set up by myself with support from PW in the conducting of these groups. Input

from Vanessa Vas from the KHP transformation programme was valuable in the development process. Dr Lisa Brighton provided expert guidance on the conducting of the PPIE focus groups and acted as facilitator in this focus group. All pulmonary rehabilitation (PR) centres involved in the development of this tool, that are identified in chapter seven provided substantial input to the focus groups as well as completing the validation process. Ongoing comments from these centres were vital to the development process. I conducted the qualitative and quantitative analyses that were part of this trial with assistance from PW.

Further detail regarding individual contributions is included in each respective chapter.

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Abstract

Lung volume reduction (LVR) therapies represent a potentially life changing treatment option for carefully selected patients with severe emphysema who derive little symptomatic benefit from traditional management plans. However, selection criteria are unclear and no formal referral pathways currently exist. This means that the number of patients undergoing LVR treatment in the UK may be disproportionate to the number eligible and that many may be missing out on these important treatments.

At present, there are two procedures available to patients that fit specific eligibility criteria for LVR that are both recognised in national and international guidelines and have a large body of robust evidence proving their efficacy. These procedures are lung volume reduction surgery (LVRS) and bronchoscopic lung volume reduction (BLVR) using endobronchial valves (EBVs). However, there is currently no published data that directly compares the two procedures to establish which is superior for those that have equipoise for either treatment.

The work presented in this thesis has the primary objective of improving outcomes and access to LVR interventions for people with Chronic Obstructive Pulmonary Disease (COPD) and addresses this within five main study chapters. The aims and structure of this thesis are outlined on the following page along with the four key hypotheses that form the basis of this work. Collectively these studies show that improved patient selection and the development of a more systematic referral pathway will improve standards of care and reduce inequalities in patients being considered for and receiving these important interventions.

Hypothesis, aims and thesis structure

The hypotheses for this work were;

1. The number of patients that receive LVR treatment is disproportionate to the number who may be eligible and therefore many may be missing out on these important treatments due to problems with current patient pathways.
2. The health benefits seen at one-year post LVRS procedure are superior to those seen one-year post BLVR.
3. Walking activity and gait parameters collected using digital measures may have utility as prognostic biomarkers, predicting mortality risk and other important clinical outcomes.
4. It is possible to implement a decision-making tool into PR programmes nationwide, that will accurately and efficiently identify individuals that are suitable for consideration for LVR procedures.

The aims of this research project were;

1) To estimate the proportion of people living in the UK that may be eligible for lung volume reduction (LVR) consideration based on NICE recommendation guidelines and review the current eligibility criteria.
2) To compare the relative effectiveness of Lung volume reduction surgery (LVRS) and brochoscopic lung volume reduction (BLVR) using endobronchial valves (EBV) for patients with emphysema, in terms of lung function, quality of life, exercise capacity and daily physical activity.

3) To review and meta-analyse the current evidence base demonstrating the longitudinal association between walking activity and gait parameters that can be measured digitally, and important clinical outcomes in COPD.

4) To develop a national LVR registry and analyse observational data collected in the registry to establish current clinical practices and track outcomes of all patients receiving LVR treatments in the UK

5) To develop a decision-making tool that can be implemented into pulmonary rehabilitation programmes to facilitate the systematic and timely referral of appropriate candidates for LVR consideration.

This thesis reports five studies;

- A study estimating eligibility for lung volume reduction referral (chapter three) presents an observational study exploring the proportion of patients completing PR at centres throughout the UK that meet the National Institute for Health and Care Excellence (NICE) 2018 guidelines for further consideration for LVR intervention, using data from the Royal College of Physicians (RCP National Asthma and COPD Audit Programme (NACAP).
- The CELEB trial (chapter four), reports the comparative effectiveness of lung volume reduction surgery for emphysema and bronchoscopic lung volume reduction with endobronchial valve placement (CELEB) using a multicentre, single blind, parallel group, randomised controlled trial (RCT) design. The analysis explores if outcomes at one-year post LVRS are substantially superior to BLVR at one-year post procedure.
- A systematic literature review and meta-analysis exploring the value of Digital Mobility outcomes (DMO's) in COPD (chapter five) explores the existing literature

base that investigates walking activity and gait parameters that have the potential to be measured digitally, as predictors of clinical outcomes in COPD. The study's objective is to evaluate if these digital measures have the potential to be adopted as prognostic indicators in people with COPD.

- The UKLVR (UK Lung Volume Reduction) study (chapter six), an observational study using data from the UK lung volume reduction registry (UKLVR), analyses clinical practices across the UK in LVR selection and treatment.
- The development of decision making aid for LVR referrals (chapter seven). This is a mixed methods study using both quantitative and qualitative methodologies to achieve an iterative approach in developing a decision-making tool that can be used by PR programmes to systematically screen COPD patient's eligibility for onward referral for LVR consideration.

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Others that have contributed significantly to this work include Mr. Winston Banya and Dr. Costas Kallis who have both provided generous support and guidance on the statistical analysis featured in this thesis. I could not have completed this without their help. Professor Pallav Shah for providing an expert opinion on my work and continuing advice on my career direction. Dr Rod Lawson for his ongoing support and wise words and Dr Ravi Mahadeva and Mr Babu Naidu who have provided support, guidance, and opportunity for me in the field on lung volume reduction.

Many have contributed to the work that makes up the research chapters in this thesis and I am extremely grateful for all help I received from; the recruiting centres involved in the CELEB trial who all put in an enormous amount of work, particularly during difficult times; The centres that contributed to the UKLVR study and the PR centres involved in the development of the LVR-PR tool, namely the Royal Brompton PR service, Harefield Hospital PR service, Guys and St Thomas' PR service and Kings College Hospital PR service, as well as those

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Finally, a huge thank you goes out to all the patients that were involved in the trials that make up this thesis. Without all of whom this work would not be possible. The part you play in advancing healthcare is invaluable and deeply appreciated.

Dedication

To my parents, for a lifetime of love, support, and encouragement, without which this would not be possible.

To my number one support team and inspiration; Danny, Georgia, and Miles.

Publications arising from this thesis

- **Buttery SC**, Lewis A, Kemp SV*, et al.* Lung volume reduction eligibility in patients with COPD completing pulmonary rehabilitation: results from the UK National Asthma and COPD Audit Programme. *BMJ Open* 2020;10

- **Buttery SC** *et al*; Lung volume reduction surgery versus endobronchial valves: a randomised controlled trial**.** *European Respiratory Journal*, Jan 2023.

- **Buttery SC**, Williams PJ, Alghamdi SM, *et al.* Investigating the prognostic value of digital mobility outcomes in patients with chronic obstructive pulmonary disease: a systematic literature review and meta-analysis. *Eur Respir Rev*. 2023 Nov 22;32(170)

- **Buttery SC**, Lewis A, Alzetani A, *et al*. UKLVR Clinical Research Teams. Survival following lung volume reduction procedures: results from the UK Lung Volume Reduction (UKLVR) registry. *BMJ Open Respir Res*. 2024 Feb 29;11(1)

- **Buttery SC**, Williams PJ, Brighton LJ, *et al.;* Development and implementation of the lung volume reduction pulmonary rehabilitation tool to identify eligibility for lung volume reduction in people with chronic obstructive pulmonary disease during pulmonary rehabilitation. *Chron Respir Dis.* January 2023, vol 20.

Other first author publications produced during this thesis

- **Buttery SC**. Getting the best from pulmonary rehabilitation. *Thorax*. 2023 Oct;78

- **Buttery SC**, Philip KEJ, Alghamdi SM*, et al*; Reporting of data on participant ethnicity and socioeconomic status in high-impac medical journals: a targeted literature review. *BMJ Open* 2022;12

- **Buttery S,** Philip KEJ, Williams P, *et al*;. Patient symptoms and experience following COVID-19: results from a UK-wide survey. *BMJ Open Respir Res*. 2021 Nov;8(1)

- **Buttery SC**, Williams P, Mweseli R, *et al*; Immediate smoking cessation support versus usual care in smokers attending a targeted lung health check: the QuLIT trial. *BMJ Open Respir Res*. 2022 Feb;9(1)

- **Buttery SC**, Zysman M, Vikjord SAA, *et al;* Contemporary perspectives in COPD: Patient burden, the role of gender and trajectories of multimorbidity. *Respirology*. 2021; 26: 419-441.

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Abbreviations

LVR	**Lung volume reduction**
LVRS	Lung Volume Reduction Surgery
BLVR	Bronchoscopic Lung Volume Reduction
EBV	Endobronchial Valve
COPD	Chronic Obstructive Pulmonary Disease
NACAP	National Asthma and COPD Audit Programme
PR	Pulmonary Rehabilitation
RCT	Randomised Controlled Trial
CELEB	Comparative Effectiveness of Lung Volume Reduction Surgery for Emphysema and Bronchoscopic lung volume reduction with valve placement
UKLVR	UK Lung Volume Reduction Registry
KHP	Kings Health Partners
PPIE	Patient and Public Involvement and Engagement
NETT	National Emphysema Treatment Trial
RCP	Royal College of Physicians
NICE	National Institute for Health and Care Excellence
6MWT	Six-minute Walk Test
ISWT	Incremental Shuttle Walk Test
MRC	Medical Research Council
ROC	Receiver Operating Characteristic
ERS	European Respiratory Society
BMJ	British Medical Journal

CT	Computerised Tomography
Pa02	Partial Pressure of Oxygen
PaC02	Partial Pressure of Carbon Dioxide
GA	General Anaesthetic
HDU	High Dependency Unit
i-BODE	Composite health status measure made up of B=BMI; O=Obstruction (FEV_1%predicted); D= Dyspnoea (MRC score); E=Exercise (ISWT)
CAT	COPD Assessment Test
RV	Residual Volume
FFMI	Fat Free Mass Index
c-PPAC	Clinical visit-PROactive Physical Activity in COPD
SD	Standard Deviation
PAL	Physical Activity Level
PA	Physical Activity
DMO	Digital Mobility Outcome
GOLD	Global Initiative for Chronic Obstructive Lung Disease

1 Introduction

1.1 Chronic Obstructive Pulmonary Disease

1.1.1 **Aetiology**

Chronic obstructive pulmonary disease is a respiratory disorder characterised by chronic and usually progressive airflow obstruction that is not fully reversible (GOLD. 2020). The most common symptoms of COPD are breathlessness, a persistent cough (which may or may not be productive of sputum) and chest tightness or wheeze. Symptoms are variable, experienced in varying amounts and have the potential to significantly affect functional ability and quality of life (Miravitlles 2017). Importantly, individuals with COPD have also been found to be at a greater risk of developing significant comorbidities (Celli 2019; Mannino 2008).

With over 3 million people dying of the disease per year (Soriano 2017; Roth 2018), and an estimated 6% of deaths worldwide, COPD is the third leading cause of mortality (Celli 2019) and consequently poses a significant public health challenge. Mortality burden is highest in low and middle-income countries which account for 90% of COPD related deaths (Quaderi 2018). This is likely a result of poor diagnosis, prevention, and treatment in these areas, coupled with having the highest prevalence of the disease (Halpin 2019). A lack of quality clinical guidelines implemented in these countries may also be a contributory factor (Tabyshova 2021). Research has suggested that deprivation and other social determinants of health are associated with mortality and COPD health outcomes (Robichaux 2023) and therefore represent an important target for future interventions.

In the UK, the true prevalence of COPD has been predicted to be between 4.9% and 6.7% but due to inconsistencies in coding these proportions may be underestimated (Stone 2023). Additionally, the combination of an increasing and ageing population means that not only is the number of COPD related deaths set to rise but also the number with more severe disease (Soriano 2017; Dijk 2020). Both have implications for vital allocation of resource and

funding. A 2023 review of COPD care in the UK revealed existing problems in diagnosis and management (Agustí 2023) with only a fifth of those with COPD receiving the basic five fundamentals of COPD care (Williams 2022). Improvements in diagnosis, holistic assessment and access to pharmacological and non-pharmacological therapies are called for (Agustí 2023).

1.1.2 **Pathophysiology and diagnosis**

The primary cause of COPD is damage to the airways caused by inhaling noxious materials, predominantly tobacco (Rabe 2017). Inhalation of a toxic substance causes oxidative stress in the airways, lung parenchyma and pulmonary vasculature which leads to chronic inflammation, tissue destruction (emphysema) and impairment of normal defence mechanisms, such as mucociliary clearance (bronchitis) (MacNee 2006). These processes may result in an accumulation of mucus, oedema and bronchoconstriction in the small airways which all contribute to the expiratory airflow obstruction that typify COPD

A diagnosis of COPD is considered based on the presence of persistent respiratory symptoms including; cough, sputum production and dyspnoea, alongside an appropriate history; over 35 years old and exposure to noxious substances (Rennard 2015; Soriano 2018). Primarily this is tobacco smoke, but other risk factors include occupational exposures, biomass fuel and ambient air pollution (Eisner 2010; Schikowski 2014). A genetic predisposition for COPD is also found in those carrying the Alpha-1 Antitrypsin Deficiency (A1AD) (Falk 1970). Those with an A1AD gene are susceptible to the tissue damage or emphysema associated with COPD due to an enhanced response to inhaling toxic substances. The heritability of COPD extends further than those with A1AD and a paper that was part of a COPD Lancet series highlights that numerous genetic variations have been associated with COPD (Stolz 2020).

Newly identified COPD susceptibility genes have gained increasing interest in genomic trials (Silverman 2020) and further work is called for in defining the genetic risk of different COPD phenotypes, including emphysema (Zhou 2013).

Greater recognition is being given to the major risk factors contributing to the development of COPD and a 2023 Lancet commission advocates classifying COPD based on these risk factors, which are; genetics, early life-events, infection, smoking, and environmental tobacco smoke and other environmental exposures (Stolz 2022b).

Confirmation of COPD diagnosis is made based on spirometry (FEV_1/FVC <0.7 post bronchodilation), traditionally using degree of airflow obstruction (percent predicted FEV_1) to grade disease severity. However, this approach has changed in more recent years and alternative approaches to staging have been proposed. For example, the use of FEV z-scores in place of FEV_1% predicted. It is thought that this measure may be superior given its appreciation for age, height, sex, and ethnicity, as well as a suggested utility in predicting severe exacerbations (Huang 2016) (Diaz 2018). Although the European Respiratory Society Global Lung Function Initiative have endorsed their application (Quanjer 2012) there is still more work to be done particularly in exploring the significance of race-specific reference values (Moffett 2023).

Novel research has also explored the potential of using high dose computed tomography (HDCT) to facilitate early diagnosis of COPD that will allow more timely intervention (Fazleen 2020). The use of HDCT is of particular utility in diagnosing emphysema in the absence of spirometry defined airflow obstruction (Ostridge 2019) and, in the context of early lung cancer screening this may be achievable (Gonzalez 2016; Sekine 2012).

Although airflow limitation is the defining feature of COPD with FEV_1% predicted most commonly used to grade disease severity, how bad a patient's condition is depends on many

other factors, physiological and psychosocial (Pumar 2014; Buttery 2021) . There has been a shift towards a more multicomponent approach to the assessment and classification of COPD which is reflected in the updated 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, incorporating exacerbation frequency and symptoms.

1.1.3 **Management of COPD**

Various models have been suggested in working towards a patient-centric precision medicine approach that gives greater attention to the unique trajectories and related aetiologies that exist under the COPD 'umbrella term' (GOLD. 2020; Guarnier 2023; Celli 2022; Stolz 2022a). Personalised medicine is a concept that has been adopted in driving up the standards of COPD care including assessment and treatment (Agusti 2014). This model considers the heterogeneity of COPD including comorbidities and different phenotypes of the disease (Agusti 2014; Brightling 2019) and allows for a more personalised approach to assessment. Treatable traits have been suggested as a means of identifying therapeutic targets that are specific to the individual based on phenotype or endotype (Agustí 2017; Dijk 2020)

1.2 Hyperinflation in COPD

Emphysema is one component of COPD that is associated with air trapping in the lungs (hyperinflation) that is resistant to most traditional therapies. Tissue destruction in the small conducting airways (alveoli) reduces the surface area available for gaseous exchange and causes a loss of elastic recoil. Consequently, the driving pressure during expiration is diminished and air becomes trapped (Gagnon 2014). Over time this causes hyperinflation of the lungs. This air trapping decreases inspiratory capacity and manifests in the COPD patient as dyspnoea and reduced exercise tolerance (Macklem 1984; O'Donnell 2006). The inspiratory capacity-to-total lung capacity ratio (IC/TLC) is used as a measure of pulmonary hyperinflation and increased hyperinflation has been found to be an independent predictor of respiratory- related and all-cause mortality in COPD (Casanova 2005). In one retrospective study that compared sniff inspiratory nasal pressure (SnIP) and IC/TLC, it was shown that SnIP may be used as a cheaper and more practical test than IC/TLC to provide comparative prognostic power in hyperinflated patients (Moore 2010).

Hyperinflation negatively impacts on the relationship between pressure and volume (O'Donnell, Laveneziana, 2014). As a result of reduced airway pressure, due to expiratory flow limitation (EFL) that causes air to become trapped, the lung must operate at increased volumes. This causes impaired respiratory mechanics including flattening of the diaphragm which effects the length/tension relationship (Polkey 1996) (Hatipoglu 1999) and also results in sub optimal accessory muscle recruitment (O'Donnell, Laveneziana, 2014; O'Donnell 2007; O'Donnell 2020; Macklem 1984).

Static hyperinflation is defined as an increased volume of air remaining in the lungs after expiration (D'Ascanio 2020) (van Geffen 2018). In patients with static hyperinflation an increased residual volume (RV) and functional residual capacity (Gosselink) will be evident on pulmonary function testing (Gagnon 2014).

Dynamic hyperinflation can be observed during exercise, when an individual is exerting themselves and respiratory rate is increased. As breathing becomes more rapid expiration is shortened and air becomes trapped in the lung (O'Donnell 2007), increasing hyperinflation and consequently worsening dyspnoea (Figure 1.1). It has been proposed that reducing static hyperinflation may increase or improve the potential of dynamic hyperinflation, and this has been associated with improved exercise capacity (Dijk 2020).

The utility of inhaled bronchodilators has been discussed in the context of hyperinflation and these pharmacological interventions have been consistently proven to improve gas trapping in COPD (O'Donnell 2015; O'Donnell and Gebke 2014) The mechanism suggested to support this is the increased functional strength of respiratory muscles and optimisation of diaphragm contractility (Hatipoglu 1999; O'Donnell 2015). Similarly, the modulating effect of bronchodilators on hyperinflation during exercise has also been endorsed (O'Donnell 1996) (Guenette 2013).

Other therapies that exist in the management of hyperinflation include pursed lip breathing (PLB) where an individual is instructed to exhale through pursed lips to reduce respiratory rate and end-expiratory volume and improve gaseous exchange (Fregonezi 2004) (Thoman 1966), There are studies that show that PLB may help alleviate dynamic hyperinflation, (de Araujo 2015; Visser 2010; Cabral 2015) but evidence of its efficacy is unfortunately scarce. Pulmonary rehabilitation and oxygen therapy are also both commonly used in the management of patients with hyperinflation.

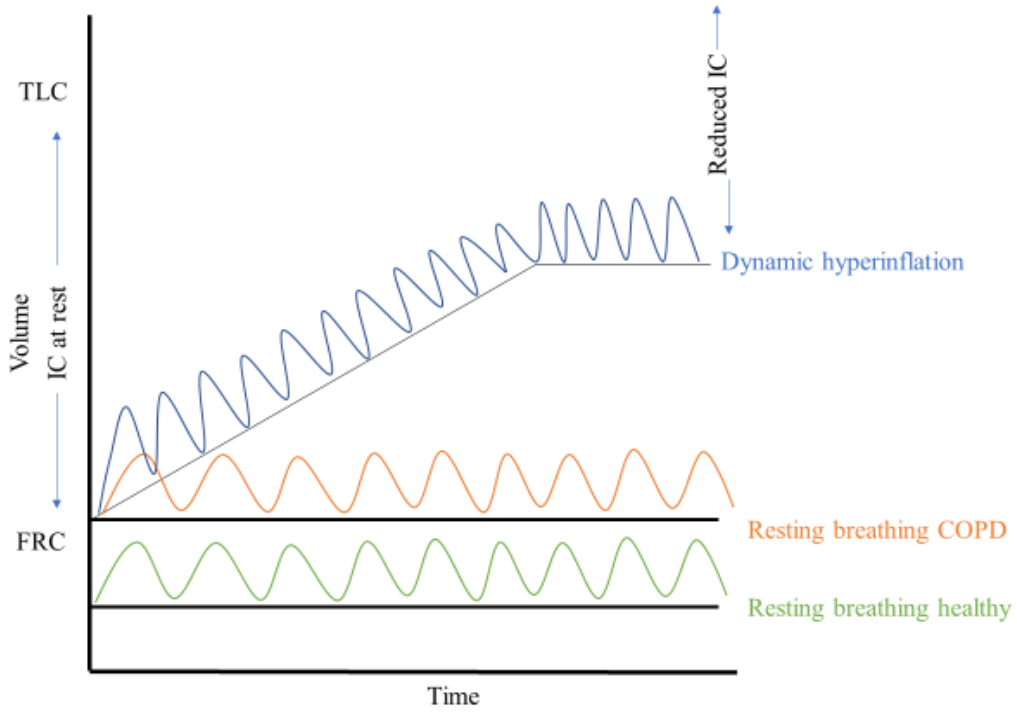
Advances in treatment options, such as lung volume reduction therapies, and the way care is delivered has meant that patients with severe emphysema now have greater treatment options and should therefore be managed using a personalised and multimodality approach to address their symptoms (Dijk 2020).

Figure 1.1 Dynamic hyperinflation

The green line represents breathing at rest in the healthy individual, at a lower lung volume than breathing at rest for the individual with COPD (orange line). In COPD where there is airway obstruction the inhaled volume of air is greater than the exhaled volume of air which results in air remaining in the lung after expiration (static hyperinflation). During an activity that causes increased respiratory rate such as exercise or anxiety the tidal volume and frequency will increase, and expiratory time will reduce (blue line). Each breath causes an increase in the end expiratory volume and results in a progressive increase in FRC and reduction in IC (dynamic hyperinflation).

Abbreviations: IC: inspiratory capacity, FRC: functional residual capacity.

Figure adapted from; Usmani OS, Dhand R, Lavorini F, Price D. Why We Should Target Small Airways Disease in Our Management of Chronic Obstructive Pulmonary Disease. Mayo Clin Proc. 2021 Sep;96(Egger):2448-2463. doi: 10.1016/j.mayocp.2021.03.016. Epub 2021 Jun 26. PMID: 34183115.



1.2.1 **Management of hyperinflation**

Although COPD is a chronic degenerative disease it is also considered a preventable and treatable disease (Halpin, Criner, 2021). Management is largely based around alleviating symptoms, reducing the frequency and severity of exacerbations, increasing exercise tolerance and optimising quality of life (Vogelmeier 2020) (Hopkinson 2019). As up to 50% of smokers are thought to develop COPD (Lundbäck 2003) (Rennard 2006), smoking cessation continues to be central in COPD care alongside immunisation (influenza and pneumococcal), inhaled pharmacological treatments, pulmonary rehabilitation and where appropriate, oxygen therapy. However, for many and particularly in those with an emphysematous phenotype these treatments are unsuccessful in ameliorating the debilitating symptoms of COPD. In these individuals, lung volume reduction therapies may be considered and in those that are suitable, can provide tremendous benefit. Lung volume reduction treatments have been developed to target the hyperinflated lung and in doing so, alleviating symptoms of dyspnoea and addressing the consequential reduction in functional capacity. It is important to note that where all other treatment options have been exhausted the possibility of lung transplantation may be explored in end-stage COPD patients, but this procedure is undergone in only a small minority of patients (Verleden 2023). The remainder of this thesis will focus on lung volume reduction therapies in the management of COPD.

1.3 Lung volume reduction in COPD

1.3.1 Lung volume reduction surgery

Lung volume reduction as a surgical approach to emphysema was first introduced in 1959 by Otto Brantigan who described it as the 'restoration of a physiological principal' (Brantigan 1959). His work suggested that removing the most emphysematous parts of the lung tissue would allow the healthier lung to expand, increase elastic recoil and restore normal chest wall mechanics, with the objective of relieving breathlessness. However, due to the high mortality rates (around 16%) reported in his case series LVRS did not take off until the early 90's led by the work of Joel Cooper. Cooper reported a much larger cohort of patients undergoing median bilateral sternotomy that achieved significant improvements at 6 months post procedure with fewer adverse events and an associated 5% mortality risk (Cooper 1997).

The increased popularity of LVRS as a treatment for severe emphysema resulted in a huge increase in the number of procedures performed and with it a vast increase in healthcare costs and medical insurance claims in the United States (US). Therefore, in the US the National Emphysema Treatment Trial (NETT) (Criner 2011a) was set up and funded by Medicare. The objective of the trial was to investigate if LVRS should be established as a safe, valuable, and funded treatment for patients with emphysema, or if it should be abandoned completely.

This landmark trial, was the largest to date multicentre COPD RCT, recruiting 1,218 patients and following them up over 24 months, investigating survival in those undergoing LVRS, in comparison to only optimal medical treatment. Lung function, exercise capacity and quality of life were also evaluated as part of this trial and all participants were required to undertake a course of PR prior to enrolment. Advantageously, there was no cross-over during the trial which meant that long-terms outcomes of LVRS could be collected.

The primary analysis of the NETT revealed that although exercise capacity was improved in those that underwent LVRS, there was no survival advantage over medical therapy (Fishman 2003). However, a secondary sub group analysis in those deemed 'low risk' (predominantly upper lobe emphysema and low baseline exercise capacity) a survival advantage was seen. The authors also emphasised that in 'high risk' individuals (non-upper lobe emphysema and high baseline exercise capacity) mortality risk was higher with less functional gain. This group were therefore deemed poor candidates for LVRS (Fishman 2001; Criner 2011a).

In 2000 the first UK based clinical RCT comparing patients undergoing LVRS with those receiving only usual medical care was published in the New England Journal of Medicine (Geddes 2000). This trial showed proven benefits of LVRS in terms of FEV_1, exercise capacity and HRQoL, but its effect on survival was not clear.

More recently, a paper has criticised the NETT analysis stating that the methodology chosen was unsuitable (Lim 2020). The authors of this paper addressed this limitation by reinterpreting the data using a longitudinal data analysis methodology and showed that, in agreement with Geddes and colleagues (Geddes 2000) LVRS does improve lung function and dyspnoea up to 5 years post procedure, and that it should feature as an important component of emphysema management in the control of symptoms.

Changes in LVRS approach were adopted in response to the high mortality rate seen in the NETT with LVRS centres taking a unilateral approach to procedures using a video-assisted thoracic surgery (VATS) in place of the more invasive median sternotomy (Goldstein 2003). However, the concerns around high operative mortality risks that had been instigated following the NETT trial (5-10%) prompted a shift in focus to the development of more novel and less invasive therapies.

1.3.2 **Endobronchial valves**

Bronchoscopic approaches to lung volume reduction were first used in the early 2000's in the form of endobronchial valves (Toma 2003). This method of reducing hyperinflation was designed as a less invasive means of reducing lung volume than LVRS, aiming to achieve similar benefits with reduced mortality risk (Shah 2014). The procedure involves using a one-way valve to occlude the airway supplying the area of hyperinflated lung (target lobe). The valves are designed to allow air to exit the lung but not to re-enter which means this area of lung deflates, reducing in size and in doing so allows the healthier surrounding lung to re-expand where it was once squashed by the hyperinflated lung. As with LVRS the overall objective of this procedure that reduces gas trapping is to restore normal lung mechanics and consequently improve lung function and other important health outcomes (Shah 2014).

Over the course of a decade many clinical trials, including six RCT's (Sciurba 2010; Klooster 2015; Davey 2015; Criner 2018; Kemp 2017; Valipour 2016; Criner 2019) were carried out, to better understand EBVs as a treatment and from these trials we learnt that EBVs produce improvements in health outcomes that are similar to those produced by LVRS. It is also understood that these results are only achieved when EBVs are used in carefully selected patients (Kemp 2017; Criner 2018). For this treatment this was found to be; those with heterogenous emphysema (Valipour 2016) (although those with a homogeneous pattern may also benefit) and complete fissures (Sciurba 2010), and those achieving complete lobar atelectasis were found to procure the greatest benefit (Herth 2012) . A judgement on this selection criteria is generally made by a specialist MDT using radiological images (HRCT) and the decision on collateral ventilation can be confirmed by Chartis procedure (see section 2.3.3) (Davey 2015; Herth 2013).

In 2019 a systematic review and meta-analysis of the literature supporting surgical and endoscopic LVR intervention was conducted (van Geffen 2019) and concluded that improvements in lung function (FEV_1% predicted: 21. 77%) and 6MWT (+49m) following EBVs were greater than those observed in trials of other interventions, such as LVRS or endobronchial coils. However, there were some shortcomings in this review that were recognised by the author. First, combining and comparing the studies in a meta-analysis was problematic due to heterogeneity in methodologies. Second, several studies included suffered from a risk of bias (due to problems with blinding) or lacked long term follow-up and therefore this conclusion cannot be used as evidence that EBVs are a superior treatment. Furthermore, although EBVs were developed to provide a safer approach to LVR, complications do exist such as the high prevalence of pneumothorax and revision bronchoscopies (Brock 2023) (van Dijk 2021; Dijk 2020). Therefore, more research is required to compare LVRS and BLVR to help inform clinical practice and guide decision making when an individual has equipoise between treatments.

1.3.3 **Indication for lung volume reduction therapy**

Lung volume reduction therapy is indicated in only a small proportion of COPD patients and careful selection is essential in identifying those who will benefit most from these treatments. This has been highlighted in numerous trials that have shown improved outcomes in specific phenotypes of patients (Criner 2011a; Herth 2016). This is illustrated in a secondary analysis of the NETT showing that only a sub group of patients receiving LVRS (those with heterogeneous emphysema with upper lobe predominance and low exercise capacity) saw a survival benefit greater than those in the control arm (Criner 2011a) and it is well understood that the benefits of EBVs are seen when performed on patients with negative CV, and complete lobar atelectasis is achieved (Herth 2016).

Guidelines released by NICE (Hopkinson 2019) suggest broad criteria for identifying suitable patients for further consideration. Those with an FEV_1% predicted <50%, who do not smoke and can walk ≥140m on a six-minute walk tests and continue to complain of limiting breathlessness despite completion of a PR programme are suggested for onward referral for respiratory review. However, aspects of these guidelines are poorly defined and therefore pose a barrier for clinicians responsible for making onward referrals.

1.3.4 **Access to Lung volume reduction services**

In 2014, a study was published that analysed the results of a survey of 65 members of the British Thoracic Society (BTS) who were considered key stakeholders in advanced COPD management. The survey asked about their knowledge around LVRS, including; indications for intervention, access to investigations, and associated morbidity and mortality risks (McNulty 2014). The key learning points from this study were that improved education was required around patient section for LVR treatments as well as greater clarity of the true risks of morbidity and mortality following LVR, and that current pathways for referral were inadequate. This work was strengthened by a qualitative piece of work carried out in 2017 investigating attitudes to LVR in patients that had undergone either LVRS or BLVR (Buttery 2017). This study highlighted the difficulties patients face when trying to access LVR services and confirmed that patients felt they had to 'fight for a referral.' This is likely down to referring physicians being unaware of the options available to patients or unsure of the criteria that would make an individual suitable for onward referral (McNulty 2014). The concept of therapeutic nihilism has also been raised in the context of LVR treatment and in particular LVRS (Zoumot 2014). This was the result of high morbidity and mortality reported in early LVRS trials (Fishman 2001) as discussed earlier. Despite this being an out of date portrayal of the risks of LVRS due to changes in treatment approaches and patient selection,

work still needs to be done to convey this message to all clinical settings. Chapter 6 of this thesis provides important contribution to this.

1.4 Extrapulmonary management of COPD

As already described, COPD is a respiratory condition that predominantly effects the pulmonary system and treatment has largely focussed on the management of symptoms and exacerbations (Vogelmeier 2020). However, COPD is now commonly regarded as a multimorbid condition with extrapulmonary manifestations including cardiovascular disease, osteoporosis, sleep disorders and anxiety and depression (Vanfleteren 2013). These comorbid diseases can contribute to how an individual experiences the burden of their COPD including disease severity, functional capacity, quality of life and survival (Vanfleteren 2013). Therefore, management of COPD, including emphysema should not only target respiratory symptoms but also focus on the prevention and treatment of extrapulmonary components. Some of the most important of these components are skeletal muscle dysfunction, exercise capacity and physical activity (Alahmari 2016).

1.4.1 **Exercise therapy in COPD**

Sedentary behaviour is responsible for much of the disease burden of COPD. People with COPD show reduced levels of PA compared to peers who do not suffer with respiratory disease and PA levels correlate with disease severity (Demeyer 2021). The cause of exercise limitation in COPD is multifactorial (Vogiatzis 2012; Pepin 2007; Gosselink 1996) but hyperinflation is thought to be a significant contributor due to an inability to increase tidal volume during exercise,(Casaburi 2015) (O'Donnell 2007). Exertional dyspnoea, reduced exercise capacity and indeed dynamic hyperinflation may be evident in the early stages of COPD (Gagnon 2014). Alongside an increased mortality risk, reduced functional capacity has been shown to be associated with a poorer quality of life and increased social isolation (Gimeno-Santos 2014) (Philip 2020; Van Remoortel 2014). The World Health organisation

(WHO) recognise the importance of reducing sedentary behaviour and increasing physical activity in the healthy population (Bull 2020) (Hämäläinen 2020) and although there are no specific PA guidelines for those living with COPD it has been defined as a crucial component of non-pharmacological management (Agustí 2023).

1.4.2 **Pulmonary rehabilitation**

Traditionally in COPD management, increasing functional exercise capacity has been targeted using pulmonary rehabilitation (PR). PR is a comprehensive exercise and education programme that was designed for individuals with chronic lung disease, restricted in their daily activities due to exertional breathlessness (Spruit 2014; NHS 2023). The concept of PR as a multicomponent and personalised exercise programme was first recognised in the late 1960's, by Thomas Petty (Petty 1969) and in 1980 the first statement on PR was published by the American Thoracic Society. In the years following there was some debate around the efficacy of PR as a valuable treatment for chronic lung disease due to doubt around its ability to induce any physiological change (Belman 1981) . Thus, an abundance of clinical trials that focussed on investigating the benefits of PR ensued.

Today, PR has a strong evidence base proving its efficacy, demonstrating benefits in exercise capacity, Health related Quality of Life (HRQoL) and exacerbations (McCarthy 2015) (Mikelsons 2009) as well as improving symptoms of anxiety and depression (Gordon 2019). In 2015 an important systematic review was published that concluded that no further RCT's comparing PR with usual care were necessary to support its worth (McCarthy 2015).

Since 2009 guidelines have been developed and the NACAP PR audit and PR accreditation scheme are in place to ensure the delivery of high quality PR that is offered to all patients with COPD in the UK, with an MRC dyspnoea score of >2 (Hopkinson 2019). In 2023 a

universal healthcare package was developed by the World Health organisation (WHO) to allow PR to be delivered around the world, promoting more equitable access to this important intervention.

Despite these efforts PR is still an underused and under prescribed resource and a report published in 2022 looking at COPD care in the UK showed that only half of patients with a COPD diagnosis report being offered a course of PR (Williams 2022). Characteristics that make an individual less likely to be offered a course of PR include being female, of increased age, greater deprivation and having certain comorbidities (Stone 2020).

Importantly, PR also forms a vital part of the LVR pathway, not only in optimising patients for these treatments but also as NICE identifies this as an appropriate setting for the early identification of those that may be further considered for an LVR intervention (Hopkinson 2019). Much of the historical research that supports PR was carried out within the context of a stable COPD population. Other and more recent research has included post exacerbation rehabilitation and other respiratory conditions (Nolan 2022; Rochester 2014; Puhan 2016), but there is minimal literature supporting pre or post LVR intervention rehabilitation or exercise training and the role that PR services might play in getting the most from these therapies.

The role of PR in COPD management and specifically LVR intervention is discussed further in chapters three and seven and future directions for research relating to PR in the context of LVR pathways is suggested.

Further issues relating to improving functional capacity in the context of COPD, and specifically in those with marked emphysema are the difficulties associated with being able to show significant improvements. It is thought that between 30-50% of those that attended PR do not see a clinically meaningful improvement in outcomes following PR (Garrod 2006;

Scott 2010). These individuals, often termed' non-responders' may not achieve the expected benefits for a variety of reasons and most frequently fail to experience changes in exercise tolerance (change in 6MWD) quality of life and symptoms of anxiety and depression (Spruit 2015; Scott 2010).

Research shows that those who experience less ventilatory limitation to exercise but greater reduction in respiratory and peripheral muscle strength are more likely to make meaningful changes following exercise training (Troosters 2001). This research may explain why those with significant hyperinflation find it so difficult to complete a course of PR and highlight the need for alternative interventions to improve functional capacity

Adjuncts to PR have been suggested, such as non-invasive ventilation (Hämäläinen) and supplemental oxygen (Neunhäuserer 2016), to negotiate the ventilatory limitations to exercise of those that have dynamic hyperinflation (Hoo 2003). The theory behind their use is that they may allow individuals to work at a high enough rate to achieve physiological changes, increase exercise capacity and reap greater benefit from PR (Hoo 2003). A number of studies have demonstrated the benefits of NIV as an adjunct to PR and a recent component network meta-analysis looking at a range of adjuncts, found NIV to be the only one that appeared to provide supplementary benefit (Ward 2023).

More novel approaches to exercise training also exist including non-linear periodised resistance training (Klijn 2013), helium hyperoxia (Eves 2009) and single leg training (Evans 2015). These techniques follow the same principles of addressing the limitations of dynamic hyperinflation but have limited evidence and significant practical barriers to support their introduction into clinical practice. The few studies that have been published exploring these novel adjuncts have all shown positive outcomes in terms of increasing exercise duration and capacity. However, more work is required to feasibly implement these potentially valuable

training techniques into clinical practice, with an appreciation of resource, time, and expertise available (Nolan 2019) (Lee 2014).

1.4.3 **Physical activity**

Traditionally, exercise capacity has been used as a measure of functional performance. This has been carried out using a formal exercise test and is often done as part of a PR programme assessment. The gold standard for exercise assessment is a Cardio Pulmonary Exercise Test (CPET). These tests are costly and often impractical and therefore field exercise tests are more frequently used in clinical practice.

The two most commonly used field tests are the 6MWT and the ISWT (Holland 2014). These tests are strenuous enough to elicit a similar cardiorespiratory response to exercise as the CPET and have both been deemed to be valid, reliable, and responsive to change (Holland 2015). The 6MWT and ISWT are discussed in greater detail in chapters 2 (main methods) and 3 of this thesis.

Although measuring physical performance using these tests tells us what an individual is able to do it does not give us a clear representation of what they actually do in everyday life which may be more important in the longer-term management of patients with COPD, and particularly for those patients that will struggle to complete a course of PR or formal exercise test.

Reduced levels of PA have been associated with worse health outcomes in COPD including more frequent hospitalisation and reduced survival (Garcia-Aymerich 2006; Garcia-Aymerich 2008). Research has clearly demonstrated whole body PA is reduced in COPD (Pitta 2005) but also that an improvement in physical capacity does not necessarily translate to an improvement in PA (Vaes 2022). Therefore, in 2014 an ERS statement was published

on PA in COPD (Watz 2014) and research interests have turned to the importance of PA in COPD management including how it can be measured and augmented, and in which individuals this may be a more useful biomarker (Vaes 2022; Koolen 2019).

A study conducted in 2020 explored the concept of physical functioning in COPD to try to understand the relationship between what a patient is able to do ('can do') and what they actually do in daily life ('do do'). The authors developed a concept that may be useful for clinicians when selecting an appropriate intervention to target physical functioning based on the individual needs of that patient (Koolen 2019).

Studies in early COPD cohorts investigating the value of introducing PA interventions much earlier have started and suggest improved prognosis and reduced exacerbations (Kim 2023).

However, recent research that explored the relationship between those that have a preserved exercise capacity ('can do') and those that engage in daily physical activity ('do do') and survival found that patients that 'can do' had a significantly lower 6 year mortality rate compared to those that do not fit into this category, regardless of physical activity level. Therefore, more research is called for in this area including in the field of LVR where we continue to use measures of exercise capacity to quantify change and no research exists to investigate how everyday life functional performance or PA is changed after LVR.

To be able to accurately quantify daily mobility, work is required in developing adequate outcomes that accurately measure PA. Currently PA is measured using either subjective questionnaires, or objectively using a pedometer or accelerometer. The former is limited by issues of recall bias (Pitta 2006) and poor correlation with objective measurements (Garfield 2012) (Pitta 2005) and the latter may be considered impractical in clinical practise as well as being subject to performance bias, whereby an individual may be more likely to overperform during the observational period of wearing a device (Casaburi 2007). The Clinical

PROactive Physical activity in COPD (C-PPAC) tool has been developed as a measure of PA that incorporates both subjective and objective components to capture a more accurate representation of daily activity, from the patient's experience (Gimeno-Santos 2015).

1.4.4 **Measurement of physical activity**

The need to standardise the measurement of PA has been recognised as an important area for research and therefore several studies were set up to validate the use of activity monitors in chronic respiratory disease. This included the European PROactive consortium. The investigations carried out as part of this work package and other trials proved PA as an important outcome in research trials (Burtin 2021) and established minimal clinically important differences (MCIDs) for commonly used PA measures (Demeyer 2014; Teylan 2019) and following this a document outlining the standardisation of PA monitoring was published (Demeyer 2021). However, work is still required to ensure reliable and accurate measurement and monitoring of PA to ensure their utility in clinical care.

1.4.5 **Digital approaches to exercise training and physical activity in COPD**

Digital approaches to PR and physical activity monitoring have been investigated, and in many centres used successfully for several years. This includes methods such as web platforms, video tele rehabilitation (TR) and virtual reality (Reilly 2023a). The duration of the COVID-19 pandemic and particularly the lockdown period saw an increase in the popularity of TR, allowing patients with chronic respiratory diseases to continue to engage in supervised exercise and reap the benefits of PR, without the need for an outpatient face-to-face session. However, the evidence comparing standard PR with TR is conflicting and a secondary responder analysis conducted in 2023 showed that in 134 patients randomised to either traditional outpatient PR or TR there was no superior short term or long term benefit in

exercise capacity and the study concluded that outpatient supervised PR remains the gold standard of care (Hansen 2023).

A 2023 BTS statement on PR established that while TR represents an alternative model of PR that may help increase uptake and completion (Man 2023) the importance of a face to face assessment is stressed due to the importance of conducting a formal exercise test that can be used to prescribe a tailored exercise programme. However, weekly remote sessions and assessments may be of utility for those that are unable or unwilling to attend an in-person class or when routine assessment in prohibited.

The statement also recognises that support is needed for both those delivering and using digital technologies to ensure that individuals that could benefit are not affected by digital exclusion. The same is also true for the introduction of digital measures of physical activity.

Mobilise-D is a European consortium study set up to develop and validate digital technologies that may be used to analyse gait and daily activity in a number of chronic diseases, including COPD(Mikolaizak 2022) (Rochester 2020). Through this work the project aims to facilitate the adoption of digital mobility outcomes (DMOs) in clinical trials and practice (Rochester 2020) and work presented in chapter seven of this thesis provides fundamental contribution towards this objective.

2 Description of methods

This chapter is dedicated to a more detailed summary of the methods used in the interventional RCT of this thesis (chapter four) or methods that are common to more than one study chapter. This includes study design, physiological and radiological assessments and patient reported outcomes. A description of the ethical approvals obtained for the research conducted during this project is also described, as well as the data sources that were used.

Methods and outcomes that apply to only one study in this thesis will be discussed within that chapter. Statistical analysis methodology will also be discussed within the relevant chapter.

.

2.1 Ethical approval

The CELEB study (chapter four) received ethical approval from Fulham Research Ethics Committee, London, UK (REC reference: 16/LO/0286) and the trial was registered prospectively; ISRCTN19684749. For the UKLVR study (chapter six) ethical approval was obtained from the Camberwell St Giles Research Ethics Committee. In addition to this, Site-Specific Assessment was submitted by each participating NHS Trust and a copy of the R&D confirmation letter was held by the central site. Chapter three received approval through the RCP audit process.

All studies were conducted in accordance with the recommendations laid out for clinicians involved in research on human subjects in the 1975 Declaration of Helsinki and Good clinical practice (GCP). All participants provided written informed consent for participation in the randomised controlled trial (chapter four). For the UKLVR study, the issue of consent is addressed specifically within the methods section of this chapter (chapter seven).

2.2 Data sources

Chapter three used data from the Royal College of Physicians (RCP) National Asthma and COPD Audit Programme (NACAP). Data was obtained and combined from the 2015 and 2017 Pulmonary Rehabilitation audit (NACAP 2015).

Chapter six uses data obtained from a larger scoping review that I was involved in, conducted as part of the multinational EU HORIZON 2020 trial, MOBILISE-D (Mikolaizak 2022; Rochester 2020).

Table 2.1: *Outcome measures featured in this thesis*

	Chapter 3	Chapter 4	Chapter 5	Chapter 6	Chapter 7
Full pulmonary function[1]		x		*	
Spirometry	*	x		*	*
CT thorax		x		*	*
Chartis measurement of collateral ventilation		x		*	
i-BODE index		x		*	
BMI		x		*	
FFM		x			
MRC dyspnoea score	*	x		*	*
CAT score		x		*	
ISWT	*	x		*	*
6MWT	*			*	*
Physical activity monitoring		x			
c-PPAC score		x			

X: Measured as an outcome as part of this thesis, *: Analysed as an outcome as part of this thesis

[1] Spirometry, gas transfer, plethysmographic lung volumes, capillary blood gases

2.3 Clinical investigations

2.3.1 **Pulmonary function testing**

Pulmonary function tests were carried out by experienced physiologists in the Royal Brompton Hospital and performed and interpreted in line with the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines (Stanojevic 2021; Miller 2005; Wanger 2005). Pulmonary function tests consisted of spirometry, gas transfer, plethysmographic lung volumes and capillary blood gases. Reference equations were derived based on the recommendations of the European Coal and Steel Community (ECSC)/ European Respiratory Society reference values (Quanjer 2012). Patients on the CELEB trial were asked to take their usual medications prior to the tests.

Spirometry was performed by asking participants to breathe in to full inspiration before performing full expiration, forcefully. Key quality criteria were adhered to, to ensure reliability and reproducibility of measures (Moore 2012). This included asking participants to repeat the manoeuvre until three attempts were within 5% of each other. The highest value obtained for FEV_1 and FVC were then recorded (Moore 2012).

Lung volumes were measured using body plethysmography and gas transfer was obtained using a single breath hold technique. During this measure, the subject was asked to inhale a known concentration of carbon monoxide (CO) and the end expiratory measure of this gas was remeasured after the breath hold, adjusting for alveolar pressures.

The equipment used to make these measurements was calibrated daily for quality assurance.

2.3.2 **High Resolution Computed Tomography (HRCT) of the thorax**

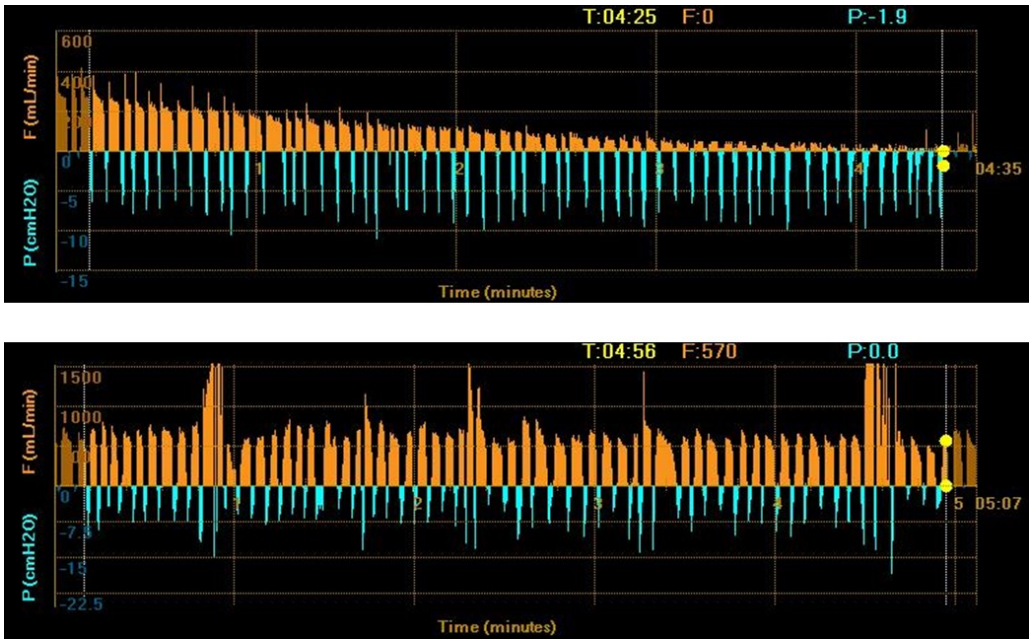
HRCT scans were performed for all participants on the CELEB trial (chapter four) at baseline, prior to enrolment on the trial and again at three months post intervention. These scans were carried out either at the recruiting site or the participants local referring hospital (baseline) as part of the diagnostic process of the LVR pathway as recommended by the NICE guidelines (Hopkinson 2019) . CT scans were carried out by staff at the Royal Brompton Hospital Radiology department and were performed per protocol, at total lung capacity (breath held at full inspiration) with volumetric images (continuous 1mm slices) stored.

2.3.3 **Chartis Assessment**

The Chartis procedure can be used to asses for the presence of collateral ventilation in individuals being considered for an LVR intervention. This procedure is carried out by an experienced bronchoscopist who inserts a balloon into the target airway to record flow and pressure. Where there is collateral ventilation (CV positive), flow (orange in Figure 2.1) will continue but where there is no collateral ventilation (CV negative) flow will gradually diminish.

Figure 2.1; Chartis readings

Orange area represents flow and blue area represents pressure. The top image shows a CV negative reading and the bottom image shows a CV positive reading



In this thesis the CELEB trial (chapter 4) utilised the Chartis assessment to evaluate participants suitability for EBV treatment. If collateral ventilation was present, then EBV treatment would not be recommended as there was no longer equipoise and the individual would be exited from the trial.

2.4 Interventional trial outcome measures

2.4.1 Individual composite outcomes of the i-BODE index

2.4.2 FEV_1% predicted

FEV_1 is the standard measure of airflow obstruction that is used universally to measure severity of COPD. It has been associated with impairment and survival and correlates with other important outcomes (Doherty 2008).

As we age FEV_1 steadily declines and a healthy, non-COPD FEV_1 measurement would be expected to decrease by around 30 ml/year, but this is increased by up to 4 times as much in those with COPD (Fletcher 1976; Tantucci 2012). Recent research has suggested that z-scores may be a more useful measure of staging COPD (Huang 2016).(Stanojevic 2010). This has been discussed further in the introductory section of this thesis.

FEV_1 has been used as a primary outcome measure in most endobronchial valve trials because it is recognised as a surrogate endpoint in COPD trials by the Food and Drug Administration (FDA) It also features as a secondary outcome in many others (Criner 2018; Kemp 2017; Davey 2015). These trials have demonstrated between 8.77% and 29.3% change in FEV_1 after EBV interventions and this is similar following LVRS. A minimal clinically important difference for FEV_1 (l) has been suggested between 100ml- 140ml which translates to around a 10% change in FEV_1% predicted from baseline (Donohue 2005; Jones 2014). In this thesis FEV_1 %predicted is measured as part of the i-BODE index in chapter four and is also considered in chapter three, six and seven.

2.4.3 **Body mass index (BMI)**

Body mass index (BMI) has been shown to be a predictor of accelerated lung function decline in COPD (Sun 2019). In this thesis body mass index was calculated using the following equation, that is universally recognised (Weir 2023);

BMI= weight (kg) /height (m)^2

In chapter four a BMI cut off of >21/≤21 was used to categorise patients when scoring the i-BODE index but an alternative cut-off of 18.5 kg/m^2 has been suggested to predict risk in those undergoing an LVR intervention and is used in chapter six (Greening 2017).

2.4.4 **The Medical Research Council (MRC) dyspnoea scale**

The Medical Research Council (MRC) dyspnoea scale is a simple measure of breathlessness that is widely used in COPD. It was developed to provide a straight forward means of defining the subjective experience of breathlessness by grading the severity of functional disability caused by breathlessness (dyspnoea). The scale consists of five statements (shown below) that are presented to the patient. The patient is then asked which statement fits most closely to the severity of their functional disability, related to their dyspnoea levels. The MRC scale has been shown to correlate with lung function parameters and other measures of dyspnoea, increasing its validity (Bestall 1999). The measure was chosen for use in this thesis due to its widespread recognition, ease, and efficiency of use

Figure 2.2 MRC dyspnoea scale

MRC Dyspnoea Scale

1. Not troubled by breathlessness except with strenuous exercise
2. Troubled by shortness of breath when hurrying on the level or walking up a slight hill.
3. Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace.
4. Stops for breath after walking about 100m or after a few minutes on level ground.
5. Too breathless to leave the house or breathless when dressing or undressing.

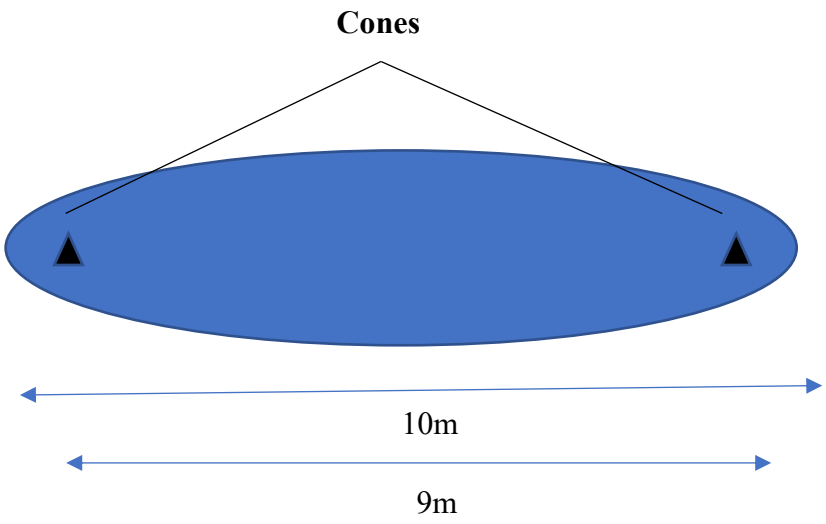
2.4.5 **Incremental Shuttle walk test (ISWT)**

The incremental shuttle walk test (ISWT) was developed as a standardised measure of functional capacity (Singh 1992) and was used in chapter four to asses exercise capacity. The ISWT has been validated in a COPD population and is recognised as reliable and sensitive in assessing change following treatment (Singh 2014). Although there are many similarities between the 6MWT and ISWT the main difference is that the ISWT is externally paced and progressive and therefore more closely mirrors the protocol for incremental cycle ergonometry, the gold standard of exercise assessment. Research shows that during a ISWT a similar physiological response to maximal exercise is provoked as during a cycle ergonometry (Hill 2012; Palange 2000). But, as a field walking test the ISWT is a more practical and less costly means of assessing exercise capacity than cycle ergonometry (Holland 2014). These factors made it a favourable choice for the RFPB funded clinical trial described in chapter four.

The subjects enrolled in the CELEB trial (chapter four) performed the ISWT according to recognised standards (Holland 2015) (Holland 2014); on a 10m walkway with two markers 0.5m from either end (Figure 2.3), using an audio recording to direct the pace. Standardised instructions were provided prior to the test and verbal cues during the test.

Figure 2.3: *Incremental Shuttle Walk test set up*

The schematic diagram illustrates the ISWT set up as per the ERS/ATS standards. Cones are set at 0.5 from each end of a 10m course to account for abrupt turns.



Adapted from; Holland AE, Spruit MA, Singh SJ. How to carry out a field walking test in chronic respiratory disease. Breathe (Sheff). 2015 Jun;11(2):128-39. doi: 10.1183/20734735.021314. PMID: 26306113; PMCID: PMC4487379.

A test was only terminated if 1) a patient indicated they were unable to continue, 2) the operator felt that the patient was not fit enough to continue, or 3) the operator determined that the patient was no longer able to keep up with the pace set (i.e. they did not reach the marking before the audio recording beeped).

Every participant was required to complete two ISWT due to the recognised 'learning effect' (McKeough 2011; Dyer 2011) and at least 30-minutes was left between the two tests to ensure recovery time. The furthest distance walked on the two tests was recorded and used to calculate i-BODE index score.

2.4.6 **i-BODE index**

The i-BODE index (Table 2.2.) was used as the primary outcome in the main RCT of this thesis. This outcome was selected as it is a valid measure of disease severity (Williams 2012) incorporating airflow obstruction (FEV_1), exercise limitation (ISWT), dyspnoea (MRC score) and body composition (BMI). Composite outcomes have been shown to provide a more meaningful way to evaluate prognosis than FEV_1 alone (Celli 2015). This is largely down to the featuring of multiple properties that are known to be important predictors of hospitalisations and mortality, in a heterogenous disease population (Corlateanu 2021) (Marin 2009) and also following LVR intervention (Imfeld 2006). The index was originally developed as the BODE index (Table 2.3) and is the most commonly used prognostic composite measure in COPD (Celli 2004). It has been used in previous LVR trials due to its association with prognosis and healthcare utilisation (Li 2019; Celli 2004) . A score between 0-10 is calculated based on four commonly used COPD outcome measures, 0 representing the best health, and 10 the worst.

The i-BODE index by comparison uses the ISWT rather than the 6MWT to assess exercise capacity and has been proved to be an equally valid predictor of mortality in COPD (Williams 2012).

Table 2.2: *i-BODE index point allocation for composites and calculation of total score*

Composite	0 points	1 point	2 points	3 points
FEV_1%predicted	≥65	50–64	36–49	≤35
Distance walked on ISWT	≥250	150–249	80–149	≤80
MRC dyspnoea score	1–2	3	4	5
BMI	>21	≤21		

Abbreviations: FEV_1: forced expiratory volume, ISWT: incremental shuttle walk test, MRC: Medical Research Council, BMI: body mass index

Table 2.3*: BODE index point allocation for composites and calculation of total score*

Composite	0 points	1 point	2 points	3 points
FEV_1%predicted	≥65	50–64	36–49	≤35
Distance walked on 6MWT	≥250	250–349	150–249	≤149
mMRC dyspnoea score	1	2	3	4
BMI	>21	≤21		

Abbreviations: FEV_1: forced expiratory volume, 6MWT: 6-minute walk test, MRC: Medical Research Council, BMI: body mass index

2.5 Other physiological measures

2.5.1 **Anthropometry**

Height (cm) was measured to the nearest centimetre using a wall mounted scale, and weight (kg) was measured using scales that were calibrated daily to ensure accuracy. Both were measured with shoes off.

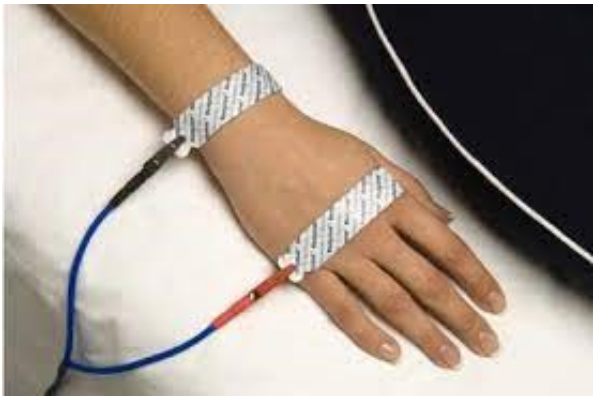
2.5.2 **Body composition**

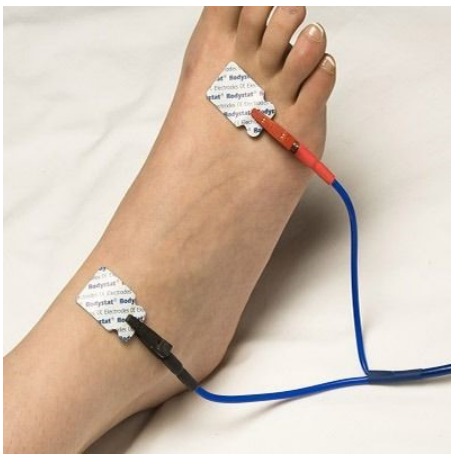
Bioelectrical impedance (BIA) was used to measure body composition using a Body stat Quadscan 4000 device (Bodystat, Isle of Man, United Kingdom). This instrument enables a quantification of body composition through the measurement of electrical current running through bodily fluids and adipose tissue between the wrist and ankle, to estimate total body water and electrical resistance.

BIA was measured according to a pre-defined standard operating procedure that required the subject to be in a supine position. To prepare for measurement subjects were asked to remove their right shoe and sock and to lie flat for a minimum of ten minutes. Electrodes were then placed on the right upper and lower limb as shown in the figures 2.4.

Figure 2.4: *Bioelectrical impedance measured using Bodystat Quadscan 4000*

Taken from; https://bodystat.com/





The rational for placing electrodes on the right upper and lower limb is explained by the increased resistance on the left-hand side, that is generated by the myocardium.

2.5.3 **Fat free mass index (FFMI)**

The fat free mass index (FFMI) was used in chapter four as a proxy of BIA, representing body composition and nutritional status. This was considered to be an important outcome for an interventional trial due to the correlations of body composition (weight loss and muscle mass) with not only exercise tolerance (Schols 1991) but also mortality (Wilson 1989; Schols 1998) that make it an important therapeutic target.

A disease specific regression equation (see below) that was developed by Steiner and colleagues and accounts for height, weight and gender was then used to provide a more meaningful estimation of body composition (Steiner 2002). The gender specific equations are provided below;

COPD females:

FFM (kg)=7.610 + (0.47 x height^2(cm)/ resistance (Brock)) + (0.184 x weight (kg))

COPD males:

FFM (kg)=8.383 + (0.465 x height^2(cm)/ resistance (Brock)) + (0.213 x weight (kg))

The Fat Free Mass Index (FFMI) was then calculated by dividing FFM by height in metres squared. A value of <15km^2 for women or <16km^2 for men is considered to represent nutritional depletion (Steiner 2002)..

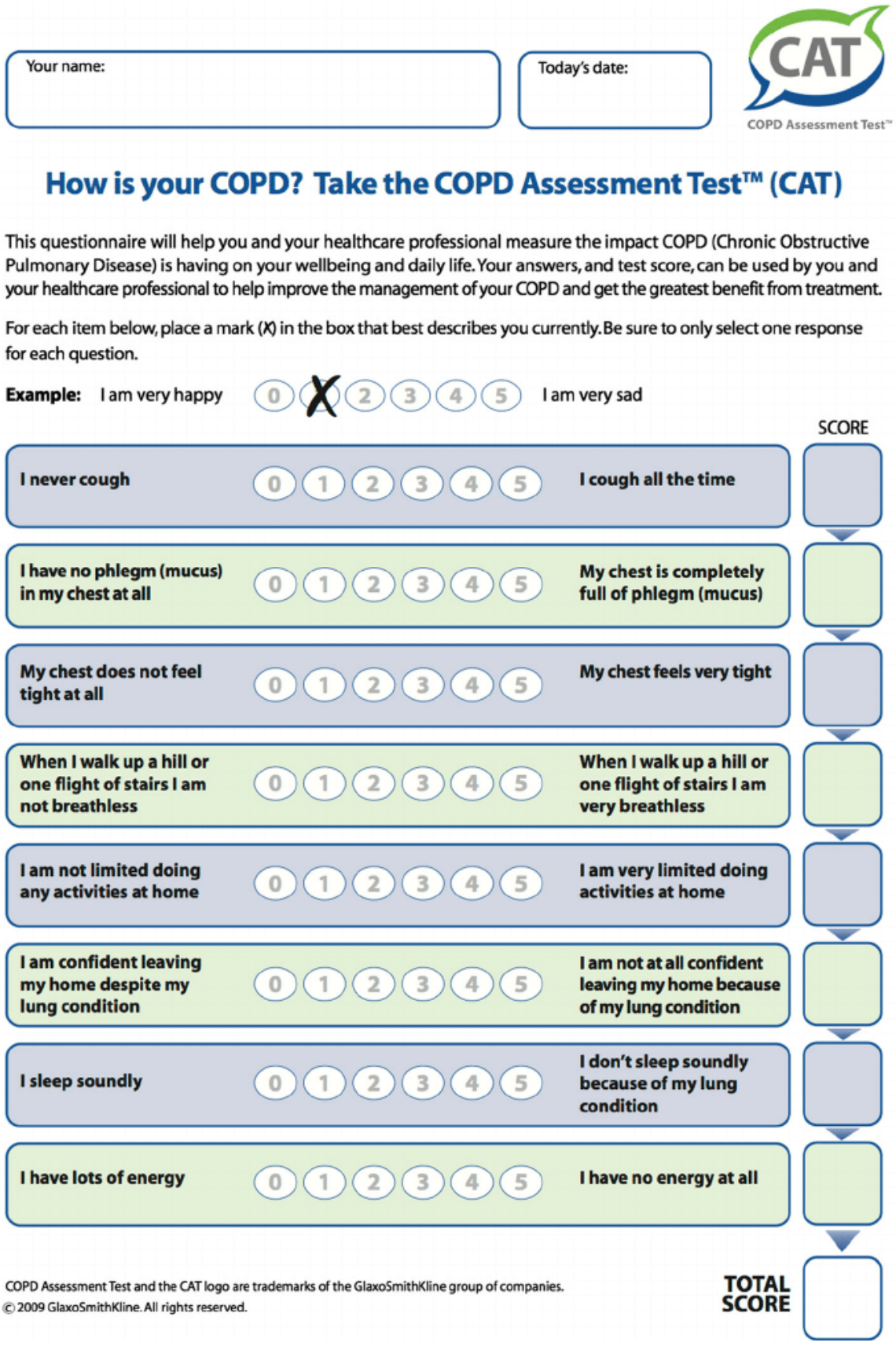
2.6 Other patient reported outcome measures (PROMs)

2.6.1 The COPD assessment test (CAT)

The COPD assessment test (CAT) is a self-reported health status measure that has been created specifically for use in a COPD population and validated in several settings (Jones 2009). The development of this measure was originally intended to help facilitate discussion between patient and clinician around important areas of COPD management. The measure involves 8 items which subjects are asked to rate on a scale of 0-5 including cough, sputum, chest tightness, functional breathlessness, sleep and energy conservation. A total score is then calculated between 0-40 based on these 8 areas, a higher score indicating a poorer health status. A change of 2 points has been shown to represent a clinically important difference in pharmacological and PR trials (Kon 2014; Smid 2017; Alma 2016; Dodd 2011; Alma 2018) but there is currently no suggested MCID for interventional trials. In more recent years the CAT has been trialled in other conditions (Daynes 2021) and as a screening tool in COPD (Liu 2023) (Stridsman 2018).

The CAT is used in chapter 4 as a measure of health status to assess the comparative change for those undergoing surgical lung volume reduction and those receiving bronchoscopic lung volume reduction.

Figure 2.5: *The Chronic Obstructive Pulmonary Disease Assessment Test (CAT)*



Your name:

Today's date:

CAT
COPD Assessment Test™

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

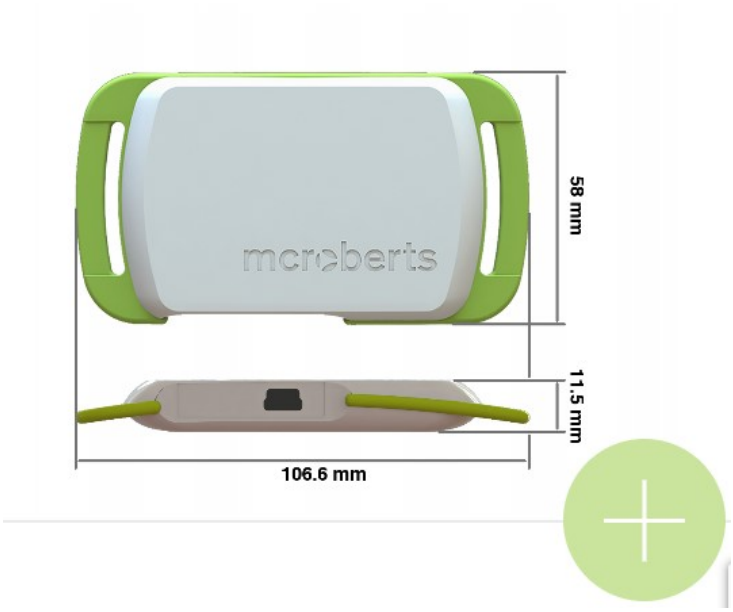
COPD Assessment Test and the CAT logo are trademarks of the GlaxoSmithKline group of companies.
© 2009 GlaxoSmithKline. All rights reserved.

2.6.2 **Assessment of physical activity**

Objective measurement of physical activity was conducted using a Dynaport MoveMonitor (McRoberts) (Figure 2.) This is a tri-axial accelerometer that has been extensively researched and validated in the measurement of physical activity and energy expenditure in a healthy population (Valkenet 2019) and in those with COPD (Rabinovich 2013; Van Remoortel 2012). Although these devices have the capacity to measure sleep movements, in this thesis the MoveMonitor was only used to measure physical activity, in the form of steps per day and vector magnitude units (VMU).

***Figure 2.6**: McRoberts Dynaport MoveMonitor*

Taken from; https://www.mcroberts.nl/products/movemonitor/



Daily step count is a widely recognised measure of physical activity in healthcare research and has been strongly associated with survival (Paluch 2022) and other important health outcomes in COPD (Gimeno-Santos 2014; Demeyer 2019). Physical activity is recognised in GOLD guidelines as an important non-pharmacological treatment in the management of

COPD (GOLD. 2020). Previous pedometer trials have found success in providing daily physical activity programmes for patients with COPD (Mendoza 2015) (Blondeel 2020) and advancements in technology means that more accurate measures can be obtained, including tri-axial accelerometery (Demeyer 2019; Demeyer 2021). However, there remains controversy around the use of activity monitors as a reliable tool to measure clinical end points (Blondeel 2020).

In this thesis the guidelines for respiratory physical activity monitoring that are set out in a recent white paper (Demeyer 2021) were adhered to. Therefore, as actigraphy was measured as a part of an interventional trial this meant a measurement was only accepted as valid if worn for ≥8 hours per day for a minimum of four days (Demeyer 2014). Daily step count between 7am and 9am was calculated by dividing the number of steps taken by the number of valid days.

Patients enrolled in the CELEB trial (chapter four) were asked to wear the monitor for seven full days following their baseline assessment and then for the same duration again at 12 months post interventional procedure. Patients were given clear instructions and demonstration on how the device should be worn and written documentation of this information was provided (Appendix 1). It was emphasised to all patients that the device should be worn for a full 24 hours and only be taken off when there was risk of the device getting wet (bathing/showering/swimming). A pre-paid envelope was provided that the patient was advised to use to return the device, after the seven wearing days.

Figure 2.7: *Movemoitor device being worn*



Taken from: https://www.mcroberts.nl/wp-content/uploads/2017/07/DynaPort-MM-Wearing-Compliance-v0.1.pdf

2.6.3 **Clinical visit PROactive Physical Activity in COPD tool (c-PPAC)**

As well as wearing the activity monitor individuals were given a C-PPAC questionnaire (Appendix 2). This outcome was developed as part of the PROactive consortium project (Demeyer, Louvaris, 2017) and validated as a method of more accurately representing experience of physical activity, from the patient's perspective (Gimeno-Santos 2015) (Dobbels 2014). The CPPAC tool combines the objective data collected via actigraphy (VMU and steps/day) with subjective experience of physical activity using two domains- difficulty and amount.

The amount domain is determined by the objectively collected PA measures (steps/day and VMU) and also several subjective questions around the amount the subjects reports to have done. The difficulty domain is made up of entirely subjective data and both sections are scored between 0 and 100. Recent work exploring the validity and responsiveness of the

PROactie tools propose an MID of 6 for the ‘amount’ and ‘difficulty’ domains and 4 for the total score domain (Garcia-Aymerich 2021).

2.7 Disruption to studies statement

The research presented in this thesis was impacted by the COVID-19 pandemic and personal circumstances.

Chapter four was affected by the requirement of the UK to lockdown at the height of the COVID-19 pandemic. This meant that many patient follow up visits were missed as social distancing guidelines were adhered to and patients isolated at home. Even after the lockdown period ended and the hospital began to allow some research visits to take place many patients preferred to continue to isolate at home and avoid the hospital setting which may have presented greater, and unnecessary risk. Furthermore, the follow up visits for the CELEB trial involved the collection of outcomes that were particularly challenging under these circumstances. For example, spirometry was a composite of the primary outcome and deemed an aerosol generating procedure. Therefore, guidelines were published by GOLD to suggest that spirometry should only be carried out in essential cases (Halpin, Criner, 2021). Although every effort was made to allow this test to be carried out remotely including an amendment to the original protocol and sourcing of hand held spirometers, the ISWT is a measure that is almost impossible to collect remotely. Consequently, calculating a total iBODE score was in many cases unachievable. Additionally, there were many issues with the collection of physical activity data. Failing of the devices used to collect this data and inability of the trial coordinator to travel to recruiting sites to troubleshoot meant that there was a lack of paired data collected to allow a meaningful analysis to be carried out. Therefore, although a chapter was initially planned that explored physical activity following LVR intervention, this was unfortunately abandoned, and the results collected are reported within chapter four. I was able to explore my interest in physical activity in chronic respiratory disease through the completion of a systematic review and meta-analysis of digitally collected mobility outcomes

and their association with prognostic outcomes in COPD. This work is presented in chapter five.

Service changes in the months following lockdown caused further disruptions to work discussed in chapters six and seven. Strategies were put in place to attempt to mitigate interferences and these will be addressed in individual chapters.

In addition to the disruptions caused by the COVID-19 pandemic, this thesis was further interrupted by the birth of my second child for which I took 12 months maternity leave from June 2021. During this time, the studies reported in this thesis were put on hold and recommenced on my return to work in June 2022.

3 Assessing eligibility for Lung Volume Reduction in COPD patients attending Pulmonary Rehabilitation

This chapter was published in BMJ Open in 2020 (Buttery 2020)

3.1 Background

Literature demonstrating the efficacy of LVR therapies for carefully selected individuals with emphysema has been presented in the introduction chapter of this thesis. Difficulties with access including identifying suitable candidates and providing treatment in a timely manner have also been discussed. One aim of this thesis is to address this challenge by tackling the current lack of systematic referral pathway.

This chapter attempts to begin to unpick these issues by estimating the proportion of patients that may be expected to be eligible for a respiratory review, identified through recommendations suggested in national guidelines (Hopkinson 2019) as part of the first step of the LVR referral pathway.

In 2019 an update of the NICE clinical guidelines for COPD management was published in which guidance on the systematic approach to identifying suitable candidates for LVR consideration was presented (Hopkinson 2019). The criteria suggested by NICE was that any patient no longer smoking, with an FEV_1% predicted of <50%, that can walk at least 140m in a 6-minute walk test (6MWT) and complains of limiting breathlessness should be considered as a possible candidate for LVR intervention. This early identification process is the first step in the LVR patient pathway and if this criterion is met onward referral for a respiratory review should follow.

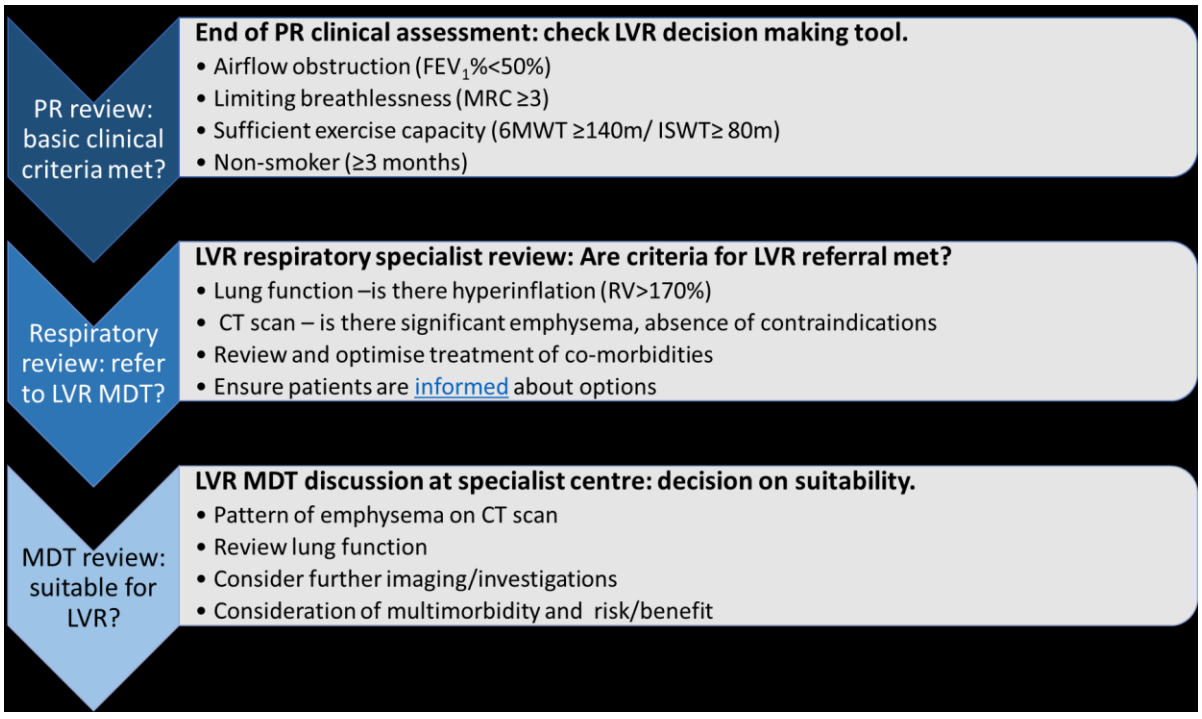
Figure 3.1 depicts the sequential steps in the LVR patient referral pathway that is endorsed by NICE. It shows the different considerations that make up the steps in a systematic lung volume reduction referral pathway.

The LVR pathway is a three-step process. The first step, which this chapter is focussed on is at the point of PR completion when COPD patients should be systematically considered for onward referral onto the next step of the LVR pathway. Step two involves a respiratory

review of referred individuals to establish extent of hyperinflation via full lung function testing and pattern of emphysema by carrying out a CT scan of the thorax. At this point comorbidities should also be evaluated, and a discussion entered between the patient and clinician around understanding and preference. Where appropriate this will lead to step three, a specialist LVR MDT evaluation of suitability for treatment including type of intervention, fissure integrity and target lobe.

***Figure 3.1**: NICE COPD lung volume reduction referral pathway*

Abbreviations: FEV$_1$, Forced Expiratory Volume in 1sec; **MRC,** Medical Research Council Dyspnoea score**, ISWT,** Incremental Shuttle Walk Test; **6MWT**, 6 Minute Walk Test; **RV,** Residual volume



NICE recommends that the initial consideration for onward referral for a respiratory review, or step one in the referral pathway should be carried out on completion of a course of PR. This is suggested as an opportune time as the multi-disciplinary and multi-component approach in PR incorporating both exercise and education mean that a patient's symptomatic management and functional capacity should be optimised (Spruit 2014; McCarthy 2015). If a patient completes PR and is still complaining of debilitating breathlessness then other potential options, including intervention should be explored. Furthermore, patients that would be suitable for LVR intervention should be routinely offered a course of PR, according to PR referral guidelines (NICE 2018) (Bolton 2013). Therefore, PR should theoretically represent a time point where all potentially eligible patients could be systematically considered. This would reflect a more equitable and fair system for patients with emphysema, to access healthcare interventions where currently barriers exist (The 2018) (Oliver 2004; Buttery 2017).

However, several points relating to this consideration criteria are unclear and when assessing patients for their eligibility, could be interpreted in a few ways. More specifically, the criteria for grading breathlessness is vague, stating no particular outcome or threshold that should be used to assess it. The assessment of exercise capacity is also lacking clarity with only 140m suggested for the 6MWT and no equivalent criteria suggested for the ISWT. Despite the two tests being the most widely used by PR programmes and often interchangeably (Wise 2005) (Brown 2007), the ISWT has some marked differences to the 6MWT and an individual that may be able to walk 140m on a 6MWT would not necessarily be expected to walk the same distance on a ISWT (Brown 2007). This is because the ISWT is designed to mimic the incremental treadmill test more closely than the 6MWT by asking the subject to increase their walking pace at equally spaced and externally paced intervals. These qualities mean that the ISWT is a maximal test of exercise capacity but does not effectively assess endurance. The

6MWT is self-paced and therefore allows the individual to utilise pacing strategies to be able to walk further over the 6-minute period and is therefore more representative of functional ability in everyday life.

These ambiguities may lead to an over or under referring of potentially eligible patients and for the purpose of this piece of work, an inaccurate prediction of the proportion of patients that may be expected to be referred. Consequently, services may either be overburdened by inappropriate referrals, or patients may miss out on referral for these important treatments. A study published in 2020 looking at a large database of COPD patients in a primary care setting (73,697) identified that only 36 (0.5%) had received an LVRS procedure despite up to 5,984 (8.1%) meeting the basic referral criteria, and of that number only around 6.9% appeared to have received a referral for secondary care assessment (Whittaker 2020). This represents a substantial mismatch in the number of referrals made and the number that may be eligible for intervention.

Therefore, this study aimed to address these issues by first suggesting appropriate thresholds for the less well-defined criteria, and then estimating the proportion of eligible patients using each of these criteria.

3.2 Methods

Pooled data from the 2015 and 2017 National Asthma and COPD Audit Programme (NACAP) Pulmonary rehabilitation reports (NACAP 2015) were studied to estimate the proportion of those completing PR in the UK (step one LVR pathway) that fit the NICE 2019 criteria (Hopkinson 2019) to be eligible for onward referral to step two on the LVR pathway.

In the first instance eligibility was judged based on criteria including patients that had completed PR, that were not current smokers, with an MRC score of ≥4, FEV_1<50% predicted, and a 6MWD or ISWT of 140m.

The same data set were then considered against different interpretations of the breathlessness and exercise capacity criteria to explore how this would affect the estimated proportions.

Firstly, the MRC score threshold was relaxed from ≥4 to ≥3, with all other criteria unchanged. Although the NICE criteria vaguely state 'limiting breathlessness' as the requirement for assessment of dyspnoea the MRC dyspnoea score was used in all iterations as this is the most commonly used measure of subjective breathlessness in COPD management and its validity has been proven (Bestall 1999). The utility of the MRC score is discussed in greater detail in the main methods chapter of this thesis.

Next, different thresholds were suggested for the ISWT and used to re-calculate the numbers fitting the eligibility criteria. Initially the calculations were done using 140m for the ISWT, to match the 6MWT. Then ≥80m was used. The rational for this relates to the category thresholds used in the BODE (which incorporates the 6MWT) and i-BODE (which uses the ISWT) (Williams 2012; Celli 2004). 140m on the 6MWT would put an individual in the highest scoring BODE category for exercise capacity (i.e. the worst health status) and on the i-BODE index the threshold for this category is ≤80m. A comparison of the two indices is

illustrated in the methods chapter (Table 2.2 ad 2.3). Therefore, a cut-off of ≥80m was used in an interpretation of the guidelines that provides an equivalent criterion for the ISWT.

The specific criteria used for each interpretation in the primary analysis are outlined below;

1) Non-smoker, FEV_1% predicted<50%, an MRC score of ≥4, and able to walk 140m on an exercise capacity test at discharge from PR.
2) Non-smoker, FEV_1% predicted of <50%, an MRC score of ≥3, and able to walk 140m on an exercise capacity test at discharge from PR.
3) Non-smoker, FEV_1% predicted of <50%, an MRC score of ≥4, and able to walk 140m on a 6MWT and 80m on an ISWT at discharge from PR.
4) Non-smoker, FEV_1% predicted of <50%, an MRC score of ≥3, and able to walk 140m on a 6MWT or 80m on a ISWT at discharge from PR.

Finally, the point of assessment was considered. NICE suggests that this should be carried out at the completion of a PR programme. However, issues related to adherence and non-completion of PR are well recognised (Augustine 2021) and have been related to characteristics including disease severity, symptomatic burden and social situation (Arnold 2006; Hayton 2013; Sabit 2008). By excluding those individuals who do not manage to complete a course of PR, perhaps because it is too uncomfortable for them, exacerbating their exertional breathlessness, may well be excluding those patients that are the most likely to be eligible for LVR intervention. Yet, it may also capture patients that have not yet made improvements that may be anticipated following rehabilitation Therefore, a post-hoc analysis was carried out using the same criteria as above but considering the MRC dyspnoea data collected at assessment, rather than at discharge.

3.3 Results

Data from 14,899 were pooled for this analysis; 7413 participants from the 2015 NACAP audit and 7476 from the 2017 NACAP audit. Table 3.1 represents the characteristics of these participants who were 47% female, mean (SD) 69(9.4) years old and the majority ex or non-smokers (75.5%). Participants on average had moderate disease severity (FEV_1%predicted 55.5 (19.9)) and health status (CAT score 19.3 (7.9)) but only a minority were prescribed oxygen therapy (8%). Just over half of PR referrals were made by a General practitioner (51%) or another member of staff working at a primary care practice and most other referrals by either a hospital consultant (21%), community services (13%) or another respiratory specialist (11%).

The findings revealed large amounts of missing data from a lack of recording individual outcomes (between 2.8 and 54.1%). Of this sample size only 32.6% (4,856) were considered against the NICE criteria in the main analysis as only 8,295 (55.7%) that were enrolled on a course had an exercise capacity test recorded and a further 3,439 (23.1%) were missing one or more of the other NICE criteria.

Data collected showed exercise capacity data completeness was poor with only around 57% having undergone an exercise test as part of their PR assessment. This was also an issue for the MRC dyspnoea score data recorded at discharge. Only approximately 46% of participants had an MRC score recorded at discharge compared to the 91% at assessment. The majority of participants fell within the MRC 3-4 category which represents a cohort who are limited by their breathlessness and would be the expected demographic of those accessing PR services.

Of the 4,856 participants considered 238(4.9%) were eligible for LVR assessment, based on the original interpretation of the NICE criteria (MRC score ≥4/ exercise capacity test 140m or

more) (Figure 3.2). However, this rose to up to 882 (18.2%) when using the most lenient criteria (MRC score ≥3/exercise capacity (ISWT) 80m or more).

A secondary analysis considering the same cohort of patients at the point of enrolment on a PR course, rather than discharge showed that up to 1,352 (27.2%) of patients fitted the eligibility criteria for onward referral (Figure 3.3).

Table 3.1: *UK Pulmonary rehabilitation participant characteristics*

	n (%)	**2015 (n=7413)**	**2017 (n=7476)**	**2015 & 2017 combined (n=14,899)**
Age **(years)**	14,886(99.9)	69(9.5)	69(9.3)	69(9.4)
Sex **(female) (n (%))**	14,889(100)	3465 (46.7)	3548 (47.5)	7,013 (47.1)
Ethnicity **(white British) (n (%))**	13,857(93.0)	6523(88.0)	6443(86.2)	12,966(87.1)
Smoking status **(n (%)) Ex-smoker/never smoked**	14,478 (97.2)	5628 (75.9)	5614 (75.1)	11,242(75.5)
BMI **(kg/m)^2**	9907(66.5)	27.5(6.6)	27.9 (6.7)	27.7(6.6)
Oxygen therapy **(n (%)) Prescribed oxygen**	14,883(99.9)	723(9.8)	513(6.6)	1,236(8.3)
Referral method **(n (%))**	14,889(100)			
GP/practice team		3810 (51.4)	3788 (50.7)	7,598(51.0)
Hospital consultant		1521 (20.5)	1498 (20.0)	3,019(20.3)
Community services		903 (12.2)	1120 (15.0)	2,023(13.6)
Hospital specialist/COPD team		841(10.6)	636 (8.5)	1,477(9.9)
Specified post		174 (2.3)	219(2.9)	393(2.6)
AECOPD early PR pathway		219(3.0)	215 (2.9)	434(2.9)
Other				
FEV_1 (litres)	8943(60.0)	1.38 (0.60)	1.42(0.63)	1.40(0.62)
FEV_1 (% predicted)	8943(60.0)	55.1 (20.0)	55.7(20.0)	55.4(19.9)
ISWT, m	4,666(31.3)	270.8(153)	276 (152.4)	273(152.6)
6MWT, m	3,740(25.1)	324.1(133)	314.6 (115.1)	319(123.9)
MRC dyspnoea score at assessment **(n (%))**	13,567(91.1)			
Grade 1		115 (1.7)	127(1.9)	242(1.8)
Grade 2		1080 (15.8)	1071 (15.8)	2,151(15.9)
Grade 3		2656 (39.0)	2648 (39.3)	5,304(39.1)
Grade 4		2328 (34.1)	2301 (34.1)	4,629(34.1)
Grade 5		643 (9.4)	598 (8.9)	1,241(9.1)

MRC dyspnoea score at discharge **(n (%))** **Grade 1** **Grade 2** **Grade 3** **Grade 4** **Grade 5**	6,831(45.8)	 177 (5.3) 1020 (30.5) 1345 (40.2) 671 (20.0) 134 (4.0)	 225 (6.5) 1061 (30.5) 1430 (41.0) 668 (19.2) 100 (2.8)	 402(5.9) 2,081(30.5) 2,775(40.6 1,339(19.6) 234(3.4)
SGRQ total score	514(3.5)	49.9 (16.6)	48.9 (17.3)	49.4(17.0)
CAT score	5,495(36.9)	19.9(7.9)	18.6(7.8)	19.3(7.9)

Abbreviations: BMI, Body Mass Index; **FEV_1**, Forced Expiratory Volume in 1sec; **ISWT,** Incremental Shuttle Walk Test; **6MWT**, 6 Minute Walk Test; **MRC,** Medical Research Council Dyspnoea score; **SGRQ,** St George's Respiratory Questionnaire; **CAT,** COPD Assessment Test.

***Figure 3.2**: UK Pulmonary rehabilitation participants meeting NICE criteria for LVR consideration (primary analysis)*

Flow diagram representing patients at discharge in the 2015/2017 PR cohorts who meet the criteria to be assessed for a possible lung volume reduction procedure depending on criteria used. - primary analysis

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; ISWT, incremental shuttle walk test; NACAP, National Asthma and COPD Audit Programme; NICE, National Institute for Health and Care Excellence; PR, pulmonary rehabilitation; MRC, Medical Research Council; 6MWT, 6-minute walk test.

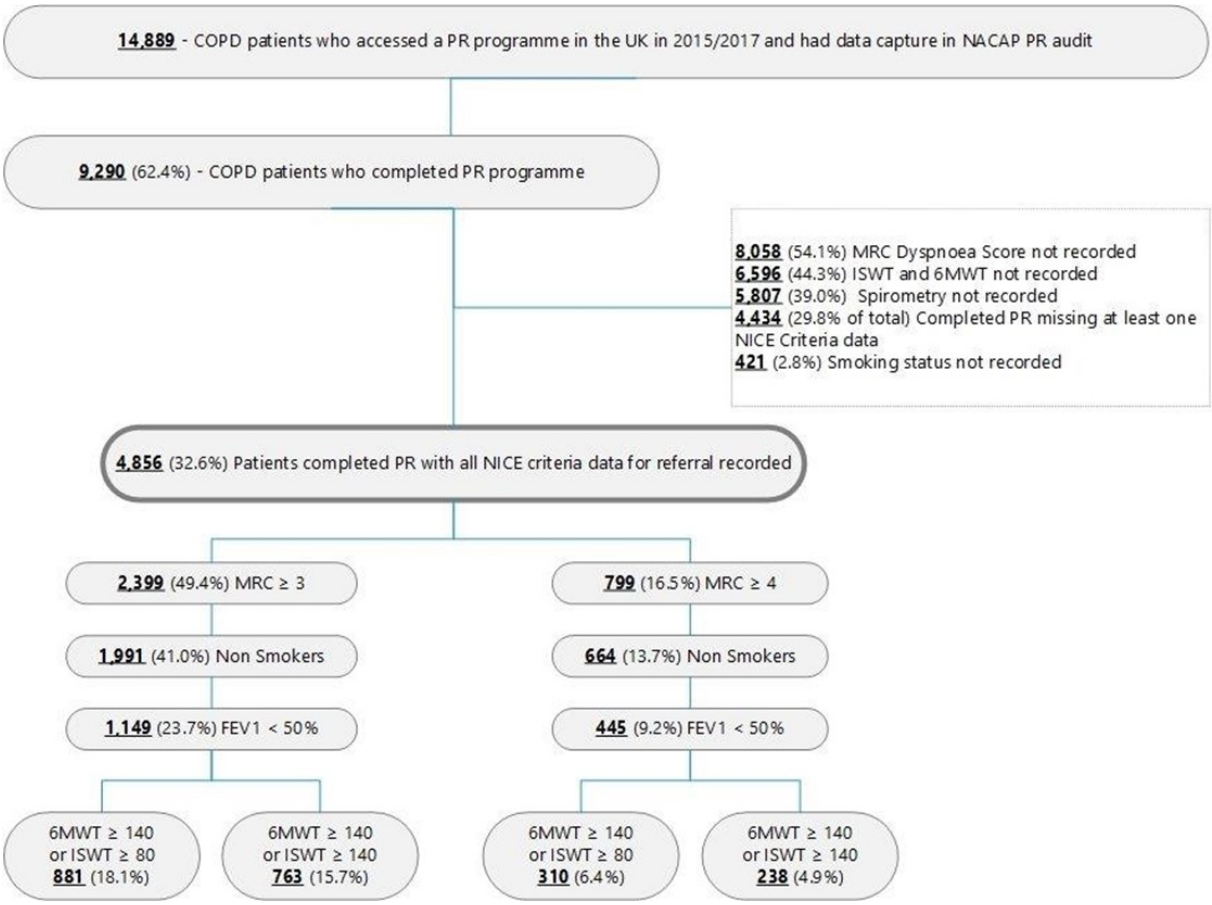
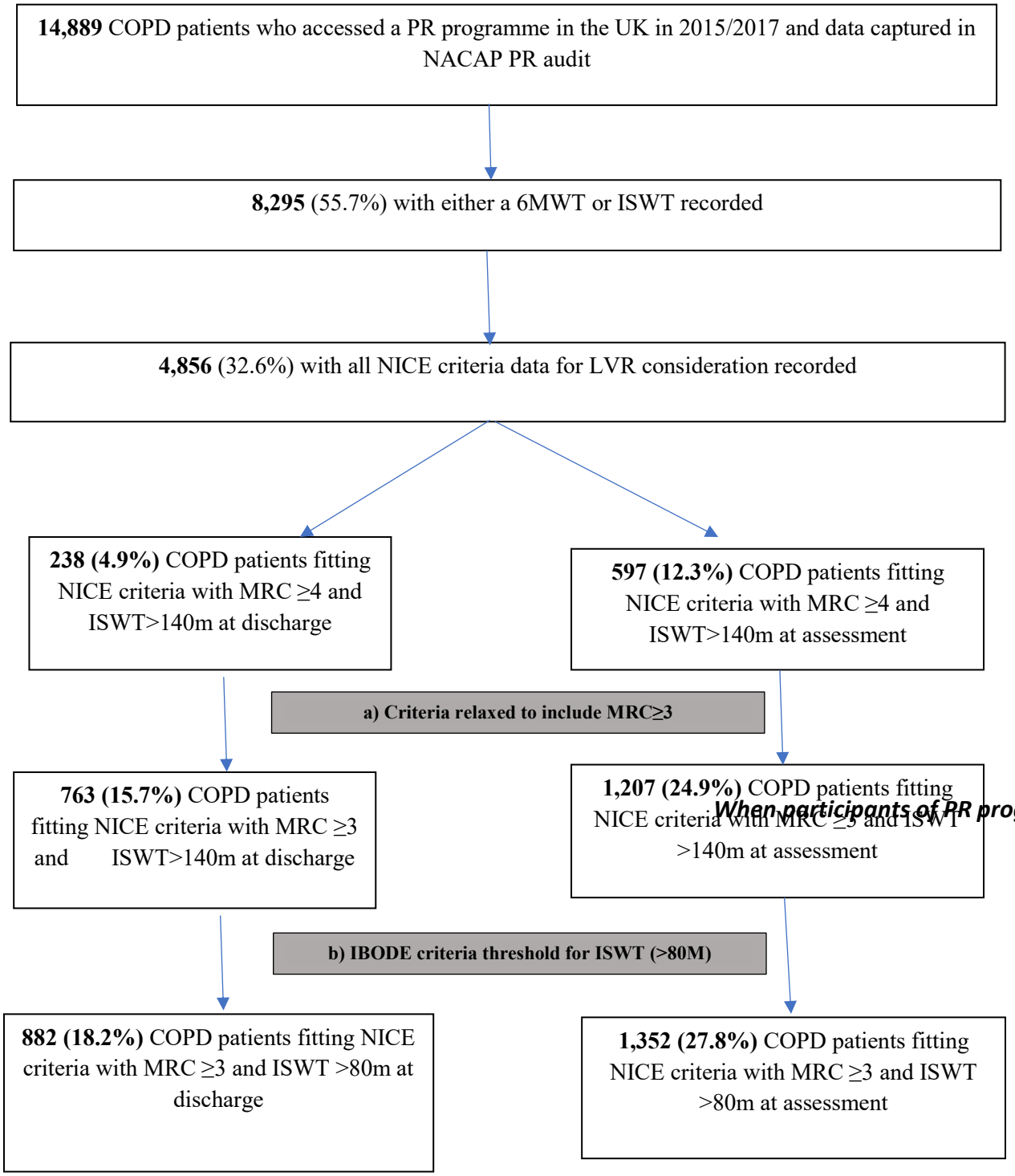


Figure 3.3UK Pulmonary rehabilitation participants meeting NICE criteria for LVR consideration: comparison between assessment and discharge (secondary analysis)

Flow diagram representing patients at discharge compared with assessment in the 2015/2017 PR cohorts who meet the criteria to be assessed for a possible lung volume reduction procedure depending on criteria used- secondary analysis



3.4 Discussion

3.4.1 **Key findings**

The analyses that were carried out as part of this study revealed firstly, that there appears to be a mismatch between the number of potentially eligible patients and the number that get referred for LVR consideration and treatment. However, it was also evident that the proportion varies according to different interpretations of key consideration criteria, that are currently unclear. This includes the threshold used to assess breathlessness and exercise capacity and the point at which assessment of criteria takes place (assessment or discharge from PR). The findings from this study show that when using a more lenient interpretation of the criteria more than three times the number of patients may be eligible for onward referral and further consideration on the LVR pathway. This represents a very broad spread and has implications for the over or under referring of individuals.

3.4.2 **Significance of findings**

Despite the observed difficulties of high attrition, incomplete data outcomes and vague consideration criteria, it may be suggested that the routine assessment of patients accessing PR, for their eligibility for LVR referral could be considered as an opportunity to improve standards of care for all COPD patients (Hopkinson 2019). It is well understood that completing a course of PR is associated with improved outcomes (McCarthy 2015). Therefore, consideration for further interventions on completion of a course of PR could be used as an incentive for patients to adhere to their programme and reap the known benefits of rehabilitation. On the contrary to this, a failure to complete PR is associated with worse long-term outcomes (RCP ; Lindenauer 2020) which may be attributable to not gaining the benefits of PR or may be because those with greater symptomatic burden are more likely to

drop out. Completion of a course of PR is commonly used as a requirement criterion for LVR intervention. If a patient does not complete a course of PR or drops out this may be interpreted as a sign that an individual's ability to cope with LVRS is reduced. However, access to PR is limited (Boutou 2014) (Philip 2019) and non-completion is common. In the NACAP dataset that was used in this study approximately 38% were lost between assessment and completion. This may be due to a multitude of reasons which could be completely unrelated to individual fitness. Literature suggests that among the most common reasons for non-adherence to a PR programme are increased disease severity and symptom burden (Hayton 2013). Patients with more severe breathlessness are likely to be the individuals that are suitable for interventions and will derive the most symptomatic benefit from LVR. However, they also may be more likely to drop out (Boutou 2014). Furthermore, as demonstrated in the introductory chapter of this thesis hyperinflated patients may not be able to train at sufficient intensities to bring about improvement through PR, finding exercise very uncomfortable and difficult to adhere to over a longer period (Ward 2023; O'Donnell 2001). To mitigate the problem of missing those patients that may be eligible for treatment but do not or cannot complete a course of PR it may be suggested that consideration for possible LVR referral should be initiated at PR assessment. As well as fairly and systematically assessing more people with COPD this approach may provide incentive and help to promote programme adherence. Finally, the time between assessment and programme completion may present an opportunity for clinicians to gather important data on comorbidities and previous investigations which may be relevant.

However, as mentioned above in the instance of this NACAP 2015/2017 data would include up to 38% more patients. Although this should not proportionally increase the number of referrals we know that when assessing the same number of patients but comparing their

outcomes collected at assessment rather than discharge more patients are likely to fit the criteria due to a lower MRC prior to rehabilitation. Therefore, work needs to be done to develop a process that captures those who are likely to drop out during the programme whilst also taking into account the improvements that are likely for some during the course of PR. It is important to note that the proportions presented in this chapter do not necessarily accurately represent the proportion of patients that should be referred to a specialist centre. Assuming this would omit a vital step in the patient pathway and generate a large number of inappropriate referrals that could in fact worsen the problem by causing a backlog and consequently, increasing wait times. Rather, that every patient should be systematically reviewed to consider whether LVR may be a potential option and if the necessary investigations have been or should be carried out in secondary care, to evaluate their eligibility, should the individual express an interest.

3.4.3 **Methodological considerations**

This study had a number of important strengths. As the data analysed was from a national audit these findings can be assumed to be representative of the UK population and therefore widely relevant. Additionally, the audit collected data from a very large pool of PR programmes and patients meaning it is likely that the findings are generalisable and provide a reasonable and reliable estimation of the proportion that may be eligible for consideration. Furthermore, the findings provide suggestions around the clarity of the NICE criteria and how different interpretations may affect the proportions eligible for referral. The proportions suggested in this study are in line with previous literature that estimated approximately 8.1% of patients from a primary care database fit basic criteria for LVRS (Whittaker 2020). The broad parameter shown in this study's primary findings (between 4.9% and 18.3%) depending on the different thresholds used for breathlessness and exercise capacity

demonstrate the importance of a more clearly defined assessment criteria to avoid the over or under referring of patients to secondary care.

Limitations of the criteria used to estimate the proportions estimated in this analysis also introduced some weaknesses. For example, the presence of co-morbidities and patient preference were not recorded and therefore not accounted for when calculating proportions. These factors are fundamental in influencing decisions around eligibility for interventions and if this data had been available, ultimately may have affected the numbers reported in the results of this analysis. For instance, those with significant pulmonary hypertension would not be eligible for an LVR intervention regardless of the other criteria assessed. Likewise, a patient fitting the functional and symptomatic criteria may simply not want to consider an intervention, preferring a conservative management plan. In these patients a referral to secondary care for further investigations in the context of LVR consideration may be considered a waste of resource.

A further limitation was the high proportion of missing exercise capacity data which excluded many subjects from being included in the analysis (44%). Exercise testing as part of a PR assessment is recommended in quality standards (Bolton 2013). Collection of this outcome is vital for both patient profiling, safety implications and exercise prescription (Ries 1994). Failure to meet this standard means that these components may not be fulfilled as well as prohibiting the consideration of individuals against basic criteria for LVR referral. As the lack of compliance with exercise testing is a known problem in PR services across the UK it has been one of the NACAP key improvement indicators (NACAP) and more recent data published after this analysis was carried out shows an improvement in the recording of exercise capacity data, nationally. This is of great significance to the LVR pathway as

walking test are not routinely carried out in secondary and tertiary care services and therefore having a formal assessment of exercise capacity to allow consideration for intervention typically relies on those measurements collected in a PR programme. This provides further justification for the integration of PR services in the LVR patient pathway.

Related to this is the lack of refined criteria for assessing or grading exercise capacity. The NACAP data shows that PR programmes across the UK use the ISWT at least as frequently as the 6MWT to assess exercise capacity. Yet, the NICE criteria provide only an exercise test threshold for the 6MWT. The COVID-19 pandemic saw many services setting up remote or virtual PR programmes when attending in-person sessions was not permitted. This has continued for some services, numerous now offering a hybrid arrangement to allow for patient preference or to cater for those that fail to adhere to programmes due to transport issues, scheduling, other major contributors to attrition rates (Wuyts 2022). With this shift in delivery mode came the need for a remote method for assessing exercise capacity. The 6MWT and ISWT can only feasibly be conducted in a clinic or lab environment due to the need for controlled settings and a large walkway. Tests such as the 5 sit to stand test (5STS) (Rosenbek Minet 2015; Oliveira 2018), 1-minute sit to stand test (Mazzarin 2018) and timed up and go (TUG) (Coquart 2017; Wilke 2015) have been explored as remote tests of exercise capacity and may offer a means of collecting exercise performance data in a more efficient manner. This could benefit those on the LVR pathway, waiting for consideration. However, these tests of course are not a replacement for the 6MWT/ISWT as they do not assess maximal exercise capacity and therefore cannot be used for exercise prescription (Holland 2020). Furthermore, there is debate around whether these tests can be safely carried out in a remote environment without clinician supervision (Holland 2020).

In the context of assessing functional capacity and the safety of a patient to undergo an intervention, other more functional test may be useful and should be explored. Interestingly, one study that used a stair climbing test to assess functional capacity in preoperative COPD patients demonstrated that a subjective measure could be reliably used to predicted post-operative complications compared to the objective test (Dankert 2023).

More work is required to explore the potential of outcomes to remotely assess exercise capacity, or functional ability, and in setting thresholds for these test for LVR eligibility criteria.

3.4.4 **Conclusions and future work**

The findings from this work show that a significant proportion of patients suitable for onward referral on the LVR pathway could be identified by PR services using NICE recommendations. However, the selection criteria, that should identify people who would benefit from a procedure but who are not at an unacceptably high risk of a poor outcome must be clearly defined. Overall, further work is indicated to explore how step one in the referral pathway can be improved, and future research should focus on the development and refining of LVR referral pathways that can be practically implemented at an appropriate time point and setting. This is explored further in chapter eight of this thesis.

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

This chapter was published in the European Respiratory Journal in February 2023 (Buttery. 2023) and a protocol for this study was published in BMJ Open in 2018 (Buttery 2018).

4.1 Background

The background to this thesis provided a detailed review of the evidence base surrounding the history of LVRS and development and uptake of bronchoscopic interventions in COPD. This overview demonstrates the strong evidence base showing that both LVRS and bronchoscopic lung volume reduction (BLVR) with endobronchial valves (EBVs) produce improvements in lung function, exercise capacity and quality of life in appropriately selected patients with emphysema (van Geffen 2019). Yet, there are no direct comparison data between the two procedures to inform clinical decision-making in people who are suitable for both, namely patients with heterogeneous emphysema and intact interlobar fissures.

As the current gold standard treatment for reducing hyperinflation in patients with emphysemas, this study hypothesised that health benefits achieved by LVRS at one-year post procedure are significantly superior to those seen at one-year post BLVR, in individuals who have equipoise for either treatment.

The aim of this chapter was to determine whether LVRS produces a significantly greater health benefit at one-year post treatment, compared to BLVR to be likely to influence choice of procedure within a clinical environment.

4.2 Methods

4.2.1 Study design and participants

Participants were recruited for this randomised controlled superiority trial between June 2016 and August 2019 from outpatient clinics at 5 centres across the UK; Royal Brompton Hospital (London), Glenfield Hospital (Leicester), Northern General Hospital (Sheffield), Golden Jubilee Hospital (Glasgow), and Barts Health (London). Patients were considered eligible for enrolment onto the trial if they fit the pre-defined eligibility criteria (outlined below). Eligible patients were then discussed at a specialist LVR MDT meeting at one of the five centres and if it was agreed that the individual was equally suitable for either LVRS or EBVs then they were invited for a screening visit where written informed consent was obtained, and baseline measures were recorded.

The study received ethical approval from Fulham Research Ethics committee, London UK (REC reference: 16/LO/0288) and was prospectively registered on clinicaltrials.gov (ISRCTN19684749). A trial steering committee was set up and met at regular intervals throughout implementation of the study. The committee had an external chairperson and provided supervision to ensure trial proceedings were carried out in accordance with the principles of Good Clinical Practice. All meetings were minuted and a memorandum of each meeting sent out to every member of the CELEB trial committee.

This was a single blind trial. Blinding of subjects was not possible due to the nature of the interventions and for practicality the study coordinator and those providing clinical care were also unblinded. However, to try to minimise bias the research staff collecting primary outcome data were blinded to intervention. Last patient visit for this study was carried out on 28th August 2020.

4.2.2 **Inclusion criteria**

- Adults diagnosed with COPD according to international guidelines (Venkatesan 2023)
- FEV_1%predicted <60%
- TLC>100%
- RV>170%
- Heterogeneous emphysema and intact fissure of target lobe based on assessment of CT thorax during MDT meeting.
- Deemed by MDT to have equipoise for either LVRS or EBV treatment.

4.2.3 **Exclusion criteria**

- FEV_1%predicted and TLco both <20%
- $Pa0_2$ <7.0 Kpa
- PaC02 >7.0 Kpa
- Collateral ventilation assessed by Chartis
- Any life limiting comorbidity
- Significant pulmonary fibrosis
- Smoking in the 3 months leading up to enrolment on the trial.

4.2.4 **Assignment of Interventions**

A detailed description of the interventions investigated in this study (LVRS and EBVs) can be found in the methods chapter. Where BLVR is used to describe treatment in this chapter it refers specifically to EBVs.

Participants on the trial were randomly assigned to either LVRS or BLVR (EBVs) on a 1:1 basis. This was carried out using a computer-generated random sequence with random block sizes, provided by Sealed envelope (London, UK). Randomisations were stratified by recruiting centre and i-BODE score (≤ 7 or > 7) to ensure an equal number in each arm with a 'poorer' health status (>7).

Randomisation was carried out immediately after undergoing a Chartis assessment to assess for the presence of collateral ventilation (CV) in the target lobe. If there was an absence of CV, then randomisation was performed, and the patient was either treated with EBVs (if randomised to this arm) or a future date for surgery was planned if the patient was randomised to LVRS. If CV was present, then the individual was exited from the trial as inclusion criteria was not met.

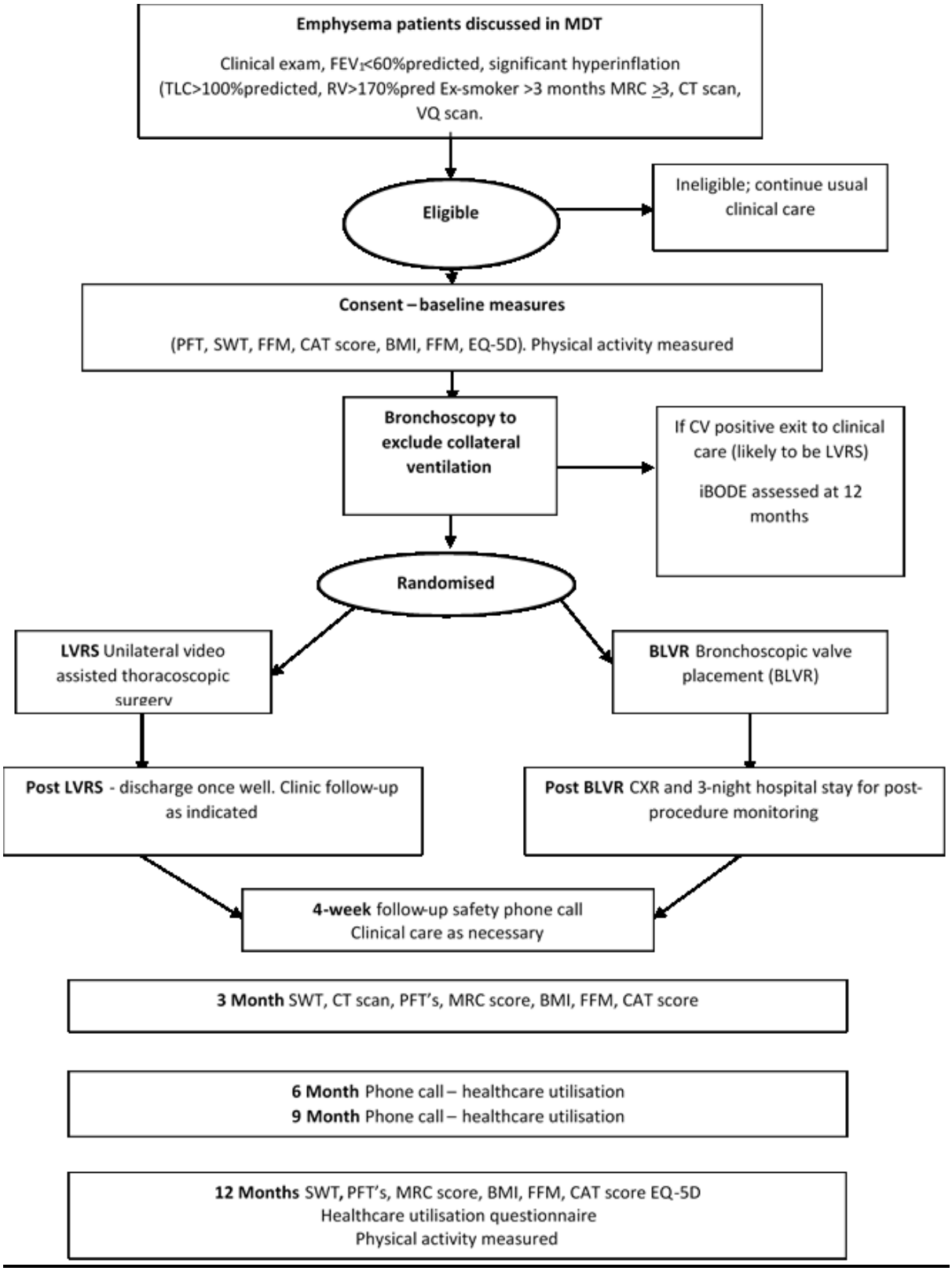
4.2.5 **Primary and secondary outcomes**

The Primary outcome for this study was the i-BODE index measured at 12 months post procedure. This is a composite measure of health status used in COPD to determine disease severity. It is made up of four outcomes that are each individually used in clinical practice to monitor health status and predict outcomes such as exacerbations and hospitalisation, in COPD. These are; B- body mass index, O- airflow obstruction measured using FEV_1% predicted, D-dyspnoea determined by MRC score, and E- exercise capacity. The I, indicates that the incremental shuttle walk test is used to measure exercise capacity in place of the 6MWT that is used in the BODE index. By combining these important outcomes into one measure it is thought that a more accurate measure of disease severity can be made, particularly in a heterogeneous disease population such as COPD. This outcome and its evidence base is described further in the methods chapter of this thesis.

To minimise the effect of bias those staff collecting the primary outcome data (BMI, FEV_1%predicted, MRC score, ISWT) were blinded to treatment arm and patients were instructed not to reveal this information. Where there were missing components of the i-BODE-index, to allow a total score to be calculated imputation was used (see statistical methods).

Secondary outcomes included; the individual components of the i-BODE index (FEV_1% predicted, BMI, MRC dyspnoea score, ISWT) RV% predicted, CAT score, FFMI and physical activity measures. The EQ-5D-5L questionnaire and a healthcare utilisation measure were also collected at baseline, three, six, nine and twelve months post intervention, via telephone, with the intent of performing an economic evaluation. The results of these outcomes are not presented in this thesis. Figure 4.1 provides a schematic outline of the baseline and follow up visits (3 and 12 months).

Figure 4.1: *Schematic diagram of trial proceedings.*



4.2.6 **Statistical analysis**

Sample size was calculated based on data from a paper published in 2006 by Imfeld et al (Imfeld 2006). This paper compared the change in BODE score at three months post LVRS in survivors and non-survivors at 5 years post procedure. In the 'survivors' arm the improvement was found to be 3.9 points and the 'non-survivors' 2.4 points. The variance between these two groups (1.5 points) was taken to represent a great enough difference to be able to conclude that LVRS is substantially superior to BLVR. Therefore, assuming a SD of 1.8 and ensuring a 90% statistical power at a 5% significance level a minimum of 34 patients in each treatment arm would be required. An expected dropout rate of 10% was accounted for, setting a total recruitment target of 76 participants.

All statistical analyses were performed using either SPSS 26.0 or STATA version 16.1 and were led by a healthcare statistician (Winston Banya). Data were analysed on an intention to treat basis, excluding those that were randomised but did not undergo any treatment. Categorical data were presented as number (%), normally distributed numerical data as mean (SD) and skewed data as median (IQR). Changes from baseline to 3 months and 12 months follow up were calculated and the treatment effect was reported as the mean of the difference (95% CI) between the 2 groups or the Hedges-Lehman estimate for skewed data. Comparisons between the two groups were done using the Chi square test or Fishers exact test for normally distributed data and Wilcoxon rank sum (Mann-Whitney) test for skewed data. Significance was set at $p<0.05$ and all statistical tests were 2-tailed. Missing data was imputed under a missing at random assumption on all data with missing variables. Values were replaced using chained equations, including the three-month i-BODE index data. For each variable 10 imputed datasets were created, and Rubin's rule was applied to obtain an overall estimate (White 2011).

4.3 Results

4.3.1 **Study design and participants**

163 patients were screened for eligibility to be enrolled on to the trial. Of these, 14 dropped out prior to enrolment due to either not meeting the enrolment criteria or declining involvement. A further 61 were excluded following a baseline assessment due to not meeting the inclusion criteria; most commonly, being CV positive (n=38) or having a low flow or indeterminate Chartis (n=9). This meant that EBVs would not be a viable treatment option and as equipoise no longer existed they would no longer meet the inclusion criteria. Other reasons for exclusion can be found in Figure 4.2.

88 eligible participants were randomised to either LVRS(n=41) or BLVR(n=47) (Figure 4.2). Baseline characteristics of the randomised participants are shown in Table 1. There were no significant differences between the two groups at baseline with the exception of exacerbations in the 12 months leading up to enrolment in the trial which were higher in the BLVR group (3, 1-4) compared to those receiving LVRS (1.5, 1-2.5) (p=0.012). Of the 88 randomised patients only 80 participants received treatment (34 LVRS / 46 BLVR). Seven participants (1 randomised to BLVR/ 6 randomised to LVRS) decided against having the procedure post-randomisation and therefore exited the trial prior to treatment. One participant randomised to LVRS died whilst on a surgical waiting list, before treatment was received`.

Figure 4.2: *CELEB trial flow diagram*

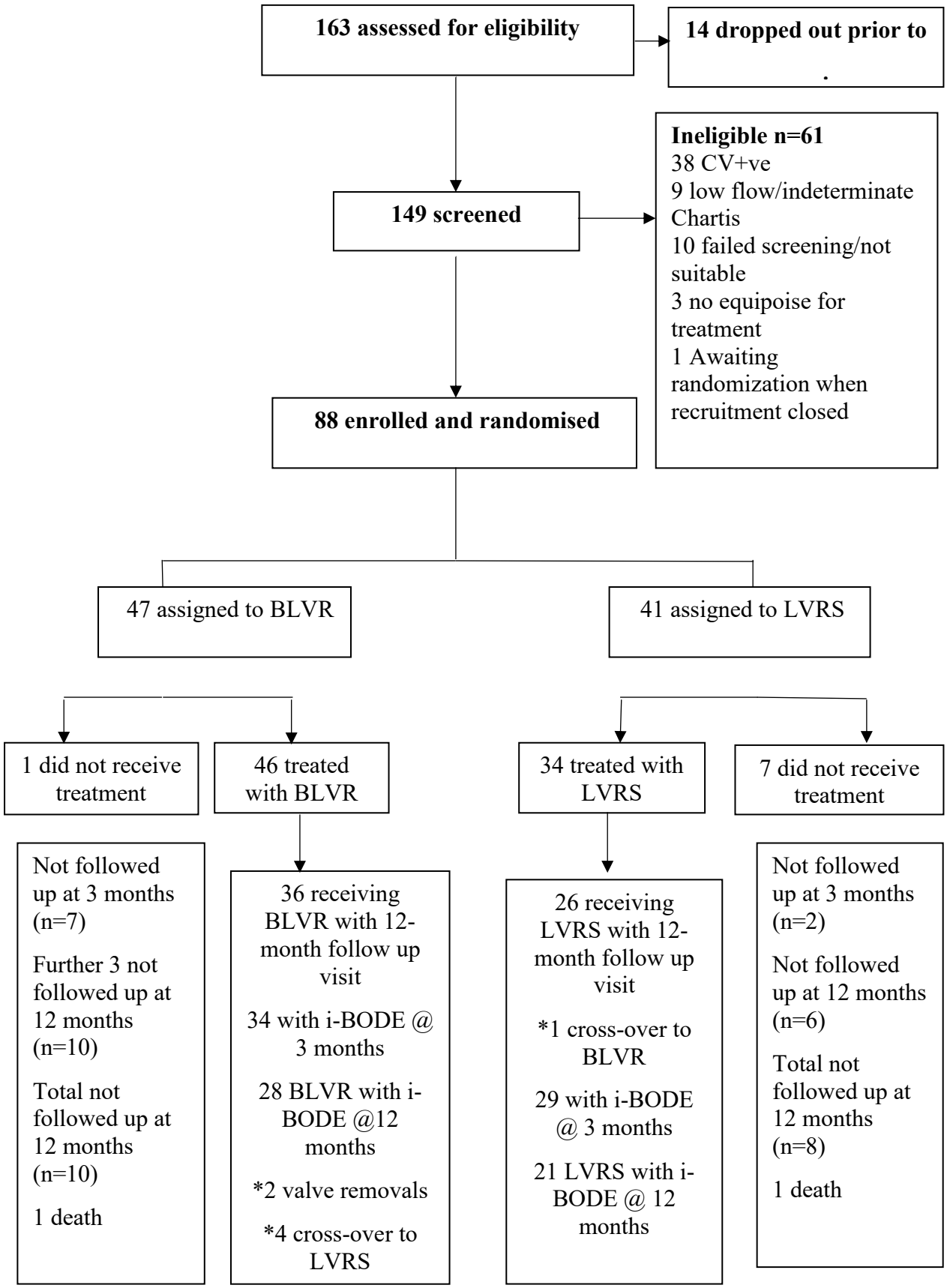


***Table 4.1**: Baseline characteristics of participants enrolled on trial: whole cohort and per treatment arm*

	All (n=88)	LVRS (n=41)	BLVR (n=47)	p-value
Age (years)	64.6 (7.7)	65.2 (7.9)	64.0 (7.6)	0.79
Gender: Female, n (%)	42 (47.7)	22 (53.7)	20 (42.6)	0.30
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)	0.012*
A&E Attendances*	0 (0, 1)	0 (0, 0)	0 (0, 1)	0.51
Hospital admissions*	0 (0, 0)	0 (0, 0)	0 (0, 1)	0.32
Hospital days*,	0 (0, 0)	0 (0, 0)	0 (0, 1)	0.28
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)	0.92
BMI ($kg/m^{2)}$	23.7 (3.7)	23.8 (3.9)	23.6 (3.5)	0.83
$FEV_{1,}$ %predicted	31.0 (7.9)	32.0 (7.7)	30.2 (8.0)	0.27
MRC dyspnoea score	4 (3, 4)	4 (4, 4)	4 (3, 4)	0.32
ISWT (m)	210 (125, 265)	200 (130, 260)	210 (120, 270)	0.79
Lung function parameters				
FEV_1(l)	0.80 (0.22)	0.81 (0.21)	0.80 (0.22)	0.26
FVC (l)	2.82 (0.81)	2.80 (0.70)	2.84 (0.90)	0.83
FVC, %predicted	86.1 (19.0)	88.2 (20.0)	84.3 (18.1)	0.34
FEV_1/FVC ratio	28.03 (24.08, 35)	28.02 (25.5, 32)	29.0 (23.89, 35.4)	0.73
TLC (l)	8.08 (1.83)	7.91 (1.87)	8.20 (1.81)	0.47
TLC, %predicted	142.0 (14.1)	142.4 (13.8)	141.7 (14.5)	0.80
RV (l)	5.3 (1.2)	5.2 (1.3)	5.4 (1.1)	0.44
RV, %predicted	240.1 (39.0)	236.9 (39.3)	242.9 (39.0)	0.49
RV_TLC ratio	64.0	63.9 (5.6)	64.0 (7.0)	0.43
FRC (l)	6.3 (1.4)	6.1 (1.5)	6.4 (1.3)	0.26
FRC, % predicted	195.5 (182, 211.5)	197.5 (182.4, 209.1)	194.5 (178.9, 214.6)	0.91
TLco, %predicted	35.8 (10.0)	35.9 (10.6)	35.7 (9.5)	0.94
Kco, %predicted	46.7 (13.9)	46.4 (14.4)	47.1 (13.5)	0.74
Other Secondary outcomes				
FFMI ($kg.m^2$)	30.9 (5.7)	30.9 (6.2)	30.9 (5.3)	0.29
CAT score	23.1 (6.4)	23.9 (6.6)	22.5 (6.1)	0.22
c-PPAC amount	28.4 (12.7)	27.5 (11.1)	29.2 (14.4)	0.73
c-PPAC difficulty	50.4 (12.8)	53.8 (11.5)	47.6 (13.4)	0.08
c-PPAC total	44.8 (12.8)	47.1 (13.4)	42.8 (12.1)	0.23
Steps per day	2551 (1463, 3812)	2809 (1455, 5398)	2292 (1471, 3450)	0.48

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 (Donaire-Gonzalez) 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.

4.3.2 **Missing data**

Survival data were available for all participants at 12 months. Outcome data were available for 71 (89%) of participants at three months (32 LVRS/ 39 BLVR) (Table 3) and 63 (79%) at 12 months (26 LVRS/ 37 BLVR) (Table 4). Complete primary end point data including BMI, FEV_1% predicted, MRC dyspnoea score and ISWT were available for 49 (61%) participants (21 LVRS/ 28 BLVR) at 12 months. A sensitivity analysis was carried out to compare characteristics at baseline between participants with complete follow up data and those without, and this showed that there were no significant differences between the two groups. This analysis can be seen in Table 2. I used this sensitivity analysis to support the use of a 'missing at random' assumption for imputation of missing data(Sterne 2009). Imputed data for 12 months follow up outcomes can be found in tale 5 and comparison between complete case analysis and imputed data can be found in Table 6a and 6b.

Table 4.2: *Baseline characteristics and relationship (p-value) of participants with and without primary outcome at 12 months follow up (sensitivity analysis)*

	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). * Self-reported in preceding year.

Table 4.3: *3 Months Follow up – based on all available data in the ITT population*

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). * Self-reported in preceding year.

***Table 4.4**: 12 Month Follow up –based on all available data in the ITT population.*

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 (10.0)	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). * Self-reported in preceding year.

***Table 4.5**: 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
FEV$_1$	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).

Table 4.6: *Primary and secondary outcomes: Change from Baseline to 12 months- complete case analysis and imputed data*

a) Complete-Case Analysis

	Difference: 12 months - Baseline		**Treatment Effect (95% CI)**	**P value**
	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
C-PPAC total	18.0 (19.7)	15.3 (14.5)	-2.7 (-24.6 to 19.2)	0.79
C-PPAC amount	17.2 (14.4)	12.0 (17.9)	-5.2 (-17.1 to 6.7)	0.38
C-PPAC difficulty	18.3 (17.3)	16.1 (16.9)	-2.2 (-15.8 to 11.4)	0.74
Steps/day	478.5 (-1166, 1102)	543 (-226, 1332)	-847.5 (-2857, to 8726)	0.31

Data are presented as mean(SD) or median (IQR).

b) Imputed data

	Difference: 12 months - Baseline		Treatment effect (95%CI)	p value
	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 dyspnoea 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

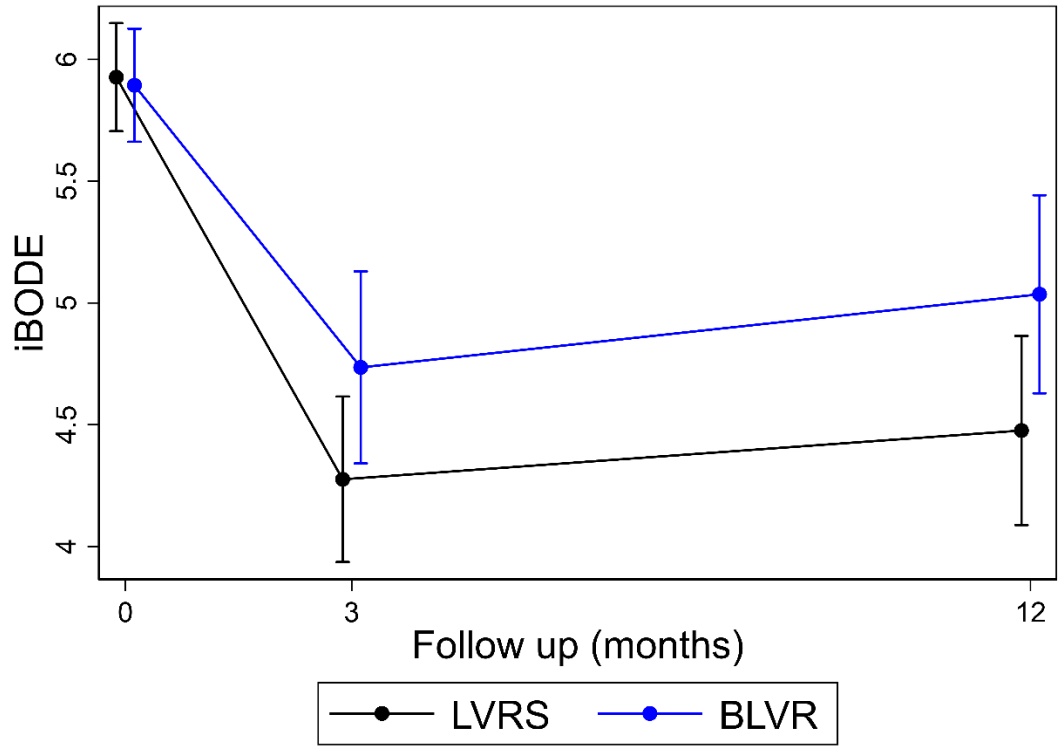
Data are presented as mean(SD) or median (IQR).

4.3.3 **Change in i-BODE score at 12 months post procedure**

Both LVRS and EBVs groups showed an improvement in i-BODE score at 12 months post procedure (LVRS: -1.10 (1.44), BLVR: -0.82 (1.61)) but there was no significant difference in these improvements, between the two groups (treatment effect: -0.27 (-0.62 to 1.17) p=0.54) (Figure 3).

Figure 4.3: *Change in i-BODE score in LVRS and BLVR treatment arms*

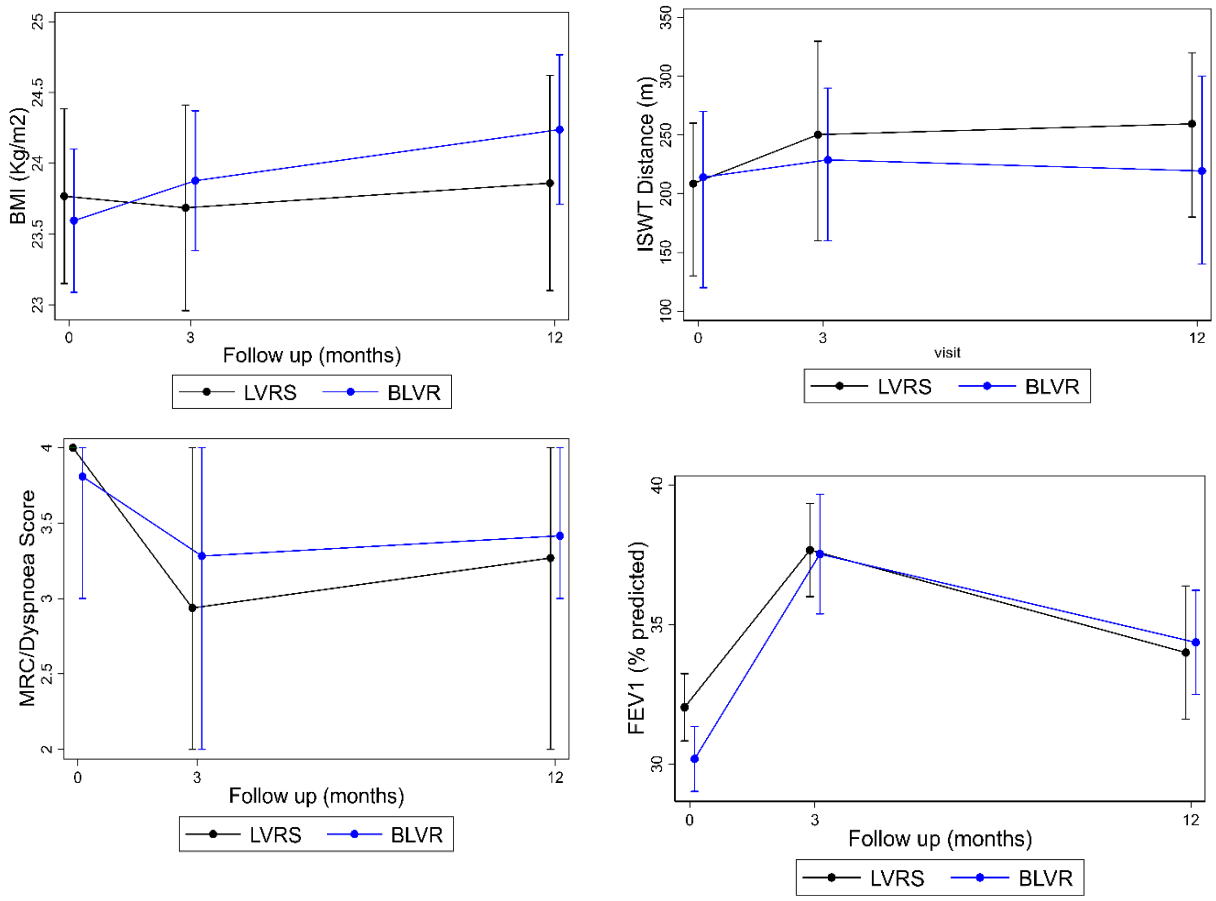
The black line shows a those in the LVRS arm and the blue line shows those in the BLVR arm. Both groups had similar i-BODE scores at baseline and there was no significant difference in change in i-BODE score over time.



Each of the four individual components that make up the i-BODE showed varying levels of improvement in the two treatment arms but there was no comparative difference seen (BMI;LVRS 0.10(1.83), BLVR 0.74(1.57): treatment effect:0.64 (-0.27 to 1.56) p=0.16; FEV_1%predicted; LVRS 1.1(9.1), BLVR 4.5(6.8): treatment effect: 3.4 (-0.8 to 7.6) p=0.11; MRC score; LVRS -0.65(0.89), BLVR -0.33(0.97): treatment effect: 0.32 (-0.80 to 0.16) p=0.19; ISWT; LVRS 27.9(60.7), BLVR -4.8(73.8): treatment effect: -32.7 (-71.0 to 5.5) p=0.09) (Table 6 and Figure 4.4).

A post- hoc analysis of responder rates (-1 point in i-BODE index) at 12 months post procedure was carried out and showed that 48.8% (20/41) in the LVRS group could be classed as responders and 46.8% (22/47) in the BLVR group. The response rate difference between the treatment arms was not significant (X^2= 0.34, p=0.85) (Figure 4.5). Waterfall plots are also provided to show the response rates in each of the four individual i-BODE components (Figure 4.6). No significant differences were seen between the two arms in responder rates for BMI, FEV_1% predicted, MRC dyspnoea score, ISWT based on the individual MID for each outcome (Figure 6).

Figure 4.4: *Change in individual i-BODE components in LVRS and BLVR treatment arms*



Figures show the following outcomes a) BMI; b) FEV_1% predicted; c) MRC dyspnoea score; d) ISWT

Figure 4.5: *Responder analysis based on Minimal Clinically Important Difference- i-BODE index score at 12 months (complete case analysis)*

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.

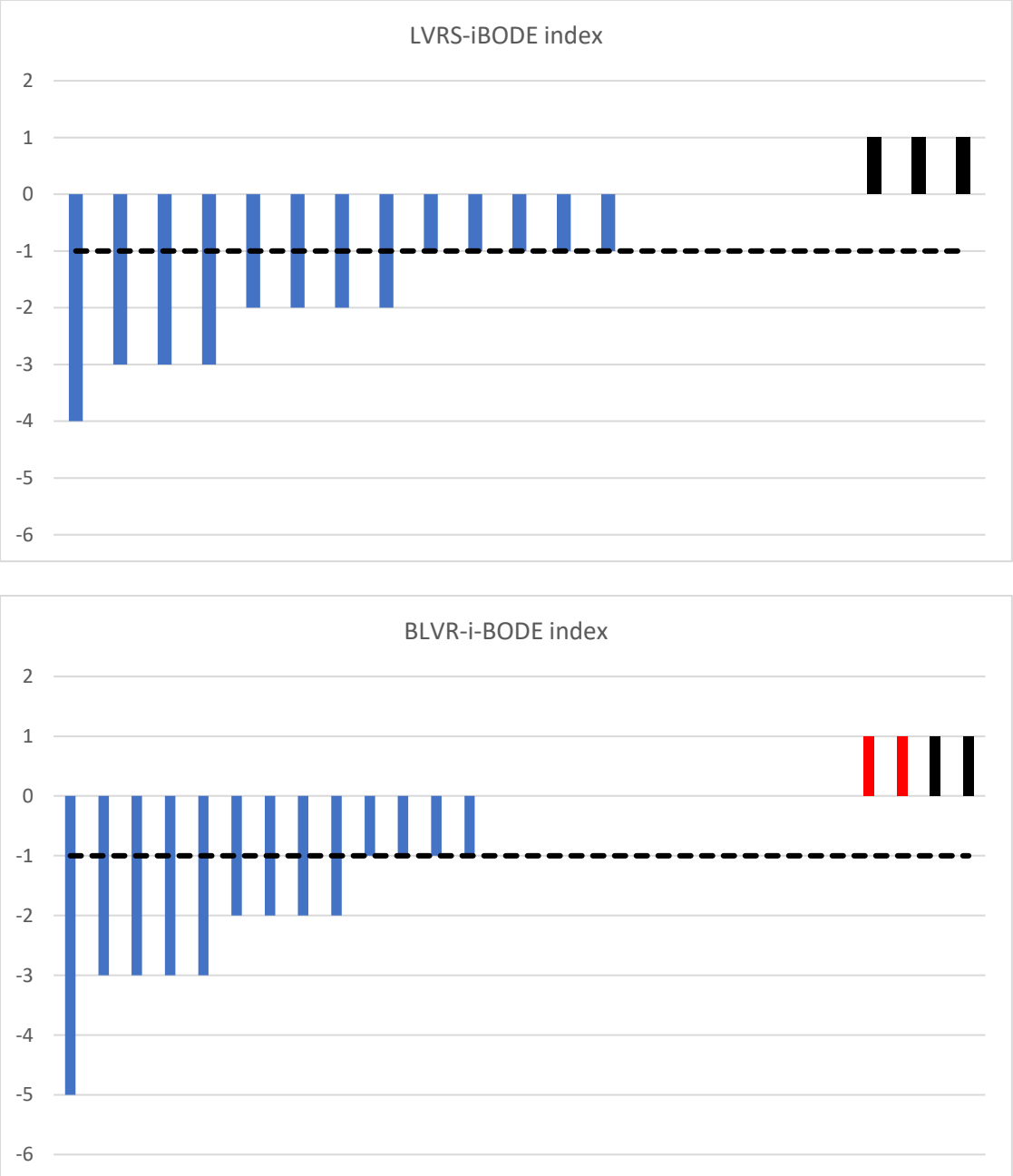
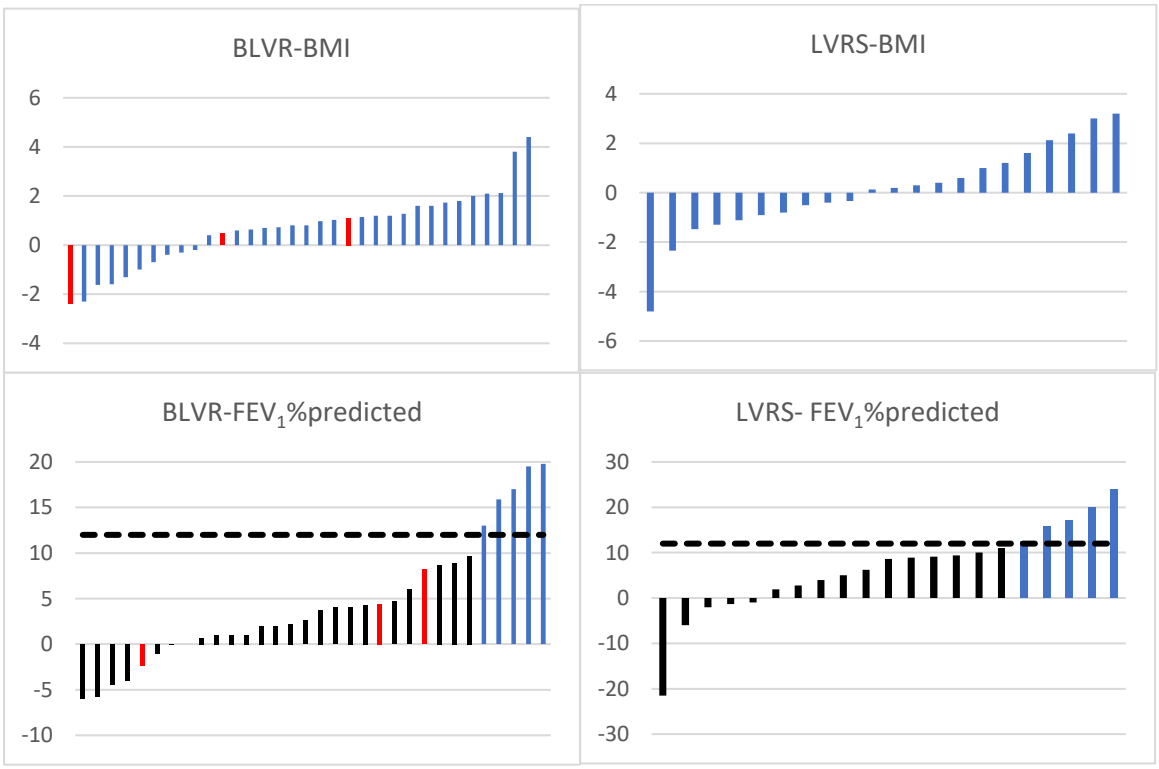
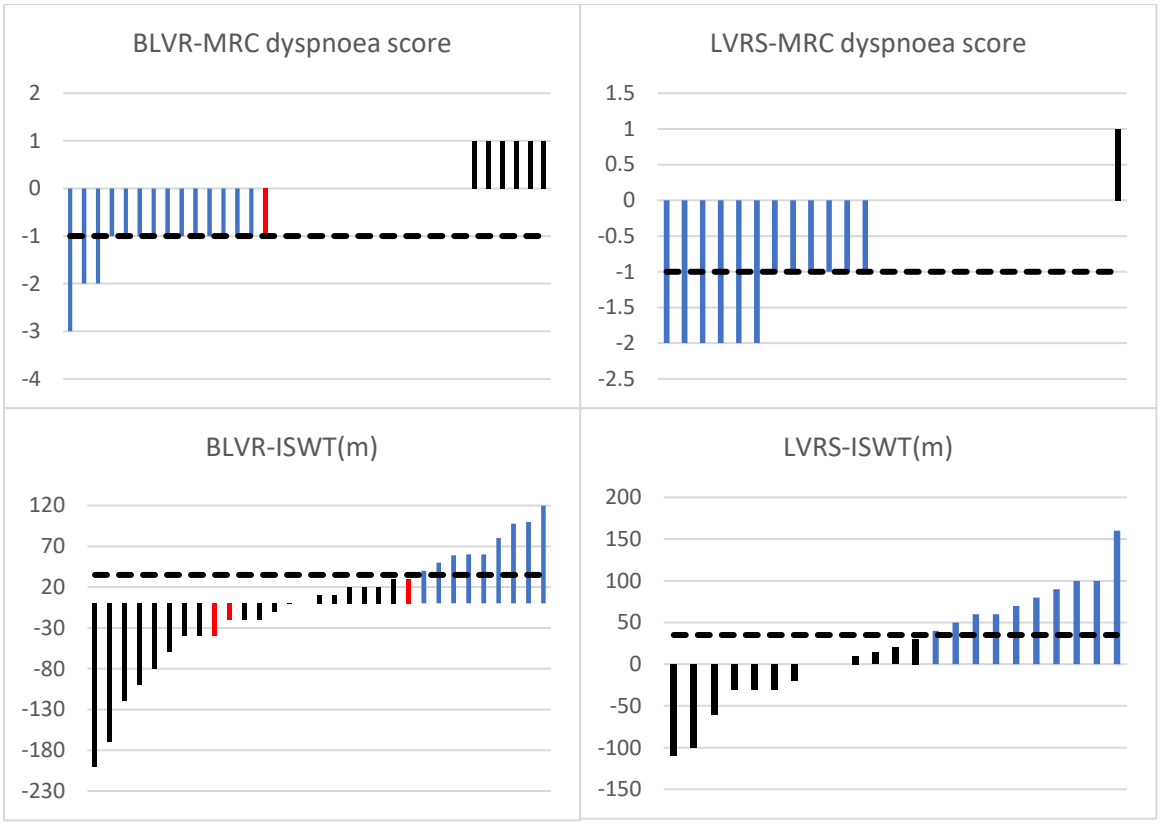


Figure 4.6: *Responder analysis based on Minimal Clinically Important Difference- i-BODE index components (complete case analysis)*

Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for the specific outcome; top: BMI: no established MID; bottom: FEV1%predicted: 12

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.





Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for the specific outcome; top: MRC dyspnoea score: -1 points; bottom: 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.

Secondary outcomes

4.3.4 Change in RV% predicted at 12 months post LVR procedure

The change in RV% predicted exceeded the MID (-6.1%) (Hartman 2012) by a large margin in both treatment arms (LVRS; -36.1 (-54.1, -10), BLVR: -30.1 (-53.7, -9)) showing a positive treatment response. There was no significant difference in change in RV% predicted between LVRS and BLVR (p=0.81) (Figure 4.7). RV% predicted responder rates in LVRS and BLVR arms were 84% and 77%, respectively.

***Figure 4.7**: Change in RV% predicted e in LVRS and BLVR treatment arms*

The black line shows those in the LVRS arm and the blue line shows those in the BLVR arm. There was no significant difference between changes in RV% predicted in either arm.

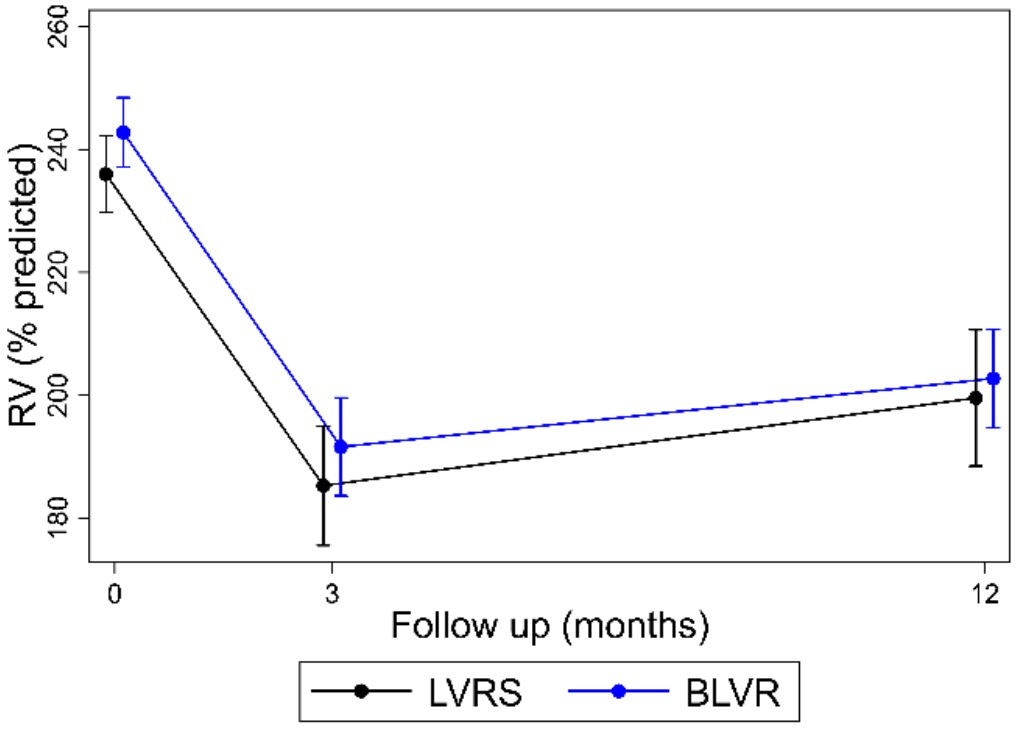
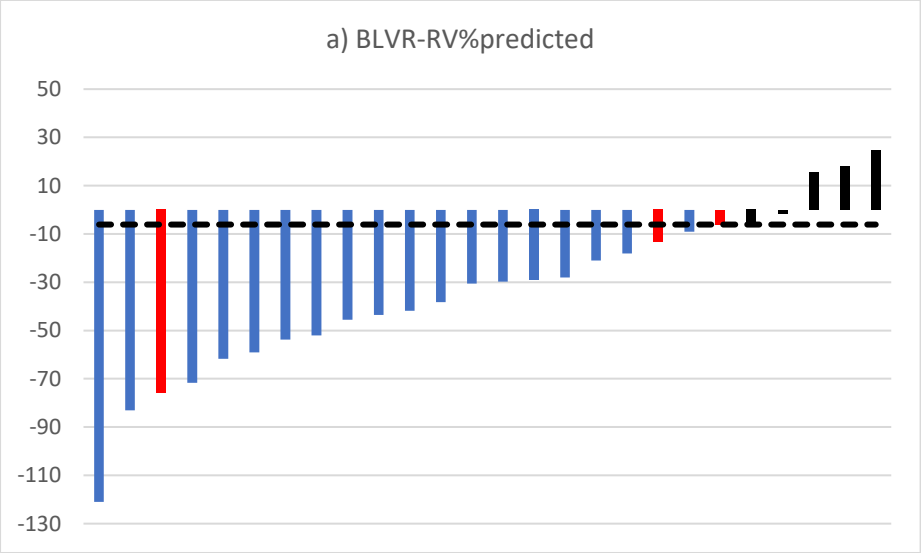
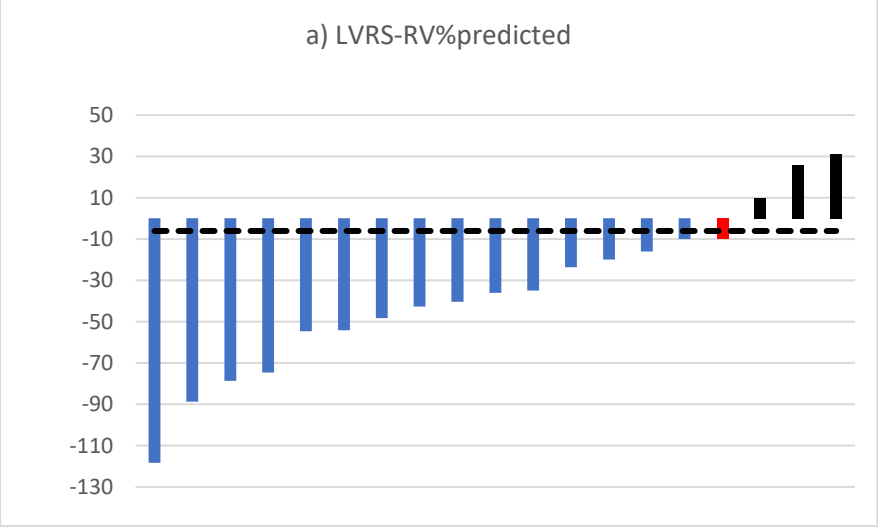


Figure 4.8: *Responder analysis based on Minimal Clinically Important Difference- RV% predicted at 12 months (complete case analysis)*

Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for RV% predicted (-6.1%)

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.





1

4.3.5 Change in CAT score at 12 months post procedure

The CAT score also showed improvement in both groups (LVRS : -7(-11, -1), BLVR: -1(-3, 2) but was the only outcome to show a statistically significant between group difference in change from baseline to 12 months follow up, and this difference favoured those in the LVRS group (Treatment effect (95%CI) -6(2 to -9), p=0.005). Only the LVRS arm made a change that reflected the MCID (-2 points). (Figure 4.9).

Figure 4.10 shows the responder analysis for CAT score in the LVRS and BLVR arms which was 68% and 40%, respectively.

Figure 4.9: *Change in CAT score in LVRS and BLVR treatment arms*

The black line shows those in the LVRS arm and the blue line shows those in the BLVR arm. The black line shows a significant change in CAT score compared to the blue line that favoured those in the LVRS arm.

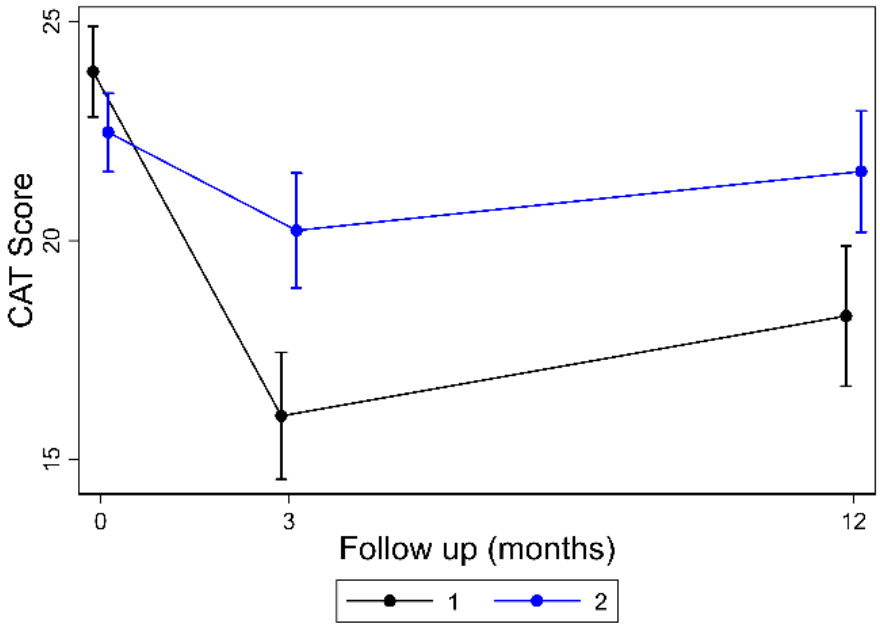
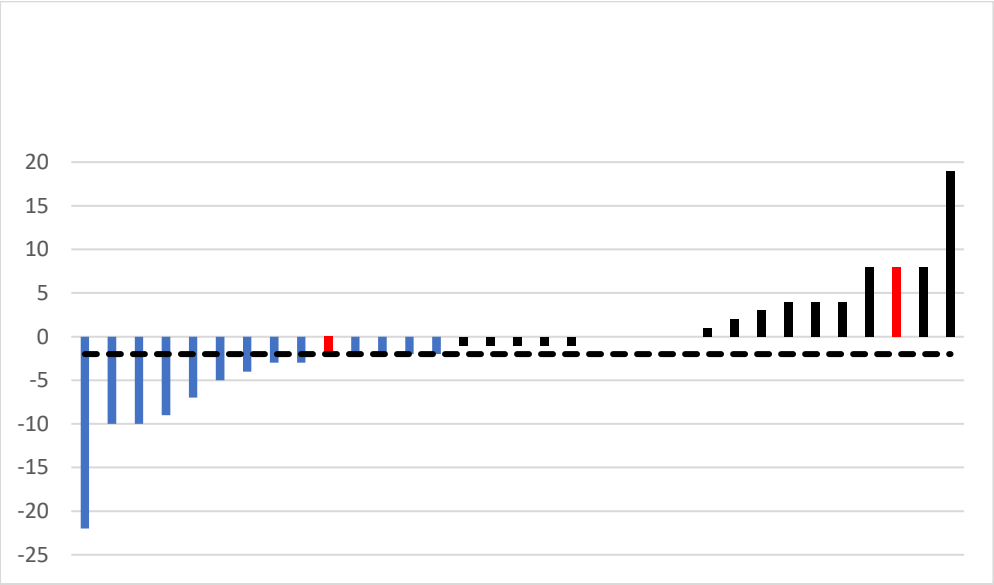
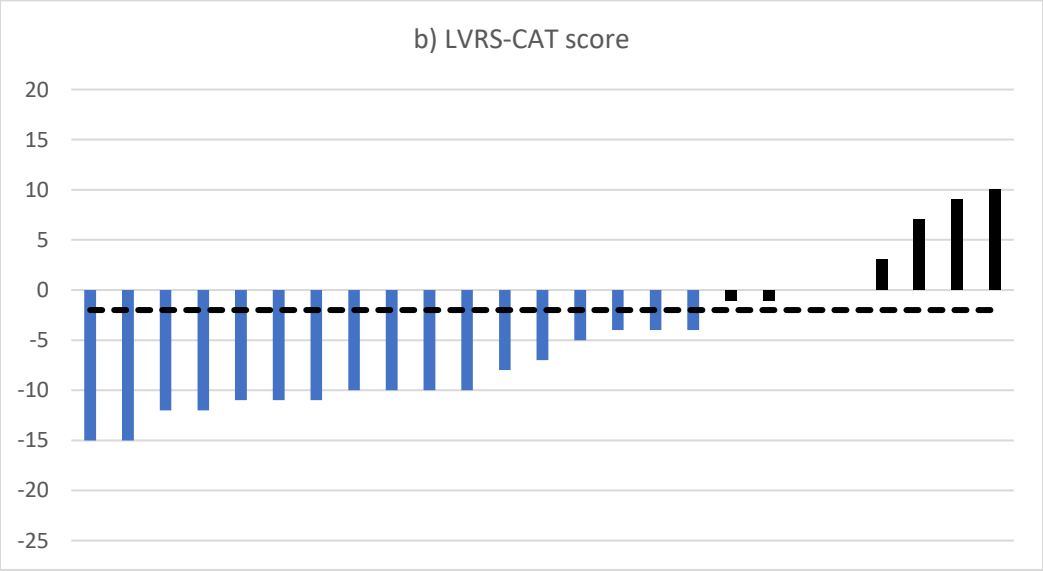


Figure 4.10: *Responder analysis based on Minimal Clinically Important Difference- CAT score at 12 months (complete case analysis)*

Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for 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.





4.3.6 **Change in Physical activity at 12 months**

The changes seen in PA post LVR intervention were similar in both groups with an improvement in both difficulty and amount. This was by a clinically meaningful amount by almost four-fold in total score, in both arms. However, this change was not reflected in the objective measurement of PA (steps/day). Both groups made a very minimal change in steps per day over the 12 months that was not clinically meaningful (1000 steps/day). It must be noted that the PA data was unreliable due to the small amount of matched data that was successfully collected.

***Figure 4.11**: Change in C-PPAC total score in LVRS and BLVR treatment arms*

The black line shows those in the LVRS arm and the blue line shows those in the BLVR arm. Both lines show a clinically meaningful change in C-PPAC score over 12 months.

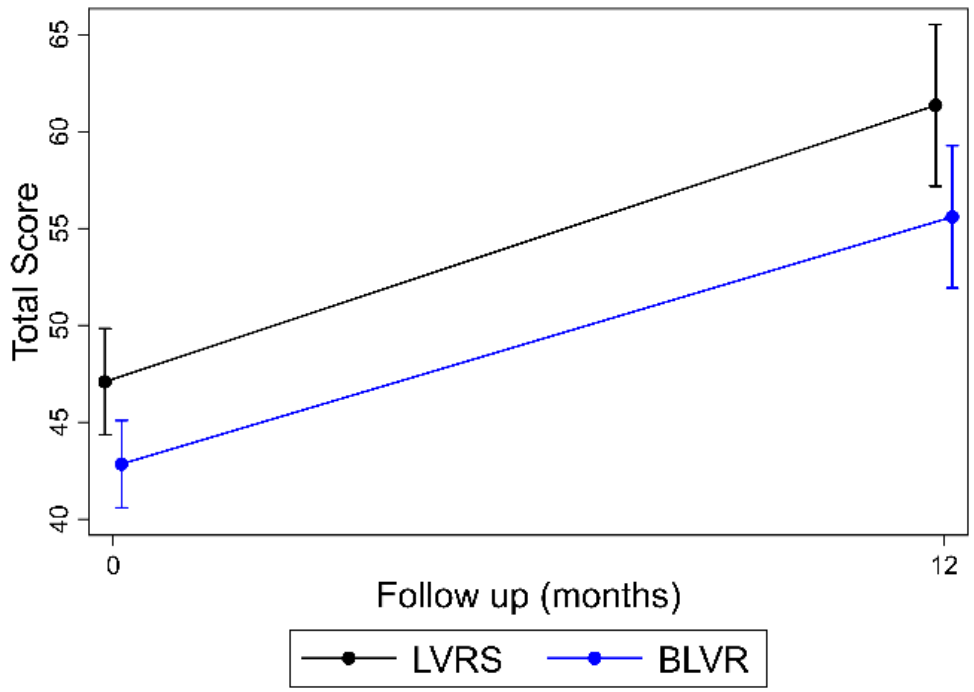


Figure 4.12: Change in C-PPAC amount score in LVRS and BLVR treatment arms

The black line shows those in the LVRS arm and the blue line shows those in the BLVR arm. Although the black line shows a greater change over 12 months there was not a significant difference between the two arms.

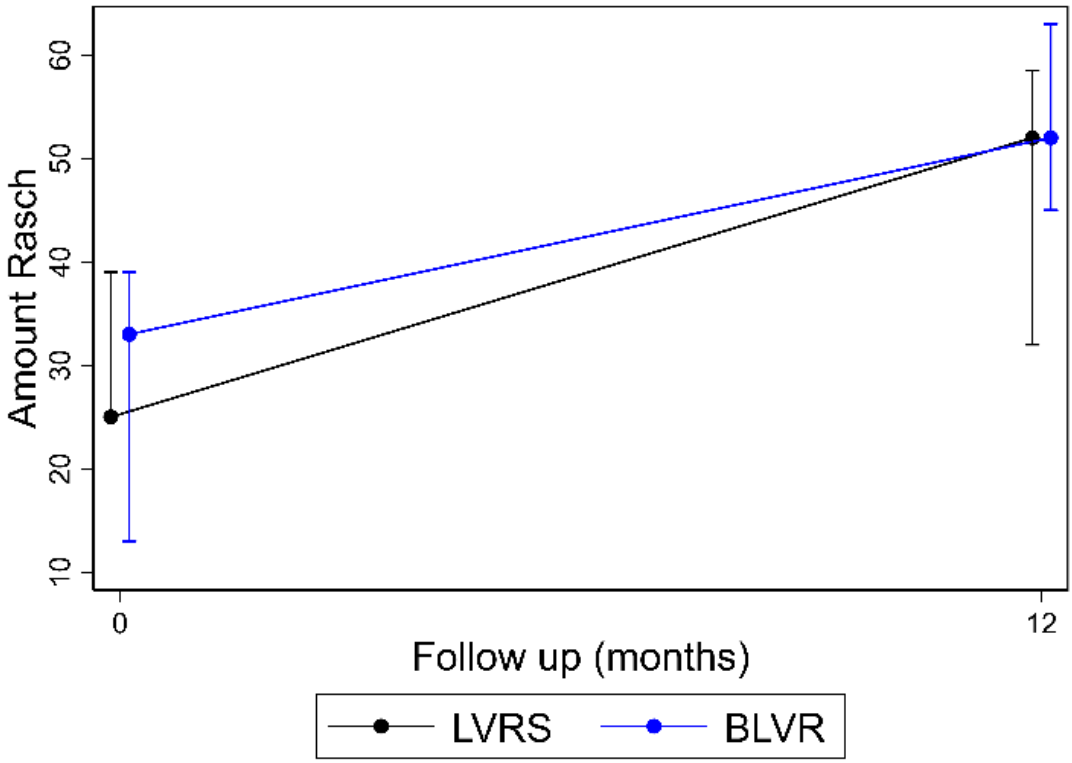


Figure 4.13: Change in C-PPAC difficulty score in LVRS and BLVR treatment arms

The black line shows those in the LVRS arm and the blue line shows those in the BLVR arm. Both lines show a similar and clinically meaningful change in C-PPAC difficulty score over 12 months.

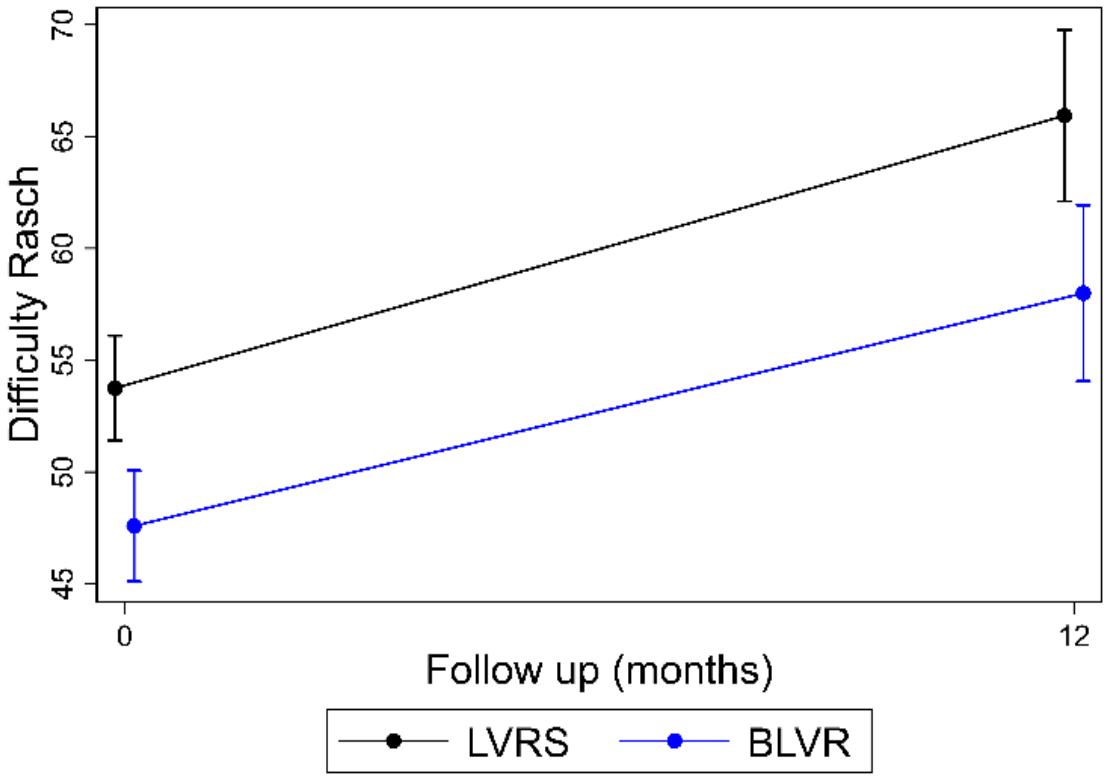
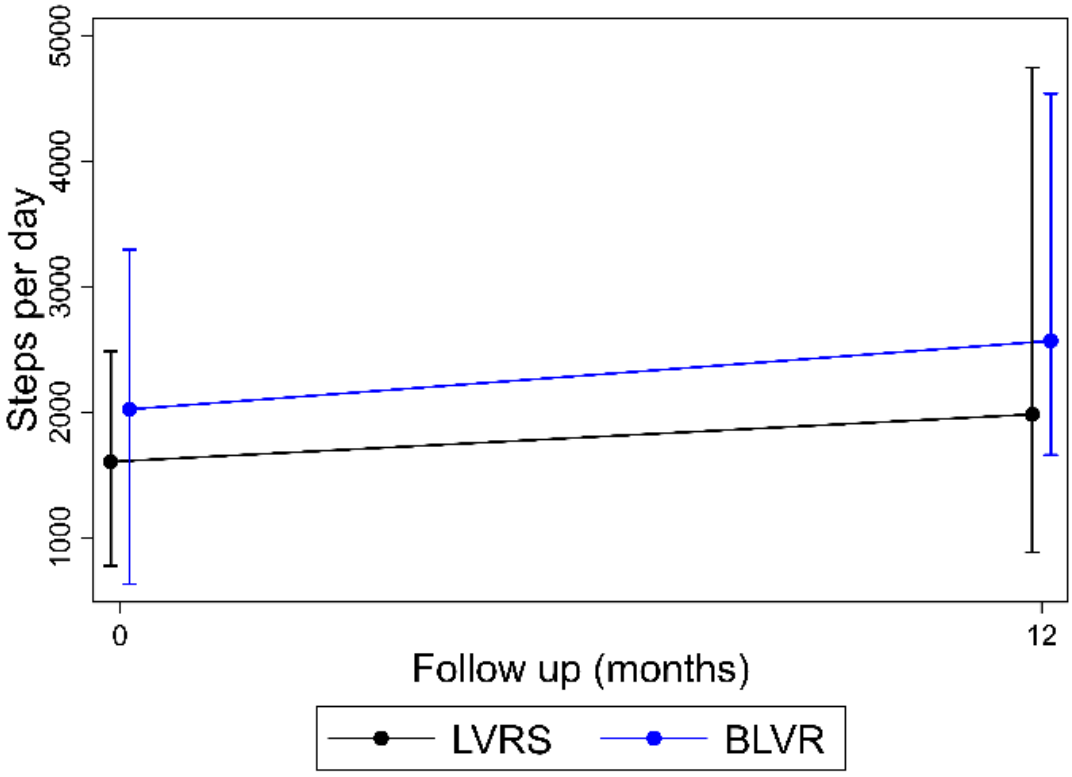


Figure 4.14: Change steps/day LVRS and BLVR treatment arms

The black line shows those in the LVRS arm and the blue line shows those in the BLVR arm. Both lines show a very minimal change over 12 months that was not significantly different between LVRS and BLVR.

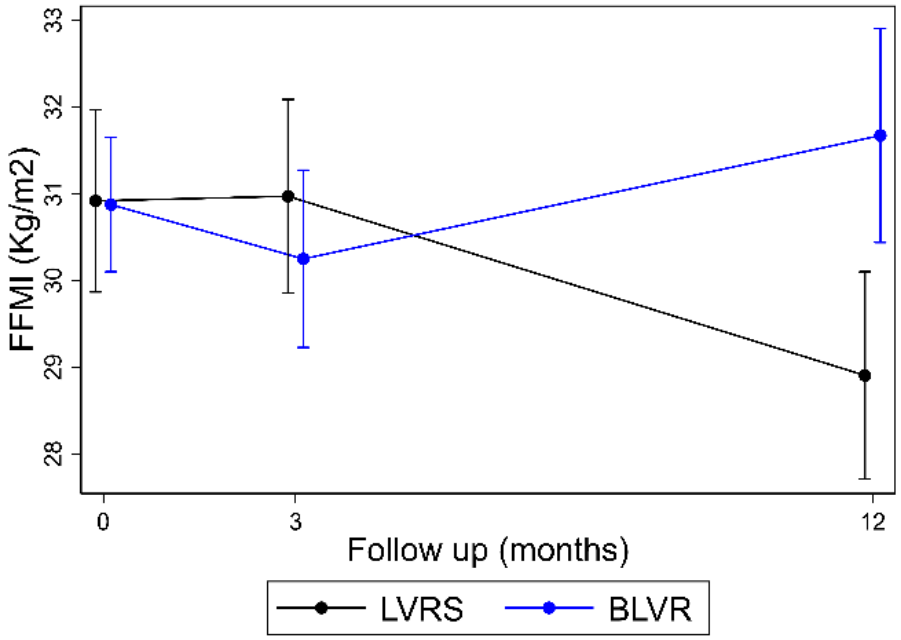


4.3.7 **Change in FFMI at 12 months post LVR procedure**

The results seen in FFMI post LVRS and BLVR were atypical. In the LVRS group FFMI appeared to remain steady at the 3 months follow up but decrease by around 2kg/m^2 at 12 months. Whereas in the BLVR group, following a mild dip at 3 months post procedure the FFMI appeared to increase 12-month post procedure. However, the changes seen were small and not statistically or clinically significant (p=0.38) (Figure 4.15). A responder analysis was not conducted for FFMI change as there is no established MCID for this outcome.

***Figure 4.15**: Change in FFMI in LVRS and BLVR treatment arms*

The black line shows those in the LVRS arm and the blue line shows those in the BLVR arm. The black line shows no intimal change in FFMI but then a drop of around 2kg/m2 by 12 months. The blue line shows an initial dip in FFMI and then two lines cross with an increase in FFMI for those in the BLVR group. These results are not significant.



4.3.8 **Procedure related details and safety outcomes**

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 as per protocol. Table 7 shows the details of LVRS procedures.

Table 4.7: *LVRS procedure details*

Procedure	**Right sided LVRS**	**Left sided LVRS**
Video assisted thorascopic surgery (VATS)	16 (47%)	14 (41%)
Robotic Assisted thorascopic surgery (RATS)	2 (6%)	0 (0%)
Thoracotomy	1 (3%)	1(3%)

A median of 4 valves (range 2-7) per subject were placed in the 46 BLVR subjects. Table 8 shows the distribution of valves placed.

Table 4.8: *BLVR procedure details*

Treatment lobe(s)	n (%)
Left upper lobe	17(37)
Left lower lobe	9(19.7)
Right upper lobe	11(23.9)
Right lower lobe	4(8.7)
Right upper and middle lobes	4(8.7)
Right middle and lower lobes	1(2.2)

There were two deaths reported during the 12 months follow up period, one in the BLVR group and this happened whilst the individual was still an inpatient following the initial procedure (44 days). The death was considered to be due to complications related to the procedure. There was one death in the LVRS arm. This occurred at 5 months post intervention due to a non-infective acute exacerbation of COPD. This death was considered unrelated to the LVRS intervention. The median length of stay in the LVRS arm was 9 (IQR 16.5) days, and in the BLVR arm 3 days (IQR 2). There were 29 respiratory related SAE's in 17 participants undergoing LVRS (50.0%) versus 35 in 18 participants receiving BLVR (39.1%), which was not found to be significantly different between the treatment arms (p=0.262, Fishers exact test).

The most common complication in the LVRS group was surgical emphysema (29.3%) and in the BLVR group the most common was pneumothorax (30.4%). Most pneumothoraces (81.8%) occurred whilst the participant was still an inpatient following the initial procedure at a median(IQR) time to onset of 2(3) days and the drain was removed after a median(IQR) of 10(12) days. In comparison 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 collapse and a further 10 (21.7%) partial collapse, whereas 10 (21.7%) were reported to have no lobar collapse. 8 patients (17.0%) in the BLVR group (17.0%) 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.

Table 9 reports the number of complications occurring in each group and the number of patients that experienced each complication, per group

Table 4.9: *Safety outcomes- LVRS and BLVR procedures*

	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

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.

4.4 Discussion

4.4.1 **Key findings**

This superiority study disproved the initial hypothesis, showing that LVRS cannot be considered a significantly superior treatment to BLVR in patients who are suitable for either treatment. There was no difference in change in health status, measured by the i-BODE score (or its individual components) from baseline to 12 months post procedure in the LVRS group, compared to the BLVR group. Although neither group achieved a clinically meaningful improvement in i-BODE score significant improvements were seen in other health outcomes at 12 months post procedure that were similar in both groups.

4.4.2 **Significance of findings**

The primary outcome for this trial, the i-BODE index was selected due to its multi-component nature. The use of a multi-index measure has been considered a more meaningful way of evaluating response to a disease modifying intervention than one outcome in isolation (Corlateanu 2021) and this is particularly significant in a heterogeneous disease population, such as COPD.

A composite measure better addresses the different phenotypic traits that may affect an individual by varying severities (Celli 2015). Most LVR trials have used FEV_1% predicted as a primary outcome (Criner 2018; Kemp 2017; Davey 2015) but LVR procedures have been developed as a palliative treatment with the aim of improving quality of life (Brantigan 1957; NICE.). Therefore, using a measure that incorporates outcomes that measure different aspects affecting overall health status may be more appropriate.

Importantly, in this study the CAT score was the only measure to show a significant difference between the two treatment arms. Future LVR studies may wish to consider the use of a quality of life measure as a primary outcome used to power the study based on its relevance to treatment outcomes, particularly from the patient perspective.

The BODE index has demonstrated associations with mortality in trials investigating LVRS (Imfeld 2006) and has also been used previously in studies investigating BLVR (Kemp 2017; Klooster, Hartman, 2017). A validation study of the i-BODE index found that the ISWT can be used as an acceptable replacement for the 6MWT and is an independent predictor of mortality in COPD (Williams 2012). Therefore, our primary outcome results that did not show any significant difference between groups indicate that health status post LVR treatment is not significantly different following either treatment and may also indicate a similar outcome for prognosis. This is supported by the survival data from this analysis.

Mortality rates in the two groups were similar with one death in each treatment arm over the 12 months follow up period. Research from analyses conducted in a larger LVR cohort, as part of this thesis found post procedural mortality rates to be numerically but not statistically higher in those undergoing LVRS (5.4%) compared to those undergoing BLVR (1.8%) (p=0.068) and similar results have been shown in previous literature (2003; Fishman 2001; Weder 2009).

The death in the BLVR arm was an unexpected occurrence due to unlikely complications following an EBV procedure. Pneumothoraces are an expected complication following EBVs and are experienced in up to 34% of patients (van Dijk 2021). When total lung volume reduction is achieved (the objective of the treatment) this can cause a pulling on the lung parenchyma. When the volume reduction is rapid this pulling can result in a rupture or tear of the lung parenchyma known as a pneumothorax. The frequency of pneumothoraces and the time of occurrence post procedure (usually within the first 72 hours) means that an inpatient

observational period has been suggested for safety precautions. The pneumothorax rate in this study (30.4%) is in line with published literature and the majority occurred in the first 48 hours post treatment and were managed straightforwardly on the ward.

Secondary outcomes showed similar improvements across the treatment arms in change in RV% predicted, FFM and physical activity. Both groups saw improvements in these outcomes at 3 and 12 months post procedure. The CAT score however, showed improvements in both groups that were significantly better in the LVRS group compared to the BLVR group. A hypothesis for this difference could be related to allocation bias whereby the higher number of drop-outs in the LVRS group after randomisation may have meant that there were a greater proportion of patients that went on to have LVRS that were satisfied with their treatment allocation (Paludan-Müller 2016).

There are conflicting opinions on the interpretation of secondary outcomes in interventional trials and care is recommended when interpreting secondary outcomes that a study is not powered for. Multiplicity may introduce an element of bias into outcome interpretation. However, Parker and Weir (Parker 2022) instead suggests practicing precision when interpreting multiple outcomes and stress the importance of not dismissing significant effects that may be valid. Nevertheless, the interpretation of a subjectively reported heath status measure in an unblinded interventional trial should be addressed with caution. Bias may be introduced based on the participants knowledge or expectations of the interventions and this is particularly important given the patients that dropped out of this trial following randomisation. Future research should investigate the comparative effect of LVRS and BLVR on quality of life in LVR intervention.

4.4.3 **Methodological considerations**

This study was influenced by several limitations and largely by the COVID-19 pandemic, that had an impact on not only delivery of the interventions but also data collection and interpretation.

Many research staff involved in data collection were required to work on COVID-19 trials or deployed to inpatient wards. Furthermore, lockdown rules prohibited patients from visiting the hospital for follow up visits. To mitigate the volume of missed data an amendment to allow the collection of outcomes over the telephone was sought and granted. However, as the primary outcome for this trial was the i-BODE index two of the composites required an in-person clinic appointment. This was overcome in one observational study with relative success by replacing the spirometry test that represents the O for obstruction with post exercise heart rate recovery (Chen 2023). This may have been more acceptable during times when aerosol generating procedures such as spirometry were being avoided in all but essential cases. The study found this modified index to have good predictive performance for one-year mortality and acute exacerbations requiring hospitalisation (Chen 2023) but this was observational data and was not within the context of LVR intervention. Furthermore, it would still have required an in-person exercise capacity assessment which was also a source of much of the missing data in the CELEB trial.

In future when designing a trial, a pragmatic approach to avoid this issue would be to select a primary outcome that does not rely on an in-patient clinic visit or as a minimum, to have a dual primary outcome with statistical adjustment for multiplicity or type 1 errors (McLeod 2019).This more flexible approach may also benefit frail patients or those that suffer from frequent exacerbations, in whom travelling to specialist centres for study visits can be challenging (McDermott 2021).

Additional to the missed study visits the study was also affected by a high attrition rate seen. This could be considered an expected outcome in an interventional trial recruiting a severe cohort of patients with chronic disease. A literature review conducting in palliative care trials found high attrition or dropout rate that was associated with high symptom burden (Hui 2013). Furthermore, difficulties in participant cross-over in interventional trials have been previously reported (Weinstein 2006; Cook 2009). However, other similar LVR trials have shown much lower drop-out rates (Kemp 2017; Criner 2018; Klooster 2015; 2003) and therefore the % seen in this study may have been consequential to the aforementioned issues relating to the COVID-19 pandemic. Still, the effect on the strength of this study's findings should be considered ad in future trials a higher dropout rate should be accounted for when calculating the sample size.

The participants that dropped out of trial prior to randomisation may have had an influence of the final results but also represent a disparity in clinical care that was not account for by this trial. Those receiving EBVs would receive treatment immediately after Chartis procedure and randomisation but at some centres the Chartis procedure was carried out by interventionalists who would not be involved in a surgical treatment. This meant a longer wait time for those randomised to LVRS as well as two separate admissions to the hospital that has implications for both patient and healthcare provider. An economic analysis comparing the two treatments is vital to determine the true utility of these treatments.

For this investigation, a sensitivity analysis imputing missing data was used as a means of addressing the missing data and underpowering of the study. However, problems associated with multiple imputation in healthcare trials and particularly the use of a missing at random assumption have been documented (Sterne 2009; Studenski 2011). These include. To address these issues an experienced healthcare statistician was consulted on model building and checking, and discussion was entered around the potential limitation of findings. Including all values predictive of the missing values in imputation models and the sensitivity analysis to

support the MAR assumption were strategies used to support analysis and interpretation of findings. Finally, a post hoc power calculation was carried out using the SD for i-BODE index in this trial (1.44) rather than that used for the original power calculation (1.8). This new calculation revealed that a sample of 20 subjects per arm would be sufficient to detect a difference which may suggest that this trial was adequately powered.

Further shortcomings of the i-BODE index as an outcome were also apparent. This composite measure transforms continuous measures such as distance walked in the ISWT and FEV_1% predicted into categories. Therefore, an individual who was closer to a category threshold at baseline is more likely to make a meaningful change (move up or down a category) at follow up, than an individual in the middle of the category. Therefore, a change in i-BODE score does not always accurately measure magnitude of change ad this may have introduced bias into our primary outcome findings.

The trial was a single, not double-blind trial and therefore an element of bias may have been introduced. However, as the outcomes reported in this study were largely objective (only the MRC dyspnoea and CAT score were subjective) lack of masking patients would have had less of an effect. Furthermore, research personnel collecting the objective measures were blinded to treatment allocation which research has shown may be more important in interventional trials than blinding of the administration of treatment.

Recruitment was slow and caused delays to trial reporting. Once of the inclusion criteria were that an individual must have been deemed to be CV negative on a Chartis assessment. However, a 2021 study suggests a threshold that can be reliably used to exclude the presence of collateral ventilation when flow rates are low (Koster 2021) and other research advocates that where a Chartis assessment is not possible due to airway collapse, the assessment of fissure integrity

using HRCT may be a viable option (Gesierich 2016). For the CELEB trial these options may have improved recruitment rates and prevented the exclusion of otherwise suitable patients.

Finally, the results from this study can only be generalised to a very specific population of patients, namely those who had equipoise for either LVRS or BLVR treatment. In clinical practice a large proportion of individuals that may be suitable for LVR intervention will be either a better fit, unsuitable, or prefer one treatment over another.

4.5 Conclusions and future work

The findings from this study did not support the hypothesis that LVRS is a substantially superior treatment compared to BLVR, in terms of health outcomes achieved one-year post procedure. Therefore, in those patients considered to have equipoise for treatment, either intervention can be considered an appropriate choice and patient preference should be paramount. These findings should provide evidence and guidance to the LVR MDT in framing treatment options for patients and guiding discussions for shared decision making between patient and clinician. A larger RCT comparing LVRS and EBVs is being carried out in Switzerland and will contribute to these findings (NCT04537182). An economic evaluation of surgical and bronchoscopic LVR intervention will be important to fully understand the comparative value of these two treatments.

5 The prognostic value of digital mobility outcomes in COPD

This chapter was published in European Respiratory Review in 2023 (Buttery, Williams, Alghamdi, 2023)

5.1 Introduction

The importance of physical activity is well known and has been examined in this thesis. Reduced physical mobility is associated with poorer health outcomes in healthy individuals as well as those with chronic disease (Musich 2018; Iezzoni 2001; Saint-Maurice 2020; Comber 2017; Creaby 2018) including COPD. According to previous literature PA is strongly associated with pulmonary function decline, exacerbations, hospitalisations, health-related quality of life, and mortality (Iyer 2018; Hopkinson 2010)((Mesquita, 2017 #519;Gimeno-Santos, 2014 #59;Dueñas-Espín, 2016 #606).

The previous chapter investigated how an intervention may augment PA and other research has also explored this hypothesis (Spruit 2015; Shioya 2018). Yet, PA is seldom measured as part of clinical care or as a primary research outcome. Typically, other measures such as pulmonary function, quality of life and exercise capacity take precedence. An obvious explanation for this is the impracticality or unreliability of traditional mobility measures.

Two types of measure are routinely used to measure mobility; subjective patient reported outcomes (PROs), or objective clinic or laboratory based physical capacity tests such as the six-minute walk test (6MWT)(Polkey 2013) and incremental shuttle walk test(Singh 2008). Both types of test suffer from limitations and may not be an accurate representation of an individual's daily walking performance in their own environment, which limits their construct validity(Fermont 2019). Reasons for this have been discussed in the previous chapter in relation to the development of the PROactive tool (Gimeno-Santos 2015) which incorporates both subjective questioning and the use of an accelerometer to objectively measure PA.

Activity monitors such as accelerometers and pedometers offer a real-world quantification of daily walking activity and gait parameters that may be used to monitor, personalise, and improve disease management (Pitta 2006; Vooijs 2015). Advances in wearable technology in

recent years means that these measurement can be conducted more comprehensively and affordably (Iqbal 2021) and this may be of utility in both a research and clinical environment. Digitally measured outcomes can be collected using a pedometer, accelerometer or using a simple stopwatch to measure gait speed in a test such as the 4-metre gait speed (4MGS) that reproduces normal walking. All are straight-forward and convenient methods of measuring walking in daily life.

However, there is still uncertainty around whether digitally measured mobility outcomes that are collected by these technologies, can be used to predicted important outcomes or events in COPD management and if they perform better than pure test of exercise capacity, that are more traditionally used.

Given this, the aim of this chapter was to present the current evidence base evaluating walking activity and gait parameters that can be measured digitally and their relationship with important clinical endpoints in a COPD population, to establish their value as predictive biomarkers.

5.2 Methods

5.2.1 Study design

A systematic literature review and meta-analysis was carried out as part of a larger scoping review conducted by the Mobilise-D trial group in November 2019 (Polhemus 2020; Polhemus 2021) and an updated search was performed in July 2021 to account for more recently published data. For this review prospective registration of a protocol online was required on the PROSPERO platform (CRD42021240146) detailing the research plan and methodology. PROSPERO is an international database of prospectively registered systematic reviews that is endorsed by Cochrane and aims to support transparency in the reporting of results and avoid reporting bias (Pieper 2022). This was an important step in the planning of this review to align with good practice measures and to avoid the duplication of a previous review question.

5.2.2 Search strategy

A scoping review was conducted to identify all relevant literature addressing the research question that is the focus of this review; 'What is the current evidence base demonstrating the longitudinal association between walking activity and gait parameters and a clinical measurement or outcome over time, in patients with COPD'. Searches of CINAHL, Scopus, Web of Science, EMBASE, IEEE Digital Library and the Cochrane Library were run for peer reviewed literature published between 1999 and July 2021. Relevant grey literature was identified from the first 100 results on Google Scholar, Open Grey, The National Information Centre's Health Services Research Projects in Progress, ACM Digital Library and ProQuest Dissertations and additional bibliographic searches of retrieved papers were conducted to identify any literature not identified by the initial scoping review.

This search strategy was carried out as part of the original scoping review conducted by the Mobilise-D review team.

5.2.3 **Eligibility criteria**

The following criteria was used to assess each study for eligibility to be included in this review;

5.2.4 **Inclusion criteria**

1. Peer-reviewed literature, grey literature, conference papers, PhD theses.
2. Study type: longitudinal (cohort) study or longitudinal analysis of the control arm of an interventional study.
3. Population: diagnosis of COPD confirmed by spirometry according to the American Thoracic Society and European Respiratory Society (ATS/ERS) criteria (Graham 2019). Studies in both stable and hospitalised patients were included but will be analysed separately.
4. Analytic method: retrospective or prospective analyses. Prediction models, univariate analysis, multivariate analyses, and machine learning models that assess the relationship between a walking activity or gait parameter at baseline and/or change over time, and a clinical outcome at follow-up.
5. Type of outcome: study outcomes had to include either mortality or a measure known to be associated with increased mortality in COPD such as healthcare utilisation (hospital admissions), exacerbations, lung function parameters, cardiovascular events, health-related quality of life (HRQoL) and functional status.
6. Included DMOs: A set of 32 DMO's that are associated with walking and were pre-selected by myself and a team of mobility experts, technologists and clinicians whom all belong to the Mobilise-D consortium. The list is inclusive of spatiotemporal

parameters, which can be broken down in three sub-categories and volume of walking. Non-linear gait patterns were excluded as were those involving dynamic balance measures. Gait analysis or measurement of any included gait parameter could be measured in a clinic, lab or real-world setting and some clinical tests were also included if instrumented with a stopwatch.

5.2.5 **Exclusion criteria**

1. Studies not written in a language spoken by any member of the Mobilise-D research team.
2. Studies with fewer than 10 participants.
3. Studies investigating subjective questionnaires or self-reported walking activity or gait parameters.

A complete list of possible walking activity and gait parameters and outcomes is provided in Table 5.1 and below is Appendix 3 provides an overview of the eligibility criteria that were used during the initial scoping review.

***Table 5.1**: Walking activity and gait parameters or DMOs, and clinical outcomes included in search strategy*

Included DMOs	**Included clinical outcomes**
Temporal Parameters **Cadence (mean, variability)** **Step time (mean, variability, asymmetry)** **Stride time (mean, variability)** **Stance time (mean, variability, asymmetry)** **Swing time (mean, variability, asymmetry)** **Single support time (mean, variability, asym.)** **Double support time (mean, variability)**	**Disease Severity measures** Dyspnoea Borg Scale Dyspnoea Visual Analog Scale Global Initiative for Chronic Obstructive Lung Disease Stages A-D Modified Medical Research Council Dyspnoea Scale Number of exacerbations
Spatial Parameters **Step length (mean, variability, asym.)** **Stride length (mean, variability)** **Step width (mean, variability)**	**HRQoL measures** Chronic Respiratory Disease Questionnaire Clinical COPD Questionnaire COPD Assessment Test Feelings thermometer St. George's Respiratory Questionnaire
Spatiotemporal Parameters **Gait speed (mean, variability)** **Stride speed (mean, variability)**	**Walking or functional assessment and physical activity measures** Endurance Shuttle Walk Test Incremental Shuttle Walk Test PROactive instruments to measure physical activity
Volume of Walking **Walking time (Daily)** **Step count** **Number, length, duration of walking bouts**	**Physiological measures** Forced Expiratory Volume 1% Forced Expiratory Volume to Functional Vital Capacity Ratio Functional vital capacity

* Mobility tests of longer duration such as 6MWT were excluded due to their limited value as DMOs in measuring gait speed. It was agreed that in 2 minutes (or less) of walking time there is less likely to be pauses and subjects are expected to hold a "stable speed". On the contrary during the 6MWT many patients will decelerate and accelerate or even stop which will lead to an invalid indication of gait speed.

Eligibility was initially assessed through abstract screening and then full text screening by a team of fully trained researchers from the Mobilise-D consortium. Training involved piloting the screening process with mock study materials and completing peer-led consistency checks for each screening phase. Records were included in the review if deemed eligible by a single reviewer, but exclusion of a record required mutual agreement by at least two reviewers. Where two reviewers disagreed a third reviewer was consulted. Reasons for exclusion were recorded for audit purposes. Duplicate records were excluded manually. The record screening for the scoping review was managed in DistillerSR (Evidence Partners, Ottawa, Canada).

5.2.6 **Data extraction**

Once included studies had been identified, data extraction was carried out independently, by two researchers who had been involved in the initial screening process (myself (SB) and Parris Williams. This process was organised and managed in Covidence 2020 a web-based software platform.

The following data were extracted;

Study characteristics: author's names, publication year, manuscript title, study design, main objective, country where study took place, funding, conflict of interest.

Sample description: sample size, age, gender, body mass index, health status, disease duration, specific questionnaire scores.

Model description; what type of model did the study use for analysis? Which covariates were included in the model? Which analytical methods were used? What clinically relevant outcomes were studied to assess the DMO's prognostic value? Did the DMO provide prognostic value with respect to the studied outcome?

As in the initial screening phase, if there were discrepancies between the initial two reviewers that could not be resolved through discussion, a third reviewer (Saeed Alghamdi (SA)) was sought.

5.2.7 **Assessing study quality and risk of bias**

To provide an assessment of the overall quality of the evidence the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) tool was used (Ryan 2016). The evidence available for each of the relationships evaluated in the review was graded according to this criterion as either high, moderate, low or very low. The tool specifies key criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias) which should be used to grade the evidence and these can also be used to justify upgrading or downgrading quality evaluations (Brozek 2021).

An assessment of bias was performed using the Quality in Prognostic Studies (QUIPS) tool. This tool has been used in previous prognostic systematic reviews and meta-analyses (Grooten 2019; Hayden 2013) and has been recommended by the Cochrane Prognosis Methods Group. A high, low or unclear risk of bias decision was made for each of the six areas included in the tool; participation, attrition, prognostic factor measurement, outcome measurement and analysis and reporting, and then an overall risk of bias based on these six domains. The overall risk of bias was used to classify a high or low-quality study.

Like other steps, the quality assessments were implemented by two reviewers (SB and PW) and a third (SA) to settle disagreements, where necessary.

5.2.8 **Statistical analysis**

Alongside the qualitative analysis a meta-analysis was performed estimating the pooled unadjusted hazard ratios (HR), 95% confidence intervals (95% CI) and p-values for associations between a DMO and a longitudinal clinical outcome. Quantitative analysis of the studies focussed on mortality investigated in participants with slow gait speed (≤0.80m/s) versus a preserved gait speed (>0.80m/s), and in participants who increased either gait speed or daily step count by a meaningful amount over the monitoring period, compared to those who did not. The effects measured in all the included studies were HRs which were then pooled, and an overall effect size estimated using a restricted maximum likelihood (REML) random effects model, as described by Raudenbush (Raudenbush 2009). This model assumes common variance of the true effect of both gait speed and step count in the individual studies, which is likely due to the differences in data collection and analysis methods used in the study methodologies. Where necessary HRs were transformed to the selected unit effect measure to allow comparisons.

Heterogeneity between studies was assessed using the Tau^2 test of variance and the I^2statistic, both as measures of inconsistency. Any analysis with an I^2 score >50% was deemed to have substantial heterogeneity. Galbraith plots were then produced to evaluate heterogeneity in effect sizes. Funnel plots were also generated to assess for the presence of publication bias and a trim and fill method used to adjust for this method (Duval 2000). Due to the small number of studies in this analysis Egger's test was used to assess for small study effects (Egger 1997).

Sensitivity analyses were carried out to further explore the presence of heterogeneity between studies, using stratified meta-analysis. For example, using only studies with a low risk of bias or a more homogenous study population.

Statistical analysis and graphical representation was performed using Stata (version 17.0), significance was set at <0.05 and results are presented as forest plots.

5.3 Results

The original search performed in November 2019 retrieved 19,672 original records and the updated search carried out in July 2021 yielded a further 1,412 records. From the combined retrieval of 21,084 records from the initial and updated search, 21 studies were identified for inclusion in this systematic review and meta-analysis. Figure 5.1 depicts the PRISMA flow diagram showing the search process and reasons for exclusion of studies is presented Table 5.2.

Figure 5.1: *PRISMA flow diagram*

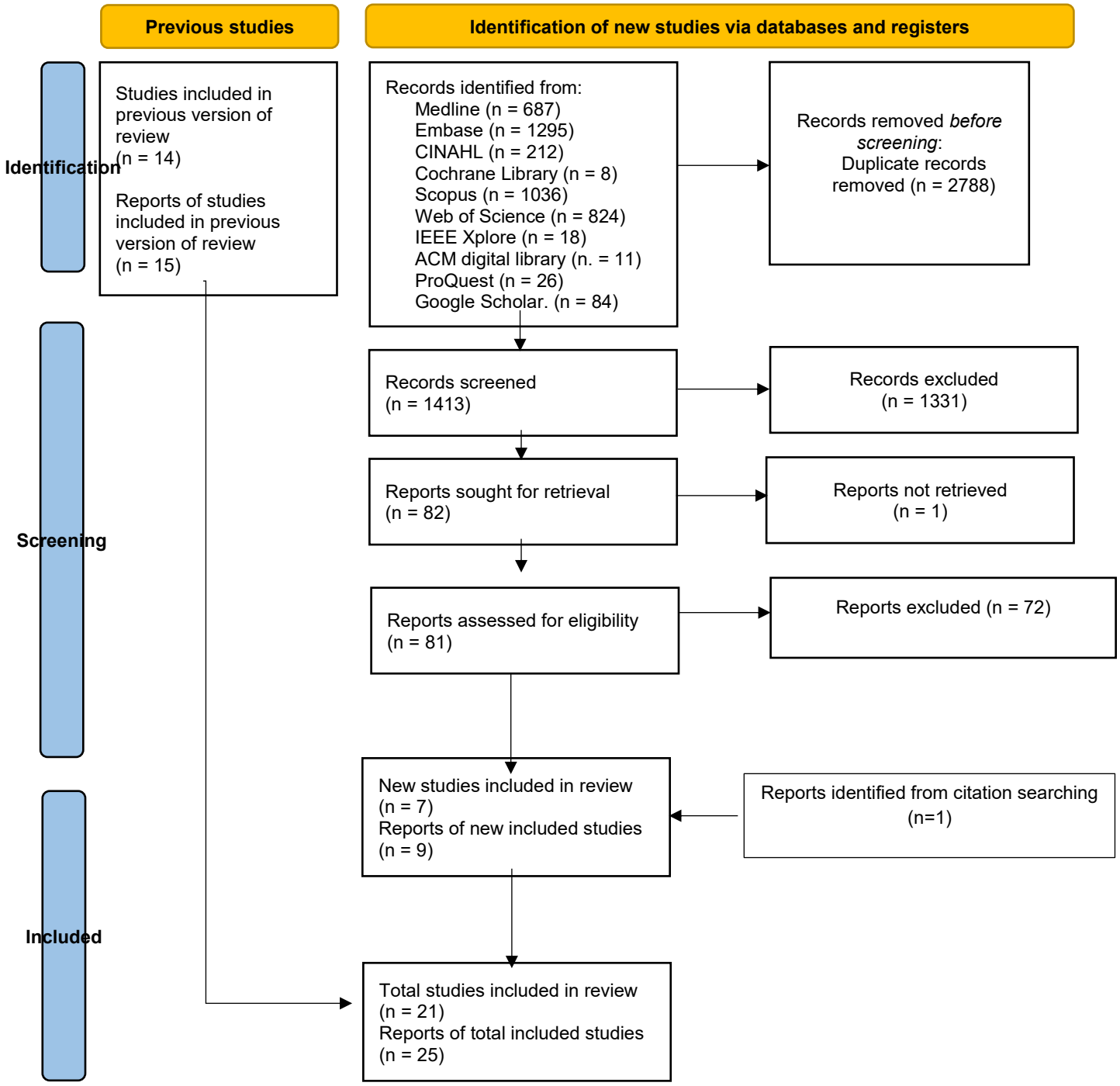


Table 5.2: *Reasons for exclusion of study from this trial*

Reasons for Exclusion	**n (%)***
The study did not address one of our research questions	23
Only excluded gait parameters were studied	8
DMOs were assessed, but only during gait initiation, turns, stair climbing, or other excluded walking motions/conditions	1
Fewer than 10 participants were included in any relevant analysis	3
The study population did not meet our inclusion criteria	1
Part of the study population met our criteria, but a sub-analysis on these participants was not conducted	2
The record studied prognostic value, but looked at DMOs as outcomes rather than variables	2
The record reported an interventional study, but it was uncontrolled, and no other relevant analysis was reported	1
The study design was a case study, case series, review, master's thesis, or other non-eligible study type	7
The record was an interventional protocol that used a DMO as an outcome that otherwise meets the criteria for RQ4	4
The record was a poster or conference abstract with insufficient information reported to know if a relevant analysis was conducted	1
The record reported identical results as another record, but to a different conference or journal	16
Full text was not available	1
The record addressed another research question from the original review, and did study the longitudinal relationship between DMOs and outcomes	42
*Records were often excluded for multiple reasons, and summed percentages exceed 100%	

5.3.1 **Characteristics of included studies**

Of the 21 studies retrieved 17 were cohort studies, 15 prospective and three retrospectives. The remaining three studies were secondary analyses of a control arm of an RCT. Of these studies five were conference abstracts that were not written up into full manuscripts. This meant that data extraction was limited and so to mitigate this limitation the authors of these studies were contacted. However, supplementary information was only provided by two study authors. The majority of studies were carried out in the UK (n=6), US (n=5) or another European country (n=5) and all were published between 2011 and 2021.

A summary of the studies included in this review are shown in Table 5.3.

Table 5.3: Summary of included studies

Study (first author, year, design)	Country	sample size	Digital Mobility Outcome	Clinical outcome	Follow up time (months)	plain text summary
(Benzo 2013) (secondary data analysis RCT)	United States	1218	gait speed	Mortality	24	significant association
(Cushen 2016) (prospective cohort)	Ireland	65	steps/day	exacerbations	0.5	significant association
(Demeyer, Louvaris, 2017) (retrospective cohort)	Europe (Belgium, Spain), United Kingdom & Brazil	758	steps/day	mortality	48	significant association
(Demeyer 2019) (prospective cohort)	Europe (Spain/ Belgium)	114	steps/day	lung Function, functional status and activities of daily living, and HRQoL	31.2	significant association in lung function and functional activities of daily living but no association with HRQoL
(Donaire-Gonzalez 2015) (prospective cohort)	Spain	177	steps/day	Healthcare utilisation	31.2	Significant association
(Durheim 2015) (secondary analysis part of RCT)	United States	326	steps/day	mortality and healthcare utilisation (time to first COPD related hospitalization)	4	significant association for univariate analysis, non-significant trend for adjusted multivariable analysis

(Fermont, Bolton, 2020; Fermont, Fisk, 2020; Fermont 2021) (prospective cohort)	United Kingdom	714	gait speed	exacerbations, healthcare utilisation	60	significant association
(Jones 2019) (prospective cohort)	United Kingdom	398	gait Speed	mortality.	12	significant association
(Kang 2018) (Secondary analysis part of RCT)	United States	63	steps/day	Mortality	60	significant association
(Kon, Canavan, 2015; Kon, Jones, 2015) (prospective cohort)	United Kingdom	213/402	gait speed	mortality healthcare utilisation (Risk of 90- Day readmission to hospital)	36	significant association
(Medina-Mirapeix 2021) (prospective cohort)	Spain	137	gait speed	exacerbations	12	significant association for univariate analysis, no association for adjusted multivariable analysis
(Nakano 2021) (retrospective cohort)	Japan	78	gait speed	mortality, healthcare utilisation, exacerbations	24	significant association
(Neo 2017) (prospective cohort)	Singapore	124	gait speed	Mortality	18	significant association
(Neumannova 2017) (prospective cohort)	Czech Republic	174	steps/day	Mortality	36	significant association
(Pilsworth 2018)	United Kingdom	448	gait speed	Mortality	12	significant association

(retrospective cohort)						
(Sievi 2019) (prospective cohort)	Switzerland	181	steps/day	exacerbations	25.2	no association
(Spacht A. 2018) (prospective cohort)	United States	53	gait speed	healthcare utilisation (readmission at 30 days)	1	no association
(Walsh 2019) (prospective cohort)	United Kingdom	472	gait speed	Mortality	36	significant association
(Walsh 2021) (prospective cohort)	United Kingdom	213	gait speed	mortality and healthcare utilisation	12	significant association
(Wan 2021) (prospective cohort)	United States	176	Steps/day	Mortality	69.6	significant association
Waschki 2011 **(Waschki 2011)** (prospective cohort)	Germany	170	steps/day	Mortality	48	significant association
(Witt 2021) (prospective cohort)	United States	70	gait speed	healthcare utilisation (Readmission at 30days)	1	no association

RCT: randomised controlled trial; ADL: activities of daily living; HRQoL: health-related quality of life. [#]: studies had records in the original search and update, and reported the same findings

Two DMOs were found to have been investigated longitudinally as predictors of clinical outcomes in COPD; (I) daily step count as a measure of volume of walking (n=9 studies) and gait speed as a measure of pace (n=12 studies). These two DMOs were the focus of this review.

The clinical outcomes observed in relation to these DMOs were mortality (n=14 studies), healthcare utilisation (hospital admissions) (n=8 studies), acute exacerbation of COPD (AECOPD) (n=5 studies), significant deterioration in lung function (n=1), health related quality of life (HRQoL)/health status (n=1) and functional status (n=1). Of these, three studies investigated both mortality and healthcare utilisation (Kon, Canavan, 2015; Walsh 2021; Durheim 2015), one studied exacerbations and healthcare utilisation (Fermont, Bolton, 2020), and one study observed the relationship between a DMO and mortality, healthcare utilisation and exacerbations (Nakano 2021). Additionally, one study looked at lung function, HRQoL and functional status and activities of daily living (Demeyer 2019). The sample size of included studies was between 53 and 1,218 participants giving a combined sample size for this review of 5,851. The participants involved in these studies were 59% male, with a mean age of 67.5 (3.3) years and FEV_1% predicted 42.8 (9.1). Most studies investigated stable COPD patients with the exception of two that recruited inpatients. Median study follow-up time was 24 months with observation periods ranging between 1 and 70 (IQR: 33).

All 21 studies are included in the qualitative analysis and ten studies are included in the meta-analysis. Reasons for studies being excluded from the meta-analysis are available in the appendix of this thesis. (Appendix 4).

In the studies investigating daily step count, walking activity was investigated in an individual's day-to-day environment using either a pedometer or an accelerometer. A range of devices were used in the included studies at either the upper arm, ankle or carried in a pocket, but the most commonly used was the SenseWear armband (Bodymedia Pittsburgh, Pennsylvania). This device is no longer available for commercial use. There was also variance in the time subjects were asked to wear devices from 10 up to 22.5 hours per day and between two to 14 consecutive days.

Gait speed was studied in lab or clinic-based assessments with either a 2-minute walk distance (2MWD) or a 4-metre gait speed (4MGS), using a stopwatch. Where a study described a '15-foot walk' this was taken to be equivalent to the 4MGS.

5.3.2 **Daily step count and mortality**

Six studies investigated the relationship between daily step count and mortality risk (Waschki 2011; Demeyer, Waschki, 2017; Durheim 2015; Wan 2021; Neumannova 2017; Kang 2018). All reported a negative correlation which was statistically significant in five of the six studies. Two studies investigated the relationship between number of steps taken per day and mortality risk but were excluded from meta-analysis as they did not report an effect estimate to allow pooling of the data (Neumannova 2017; Kang 2018). These two studies showed similar findings, showing that maintaining a daily step count of at least between 3000-4000 steps/day may be protective against mortality.

The remaining four studies were combined in a meta-analysis and showed that a greater daily step count was associated with a reduced mortality risk, per 1000 steps (HR:0.81, 95% CI: 0.75-0.88) (figure 5.2). Heterogeneity in this meta-analysis was of low significance (I^2: 37.10%, T^2: 0.00) and funnel plots showed visual asymmetry (Figure 5.3). Based on results

from Egger's test publication bias was not present in this analysis (p=0.077) and results from a trim and fill estimator supported these findings.

Figure 5.2: *Association between daily step count and all-cause mortality in COPD*

Hazard ratios (HRs) are presented with 95% confidence intervals. The red line is the average effect estimate. The black line shows no effect. REML: restricted maximum likelihood.

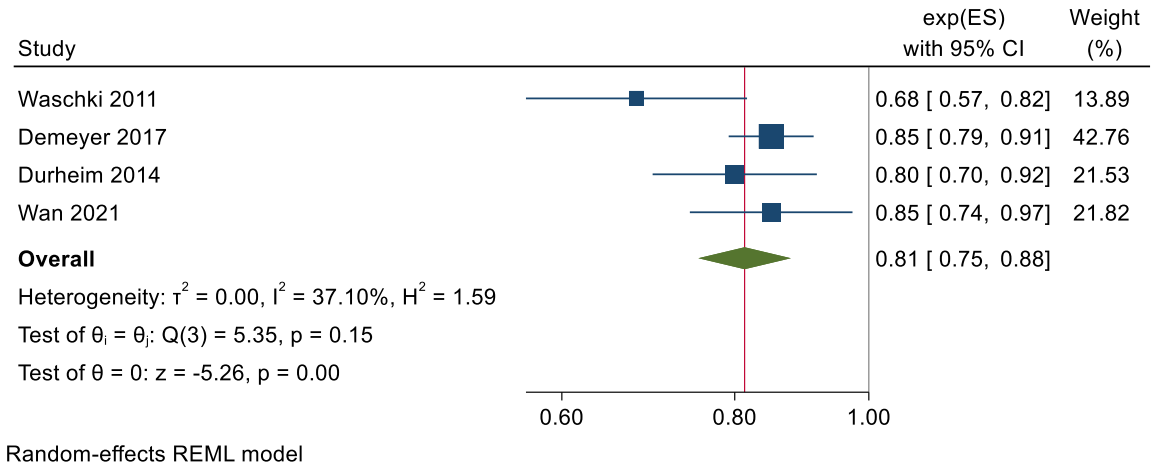
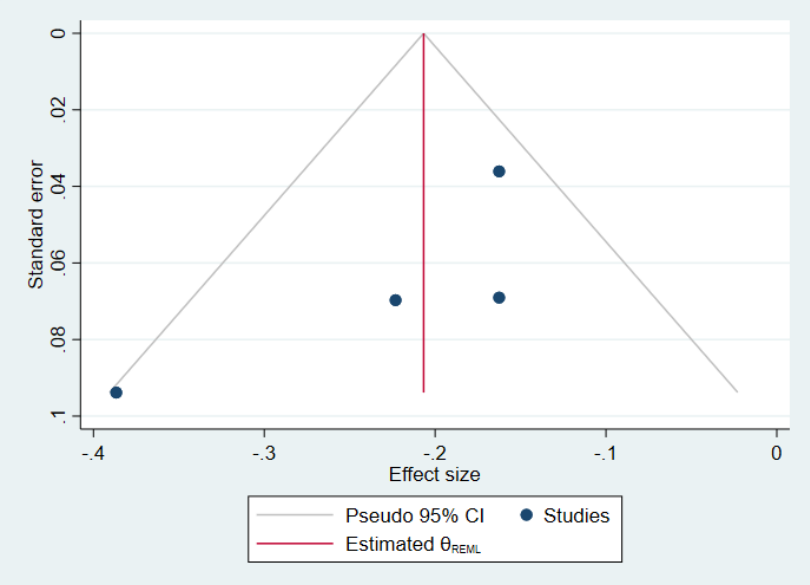


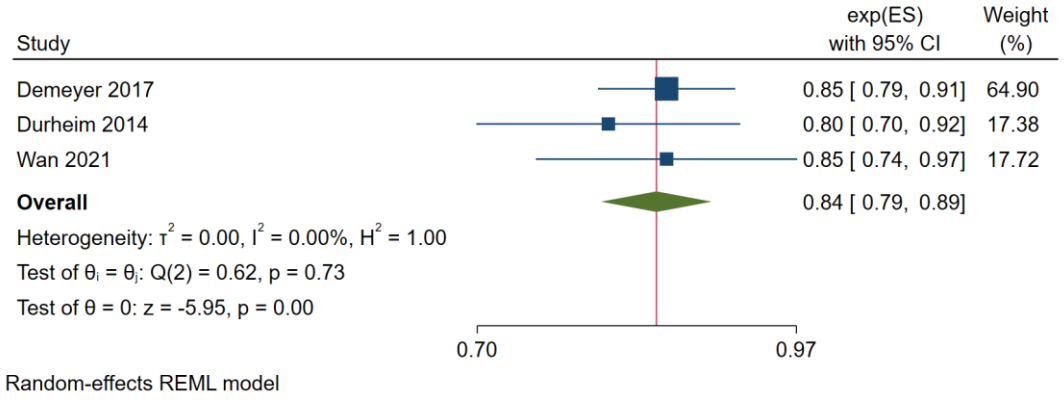
Figure 5.3: *Publication bias of studies reporting on association between daily step count and all-cause mortality in a COPD cohort*



Sensitivity analysis removing one study from the analysis that used 1,845 steps/day (a half SD) as a cut off, rather than the 1000 steps used in other studies did not substantially impact the overall effect size (HR: 0.84, 0.79-0.89) (figure 5.4).

Figure 5.4: *Association between daily step count and all-cause mortality in COPD- sensitivity analysis*

Hazard ratios (HRs) are presented with 95% confidence intervals. The red line is the average effect estimate. The black line shows no effect. REML: restricted maximum likelihood.



5.3.3 **Gait speed and mortality**

Nine studies investigated the relationship between gait speed and mortality risk (Kon, Canavan, 2015; Fermont 2021; Jones 2019; Neo 2017; Walsh 2021; Walsh 2019; Nakano 2021; Benzo 2013; Pilsworth 2018). Kon et al and Walsh et al reported data from the same cohort (Kon, Canavan, 2015; Kon, Jones, 2015; Walsh 2021) or cohorts with significant cross-over (Walsh 2019; Kon, Canavan, 2015; Kon, Jones, 2015), so only analyses by Kon et al were chosen to be included in meta-analyses as statistical representation from these papers could be compared with those in other studies. A further two studies were excluded from meta-analysis due to insufficient reporting of data to allow comparisons (Jones 2019; Pilsworth 2018). Both were conference abstracts with large sample sizes and importantly supported the hypothesis that gait speed is associated with mortality risk, but one did not report define how gait speed was measured or given an effect size and one did not state a threshold to define slow gait speed.

Three studies combined in meta-analysis explored the association between a slow gait speed (<0.8m/s) (versus a preserved gait speed (≥0.8m/s)) and survival and showed that there was a strong associated between the two outcomes (HR: 3.55, CI 1.72-7.36) (figure 5.5). However, heterogeneity between the three studies was high (I^2:66.71%) and funnel plots showed that publication bias was likely (figure 5.6).

***Figure 5.5**: Association between gait speed and all-cause mortality in COPD*

Hazard ratios (HRs) are presented with 95% confidence intervals. The red line is the average effect estimate. The black line shows no effect. REML: restricted maximum likelihood.

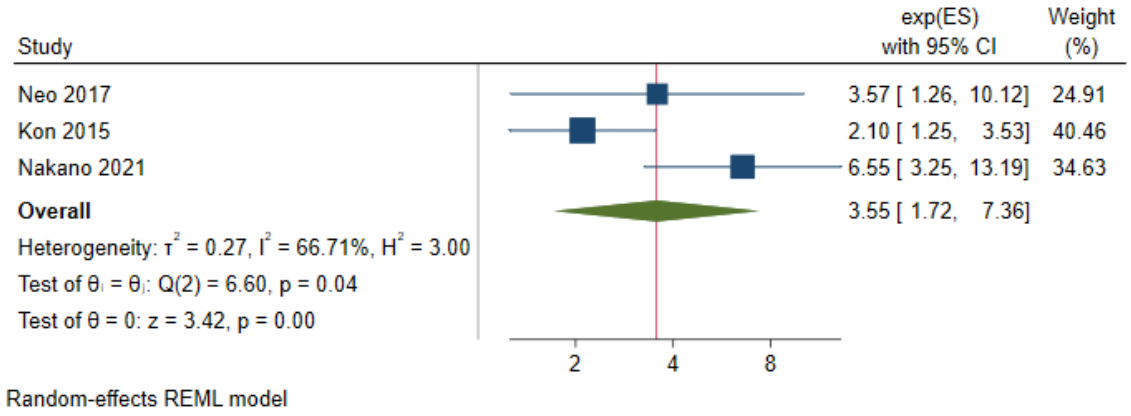
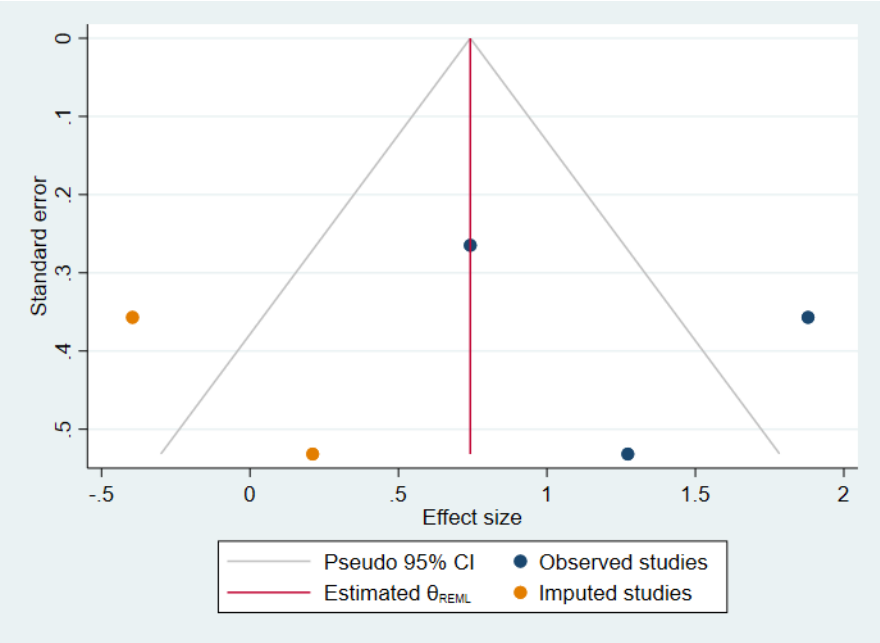


***Figure 5.6:** Publication bias of studies reporting on association between gait speed and all-cause mortality in a COPD cohort*



A sensitivity analysis removing one study from the analysis (Neo 2017) that used 2MWD rather than 4MGS as used in the other studies caused a slight decrease in the effect size (HR: 3.62, CI 1.19- 11.03) (figure 5.7) but resulted in an increased heterogeneity ($I^{2:}$ 84.73%) and greater uncertainty. A further sensitivity analysis removing a study that sampled hospitalised patients (Nakano 2021) increased the effect size (HR: 2.33, CI 1.47-3.71) (figure 5.8) with no heterogeneity (0.00%) between the included studies.

Figure 5.7: *Association between gait speed and all-cause mortality in COPD- sensitivity analysis (4MGS)*

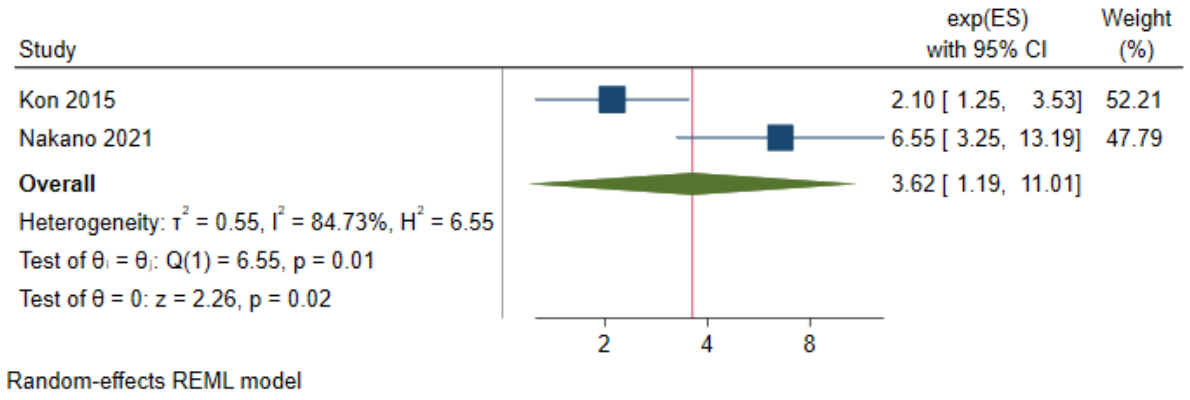
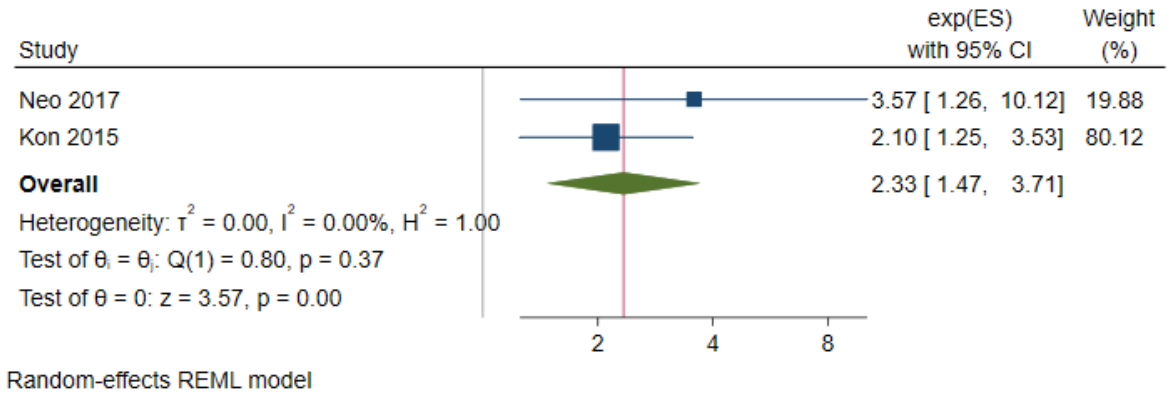


Figure 5.8: *Association between gait speed and all-cause mortality in COPD- sensitivity analysis (hospitalised patients)*



Hazard ratios (HRs) are presented with 95% confidence intervals. The red line is the average effect estimate. The black line shows no effect. REML: restricted maximum likelihood.

Two studies showed a strong relationship between declining gait speed and survival (HR: 7.55, CI 1.11-51.3) (figure 5.8) but heterogeneity between these studies was estimated to be high (I^2:76.12%) and publication bias likely (figure 5.9).

Figure 5.9: *Association between declining gait speed and all-cause mortality in COPD*

Hazard ratios (HRs) are presented with 95% confidence intervals. The red line is the average effect estimate. The black line shows no effect. REML: restricted maximum likelihood.

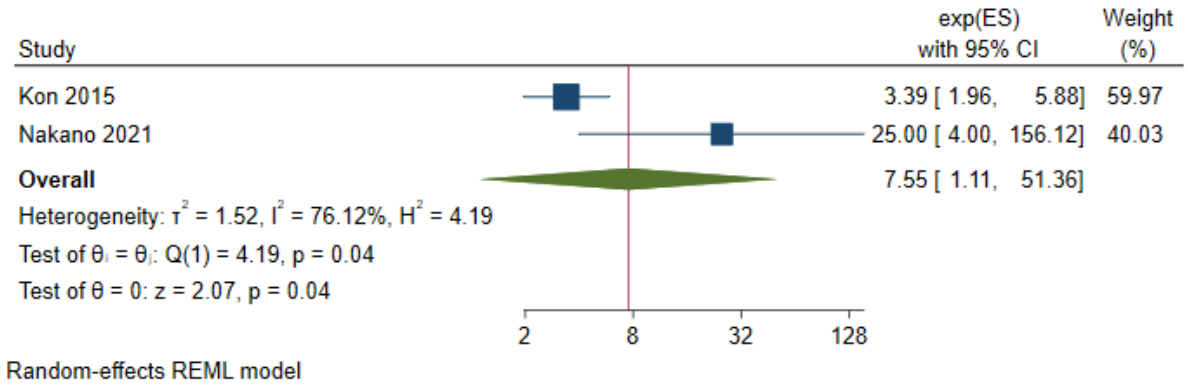
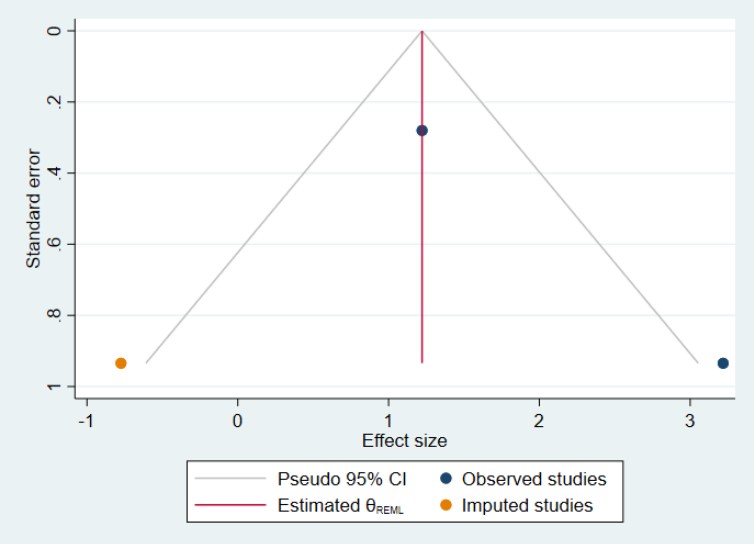


Figure 5.10: *Publication bias of studies reporting on association between declining gait speed and all-cause mortality in a COPD cohort*



A further study was included in this review but excluded from meta-analysis due to the use of the Short Physical Performance Battery (SPPB) to describe gait speed (Fermont 2021). This study used point change in SPPB rather than m/s as in all other included studies and therefore quantitative comparison was not possible. This study supported the meta-analysis results showing that declining gait speed is associated with mortality risk in people with COPD.

5.3.4 **Digital mobility outcomes and exacerbations**

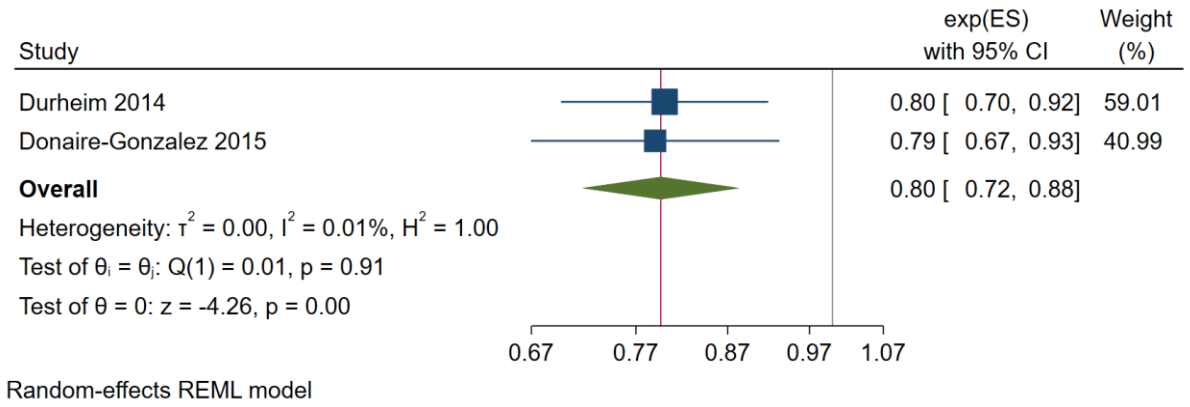
Five studies reported associations between walking activity or a gait parameter and the occurrence of an AECOPD. Two studies investigated the relationship between steps/day and AECOPD with conflicting conclusions (Cushen 2016; Sievi 2019). Sievei et al, found there to be no relationship between steps/day and exacerbation risk in a stable but severe COPD cohort (coefficient 58.4; CI: -189.3, 72.5) but in a study of inpatients hospitalised with an AECOPD an increased daily step count (≥396 steps) was found to be associated with fewer subsequent exacerbations at 14 days post discharge from hospital (AUROC 0.66, 0.46-0.82). These studies were not meta-analysed due to differences in associations reported on (daily step count versus change in daily step count).

Three studies looked at gait speed and AECOPD, with all reporting significant associations (Fermont, Bolton, 2020; Nakano 2021; Medina-Mirapeix 2021). One study reported having an AECOPD and the time to first AECOPD post hospital discharge were both positively associated with a slower gait speed (Nakano 2021). These findings were supported by those reported in Fermont et als, study but in patients that suffered an exacerbation that required hospital admission. Although Medina-Mirapeix also found an association their finding show that this did not remain significant when the authors adjusted for age and exacerbations in the previous year. A meta-analysis was not performed for this association due to inconsistencies in data analysis and reporting methodologies.

5.3.5 **Digital mobility outcomes and healthcare utilisations-readmission to hospital**

Two studies found that there was a negative correlation between steps/day and healthcare utilisation that when combined in meta-analysis suggest that for a 1000 steps/ day decrease a 20% greater risk of hospitalisation may be expected (HR:0.80 CI 0.72-0.882) (Figure 5.9).

Figure 5.11: *Association between steps/day and healthcare utilisation in COPD*



Heterogeneity between these studies was insignificant (0.01%) and publication bias was shown to be unlikely.

There were five studies that explored the association between gait speed and healthcare utilisation (Kon, Jones, 2015; Fermont, Fisk, 2020; Fermont, Bolton, 2020; Witt 2021; Spacht A. 2018). There was only one study that found no significant relationship between gait speed and healthcare utilisation but this was in a small sample and over a short observation period (30 days) (Witt 2021). Meta-analysis of two studies showed that a slower gait speed (<0.8 m/s) was associated with an increased admission risk.(Witt 2021; Kon, Jones, 2015) with patients being three times more likely to be readmitted to hospital in the short-term (90 days) (OR:3.36, CI 1.42-7.94; I^2=0.00%) (Figure 5.12 and 5.13) There were two further studies that supported this finding (Fermont, Bolton, 2020; Fermont, Fisk, 2020) but could not be included in quantitative analysis due to differences in reporting methods (median 4MGS and point change in 4MGS as part of the SPPB, respectively).

Figure 5.12: *Association between declining gait speed and healthcare utilisation in COPD*

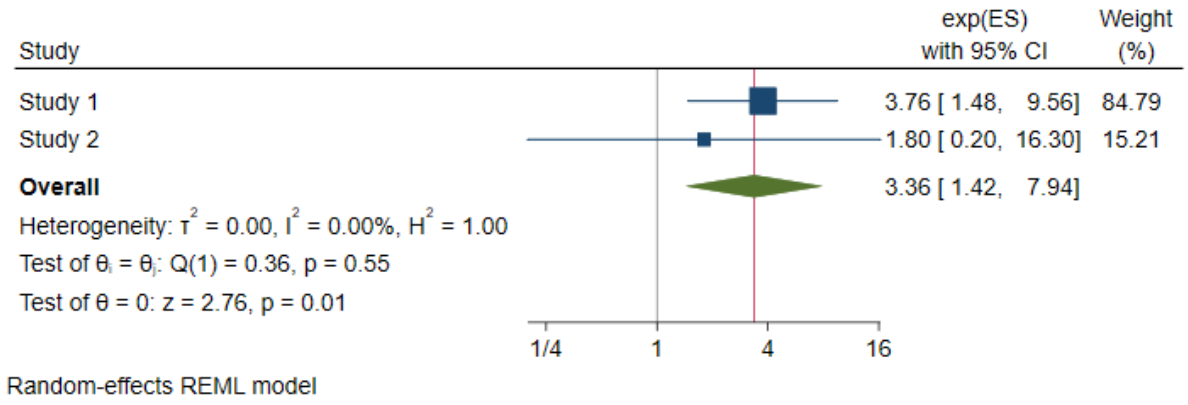
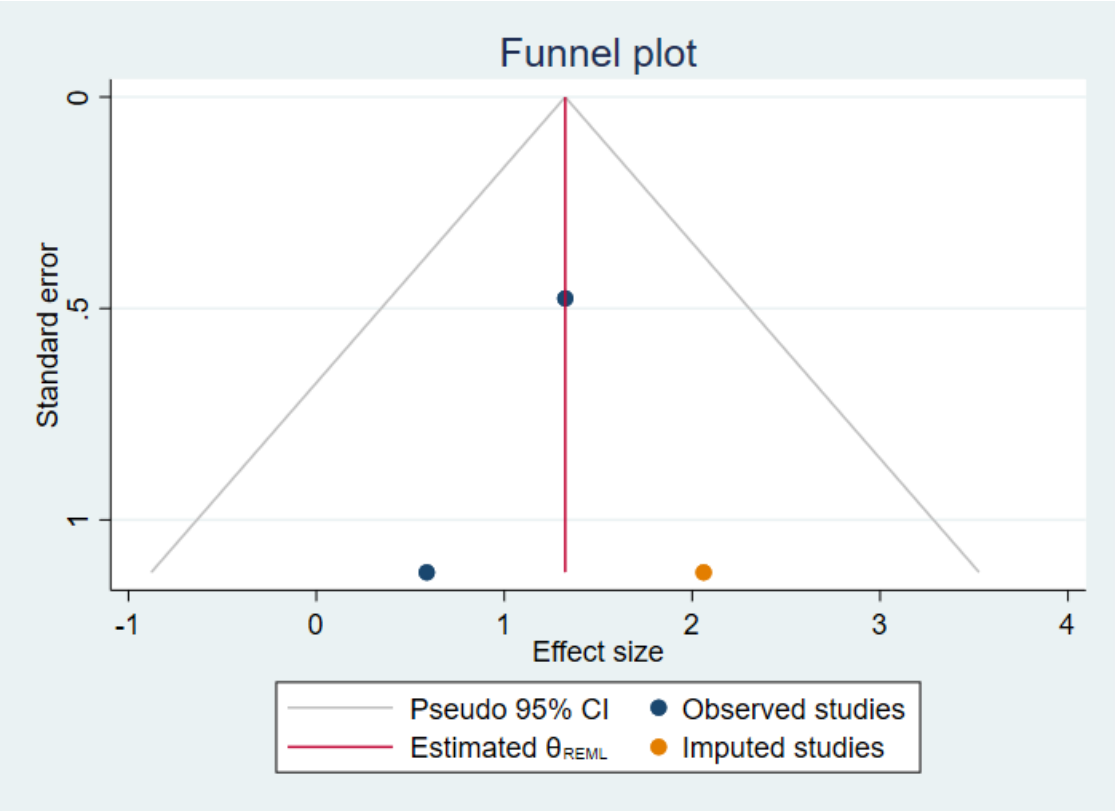


Figure 5.13: *Publication bias of studies reporting on association between declining gait speed and healthcare utilisation in a COPD cohort*



5.3.6 **Digital mobility outcomes and other clinical outcomes**

One study was identified that investigated relationships between a DMO and alternative clinical outcomes. Demeyer et al studied steps/day in relation to decline in lung function parameters, health status (using the St George's Respiratory Questionnaire) and functional exercise capacity (using 6MWD). Associations were found for lung function parameters, but only for the symptoms score of the SGRQ, no other domains or for exercise capacity.

5.3.7 **Critical appraisal of evidence- quality and risk of bias**

Grading of the evidence was found to be of overall moderate to low quality. The studies included were largely observational cohort studies which are deemed to be lower quality evidence that RCTs due to methodological limitations. The inclusion of conference abstracts may also have influenced the overall quality of the evidence (table 5).

Assessment of the risk of bias showed eleven of the studies to be at high risk of overall bias. The domains contributing most frequently to this judgement were participation, prognostic factor measurement and confounding. However, most studies deemed to be at a high risk of bias were given this (figure 5.13).

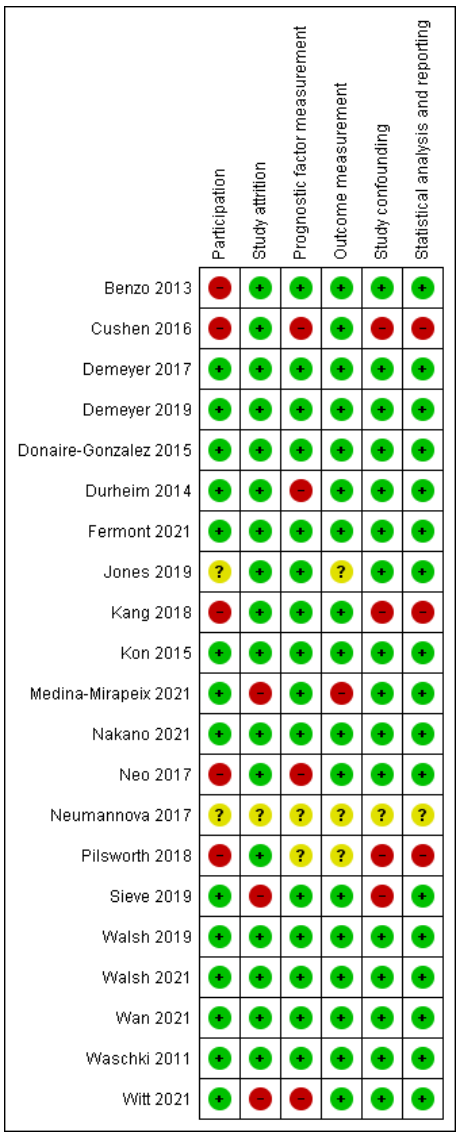
***Table 5.4**: GRADE certainty of evidence summary of findings table*

Participants/studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence GRADE
Daily step count and mortality						
1,629 **6 cohorts**	moderate risk of bias	no serious inconsistency	serious indirectness	no serious imprecision	strongly suspected	⨁⨁⨁⊙ **MODERATE**
Gait speed and mortality						
3,177 **7 cohorts**	high risk of bias	serious inconsistency	serious indirectness	serious imprecision	strongly suspected	⨁⨁⊙⊙ **LOW**
Daily step count and healthcare utilisation						
288 **1 cohort**	high risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⊙ **LOW**
Gait speed and healthcare utilisation						
1,075 **4 cohorts**	moderate risk of bias	serious inconsistency	serious indirectness	no serious imprecision	undetected	⨁⨁⨁⊙ **MODERATE**
Daily step count and exacerbations						
224 **2 cohorts**	high risk of bias	serious inconsistency	serious indirectness	no serious imprecision	undetected	⨁⨁⊙⊙ **LOW**
Gait speed and exacerbations						
929 **3 cohorts**	moderate risk of bias	serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⊙⊙ **LOW**
Daily step count and lung function, HRQoL, functional status/ADL's						
114 **1 cohort**	high risk of bias	no serious inconsistency	serious indirectness	no serious imprecision	undetected	⨁⨁⊙⊙ **LOW**
Gait speed and cardiovascular events						
714 **1 cohort**	low risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨁ **MODERATE**

All outcomes started with a baseline GRADE rating of low. Daily step count and mortality marked up due to large magnitude of effect; gait speed and healthcare utilisation marked up due to large magnitude of effect; gait speed and cardiovascular events marked up due to large magnitude of effect. GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HRQoL: health-related quality of life; ADL: activities of daily living. ⨁: GRADE quality criteria met; ⊙: downgrading for decreased quality based on quality criteria

Figure 5.14: *Risk of bias summary*

Green= low risk of bias, red= risk of bias and yellow= indeterminate risk.



5.4 Discussion

5.4.1 **Summary of findings**

The key finding from this literature review and meta-analysis is that daily step count and gait speed collected as DMO's both show longitudinal association with survival in a COPD population, demonstrating their potential value as prognostic digital biomarkers. There was also evidence to indicate relationships between these DMOs and other important clinical outcomes such as healthcare utilisation and exacerbations. However, these findings must be considered in the context of a low number of studies with substantial heterogeneity in methodologies.

5.4.2 **Significance of findings**

This is the first review that explores the relationship between DMOs and clinical endpoints in COPD and therefore the results provide novel insights into the potential value of these measures as predictive biomarkers. Although there are other reviews and meta-analyses that have previously explored the value of DMOs these studies largely appraise the psychometric properties of outcomes that can be collected digitally (Rist 2022; Johnston 2017), or investigate them as part of physical activity promotion interventions (Reilly 2023b; Vetrovsky 2021; Reilly 2023a).

These findings offer valuable contribution to strengthening the evidence base around the adoption of DMOs within a clinical and research environment, providing a convenient and reliable way to measure real-world mobility (Mikolaizak 2022). Although there is a long list of potential DMOs which were considered for this review (table 1) only 2 were found to have been assessed longitudinally in COPD; steps/day and gait speed. The significance of other walking activity and gait parameters has been recognised within long term conditions in

general and indeed within COPD care (Iwakura 2019). Walking cadence, for example has been shown to be associated with physical capacity (6MWD) (Shioya, 2018 #7). Furthermore, with the strong public health emphasis of reducing sedentary time in the general population (Owen 2011; Carr 2013; Healy 2011; Wilmot 2012; WHO 2020), duration of walking bouts is becoming more widely studied in a COPD population. However, due the lack of longitudinal observational studies investigating these measures in COPD this review can only comment on the prognostic value of steps/day and gait speed. This highlights a research gap which should be noted as other DMOs may show greater correlations with clinical outcomes and hence, be better prognostic indices.

Of note, physical activity (PA) parameters that were not walking specific, such as those evaluating total quantity or intensity of PA (e.g. vector magnitude units (VMUs) or time in moderate to vigorous physical activity (MVPA) were not considered gait DMOs for the purpose of this study and therefore, not included. However, previous literature reviewing PA parameters that was not restricted to the a priori decided digital measures supports our findings (Gimeno-Santos 2014).

The 4MGS and 2MWD, as measures of gait speed, were taken to be representative of normal continuous walking, based on the instructions given during the test. Conversely, the 6MWT was not and studies using this test were excluded from this review. This is because the 6MWT is longer in duration and therefore may include a greater number of pauses or changes in pace which would not allow for an accurate estimation of normal walking pace. Measures such as 4MGS are of utility in assessing gait as they are quick and simple to administer and require only a small amount of space and resource. This is also true for daily step count which can be measured routinely, with relative ease using a small device that causes minimal interruption to daily life. Due to their practicability and potential to be collected digitally, measures such as these could be of greater clinical value in monitoring and identifying

patients at high risk for significant events such as AECOPDs, admissions and mortality (Fermont 2019; Johnston 2017).

Findings suggested that increasing daily step count by 1000 steps/day could be associated with a decrease in mortality risk of between 19% and 23%, and also a reduction in healthcare utilisation to a similar extent. However, it is important that in evaluating the results causality is not assumed. Many of the included studies used a between-patient, rather than within-patient design and thus, to confirm this relationship, would need to be evaluated in prospective interventional trials.

A low total number of daily steps (between 3,000 and 4,000) also appeared to be associated with an increased mortality risk. However, the studies that reported these findings were lacking vital information including participant characteristics, methodology and reporting of statistics which meant meta-analysis could not be conducted. In previously published literature investigating PA levels in healthy older people, a link was found between the number of steps taken per day and survival. As the number of steps/day increased mortality rates decreased but this correlation was only sustained up to a threshold of 6,000-8,000 steps/day (Paluch 2022). Reference points such as these and those suggested in this study's findings may be useful when monitoring and quantifying an individual's activity levels or when discussing the importance of increasing or maintaining PA with a patient and may be facilitated with a simple pedometer. A study investigating the use of a pedometer in a COPD cohort, compared to a control group receiving only PA encouragement found that the pedometer group had significantly greater improvement in steps/day and that this was associated with fewer exacerbations (Mendoza 2015).

Despite the large effect size of steps/day on mortality that was shown in the pooled analysis of this review, the linearity of this association still requires further investigation. Of note,

although related, the impact of physical capacity (what people can do) and physical activity (what people actually do) may have different prognostic value (Vaes 2022).

Although the association between gait speed and survival was significant there was low quality evidence to support this. Digitally assessed gait speed has previously been found to be a reliable indicator of age-related decline associated with important health outcomes and other measures of function (Kon 2013; Soltani 2021; Abellan van Kan 2009; Studenski 2011). Additionally, its utility as a gait parameter estimating real-world walking speed measured using an activity monitor has been demonstrated (Soltani 2021). The large effect size we found between a reduction in gait speed and mortality suggests that it may be used to monitor and highlight deterioration over time, signalling when intervention is indicated. Additionally, a slow gait speed could categorise hospitalised patients who are at higher risk for readmissions and therefore may be candidates for community care or services such as hospital at home. Interestingly, removing the only study that evaluated mortality risk and gait speed in hospitalised patients yielded the greatest effect size and therefore this association cannot be generalised to hospitalised COPD patients. This highlights an important area for future research.

The relationship between mobility and admissions has been explored previously (Garcia-Aymerich 2003; Garcia-Aymerich 2006) but in studies using subjective measures to quantify physical activity level, of which problems of overreporting are well-known(Pitta 2005). Pitta et al, found that when patients were asked to estimate the amount of time they spent carrying out activities their estimations did not correspond to objective measures(Pitta 2005). An important study that contributes to this evidence base is that of Garcia-Rio and colleagues (Garcia-Rio 2012) investigated the relationship between exacerbation rate and physical activity more broadly. They found that amount and intensity (VMU) of daily activity was

predictive of admission rate and considering that walking makes up a substantial amount of physical activity this provides important context to this work.

Other studies that were identified in the review explored relationships between walking activity and gait parameters and other clinical outcomes (AECOPDs, lung function parameters, HRQoL and function) but in these outcomes data was sparse and therefore difficult to draw meaningful conclusions from. These outcomes are of significance as they are routinely used in both clinical practice and research studies as important health outcomes. In the past there has been a focus in COPD care on improving symptoms and reducing exacerbations (Vogelmeier 2020) and this has been discussed in the background to this thesis. With a greater awareness of the full burden of COPD comes an appreciation of the importance of health-related quality of life (Hurst 2021) and its relationship to health trajectories (Esteban 2022).

Recent findings from a pooled analysis found that increasing steps/day by as little as 750 steps may be associated with an improvement in quality of life in people with COPD (Driver 2022) and this is supported by previous work suggesting a minimum importance difference of between 600 and 1100 steps/day following PR (Demeyer 2016). Greater research is indicated in more routinely used clinical outcomes such AECOPD, lung function, HRQoL and functional status to provide clarity around the utility of steps/day, gait speed or other walking activity and gait parameters in predicting these outcomes.

5.4.3 **Methodological considerations**

There are three main limitations within this study that require the results to be interpreted with some caution. First, the small number of included studies, that was further limited during meta-analysis and meant that sub-analyses could not be conducted. This may be

caused by a restrictive inclusion/exclusion criterion or represent a gap in the research literature. Nevertheless, this must be recognised when evaluating the robustness of the conclusions that can be drawn from this analysis.

Second, the quality of the included studies. A large majority of the studies were observational studies which are considered to be of lower quality evidence than the gold-standard RCT. It has been argued that observational studies are at a greater risk of publication bias due to a lack of preregistration and mandatory protocol preparation. Consequently this can make it difficult to identify unpublished studies or other reporting biases (Metelli 2020).

There was also a proportion of included studies that were conference abstracts, and, in these, it was often difficult to assess the presence of bias due to restricted reporting of methodologies. There is debate around whether research abstracts should be included in systematic reviews due to the labour-intensive task of searching for such records (Hackenbroich 2022). Additionally, the absence of peer review of unpublished studies puts the reliability of their results under scrutiny and there is typically a lack of detail in methodologies and analysis (Scherer 2019). However, including abstracts may address the dilemma of publication bias and where research is sparse may help to strengthen conclusion. These reasons, particularly the latter provide the justification for inclusion of abstracts within this review.

Recognition of the wide confidence intervals that were reported in meta-analyses, particularly in those analysing gait speed indicates poorer precision of the effect estimate. This may be down to limitations associated with the lack of consistency in methodologies for measuring gait speed which has been described previously (Studenski 2011).This was also a problem in studies measuring walking activity. For example, the type of device used to measure daily step count, the location it was worn and the duration of time it was worn all introduce

diversity and potential bias when pooling data. An international task force has published recommendations for working towards a common framework in objective measurement of PA (Demeyer 2021) and this will facilitate increased quality of associated research trials.

Third, expands on the previous point drawing on the heterogeneity of the included studies in terms of methodologies used for analysis, and study design. Heterogeneity was a limitation that to some extent should be anticipated when conducting a meta-analysis but must still be noted and quantified (Higgins 2008). It is suggested that the degree of heterogeneity should be considered, whether it is acceptable and then how it should be handed during analysis (Higgins 2008). The greatest source of inconsistency within this analysis was the range of disease severities observed by the studies, whether they included stable or hospitalised patients, different outcomes measuring gait speed, and a lack of commonality in confounders. This was particularly evident in those observing the relationship between gait speed and mortality. For example, the majority of studies investigated gait speed using the 4MGS, an instrument that has been extensively studied in a COPD population with its validity and reliability confirmed (Kon 2014; Kon 2013). However, a few studies instead used the 2MWD which made quantitative comparison difficult. Unfortunately, three of the largest studies that were identified for this review could not be included in the quantitative analysis due to reporting limitations (Pilsworth 2018; Jones 2019; Benzo 2013) which means effect estimates may actually be underestimated.

The concept of clinical heterogeneity in systematic reviews has been recognised and the need for a methodical practise for exploring has been called for. Variances in this study were addressed in several ways; 1) by transforming unit effects where necessary to allow more studies to be combined in the same meta-analysis 2) using a model that accounts for and acknowledges heterogeneity in trials (Raudenbush 2009) 3) using a statistical test of heterogeneity (I^2 test) to quantify variance against a pre-defined acceptable threshold, and 4)

conducting sensitivity analyses, removing studies and assessing how the magnitude of effect is changed.

Finally, this study focussed on reviewing the available evidence, but several important points that were outside of the scope of this study do require future consideration; the sensitivity and specificity of the associations found, the impact of confounders that may not have been accounted for but may have played a role in the associations, and evaluation of other characteristics to are vital in confirming the value of DMOs as predictive digital biomarkers (Califf 2018; Fermont 2019).

5.5 Conclusions and future work

The existing evidence on the prognostic value of walking activity and gait parameters in COPD is scarce and limited to a few studies observing gait speed and daily steps. These studies show heterogeneity in methodologies and data analysis making pooling of data complex. Findings presented here provide important evidence that walking activity and gait parameters, specifically daily step count and gait speed are associated with mortality risk and other important clinical outcomes for people with COPD and may have value as prognostic indicators or outcome measure in clinical trials. Future research should focus on validating gait speed and other DMOs (cadence, duration of walking bouts, gait variability etc) prognostic ability in larger studies and using standardised methodologies that can be compared across studies.

6 Setting up a national lung volume reduction registry- the UKLVR study

6.1 Introduction

The introductory chapters of this thesis review the strong evidence base supporting the efficacy of LVR treatments for carefully selected individuals with severe emphysema. However, much of the existing data, particularly for the more novel bronchoscopic treatments such as endobronchial valves are taken from clinical trials. These trials are often funded by commercial companies that manufacture the devices used in the trials and allow for additional funding and resource for clinician time and clinical investigations. It is important that the benefits seen in these trials are reflected in everyday clinical care. For this reason, the importance of real world data in the endorsement of interventions is firmly established and considered essential (Halpin 2023; Arlett 2022; Cave 2019), and this has been emphasised previously in chapter 3 of this thesis.

To uphold this, NICE suggested in 2018 as part of the interventional procedure guidance that all novel interventions should be performed with special arrangements for governance, consent and audit or research, as well as a requirement for an MDT setup collecting lung function, breathlessness, quality of life, exercise capacity and safety outcome data (NICE. 2004).

As part of the work planned for this thesis in addressing this mandate whilst working towards improved patient access and outcomes for LVR interventions, a national LVR registry was set up. The UKLVR registry was designed to collect clinical data on all LVR procedures being carried out at specialist LVR centres across the UK with the intention of supporting the MDT infrastructure, endorsed by NICE and developing a national framework for delivering LVR treatment.

In this chapter I aim to analyse and interpret the data of all procedures entered in the UKLVR registry thus far with the objective of facilitating clinical audit, supporting the development of treatment pathways and addressing clinical research questions, such as; does the response to LVR treatment in clinical practice match those seen in research trials?, What are the complication rates of different procedures?, and does long term survival differ in individuals undergoing different treatments? E.g. bronchoscopic or surgical?

6.2 Methods

6.2.1 **Study design**

This observational study was set up with ethical approval from Camberwell St Giles Research Ethics Committee (16/LO/1107). Where retrospective data was entered the need for patient consent was waived but for prospective data entry patients were asked to provide written informed consent. This approach to consent was agreed to avoid unnecessary bias or exclusion of data from retrospective patients that do not respond to telephone or postal contact. However, Confidential Advisory Group (CAG) approval would be needed to allow the use of identifiable data in the analysis. As this was not sought, no identifiable data will be presented in this chapter.

The registry was set up with financial support from Asthma+Lung UK and sponsorship from Imperial College, London. Inception of the registry was planned with patient and public involvement via the Asthma +Lung UK Breath Easy groups. Discussions indicated that patients were supportive of this project and recognised the need to ensure that new treatments are introduced and delivered in a rational away. The registry platform was developed collaboratively between the study team at the Royal Brompton Hospital and a software development company (Westcliffe Solutions). Multiple iterations of the database were

produced in the process of developing the UKLVR registry. Westcliffe Solution created the final version of the database and continue to host the online platform including managing information governance and server security.

6.3 Participating centres

Any specialist centre undertaking LVR procedures in the UK was eligible to be involved in this study. A principal investigator for each centre was required to contact the trial coordinator at the Royal Brompton Hospital (SB) who would arrange trial set up with support from the recruiting centre's Research and Development department. Training was then provided to the research staff at each individual recruiting centre either virtually or face-to-face depending on individual site preference and convenience. Training was focussed on practical use of the online registry and accurate inputting of data, as well as covering the consent process. All research staff at centres involved in this study were made aware that support with accessing and using the registry could be sought at any point during the trial and a contact number and email address was provided.

6.3.1 **Data collection and outcomes**

The UKLVR registry collects data on adult patients with a diagnosis of COPD, undergoing an LVR procedure (either surgical or bronchoscopic) at a participating centre. This study covers procedures carried out between January 2017 and June 2022.

Any centre carrying out LVR procedures was eligible to be involved in the study and could register their interest by contacting the trial coordinator directly. Training was provided to sites to aid with data collection, registry use and the consent process for the trial.

Adult patients with COPD, undergoing an LVR procedure (either surgical or bronchoscopic) were eligible for the present analysis if their procedure had been carried out between January 2017 and June 2022. Survival data was collected from the NHS Spine up until February 2023. The present analysis includes data from 14 UK centres that are currently inputting data into the registry. A list of sites entering data into the UKLVR registry can be accessed in Table 6.2.

The registry was set up to collect baseline data (pre LVR procedure), details relating to the procedure received, and outcome data (post procedure) to be collected at three and 12 months following an intervention. The option to collect longer term data (24 and 36 months) was also available but not a requirement of the study. Survival data for patients entered into the database was obtained from the NHS spine up to February 2023. A summary of the data points collected by the registry can be seen in Table 6.1.

Participant characteristics were assessed in terms of several established risk criteria to explore the proportion of procedures that are being carried out in higher risk individuals the UK and to also be able to compare this with survival data.

First, the BODE/i-BODE index was used. An overview of these measures can be found in the main methods chapter of this thesis. Next, was the Glenfield BFG score. This is an established predictor of risk that was designed for use in patients undergoing LVRS. The tool categorises people as low, medium or high risk following LVRS based on their FEV_1%predicted, TLco and BMI (Greening 2017). Finally the proportion of patients undergoing a procedure with both an FEV_1% and TLco <20% was also determined as a measure of risk based on results from the NETT study (Criner 2011a). Of note, Tlco is the lung function parameter that has been found to have most prognostic significance in COPD (Boutou 2013).

A comparative analysis of proportions of low, high and medium risk patients that are undergoing LVRS and EBVs in the UK was performed using these risk indices.

6.3.2 **Statistical analysis**

A descriptive analysis of outcomes for all LVR treatments inputted into the registry is presented in the results section of this chapter. Quantitative representation of variables will be either mean (SD), or median (IQR) where data are not normally distributed. Categorical variables are reported as number and percentage (%). Statistical analysis will estimate between treatment comparisons using the t-test for normally distributed data and Mann Whitney U test for non-normally distributed data. For categorical data, the X^2 or Fishers exact test will be used. Kaplan Meier survival curves will also be composed for mortality data and Cox proportional Hazard modelling used to estimate hazard ratios. The Kaplan Meier analysis was chosen to provide a graphical representation (curve) and visual comparison of the two groups' survival over the follow-up period. Cox regression analysis allows formal comparison of the two group's survival over the follow-up period, and the addition of adjusting covariates that may affect survival to be added to a statistical model (Bewick 2004). Patients were considered to be at risk from time of procedure until either date of death or end of follow up period (73 months/6 years) and death was defined as all-cause mortality during the follow up period. Univariable cox regression analysis was carried out investigating the relationship between treatment (LVRS/EBVs) and other cofounding variables: age, gender, FEV_1%predicted, RV% predicted, CAT score, pattern of emphysema, and BMI, and survival. In addition, a multivariable analysis including all confounders was performed. Breathlessness and exercise capacity were also considered important baseline cofounders but due to the large amount of missing data were not included in the main regression analysis.

A sensitivity analysis was carried out including MRC dyspnoea score and exercise capacity (distance walked on either 6-minute walk test (6MWT) of incremental shuttle walk test (ISWT)), in the univariate analysis. The proportional hazards assumption was applied based on Schoenfeld residuals method (Grambsch 1994; Hess 1995) with no significant violations found ($p=0.205$). For all statistical tests, a significance of $p<0.05$ was set. Data presented in this chapter were analysed using IBM Statistical Package for Social Sciences (SPSS, New York, USA) version 28 and Stata version 17.0 (StataCorp, College Station, TX, USA).

***Table 6.1**: Data points collected by UKLVR registry*

Type of outcome	Outcome	Time point collected
Patient demographics	Date of birth, gender, hospital and NHS numbers, consent for data sharing	Baseline
Initial assessment	Date of MDT discussion, data of CT scan, date of lung function tests, date of VQ scan and perfusion data, pattern of emphysema, target lobe, fissure integrity. MRC score, CAT score, SGRQ (symptoms, activity, total), Exercise capacity tests, height, weight, BMI, FFMI, full lung function tests, arterial blood gases,	Baseline
Procedure	Date of admission, date of procedure, date of discharge, type of intervention.	Baseline
Endobronchial valves	Chartis assessment outcome, lobe treated, number of valves, type of sedation, confirmation of post procedure chest x-ray.	Baseline
Lung volume reduction surgery	Target lobe(s), approach, lobectomy performed? ITU admission, days on ITU/HDU, Invasive ventilatory support required? Days with drain, reoperation required,	Baseline
Endobronchial coils	Lobe treated, number of coils placed, confirmation of post procedure X-ray, decision made to not proceed to other side, number of coils placed.	Baseline
Adverse events: NICE audit	Date of follow up, months since initial procedure, survival data, date of death, cause of death, adverse event data.	3 and 12 months (optional 24 and 36)
Follow up data	CT scan, MRC score, CAT score, SGRQ (symptoms, activity, total), Exercise capacity tests, height, weight, BMI, FFMI, full lung function tests, arterial blood gases,	3 and 12 months (optional 24 and 36)

6.4 Results

In this chapter data on 541 patients undergoing LVR will be presented. The majority of patients entered into the databased had undergone either LVRS 244(44.9%) or EBV placement 219(40.9%). There were 65(12%) who underwent endobronchial coil treatments (EBC), 9(1.8%) that had bullectomies and 4(0.7%) who received bronchoscopic thermal vapour ablation (BTVA) treatment (Table 6.2) .386(71.0%) were described as having a heterogeneous pattern of emphysema on their CT thorax and 155(28.5%) had a homogeneous pattern. 60(38.7%) of the patients described as having homogeneous emphysema were treated with EBVs and 55(35.5%) underwent LVRS. 69(13.0%) of patients in the registry were recorded as having alpha-1 antitrypsin deficiency, and of these 35(50.7%) had EBVs, 26(37.7%) LVRS, 7(10.1%) EBCs, and 1(1.4%) had BTVA (Table 6.2).

People undergoing BTVA and bullectomy were excluded from further analysis due to the very low numbers in these groups which would make drawing meaningful conclusions difficult. Furthermore, the small numbers of patients in these groups may cause the individuals to be identifiable and consent has not been obtained for this.

The analysis presented concerns only LVRS and EBV interventions as these are the most commonly performed LVR interventions as well as the only ones to be clinically commissioned. For these reasons, these treatments are the primary focus of this thesis and this chapter. Although Endobronchial coils (EBCs) had a greater number of entries in the database (n=65) these treatments have been excluded from further analysis as EBCs are no longer available outside of clinical trials in the UK. Some basic descriptive data relating to EBCs are presented at the end of this section.

Table 6.2: *All procedures entered in UKLVR database and carried out per centre*

Patient data collected	All n= 541	LVRS n=244 (44.9%)	EBV's n=219 (40.9%)	EBC's n=65 (12%)	Bullectomy n=9 (1.8%)	Steam treatment n=4 (0.7%)
Centre:						
Addenbrookes	27 (5.0)	19 (7.8)	8 (3.7)	0 (0)	0 (0)	0 (0)
Birmingham	55 (10.2)	18 (7.4)	27 (12.3)	10 (15.4)	0 (0)	0 (0)
Bristol (BRI)	20 (3.7)	1 (0.4)	11 (5.0)	8 (12.3)	0 (0)	0 (0)
Glenfield	79 (14.6)	49 (20.1)	21 (9.6)	7 (10.8)	2 (22.2)	0 (0)
Golden Jubilee	10 (1.8)	4 (1.6)	3 (1.4)	2 (3.1)	1 (11.1)	0 (0)
Liverpool	23 (4.3)	15 (6.1)	8 (3.7)	0 (0)	0 (0)	0 (0)
New Cross	15 (2.8)	7 (2.9)	8 (3.7)	0 (0)	0 (0)	0 (0)
Northern General	17 (3.1)	8 (3.3)	9 (4.1)	0 (0)	0 (0)	0 (0)
RBHT	244 (45.1)	118 (48.4)	94 (42.9)	25 (38.5)	6 (66.7)	1 (25.0)
Preston	6 (1.1)	0 (0)	0 (0)	3 (4.6)	0 (0)	3 (75.0)
Southampton	36 (6.7)	4 (1.6)	22 (10.0)	10 (15.4)	0 (0)	0 (0)
Southmead	6 (1.1)	1 (0.4)	5 (2.3)	0 (0)	0 (0)	0 (0)
Nottingham	3 (0.6)	0 (0)	3 (1.4)	0 (0)	0 (0)	0 (0)

Data presented as n (%). LVRS: Lung volume reduction surgery; EBVs: Endobronchial valves; EBCs: Endobronchial coils

6.4.1 **Baseline characteristics of people undergoing LVR**

First, I present the baseline demographics of patients entered into the registry this is shown in Table 3. Patients were 42% female with a mean(SD) age 64.8 (8.54) and generally had a healthy BMI: mean (SD) 24.2(4.4) kg/m^2. BMI is an important predictor of outcome following LVR as research shows that those with a lower BMI prior to their procedure may be at higher risk of post procedural complications and have poorer survival following LVRS (Greening 2017; Fernandez-Bussy 2020). The research base demonstrating associations between BMI and prognosis in COPD and LVR is presented in the main methods chapter.

Table 4 shows the baseline lung function parameters of the whole UKLVR cohort and broken down per treatment (LVRS and EBV). In those undergoing LVRS 88.5% had lung function test results recorded, compared to 89.5% in the BLVR group.

According to GOLD guidelines patients in the database had moderate to severe airflow obstruction with a mean(SD) FEV_1 31.8(12.1) %predicted. The final column in Table 4 compares the parameters between the two groups and shows that baseline lung function outcomes were similar between the two groups. The only parameters to reach a statistically significant difference between LVRS and EBVs groups was FVC (l), which was greater in the LVRS arm, representing less severe disease (LVRS: 3.10 (2.02) vs BLVR: 2.79 (0.89) p=0.04) but as this difference was in isolation it was unlikely to represent an important variance.

***Table 6.3**: Baseline characteristics of patients entered in the UKLVR registry*

	All **n=541**	**LVRS** **n=244**	**EBV's** **n=219**	**Missing data**
Gender n (%Female)	222 (41.8)	94 (38.5)	91 (41.6)	3(0.6%)
Age (years)	64.8 (8.54)	63.4 (8.58)	65.9 (8.31)	18(3.9%)
BMI kgm^{-2}	24.2 (4.4)	24.6 (4.6)	24.2 (4.3)	126 (23.3%)
FEV_1%predicted	31.8 (12.1)	32.1 (12.1)	31.2 (11.6)	61 (11.3%)
RV% predicted	224.2 (51.3)	220.2 (51.5)	225.4 (52.4)	84 (15.5%)
TLco% predicted	36.1(18.0)	37.0 (16.2)	35.9 (18.8)	83(15.3%)
MRC dyspnoea score	4.0 (0.89)	3.7 (0.85)	3.8 (0.87)	147 (27.2%)
Pattern of emphysema **Heterogeneous/Homogeneous**	386 (71.0)/155 (28.5)	190 (77.9)/ 54 (22.1)	159 (72.6)/ 60 (27.4)	0(0.0%)
Alpha1-antitrypsin deficiency **Yes**	69 (13.0)	26 (10.7)	35 (16.0)	252(49.9%)

Data are presented as n (%) and mean (SD). LVRS: Lung volume reduction surgery; EBVs: Endobronchial valves; EBCs: Endobronchial coils; BMI: body mass index; FEV_1: forced expiratory volume in 1 sec; RV: residual volume; MRC: medical research council

Table 6.4: *Baseline lung function characteristics*

	Whole cohort	LVRS	EBVs	P value
FEV_1 (L)	0.87 (0.42)	0.90 (0.44)	0.85 (0.39)	0.23
FEV_1%	32.3 (11.7)	32.2 (11.9)	31.4 (11.3)	0.46
FVC (l)	2.91 (1.52)	3.10 (2.02)	2.79 (0.89)	0.04
FVC% predicted	101.7 (375.0)	123.5 (558.7)	83.4 (23.9)	0.31
TLco% predicted	36.1 (18.0)	37.0 (16.2)	35.9 (18.8)	0.56
Kco% predicted	46.5 (17.1)	48.2 (16.3)	46.5 (15.4)	0.31
TLC (litres)	8.9 (10.6)	8.24 (4.28)	10.0 (15.7)	0.57
TLC%predicted	134.2 (20.7)	133.7 (21.1)	133.9 (21.5)	0.93
RV (litres)	5.43 (9.61)	4.94 (1.37)	6.10 (14.7)	0.31
RV% predicted	223.8 (51.1)	220.4 (51.4)	225.4 (52.4)	0.34
RV/TLC	67.1 (30.3)	64.6 (22.1)	68.9 (37.8)	0.19
FRC% predicted	188.6 (38.4)	186.8 (42.9)	191.0 (34.7)	0.36
FRC (litres)	8.50 (20.4)	9.25 (24.2)	8.04 (18.1)	0.63
Pa02	10.0 (1.84)	10.0 (1.81)	10.1 (1.76)	0.76
PaC02	5.27 (0.93)	5.22 (0.99)	5.26 (0.90)	0.77

Data are presented as mean(SD). FEV_1: forced expiratory volume in 1 sec; FVC: forced vital capacity; TLco: carbon monoxide transfer factor; Kco: carbon monoxide transfer coefficient; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; Pa02: partial pressure of oxygen; PaC02: partial pressure of carbon dioxide

6.4.2 **LVR assessment pathways**

Next, I wanted to investigate the length of time that patients wait between being discussed at a specialist MDT meeting, having specialist investigations (CT scan, VQ scan and PFTs) and receiving their treatment, to begin to identify if and where there are delays in the patient pathway. Most of the patients in this study, 414(89.4%) that underwent either LVRS or EBV, were reported to have been discussed at a specialist MDT meeting prior to a decision being made on their suitability for treatment. The median(IQR) time between being discussed at an MDT meeting and receiving treatment was 175(195) days, or almost six months. A significantly longer delay between these time points was seen for those undergoing LVRS (LVRS=198(198) vs EBVs = 150(161) p=<0.001).

Only 126(24.3%) of patients were documented as having pulmonary function test (PFT) investigations within three months prior to receiving their treatment. The median length of time between having a PFT and receiving a treatment was 195(233) days which is over six months. Three months is usually suggested as an acceptable period as it allows enough time for busy clinical services to allocate an appointment whilst being unlikely to see a significant change in results. Previous research in COPD cohorts has demonstrated the average FEV_1 decline per year and in a cohort comparable to ours could be expected to be between 56-59ml/year (Tantucci 2012). A change over six months could mean that a patient would go from being a low or medium risk candidate to be considered high risk, or potentially mean they no longer fit the eligibility criteria to undergo a procedure.

428(92.4%) had a CT scan date recorded prior to treatment with a median of 219(259) days between having the scan and receiving intervention. 339(73.2%) had undergone a nuclear medicine ventilation-perfusion isotope (VQ) scan and the median length of time between investigation and treatment was 248(231) days. Although those receiving LVRS waited longer between receiving treatment and all steps of the pathway than those undergoing a

bronchoscopic treatment, there was only a significant between-group difference in CT scan and PFT wait times (CT scan: LVRS: 242(270)/BLVR:199(258) (p=0.038) (PFTs; LVRS: 221(245)/ BLVR :153 (p=<0.001). Although statistically significant, this time difference is unlikely to have led to clinically altered outcomes.

Table 5 shows the time (days) between initial MDT discussion, CT scan, VQ scan and PFTs for patients undergoing LVRS or EBV treatment.

Table 6.5: *Treatment related data for whole UKLVR cohort and per treatment (LVRS/EBVs)*

	All n=463	LVRS n=244	EBVs n=219	p-value
Discussed at MDT meeting: **Missing data** **Yes** **No** **Time between MDT and treatment (days)**	 18 (3.9) 414 (89.4) 31 (6.7) 175 (195)	 11 (4.5) 221 (90.6) 12 (4.9) 198(198)	 7 (3.2) 193(88.1) 19 (8.7) 150(161)	 <0.001
CT scan **Missing data** **Yes** **Time between CT scan and treatment (days)**	 35 (7.6) 428 (92.4) 219(259)	 20 (8.2) 224 (91.8) 242(270)	 15 (6.8) 204 (93.2) 199(318)	 0.220
VQ scan **Missing data** **Yes** **Time between VQ scan and treatment (days)**	46 (9.9) 339 (73.2) 248(231)	16 (6.6) 188 (77.0) 259(241)	30 (13.7) 151 (68.9) 231(217)	 0.105
PFTs **Missing data** **Yes** **Time between PFTs and treatment (days)**	 51 (11.0) 412 (89.0) 195(233)	 28 (11.5) 216 (88.5) 221(247)	 23(10.5) 196 (89.5) 153(212)	 <0.001

Data are presented as n (%) or median (IQR). LVRS: Lung volume reduction surgery; EBVs: Endobronchial valves; MDT: Multidisciplinary team; CT scan: computer tomography scan; VQ scan: Ventilation perfusion scan; PFTs: Pulmonary function tests.

6.4.3 **LVRS**

209(87.1%) of the LVRS treatments were done via a video assisted thoracoscopic (VATS) approach and 71(29.6%) had a lobectomy. The VATs approach is generally the preferred surgical method universally due to it being a more cost-efficient (Ko 1998) procedure that allows a quicker postoperative return to function (Kösek 2020). Research presented in the introductory chapter of this thesis suggests conflicting evidence around the comparative morbidity following either VATs or median sternotomy (McKenna 2004; Ko 1998). 18(7.5%) LVRS patients were admitted to the intensive care unit (ICU) post treatment and 15(6.3%) required ventilatory support. The median length of time post-surgery with an intercostal drain was 11 days. These proportions are in line with previously reported cohorts (Lacour 2018).

6.4.4 **EBVs**

Prior to EBV treatments, 143(66.5%) were reported to have had a Chartis (PulmonX, Redwood City, CA, USA) procedure to confirm whether collateral ventilation (CV) was present. An in-depth explanation of this procedure is presented in Chapter 2: Methods. Of these 14(9.9%) had an indeterminate result compared to 122(85.3%) with a negative result. 7(4.8%) were treated with EBV despite having been recorded as CV positive. The importance of fissure completeness or collateral negative status has been emphasized and associated with a lack of clinically meaningful benefit from EBVs (Koster 2021; Klooster, Slebos, 2017; Gompelmann 2013).

On average patients received 4 valves (range 1,7). 153(69.9%) were carried out under general anaesthetic and 55(25.1%) under sedation. Preference for sedation is usually based on specific site guidelines and facilities but either approach is acceptable (Slebos 2017). An

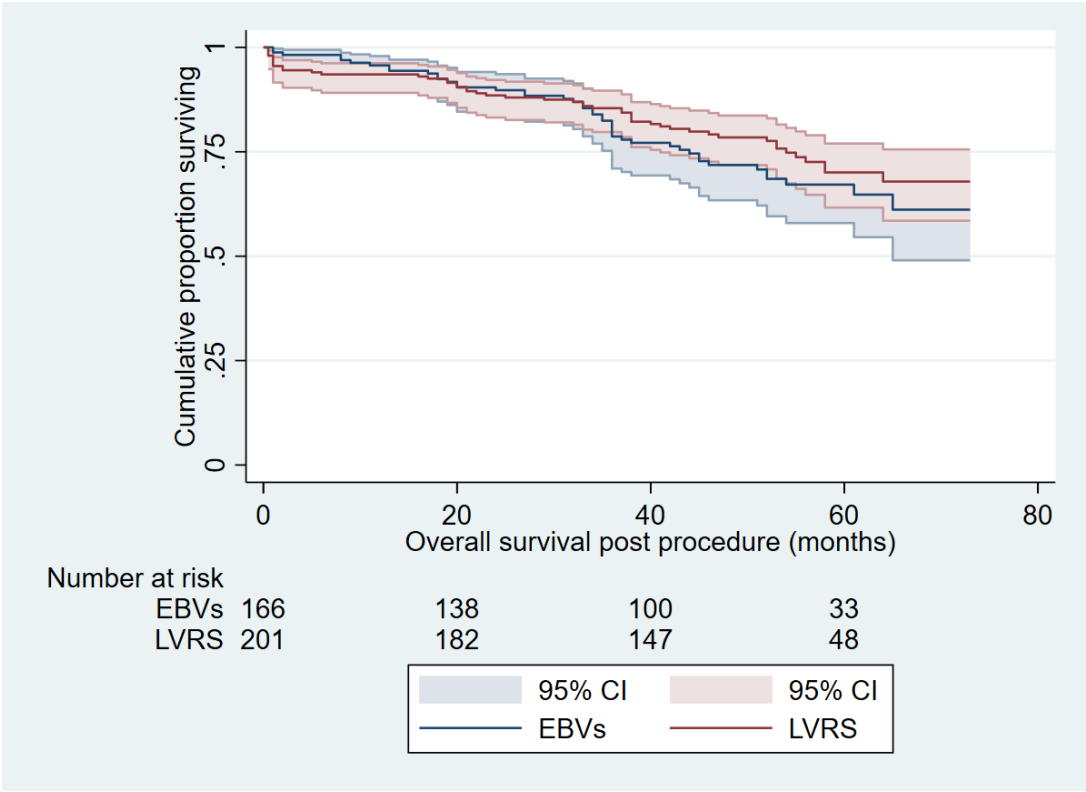
Australian observing differences in anaesthetic approach concluded that GA may offer preferable conditions for EBV placement for both patient comfort and length of procedure time (Thiruvenkatarajan 2018). Only 2 patients did not have a CXR post intervention recorded (0.9%). This is an important safety precaution that is recommended to screen for early post procedural pneumothorax (Slebos 2017; van Dijk 2021). 27(12.3%) patients were reported to have a post-procedure pneumothorax, 7(3.2%) of which occurred after hospital discharge.

The median(IQR) length of stay post procedure was unsurprisingly, significantly longer for those that received LVRS at 12 days compared to the 4 days for those who had EBVs (p=0.01).

6.4.5 **Outcomes post-procedure**

There were 95 deaths during the follow up period to February 2023; 50(10.8%) in the LVRS group, and 45(9.7%) following EBVs. Kaplan-Meier survival curves did not differ between the two groups (Figure 6.1) (Log rank=1.028, p=0.298) and unadjusted cox regression analysis showed no significant difference between the groups (HR:1.24 (95% CI 0.83-1.85, p=.301). Early post-procedural deaths (0-90 days) were numerically higher in the LVRS group (5.5% vs 1.8%) with four (1.6%) deaths during the perioperative (30 day) period following LVRS, and 7(2.9%) in the 31-90 days post procedure, and no periprocedural deaths in the EBV group but 3(1.4%) 30-90 days post procedure. But this difference was not statistically significant (p=0.068).

***Figure 6.1**: Survival following lung volume reduction procedures in UKLVR cohort*



Kaplan Meier survival analysis showing absolute survival between patients undergoing either LVRS or BLVR. The blue (LVRS) line shows significantly more deaths between 0-90 days compared to the red (BLVR) line. At around 20 month the two lines meet and then from around 20 months LVRS has a non-significant survival advantage.

In summary, there were significantly more early post-procedure deaths (0-90 days) in the LVRS arm compared to EBVs but at around 20 month the two lines on the Kaplan-Meier curve lines (Figure 6.1) meet and from this point the LVRS group have a non-significant survival advantage. The adjusted HR 1.30 95% 0.86 -1.98 p=0.216 showed no evidence that time modifies the treatment effect (Table 6.6). This statistical analysis would normally be presented with a median survival time. To calculate this at least 50% of subjects would have to have to be exposed to the risk (died). As this percentage was not reach a median survival time cannot be calcuated but 5-year survival was estimated to be 75% following LVRS and 73% following EBVs.

Next individual covariates were assessed for their association with survival and LVR treatment. The covariates that were shown to be associated with an increased risk for mortality in the univariate analysis were age, gender (being male was protective) and airflow obstruction (a higher FEV_1% predicted was protective). (age: 1.06 95%CI 1.03-1.09 p= =<0.001, gender: HR: 0.62 95%CI 0.40-0.96 p=0.032, FEV_1%: HR:0.98, 95%CI 0.96-0.99 p=0.003). However, the multivariate analysis showed that only age and FEV_1 remained significant model (age 1.07 95%CI 1.04-1.11 p=<0.001, FEV_1%HR: 0.97, 95%CI 0.96-0.99 p=0.002) (Table 6.6).

A further sensitivity analysis was carried out including two other important potential confounders- MRC dyspnoea score and exercise capacity. These were not included in the main analysis due to high percentage of missing data which may cause bias. The result of this analysis suggested that the level of patient reported breathlessness (MRC dyspnoea score) had a significant association with survival (Table 6.7) but this must be interpreted with caution due to the aforementioned issues.

Table 6.6: *Univariate and multivariable Cox- regression analysis investigating predictors of survival following LVR*

	Patients (n=367)	Unadjusted HR (95%CI)	P value	Adjusted HR (95% CI)	P value
Gender (male as reference)	349	0.62 (0.40-0.96)	0.032	0.81 (0.50-1.31)	0.393
Age	355	1.06 (1.03-1.09)	<0.001	1.07 (1.04-1.11)	=<0.001
Pattern of emphysema (homogeneous)	349	1.02 (0.65-1.60)	0.935	0.93 (0.59-1.49)	0.775
Fev_1%predicted	347	0.98(0.96-0.99)	0.003	0.97 (0.95-0.99)	0.003
RV% predicted	347	1.00 (1.00-1.00)	0.122	1.00 (1.00-1.01)	0.006
CAT score	348	1.00 (0.99-1.02)	0.738	1.01 (0.99-1.02)	0.620
BMI	347	0.99 (0.97-1.01)	0.157	0.98 (0.96-1.00)	0.092
Treatment arm (LVRS/BLVR)	367	1.24 (0.83-1.85)	0.216	1.10 (0.72-1.67)	0.661

Hazard ratios, 95% confidence intervals and p values estimated from univariable and multivariable cox models.

LVRS: Lung volume reduction surgery; EBVs: Endobronchial valves; BMI: body mass index; FEV_1: forced expiratory volume in 1 sec; RV: residual volume

Table 6.7: *Sensitivity analysis- Univariate and multivariable Cox- regression analysis*

	Patients (n=367)	**Unadjusted HR (95%CI)**	**p value**
MRC dyspnoea score	263	1.52(1.10-2.08)	0.010
Exercise capacity (6MWT/ISWT)	164	1.00 (1.00-1.00)	0.077

Sensitivity analysis- Univariate and multivariable Cox- regression analysis investigating predictors of survival following LVR with MRC dyspnoea and exercise capacity in models

Hazard ratios, 95% confidence intervals and p values estimated from univariable and multivariable cox models.

LVRS: Lung volume reduction surgery; EBVs: Endobronchial valves; BMI: body mass index; FEV_1: forced expiratory volume in 1 sec; RV: residual volume;6MWT: 6-minute walk test; ISWT: incremental shuttle walk test.

*for exercise capacity either 6MWT or ISWT was used depending on which one had been recorded for an individual

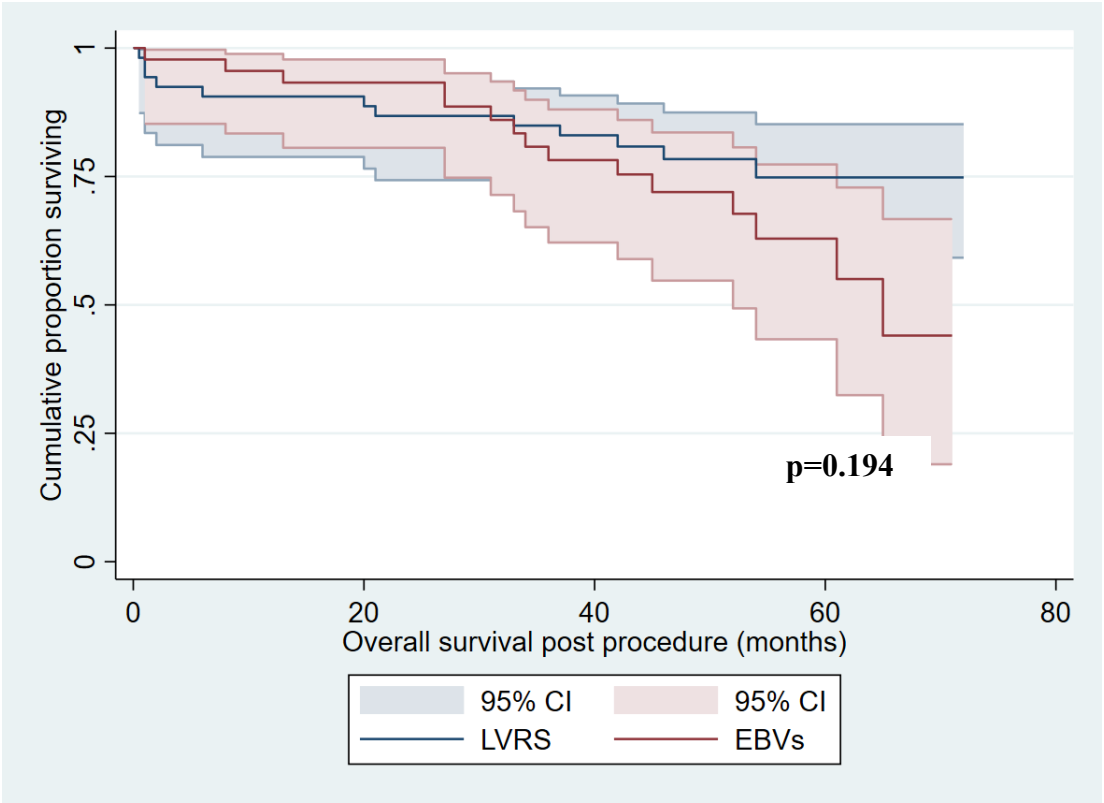
6.4.6 **Survival in patients with Homogeneous emphysema (sub-analysis)**

Among the 115 patients with homogeneous emphysema there were 27(23.5%) deaths in the follow up period; 12(20%) in the LVRS group and 15(27.3%) in the BLVR group (p=0.194). There was one perioperative death in the LVRS group and one in the 90-day post intervention period in the BLVR arm (Figure 6.2).

6.4.7 **Survival in patients with alpha-1 Antitrypsin deficiency (sub-analysis)**

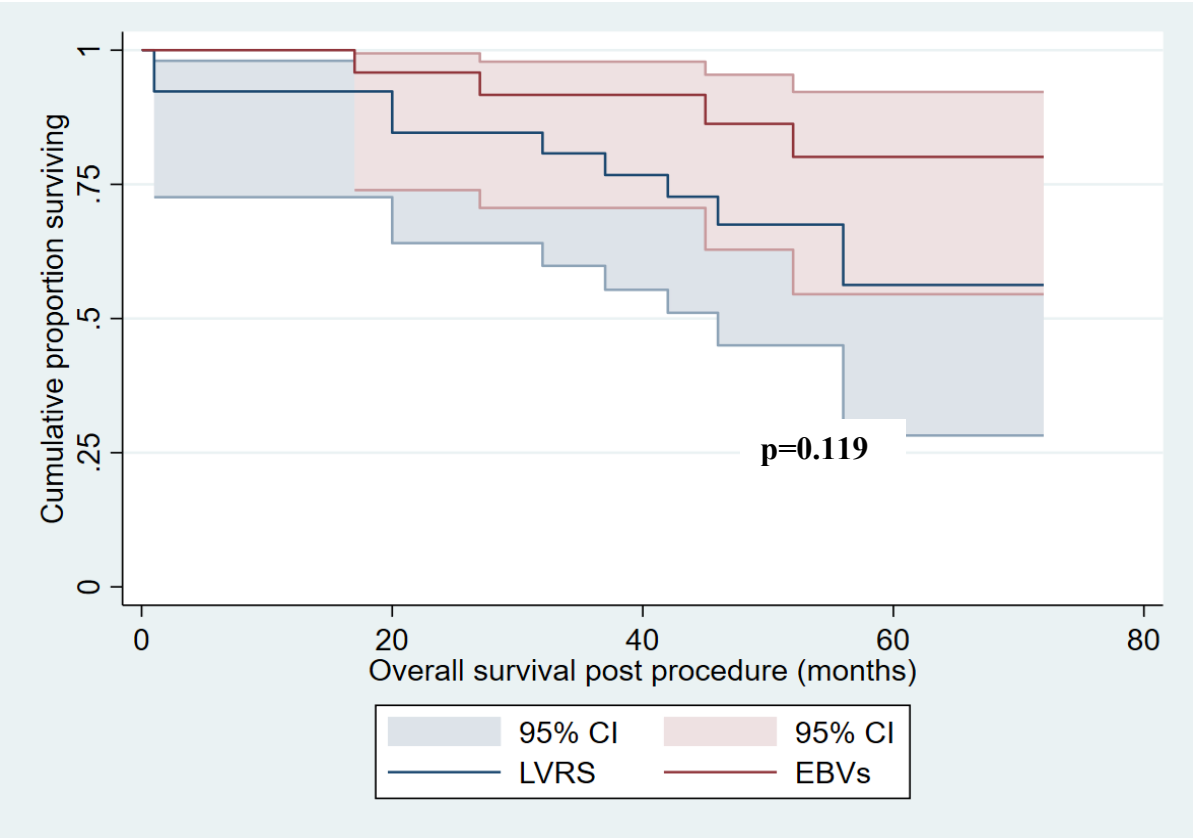
In 61 patients with an alpha-1 antitrypsin deficiency there were 12(17.4%) deaths in the follow-up period; 8(30.8%) in the LVRS group and 4(11.4%) in BLVR (p=0.119). One death following LVRS was in the 90-day post-operative period. The median survival time was 2.8 years following EBVs and 2.9 years following LVRS (Figure 6.3).

***Figure 6.2**: Survival following lung volume reduction procedures in patients with a homogeneous pattern of emphysema*



Kaplan Meier survival analysis showing absolute survival between patients with a) homogeneous pattern of undergoing either LVRS or BLVR.

***Figure 6.3**: Survival following lung volume reduction procedures in patients with alpha-1 antitrypsin deficiency*



Kaplan Meier survival analysis showing absolute survival between patients with alpha-1 antitrypsin deficiency, undergoing either LVRS or BLVR.

Follow-up data were entered in the register for 221/541(40.9%) participants. There were 136 follow ups entered between 0-3 months post procedure, 134 between 3 and 12 months, 40 between 12 and 24 months and 12 up to 36 months. Table 8 describes the complications recorded for each LVR treatment.

Table 6.8: *Complications following LVRS and BLVR*

Complication	Whole cohort (n=289)	LVRS (n=118)	EBV's (n=171)	p-value
Haemoptysis	12 (2.6)	0 (0)	12 (5.5)	0.002
Pneumonia	33 (7.1)	12 (4.9)	21 (12.3)	0.568
Pneumothorax	31 (6.7)	11(4.5)	20 (9.1)	0.518
Pneumothorax occurring after hospital discharge	9 (1.9)	3 (0.8)	8 (3.2)	0.534
Valve expiration, aspiration, or migration	10 (2.2)	n/a	10 (4.6)	n/a
Bronchospasm	1 (0.2)	0 (0)	1 (0.5)	1.000
Exacerbation of COPD	75 (16.2)	26 (10.7)	49 (22.4)	0.198
Post-operative pain	13 (2.8)	11 (4.5)	2 (0.9)	<0.001
Hospitalisations (up to 12 months post procedure)	42 people (12.5)/ 52 admissions	13 people (14.3)/ 17 admissions	29 people (22.3)/ 35 admissions	0.120
Hospitalisations requiring NIV (up to 12 months post procedure)	5 people (1.1) 7 NIV admissions	0 (0)	5 people (2.3)/ 7 admissions	0.059
Hospitalisations requiring intubation (up to 12 months post procedure)	6 (1.3)	1 (0.4)	5 (2.3)	0.215
Survival analysis	**Whole cohort (n=367)**	**LVRS (n=201)**	**EBV's (n=166)**	
Death	95 (25.9)	50 (24.9)	45 (27.1)	*0.298
Death within 0-90 days of procedure	14 (3.8)	11 (5.5)	3 (1.8)	0.068

Data are presented as n (%). LVRS: Lung volume reduction surgery; EBVs: Endobronchial valves; Post-operative pain defined as pain requiring medication more than one month after discharge from hospital. Perioperative defined as 0-30 days post procedure. Mortality was evaluated up to February 2023 in those undergoing a procedure between January 2017 and June 2022.

6.4.8 **Completeness of selection criteria**

According to the NICE guidelines, the basic recommendations for selecting patients who may be eligible for LVR include being a non-smoker, having at severe or very severe airflow obstruction (FEV_1<50%), dyspnoea that limits daily life, and a sufficient exercise capacity for the procedure to be undertaken safely (6MWD >140m or ISWT >80m). Therefore, to comply with best practice guidelines, all these data points should be recorded for every individual as part of their LVR assessment and therefore, every patient entered into the database. An assessment of proportions of missing data for the four criteria showed the following amount of missing data; FEV_1%predicted: 55(11.9%), smoking status: 89(19.2%), MRC dyspnoea score: 137(29.6%), ISWT or 6MWT: 257(55.5%). Although the mean of each of these four individual outcomes fit within the criteria thresholds that are recommended by NICE (NICE. 2018) 48(10.1%) of patients did not meet one of more of the NICE criteria. This is demonstrated in Table 9. Only 252(54.4%) of patients in the registry had an exercise capacity test recorded as part of their LVR assessment and a the 6MWT was more frequently used to assess exercise capacity than ISWT: 179(86.9%) 6MWT and 76(36.9%) ISWT, 3(0.6%) patients had both. The mean(SD) distance achieved on these tests was 280(102.6) m for the 6MWT and 244(117.8) m for the ISWT which translate into the same category on the BODE and i-BODE index. Of those patients with a walking test recorded 40(19.3%) were able to walk a distance that would put them at the least severe threshold on the BODE/i-BODE index; 5(7.1%) walking >350m on the 6MWT and 35(25.5%) walking >250m on the ISWT.

Table 6.9: *Compliance with NICE recommendation criteria*

		Whole cohort (n=463)			LVRS (n=244)			EBVs (n=219)	
	n (%) meeting NICE criteria	**n (%) Not meeting NICE criteria**	**n (%) missing criteria**	**n (%) meeting NICE criteria**	**n (%) Not meeting NICE criteria**	**n (%) missing criteria**	**n (%) meeting NICE criteria**	**n (%) Not meeting NICE criteria**	**n (%) missing criteria**
Smoking status	371 (80.1)	3 (0.6)	89 (19.2)	191 (78.3)	1 (0.4)	52 (21.3)	180 (82.2)	2 (0.9)	37 (16.9)
FEV1	432 (93.3)	26 (5.6)	55 (11.9)	227 (93.0)	14 (5.7)	27 (11.1)	205 (93.6)	12 (5.5)	28 (12.8)
MRC	303 (65.4)	23 (5.0)	137 (29.6)	161 (66.0)	14 (5.7)	69 (28.3)	142 (64.8)	9 (4.1)	68 (31.1)
Walking test	187 (40.4)	19 (4.1)	257 (55.5)	81 (33.2)	10 (4.1)	153 (62.7)	106 (48.4)	9 (4.1)	104 (47.5)
6MWT	56 (12.1)	14 (3.0)	393 (84.9)	33 (13.5)	9 (3.7)	202 (82.8)	23 (10.5)	5 (2.3)	191 (87.2)
ISWT	131 (28.3)	6 (1.3)	326 (70.4)	48 (19.7)	1 (0.4)	195 (79.9)	83 (37.9)	5 (2.3)	131 (59.8)

Data are presented as n (%) LVRS: Lung volume reduction surgery; EBVs: Endobronchial valves; NICE: National Insitite of Clinical Excellence; FEV_1: forced expiratory volume in 1 sec; MRC: medical research council; 6MWT: 6 minute walk test; ISWT: Incremental Shuttle Walk Test.

6.4.9 High risk patients

Characteristics of patients in the registry were compared against predictors of risk that are commonly used in LVR management, including the BODE/i-BODE index, the BFG score and FEV_1 % predicted/TLco <20%.

6.4.10 **BODE / i-BODE index**

Around 70% of patients fell within the 3-6-point category on the BODE/i-BODE index, which according to previous research would give a COPD patient on usual medical management a 57-67% 4-year survival rate. There which much smaller proportions (10%) in the category that would have an expected 80% survival which is appropriate given that these procedures are best suited to those with severe disease and are often considered palliative treatments. Given this, there were a substantial number (19%) in the highest risk category- those with an 18% survival risk over 4 years, if no intervention is undergone.

6.4.11 **BFG score**

There were no patients in this registry receiving an LVR treatment that would be considered 'high risk' when assessed against the Glenfield BFG score criteria. 39(12.5%) would be considered medium risk and 273(87.5%) low risk patients (Table 10). Broken down per individual criteria that make up the high-risk score, 151(48.4%) patients had an FEV_1 <0.71L, 22(7.1%) a BMI<18.5 5kg/m^2 and 26(8.3%) a TLco<20%.

6.4.12 **FEV_1 /TLCO<20% predicted**

4 patients (1.1%), 1 LVRS and 3 EBV (p=0.54), had both FEV_1 and TLco below 20% predicted.

Table 10 shows the risk data broken down per individual criteria that make up each of the risk scores, demonstrating that there was no significant difference between the two different treatments in terms of any of the risk predictors.

Table 6.10: *Risks associated to procedures carried out; 4-year survival rates based on BODE/i-BODE score, Glenfield BFG score, other important risk predictors*

Risk criteria	Number (%) all procedures (n=463)	Number (%) LVRS (n=244)	Number (%) EBV's (n=219)	P value
BODE/i-BODE index	(n=177)	(n=80)	(n=99)	
0-2 points (80% survival)	18 (10.12	8 (10.0)	10 (4.6)	0.95
3-4 points (67% survival)	59 (33.3)	27(33.8)	32 (32.3)	0.65
5-6 points (57% survival)	67 (37.9)	30 (37.5)	37 (37.4)	0.69
7-10 points (18% survival)	33 (18.6)	15 (18.8)	18 (18.2)	0.97
BFG score components	(n=132)	(n=163)	(n=149)	
FEV1 < 0.72	151 (48.4)	73 (44.8)	78 (52.3)	0.26
BMI <18.5	22 (7.1)	13 (8.0)	9 (6.0)	0.56
TLco <20%	26 (8.3)	11 (6.7)	15 (6.8)	0.40
BFG score	(n=312)	(n-163)	(n=149)	
High risk (4-5)	0 (0)	0 (0)	0 (0)	0 (0)
Medium risk (2-3)	39 (12.5)	20 (12.3)	19 (12.8)	0.95
Low risk (0-1)	273 (87.5)	143 (87.7)	130 (87.2)	0.95
FEV_1/TLCO	(n=359)	(n=190)	(n=169)	
FEV_1 and TLco <20% predicted	4 (1.1)	1 (0.5)	3 (1.8)	0.54

Data are presented as n (%). LVRS: Lung volume reduction surgery; EBVs: Endobronchial valves; BMI: body mass index FEV_1: forced expiratory volume in 1 second; TLco: transfer capacity of the lung

6.4.13 **Endobronchial coil (EBCs) data**

There were 112 EBC procedures in 65 cases. Median (IQR) LOS post EBCs was 2 days for the first treatment and 2 for the second treatment, giving a combined number of hospital days post procedure of 4 (2.3). An average of 10 (range 4-18) coils were placed in the first treatment received and 8 (range 4-18) in the second. A decision not to proceed to the second treatment was made in 18(28.6%) patients and the mean (SD) number of days between first and second treatment was 77(122). There were 25 deaths reported in participants receiving EBC's, none of which were within the perioperative period (0-30 days), but one occurred at 47 days post procedure. 2 patients experienced haemoptysis, 3 pneumonias, 4 bronchospasms and there were 19 COPD exacerbations in 10 people. There were 14 hospitalisations, and 1 further hospitalisation requiring intubation

6.5 Discussion

6.5.1 **Key findings**

The findings discussed in this chapter, analysing data from the UKLVR registry provide key insights into the standard of practice in the UK for LVR interventions, measured against national guidelines. The data show that compliance with these guidelines is high with the majority fitting NICE eligibility criteria and only a small proportion fitting criterion to be deemed high risk. Furthermore, most procedures are being carried out after being discussed by a specialist LVR MDT, a standard that has been endorsed by both NICE and in clinical commissioning recommendations. Other key findings were that those undergoing LVRS and EBV have similar characteristics at baseline, and that long-term survival does not differ between the two procedures. There were some gaps in data collection, in particular objective assessment of exercise capacity which may indicate an area for increased clinical resource. Results from this chapter showed substantial delays in the LVR pathway that was most marked in those undergoing LVRS. A lack of timely reassessment of lung function and imaging prior to procedure meant that unnecessary hold ups were faced that may be critical for some.

6.5.2 **Significance of findings**

As highlighted above, data showed patients that had been selected for either LVRS or EBV did not appear to differ in terms of disease severity. This supports previous research but is the first-time clinical data has been compared. EBVs are often thought of as the less risky procedure and therefore it may be assumed that those with more severe disease have a greater likelihood of being offered this treatment. However, these results do not support this and suggests that decisions between procedures are being based appropriately on the pattern of emphysema, the completeness of interlobar fissures and individual preference.

Results from this database of patients also support the perception that LVRS carries a greater short-term risk with 5.5% dying at 90 days post procedure in the LVRS group and 1.8% following EBVs. These results are comparable to previously reported safety data for LVRS (Weder 2009; Fishman 2001) and EBVs (Kemp 2017) . However, it is important to stress that overall survival longer term did not differ statistically, suggesting that once the immediate peri-operative period has been exceeded, higher risks do not extend into the medium to long term. The 5-year survival post-procedure for people entered into UKLVR was 75% following LVRS and 71% following EBVs. This is within the 63-78% range previously reported for LVRS(Thuppal 2021; Fujimoto 2002) and 75% for EBVs (Hartman 2019; Hartman 2022) in previous cohorts.

There was a longer length of stay following surgical intervention (LVRS 12 days vs EBV 4 days). Once again, this is an expected difference and in fact those receiving EBVs often remain in hospital longer than necessary as a safety precaution due to the risk of pneumothorax. If this precaution could be managed safely in the home, then bed days following EBVs could likely be decreased. The difference in LOS between the two treatments has important health economic implications when comparing LVR treatments and should be explored further.

The need for specialist MDTs and careful patient selection to ensure the best results from LVR procedures is widely acknowledged (Rathinam 2014; Chew 2018; Oey 2018; Hartman 2021). Similar multi-centre open label registries have been set up in Germany (Lung Emphysema - Registry (LE-R))(Lenga 2021) and the Netherlands (Bronchoscopic EmphysemA Treatment in THE NetherLands (BREATHE-NL) (ClinicalTrials.gov Identifier: NCT02815683) that also collect nationwide data on patients undergoing LVR procedures. Our registry data demonstrate that the majority of LVR cases were being considered by a specialist MDT and that patients receiving LVR treatments in the UK generally meet the NICE recommendations set out for selection (NICE. 2018) with only small amounts of missing data for these criteria.

Objective assessment of exercise capacity was the exception to this with over 50 % of data missing for this outcome. The registry is currently entirely voluntary, and this means the absence of clinical data points does not necessarily indicate that appropriate investigations were not conducted. This is an obvious limitation of the registry's function and emphasises the import of encouraging both the time and personnel to maintain registry information.

Long delays were observed between assessment, MDT discussion and procedures, particularly for those undergoing a surgical procedure. This may be because the COVID-19 pandemic added further pressures to surgical waiting lists although much of the data were collected prior to the pandemic.

One approach to this is consolidating the role of PR services in the LVR pathway(Buttery 2020). People meeting the basic eligibility criteria for LVR who still experience limiting breathlessness at the end of PR should be assessed systematically for suitability (presence of hyperinflation, emphysema on CT thorax and absence of exclusion criteria such as pulmonary fibrosis)(Hopkinson 2019; Buttery 2020). Specialist LVR services should also have capacity to perform all necessary investigations, to ensure that procedures are performed in a timely way. Of note, the period covered in the registry includes that of the COVID-19 pandemic and the inevitable disruption to clinical practice caused by this. It is well recognised that the pandemic has in some circumstances had a profound effect on surgical waiting lists, particularly for benign disease. This is a real cause for concern, especially when dealing with a cohort of patients where there is a limited therapeutic window for intervention before the risks associated with declining physiological status make these interventions impossible.

The patients in this registry had comparable baseline lung function measurements, regardless of intervention that are comparable to those seen in trial cohorts (Kemp 2017; Criner 2011b; Criner 2018). Nevertheless, these levels (particularly airflow obstruction and hyperinflation)

are substantially worse than those at which guidelines suggest LVR ought first to be considered. As discussed in the introduction to this chapter, timely referral is key in receiving an LVR intervention at the point that an individual will get the greatest benefit from the procedure. The findings from this study further support this thinking by highlighting the delays that may be encountered along the patient pathway. The severity of individuals undergoing these treatments may indicate that many suitable candidates are missing out on these treatments or indicate that people are waiting longer than necessary.

However, the majority of cases (>90%) were carried out in patients not considered to be at high risk, according to a range of criteria. Again, this may be due to delays in a referrals being made and previous research illustrates that individuals have had to 'fight to get a referral'(Buttery 2017). In addition, patients being discussed in a specialist MDT may require further work-up for a procedure to address multi-morbidity before finally determining their eligibility. Identifying and treating multimorbidity is the fifth of the Five Fundamentals of COPD Care set out by NICE guidance for COPD, but a significant proportion of COPD patients do not receive adequate attention to this (Cumella 2021; NICE. 2018).

6.5.3 **Methodological considerations**

The data presented here come from a network of specialist centres across the UK carrying out LVR procedures, and therefore the results can be generalised in a broad population and a variety of settings. The importance of real world trials investigating the effectiveness of interventions in clinical practice has been endorsed carried in pharmacological interventions (Vestbo 2016; Halpin, Worsley, 2021) but is equally important in establishing more novel non-

pharmacological such as LVR to explore their efficacy in heterogeneous populations (Arlett 2022; Cave 2019; Halpin 2023).

Observing a large number of LVR procedures within clinical practice confirms that patient selection criteria and outcomes post intervention are comparable to those seen in research trials. Furthermore, the results of this data analysis report on procedures that were carried out in all severity levels, rather than excluding higher risk patients as is often the case in clinical trials.

We do acknowledge several limitations. Firstly, it is possible that some errors exist in data entry. For example, some patients receiving treatments may not have been entered in the registry and therefore our results may not reflect the entire population of people receiving these treatments. Additionally, the database did not dictate that all data must be completed, therefore there was a large proportion of data entry that was incomplete which may bias our results. For example, when considering the proportion of patients that had been recorded as 'not discussed at an MDT meeting' it was evident that they were from centres that had discussed other patients at an established MDT, raising the possibility of a data entry error.

Secondly, although survival data were complete, limited amounts of follow-up data were entered, which may have led to an underestimate of adverse events post LVR. A more streamlined dataset, collecting only the most fundamental information to guide good practice should be considered going forward. The UKLVR data only includes those proceeding to an intervention and may not capture the full range of patients being discussed at MDT. An MDT-based audit registry rather than the current procedure-based approach should be implemented.

6.6 Conclusion

In summary, the UKLVR registry provides a database for recording all LVR procedures carried out across the UK. The results from this analysis confirm that procedures that are being carried out are generally being conducted in line with quality standards set out by NICE with only a

small number of high-risk cases being performed. Future research should focus on streamlining and standardising the LVR pathway and promoting routine long-term follow up and data collection of LVR procedures.

7 Integrating Pulmonary Rehabilitation into specialist COPD services: Developing a tool to aid decision making

This chapter was published in Chronic Respiratory Disease in 2023 (Buttery, Williams, Brighton, 2023).

7.1 Introduction:

This chapter explores the potential of developing a tool to support clinicians working in PR to operationalise the NICE 2019 COPD guidelines, recommending the systematic consideration of COPD patients completing PR for onward referral on the LVR pathway (Figure 3.1, chapter 3).

The work presented in this thesis has demonstrated the important role of LVR in COPD management but also the existing issues with accessibility. Chapter 3 particularly (Figure 3.2) highlighted the proportion of patients completing a PR programme that may be suitable for a respiratory review to investigate suitability for LVR intervention (up to 18.4%), and the mismatch with the estimated number of procedures carried out each year (Whittaker 2020). This initial step in the LVR patient pathway although endorsed by NICE is not routinely carried out across the UK. This is likely due to time-constraints of busy clinicians but also lack of clarity on which specific characteristics would indicate a referral may be appropriate and when and how a referral can be made(McNulty 2014). Consequently, referrals are often made too late meaning that a patient is outside the 'treatment window' and has deteriorated to a point where an intervention cannot be carried out safely. LVR interventions are best suited to patients with severe emphysema but are often contraindicated in those with very severe disease. Qualitative work looking at individual experience of LVR interventions found that patients had to 'fight for a referral'(Buttery 2017). Additionally, long waits on surgical waiting lists and for vital investigations have been demonstrated in this thesis (see chapter 6). Significant delays at all steps in the LVR patient pathway mean that eligible patients may miss out on these important treatments.

In 2019 NICE updated the COPD guidelines (Hopkinson 2019) and set out a recommendation for the routine consideration of patients completing a course of PR for onward referral for a respiratory review in a secondary care setting. The three step LVR pathway is discussed in

chapter three and a visual representation is shown in Figure 3.1 (chapter 3). To briefly recap, the first step, which this chapter is focussed on is at the point of PR completion when COPD patients should be systematically considered for onward referral onto the next step of the LVR pathway. The following steps are; Step two, following initial identification, at the completion of a PR programme the patient should be referred for a respiratory review in a secondary care setting. This specialist review will consist of further investigations, as necessary to assess for, severity of emphysema, hyperinflation, and a review of comorbidities. At this point it is also suggested that a discussion between the patient and clinician is entered to explore preferences. If criteria are met and no contraindications exist at this point, then a referral to a specialist LVR centre should be made (step three). During step three a decision will be made on the individuals eligibility for intervention, by a specialist LVR MDT. This will involve identification of a target lobe and method of LVR treatment and there will also be an assessment of fissure integrity, to determine if endobronchial valves are a viable treatment.

However, currently there are barriers to achieving the first step of this pathway. This is largely due to PR services in the UK being oversubscribed putting clinicians working in these programmes under pressure. Although this has been a historical problem and recognised in the NHS Long term plan and National PR audit (NHS 2019; NACAP) pressures have been worsened following the COVID-19 pandemic due to both a backlog of patients waiting for assessment and increased post COVID-19 infection referrals (Thornton 2020; Vallier 2023). Therefore, the process for systematically considering COPD patients accessing a PR programme needs to be straight-forward, methodical, and not put further burden on busy clinicians.

The aim of this chapter was to develop a decision-making support tool that could be feasibly embedded into PR programmes nationally, to facilitate the systematic consideration of people

with COPD for onward referral for a respiratory review of their suitability for LVR intervention, as recommended by NICE.

7.2 Methods

7.2.1 Study design and participants

This was a mixed-methods study using an iterative approach that was based on a modified-Delphi method. The Delphi process was originally developed as a structured survey-based research methodology with the objective of pulling together repeated individual responses via a survey, to reach unanimity on an issue where there is a lack of consensus (Thangaratinam 2005; Goodman 1987). This research method has been favoured as a means of bringing together key individuals to communicate ideas around a complex problem or topic and reach a solution, collectively (Manley 2013) and for this reason is often used in policy making (Turoff 1970). A key feature of a standard Delphi process is that it should involve at least three iterations of a survey (Santaguida 2018) (Hsu 2007). The modified method that has been used in this study was chosen due to the limitations of using only survey responses and no in-person meetings, largely the missed opportunity for deeper discussion and understanding of important topics. The modified Delphi approach allows the addition of face to face meetings enabling richer discussion around key concepts between stakeholders with differing viewpoints and experiences, mitigating the potential of a biased consensus (Murphy 1998).

There were four steps involved in the development process

1) Initial tool development via individual surveys
2) Stakeholder consultation group interviews and analysis
3) Assessing external and content validity
4) Piloting the tool.

A nominal group technique (NGT) was used to gain consensus on tool development using a partnership-based approach. The NGT combines qualitative and quantitative data collection, in a structured manner and whilst allowing consideration of many different perspectives

(patients, clinicians, service providers) manages to deal with some of the limitations that are associated with the Delphi technique such as the' focussing effect' where a single train of thought or perspective is followed and opposing or contrasting views are overlooked (Gallagher 1993). The NGT aims to encourage all stakeholders to voice their opinions and avoid only the most dominant characters controlling the direction of the development process. In this study the survey was used as a means of equally including views from clinicians at different levels and different specialities and discussion was only entered once the main domains had been decided. It was important that during these stakeholder groups there was not one person dominating or influencing the discussion and that all members of the group had equal input. We ran clinician and patient groups separately to avoid dominance of the 'expert view'. The NGT has been used in policy making and guideline development (Murphy 1998; Gallagher 1993) and its principles were also fitting for developing a decision-making tool such as this one.

To avoid any further bias based on allowing my own perspectives to take precedence, a partnership-based approach to development was adopted (O'Cathain 2019; O'Cathain 2019). This allowed equal influence of my ideas, other researchers, clinicians, and members of the public to make decisions.

Each step was planned and guided by the 6SQuID development framework. This framework was intended to provide a pragmatic but systematic way of approaching the process of developing an effective intervention that is based around six steps (Wight 2016). The first step involves identifying the problem and what the issues around it may be. This step was established in the early stages of this work and introduced in chapter 3. Steps two and three deal with identifying the factors that can be addressed or changed and the mechanisms of doing this. Again, this was preliminary work conducted as the basis of this study and is discussed in the background section of this chapter. Steps four, five and six form the basis of the

development process of this tool and involve; clarifying how the tool may best be delivered as well as any barriers, testing and adapting the intervention as necessary and finally, collecting evidence of the effectiveness of the intervention. These steps will be discussed in more detail in the contents of this chapter and referred to as steps 1-4.

Although this framework was designed for developing healthcare interventions and this is not categorically an 'intervention,' following a planned and structured framework should improve the uptake of such a tool by ensuring key concepts are addressed, such as feasibility, acceptability and fidelity (Klaic 2022). The importance of frameworks in developing complex healthcare interventions is acknowledged in guidance from the National Institute of Health Research (NIHR) and Medical Research Council (Skivington 2021), to maximise and improve the efficiency of research (Skivington 2021). The 6SQuID framework was chosen for this project as although this work does not specifically involve the development of a complex intervention, rather a component of one, this framework has wider applicability and employs a pragmatic approach.

The clinicians and members of the public involved in the development process were recruited based on purposive sampling in order to select specific individuals who may be more suitable for the objective of the task based on characteristics such as experience, expertise or credentials (Palinkas 2015). This sampling method was chosen due to the specialist subject of interest for this group and the qualitative methodologies used. Purposeful selection is more commonly associated with qualitative techniques whereas quantitative analysis typically uses randomised sampling (Patton 1990).

7.2.2 **Development process**

Step 1: Expert survey

An online survey was conducted via SurveyMonkey (Momentive Inc, San Mateo, California, USA). The survey can be found in Appendix 6 and includes both open and closed questions to collect qualitative and quantitative data based on a scoping review of the literature and existing COPD and LVR guidelines that the survey included questions about professional identity, confidence in identifying patients for LVR, involvement in an MDT and/or PR programme, and views on the necessity of certain measures being included in a decision-making tool. The purpose of the survey was to gain an understanding of the demographics of respondents and fundamentally to collect a preliminary consensus on the most important domains that should be included on a decision-making tool. The information gathered from this survey would also be used to inform the next step of the development process.

Clinical stakeholders from across the UK, were identified and invited to take part in the survey via an email explaining the current clinical problem, the purpose of the survey, and how their responses would be used. A variety of specialists including respiratory physicians, thoracic surgeons, specialist respiratory physiotherapists, interventionists, and specialist nurses were recruited if they; (i) had been involved in the CELEB trial (chapter 4) (Buttery. 2023), (ii) if they were part of a clinical service participating in the King's Health Partners transformation project, (iii) if they were known to the research team as a clinical stakeholder in either an LVR or PR service.

The quantitative analysis of closed ended questions asked in the survey, converted responses into numerical values (n %) to allow trends to be identified. The final question of the survey was open and allowed free text. This was included to encourage individual views to be expressed and to begin to explore concepts at a deeper level. Each comment was considered on

an individual basis by myself and a second researcher (NSH) and along with the quantitative data were used to inform the preliminary working outline of the LVR-PR tool

Step 2: Stakeholder consultations

Step two of the development process was incorporated to gain a richer understanding of the themes around developing the proposed tool from a diverse group of stakeholders. Groups that encouraged free thought and dialogue using semi-structured interviews and informal discussion were set up to define individual item saliency and explore barriers associated with implementing such a tool.

i) Clinical focus group

A clinical stakeholder focus group was set up inviting, via email individuals who would either be responsible for completing the tool at the end of a course of PR or would need to be familiar with using it. The format of this group was a brief introduction from the group chair explaining the purpose of the meeting and ground rules, introductions from all present and a presentation of the preliminary working tool followed by a semi-structured interview lead by the meeting moderator. The semi-structured interview was intended to facilitate discussion between participants, focussing on feasibility and usability of the tool and any barriers or extra training they felt might be required. The content of this meeting was informed by the quantitative and qualitative data collected from the survey in step 1.

I moderated the clinician focus group based on previous experience in running focus groups and qualitative research. Paraphrased field notes and transcription was carried out by PW (clinical academic), who also has experience in qualitative research methods. The chair for this group was NSH (professor of respiratory medicine), an expert clinician in this field with experience in qualitative research methods including conducting focus groups.

Paraphrased transcription of recorded meetings was carried out immediately after, and recordings were then destroyed.

ii) Patient and public involvement

A second stakeholder meeting was conducted to capture the view of the patients that may be affected by implementing such a tool. This meeting was set up as a patient and public involvement and engagement (PPIE) event using a purposive sampling of members of the public that were already part of an existing Pulmonary Rehabilitation Public Involvement Group. It was thought that purposefully selecting or recruiting a group that had COPD and prior experience of the PR environment would allow a greater understanding of the issues that might be encountered and a deeper exploration of their personal feelings in this context. Members of this group were invited via email and attended an online Microsoft Teams meeting that was moderated by LB (postgraduate researcher), an expert in PPIE with specialist interests in online PPIE forums. I acted as chair for this meeting and as was the case in the previous stakeholder meeting, PW collected paraphrased transcriptions. No recordings or direct quotes were taken from this meeting, but verbal consent was obtained for the reporting of the general themes discussed.

During this meeting members of the public involved in the PPIE group were shown and asked for comment on the online text and video recorded resources that have been developed as part of this project in partnership with Asthma + Lung UK. Printable educational resources and digital resources can be accessed online at the link provided in Appendix 9.

Issues raised in the clinical focus group were used to influence further informal discussion during the PPIE group. The outline of the PPIE meeting can be seen in Appendix 8.

There were no pre-established relationships between any members of the research team or the PPIE group but there were professional relationships between some members of the clinical

focus group and researchers. Reimbursement for time was available for members of the PPIE group.

Those involved in stakeholder groups were briefed on the purpose of the group prior to attending as well as being sent a copy of the tool, to allow thought and ideas to be formulated individually before being influenced by other participants.

A thematic analysis framework based on content analysis, was followed for evaluation of the clinician focus group. This process involves data collection, familiarisation of the data and then drawing themes. Familiarisation of the data was carried out through both individual study and then group discussion and this is where themes were drawn, as a group. Reporting of the results of the focus group was done in accordance with the CORE-Q guidelines for qualitative research (Tong 2007).

No explicit consent was taken for the collection or reporting of direct quotes or recording of the PPIE meeting. Therefore, only the themes derived from informal discussion are presented. In contrast to the more systematic focus group evaluation that is based around thematic analysis (Hoddinott 2018) reporting of the findings from the PPIE group will follow the Guidance for Reporting Involvement of Patients and the Public Short Form (GRIPP2-SF) (Staniszewska 2017).

Step 3: Assessing validity

The third step in the development process was dedicated to evaluating the validity of implementing the tool in a clinical setting. Two types of validity were tested; face validity and content validity.

Face validity was investigated to explore the degree to which the LVR PR tool and each component of it, achieves what it is set out to based purely on its face value (Roy 2023; Bolarinwa 2015) (i.e. can be used in a clinical environment to identify suitable patients for

onward referral). This type of validity was evaluated in several stages. First the tool was sent to members of four PR services within London, all part of the Kings Health Partnership transformation programme (Royal Brompton Hospital, Harefield Hospital, Kings College Hospital and Guys and St Thomas' Hospital). Clinicians at these sites were asked to comment on the tool in terms of feasibility of using the tool in their specific service and any more general perceived issues.

Secondly, the tool was presented at two meetings that had been specifically set up with PR services in different geographical locations to discuss the LVR PR tool and gain qualitative feedback. These meetings were conducted at PR centres that had not been used in any previous stages of the tool development. Finally, discussion at a regional West Midlands specialist LVR meeting was used for further feedback. These steps were intended to ensure the utility of the tool within variable settings, for example community and hospital-based PR programmes. As no consent was taken at these meetings only the key points from general discussion have been presented, rather than direct quotes. A list of PR centres that were consulted during this process can be found in Appendix 7.

To assess content validity two clinicians from each centre involved in the KHP transformation programme, who were involved in the PR service at their site but had not been involved in any previous stage of the development process were asked to rate it using the Content Validity Index (CVI) questionnaire. Content validity was investigated to assess if the tool represents all aspects of the process of considering a patient for onward referral on the LVR pathway, within a PR setting. The CVI tool was selected to assess content validity based on it being the most widely used index when evaluating a tool using a quantitative method (Shi 2012) and also due to its previous use in the development of a clinical tool by Corner et al (Corner 2013).Those individuals that were asked to rate the tool using the CVI were sent an email with detailed instructions of the purpose of the exercise, including a background to the development of the

LVR PR tool and also how rating should be conducted. Briefly, they were asked to score each individual item using a four-point scale (not relevant, item needs some revision, relevant, very relevant) and it was stressed that scoring was to be carried out individually without group deliberation or discussion. Scores collected from each individual were then used to calculate an I-CVI score (validity of each individual item included in the tool) and an S-CVI score (an overall scale validity score) and a mean of these scores would be calculated to determine the overall CV of the tool. An I-CIV score of ≥0.78 is considered indicative of agreement that the individual item is valid for inclusion and a S-CVI of ≥0.80 suggests that the tool under assessment can be deemed valid and all items are relevant for inclusion (Polit 2006).

Step 4: Piloting the tool

Between December 2021 and December 2022, the tool was piloted at the 4 hospitals in London that had been involved in the development process (Royal Brompton Hospital, Harefield Hospital, Kings College Hospital and Guys and St Thomas' Hospital). This step was intended to practically assess its feasibility in a clinical environment and detect any limitations that had not been picked up in previous stages of the development process. PR programme leads at these centres were asked to consider every patient at discharge from PR, against the basic criteria on the final version of the LVR tool. Originally all sites were asked to collect anonymised data on whether a patient fit the criteria and a standardised spreadsheet was circulated that would allow clinicians to categorise patients as either having completed PR and may be a suitable candidate, did not complete PR but may be a suitable candidate, or is not a suitable candidate. The intention was to find out whether it would be possible to match every patient accessing a PR programme to one of these categories, in an efficient manner. However, there were interruptions in some of the PR services involved in this study caused by the COVID-19

pandemic which meant changes in the delivery of their services. Therefore, no patient outcome data were collected during this step, only comments on the clinician's opinion and experience of using the tool as a decision-making aid, alongside the educational resources that had been developed as part of this study. As with other steps all comments were considered on an individual basis by the project team (SB, PW and NSH) and changes were implemented as appropriate.

7.3 Results

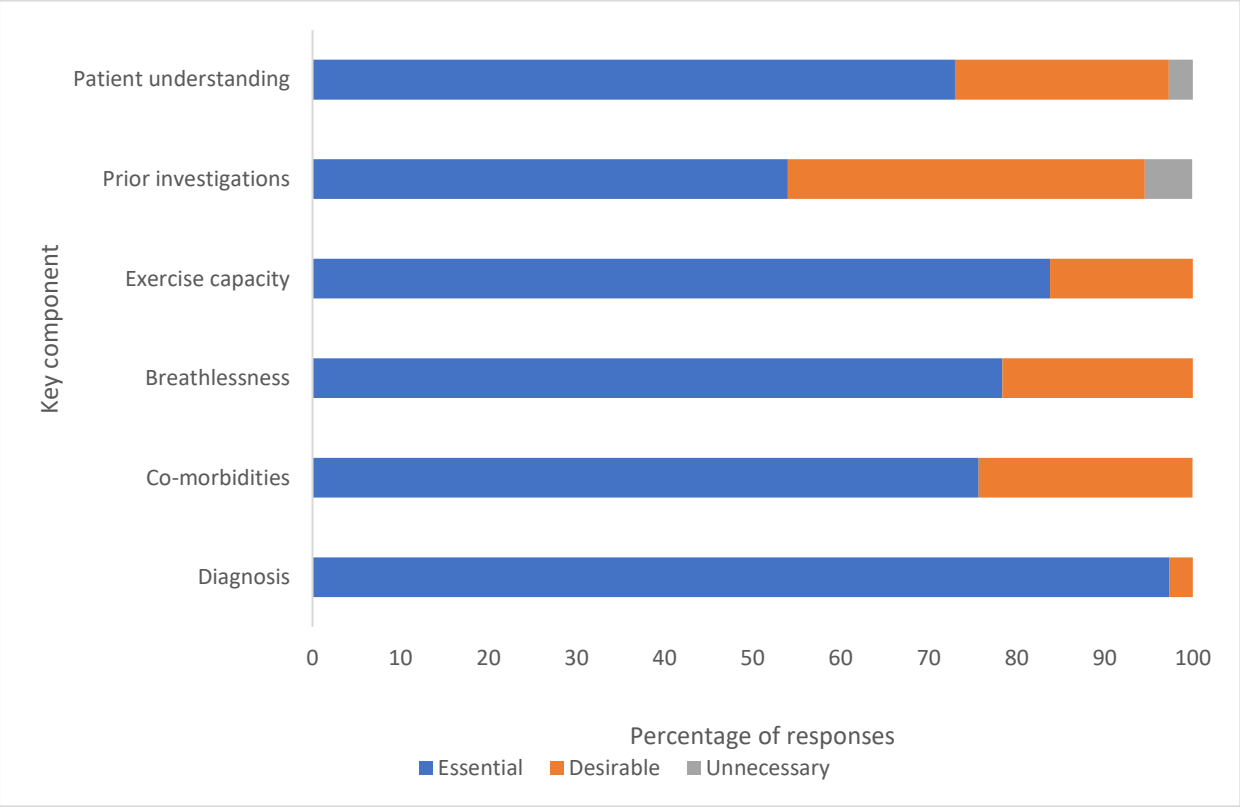
The expert survey was sent out to 40 clinicians on 23rd June 2020. 37 of the 40 clinicians (92.5%) responded to the online survey and this consisted of 13 consultant physicians, 9 consultant surgeons, 12 respiratory specialist physiotherapists, 1 specialist respiratory nurses and 1 specialist trainee in lung intervention. Although the survey was anonymous basic demographic characteristics were collected and showed that 51.4% of respondents were female and the majority (73%) within the 35-54 years age bracket (13 (35% 35-44 years and 14 (38% 45-54 years). Among the respondents only 60% reported being involved in an LVR MDT and 51.4% directly involved in a PR programme. Of this proportion, 37.8% were involved in the PR referral process which may have meant making patient referrals to PR, and the remaining 10.8% represented those clinicians that would receive LVR-PR outcome referrals. Therefore, there was representation from all important stakeholders in step one of the LVR patient pathway.

When asking how confident responders felt in identifying patients who might be suitable for LVR (0=not confident at all. 10= very confident), the mean response was 6.2 with a range between 1 and 10. This shows that there was not a selection bias of only those with a very

specialist interested in LVR or a than average higher baseline knowledge compared to the typical clinician that would be a potential user of such a tool in the future.

Respondents were then asked to rate perceived importance of six key components that had been informed by literature/guidelines in LVR assessment. Participants could answer either ‘essential’, ‘desirable’ or ‘unnecessary’ and all respondents provided a rating for all six components. Figure 7.1 describes responses to this.

Figure 7.1: Key components of a LVR-PR decision support tool



Key components suggested and rated by survey responders. Blue=criteria regarded as essential, orange= criteria regarded as desirable, grey= criteria regarded as unnecessary.

Diagnosis was unsurprisingly voted as the most important of the components with 97% rating it essential. Exercise capacity, breathlessness and comorbidities were also considered essential by most respondents- 84%, 78% and 76%, respectively. Patient understanding was considered of lower priority with 72% rating it essential and prior investigations was thought to be of lowest significance with 54% voting it essential while 5% felt it was unnecessary. Only the prior investigations (5.4%) and patient understanding (2.7%) domains received votes for being 'unnecessary'.

Below, the comments that were collected from the open question in the survey are summarised and presented in Table 1. The comments are grouped by common topics and were then taken forward to either inform the preliminary working tool or plan further exploration in the stakeholder groups. This included concerns raised around; the upskilling of PR healthcare professionals in LVR education, issues relating to implementation of the tool in clinical practice, increased referrals to secondary care and increasing workload for PR services.

Table 7.1; Comments from open ended survey questions

Domain	Responder feedback
Further suggestions for inclusion in an LVR decision making tool	Exacerbation frequency/sputum; optimisation of management; smoking history/ smoking status/smoking cessation; BMI; substance misuse; lung volumes; previous interventions; patient motivation; oxygen saturations/ ABG's; up to date CT scan.
Agreement on need for a tool	'If there are clear criteria it seems like a sensible approach' 'Should be routine part of discharge assessment' 'This is how we initially wanted to target patients when starting our MDT.'
Concern over increased referrals to secondary care	'need to be clear pathways to a specialist clinic for investigation, discussion and selection. A good tool I think therefore would be expected to screen out those clearly unsuitable, and the screening out should be reliable. Those screened in will include a significant number of people ultimately not suitable for LVRS after further testing.' 'Need to ensure that the capacity for timely review in secondary care exists right from the initiation of any tool, otherwise engagement in the process will be low' 'It may well create unprecedented demand!'
Concern over increased workload for PR services	'The work needs to be easy for the rehab team itself and easy to encompass as part of final assessment process, but is likely to create workload for selection clinics, in excess of the increased procedures'
Concern over raising sensitive topics with patients	'Advanced procedures are emotive for patients- potential for a quick and potentially life changing 'fix'. However, as we know benefit depends on accurate patient selection. The initial conversation is key to manage expectations and to be clear that teams do procedures that are likely to benefit patients' 'Change of focus, from self-management to interventions'
Need for further training/educational resources	'Never had any training or information on this so would need some!' 'little plain English summaries of available LVR procedures exist for HCPs and/or patients' 'If the tool was virtual, perhaps a video explanation may be of great value.'

7.3.1 **Stakeholder consultation groups**

Focus group one was attended by 12 clinical stakeholders working in PR programmes and part of the King's Health Partners Transformation programme. This group included 5 band 8 and 2 band 7 physiotherapists, 2 exercise practitioners, 1 band 7 clinical nurse specialist, 1 reader in rehabilitation and 1 professor of respiratory medicine. The main take away discussion points from this meeting were; streamlining the tool to ensure it could feasibly be implemented and accepted in busy PR environments; access (or lack of) to clinical information and investigations, and issues around introducing LVR therapies to patients in a PR setting (Table 2). This final discussion point was raised with clinicians having concerns around the sensitivity required in broaching a potential treatment that can often be thought of as a life changing or 'last resort' treatment, to a group of patients, most of whom will not go on to fit the specific selection criteria.

The take away points from this group were in keeping with the results from the survey and were used for further development of the tool and in preparing for the second patient focus group.

Table 7.2: *Focus group one summary*

Theme	Qualitative comments	How addressed
• *Streamlining the tool*	"Everything there we would normally capture and that would probably be across the board, most of this is covered in our assessment and I assume that is the same with everybody else" (physiotherapist).	None required
	"It's not a massive amount of patients to have to refer back, based on the evidence up to around 20%, so 1 in 5" (physiotherapist).	None required
	"If this is going to be used nationwide, then the information required needs to be really simple. So, for example making sections very specific and using tick boxes" (physiotherapist).	Each domain split into specific sections with specific information required added to 'notes' column.
	"If the tools purpose is to consider individuals and for most people they won't be eligible based on the literature, then the ordering should be based on the things that are going to quickly exclude people based on what we know for that population" (reader in rehabilitation).	Ordering of tool amended to screen out patients more efficiently.
	"Should there be some information for the original referrer on what to do next" (exercise practitioner).	Sentence added to the bottom of table 2 (LVR-PR tool).
	"If we can get more simplicity on what are the key inclusion criteria or the key discriminators on what can identify this early" (physiotherapist).	Addressed in identifying key domains.
	"better off having a smaller number of things to tick off" (exercise practitioner).	

		Section on previous investigations scaled down and two sections categorised as desirable rather than essential.
• *issues around introducing LVR therapies to patients in a PR setting.*	"Are the clinicians aware of the procedures and how they would have this conversation with their patients?" (nurse practitioner). "I have a concern on how the patient will interpret the information that is sometimes complicated. We have some examples of Patients that have been very frustrated about why the treatments are not for them and why they are not suitable for the pathway" (physiotherapist). "We used to have LVR in one of our education sessions but we actually removed it from our general education because most people we were talking to weren't eligible for it and yet we were sort of teasing them with what treatments might have been available if they were ten years younger". (physiotherapist). "Currently this is done very ad hoc and very individual to the patient. Usually it is sparked by them asking us if we have any in depth conversation. It's not something we go into at very great depth with any of our patients, at the moment" (physiotherapist). "The level of staff- You may have band six and potentially band fives seeing these patients, so we need to cover all boundaries" (physiotherapist). "It would be a significant add on to an assessment time to have an in-depth conversation. I think it would be better to raise it and give a leaflet that the patient can then read themselves" (physiotherapist).	Development of educational resources for clinicians. Development of quality educational resources for both clinician and patient. PPPIE group suggest that more information on potential treatment options is desirable. Therefore, brief interventions suggested alongside signposting. Guidance on introducing to patient and signposting (resources developed). Upskilling of workforce to provide baseline knowledge of LVR procedures to all working in PR services.

	"It requires the right environment, the right conversation and the patient to reflect upon the information given to them so we really need to consider how it is delivered" (physiotherapist).	Brief introduction and signposting recommended within the too
• *access to clinical information and investigations*	"We don't always get the information on whether patients have had echo's or CT scans done, only if referral has come from a consultant. GP or respiratory nurse referrals would not have this information, without digging around and having to get back in touch with a referrer. Unless it would be acceptable to ask the patient?" (physiotherapist). "if the rehab professional has to collect information on CT scans and all that then they will need to have that document prepped almost before they see them at the post rehab assessment" (physiotherapist).	Investigation information downgraded to desirable rather than essential and space to just tick if has been done and/or add further detail if available. As above. Now not essential for referral to avoid unnecessary burden on PR services.

Consultation group two was attended by 10 patients (5 female/5 male), all of whom were members of the Pulmonary Rehabilitation Public Involvement Group. All members of the public were retired and had been through at least one course of PR. Two attendees had completed more than one course. Two of the group had been considered for an LVR procedure and one had undergone a procedure. This diversity provided important contribution from stakeholders that had experience of being introduced to LVR therapies and those that did not. The key points that arose from this meeting were the need for clearer information on LVR procedures for patients, the clinician's role in considering eligibility, and how educational resources should be delivered. Comments from this group were used in conjunction with focus group one, to understand the importance of how information is delivered and will also be used to further develop current educational resources. For example, members of this group indicated a preference for a question and answer style interview approach to the video resource that makes greater used of visual aids.

Difference in opinions between the two stakeholder groups on how the sensitive topic of LVR therapies are introduced and discussed with patients, within a PR environment was used to inform the 'patient' domain of the tool. It was decided that clinicians should not be involved in in-depth conversations or decisions around patient preferences. Instead, they could provide a very brief introduction to patients, requiring only a baseline knowledge of the interventions, and then direct them to additional written or online resources. For this to be effective, it was agreed that quality information would need to be available to signpost patients to and therefore patient resources were refined and included as part of this tool (Table S1). The need for a nationwide training programme was also raised. Although this was outside of the scope of this project this is something that should be considered in the implementation phase of this tool.

7.3.2 Assessing feasibility and validity of the tool

Of the 14 centres that were asked for comment on the tool, all felt that it could feasibly be implemented into their service and that the information needed to complete the tool was already routinely collected as part of their assessment process. This was with the exception of the 'prior investigations component' where there was significant discussion and disparity around the ability of services to collect information to complete this section.' Some clinicians were of the opinion that collecting information on previous CT scans, lung function tests etc was feasible, some thought this would require a great deal of work and whilst others thought that it was unachievable. Eventually consensus was achieved, and it was agreed that the guidelines for this section should include more clarification around which investigations and what timelines were important, and that this should not be a compulsory part of the tool. This would mean that there would be less likelihood for clinicians to completely skip the identification process due to it being a timely task.

On the whole professionals felt comfortable to introduce the tool to patients as part of their educational programme and signpost them to additional educational online resources or provide them with an Asthma + Lung UK leaflet. Clinician educational resources from Asthma + Lung UK were welcomed by those who lacked confidence in their baseline LVR knowledge. Although comments collected were generally supportive of the tool's feasibility, further suggestions collected at this point have been collated in Table 7.3 along with additional comments collected at stage 4.

The results from the content validity assessment showed that the LVR decision making tool had an S-CVI score of 0.95 and that each individual item achieved a score of 0.78 or greater. This suggests that the tool can be considered valid and that no individual items needed deleting or revising at this point (Table 3).

Table 7.3: *Content Validity Index data*

Item	Rate r1	Rate r2	Rate r3	Rate r4	Rate r5	Rate r6	Rate r7	Rate r8	Rate r9	(n) in agreement	Item CVI (I-CVI)
1	**3**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**9**	**1.00**
2	**3**	**4**	**4**	**4**	**2**	**4**	**4**	**4**	**4**	**8**	**0.89**
3	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**9**	**1.00**
4	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**9**	**1.00**
5	**2**	**2**	**4**	**3**	**3**	**4**	**4**	**4**	**4**	**7**	**0.78**
6	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**9**	**1.00**
Mean CVI											**0.95**

CVI: Content Validity Index; Agreement = rating an item as either relevant or very relevant.

Item: 1=Diagnosis; 2= Comorbidities; 3= Breathlessness; 4=Exercise capacity; 5= Prior investigations; 6= Patient

Item CVI: 1=not relevant, 2= item needs some revision, 3= relevant, 4=very

Table 7.4: The Lung Volume Reduction Pulmonary Rehabilitation tool (final version)

	Referral consideration	When	Notes
Diagnosis:	Do they have COPD?		
	Is FEV_1 ≤50% predicted	Assess at beginning or obtain data.	**FEV_1(l): FEV_1 % pred:**
	Smoking status	Assess at beginning (and end)	
Breathlessness	MRC dyspnoea score	Assess at end**Consider criteria to flag as possible at baseline? MRC 4 or 5*	**MRC score:**
Exercise capacity	Walking distance	Assess at end **Consider criteria to flag as possible at baseline <300m?*	**ISWT:** **6MWT:**
Patient	Has the patient been introduced to LVR? □ Asthma+Lung UK resource/leaflet provided	Ask at baseline **Consider criteria to flag as possible at baseline?*	
Comorbidities	Do they have a condition that limits survival or ability to benefit from LVR?	Assess at beginning or during programme	**Malignancy** **Frailty** **Severe heart failure**
Prior investigations **(only if available)**	Have they had a CT scan? (ask patient)	When and where was it performed?	
	Have they had detailed lung function? (ask patient)	When and where was it performed?	
	Have they had an echo? (ask patient)	When and where was it performed?	

Please tick or copy and paste one statement from below into your discharge summary and attach any relevant notes.

Green = essential consideration criteria, Red= desirable consideration criteria

Table 7.5: The Lung Volume Reduction Pulmonary Rehabilitation (LVR-PR) text

☐ This person has completed PR – **based on NICE criteria they are sufficiently limited by breathlessness to be considered for a respiratory review to see whether a lung volume reduction procedure might be beneficial.**

- Formal diagnosis of COPD
- FEV_1 ‹50%
- MRC ›3
- 6MWD ›140m or ISWT ›80m
- Not a current smoker
- They do not fall outside the established safety criteria and do not appear to have any major co-morbidities that would mean that they are not likely to be suitable.
- LVR therapies have been discussed with the patient in broad terms and they have been given the BLF leaflet Lung volume reduction procedures for emphysema
- They report they have had a CT scan of their chest previously Y/N/DK
  - If Y when and where or NK
- They report they have had lung volumes measured (body box) previously Y/N/DK
  - If Y when and where or NK
- They report they have had an echo previously Y/N/DK
  - If Y when and where or NK

☐ This person has not completed PR but may be suitable for LVR referral based on baseline assessment- **based on NICE criteria they are sufficiently limited by breathlessness to be considered for a respiratory review to see whether a lung volume reduction procedure might be beneficial.**

- Formal diagnosis of COPD
- FEV_1 ‹50%
- MRC ›3
- They do not fall outside the established safety criteria and do not appear to have any major co-morbidities that would mean that they are not likely to be suitable.
- Not a current smoker
- LVR therapies have/have not been discussed with the patient.
- They report they have had a CT scan of their chest previously Y/N/DK

- If Y when and where or NK
- They report they have had lung volumes measured (body box) previously Y/N/DK
  - If Y when and where or NK
- They report they have had an echo previously Y/N/DK
  - If Y when and where or NK

☐ This person does not meet the criteria to be considered for a respiratory review to see whether a lung volume reduction procedure might be beneficial (tick all that apply)

- No formal diagnosis of COPD
- $FEV_1 > 50\%$
- MRC < 3
- Their exercise capacity is too limited for a procedure to be undertaken safely
- They are a current smoker

Table 7.6: *Final qualitative comments from clinicians piloting the LVR PR tool*

Key component	**comment**	**How the comment was addressed**
1. Diagnosis	Assumes the PR physiotherapist would know that the diagnosis requires obstructed spirometry (i.e. obstructed FEV1/FVC) I think this specific point should be included for clarity (e.g. ratio ‹ 0.7). Does the diagnosis only specify COPD, or do we include ACOS/ FEV ‹50%? Most lung functions collected are over 1 year old – does this matter?	Further detail added to diagnosis section to collect FEV_1% predicted (‹505) and FVC. If FEV_1% predicted is ‹50% a patient may still be deemed eligible, regardless of when the measure was taken.
2. Breathlessness	MRC score – note would not meet inclusion for most PR regimes except after exacerbation Is it to flag at baseline if MRC is 4 or 5? Or is it post PR that MRC is 4 or 5? patients mention this changes at the time of year the question is asked	MRC score set based on NICE recommendations (limiting breathlessness). Detail regarding time point (assessment/discharge) added.

	3. Exercise capacity	End of what? Lowest acceptable limit? / is there a lower limit? Or a change required from baseline to post-PR? Patients may miss beeps on ISWT due to other limitations rather than breathlessness i.e. leg pain etc	Detail added to tool and output summary to clarify exercise capacity.
	4. Comorbidities	Neuro/ vascular history taken into account? Peripheral Vascular Disease/ Cardio Vascular Disease/ Multiple Sclerosis – would impact ability to complete rehab/ acceptance criteria of other services? Severity of heart failure may not be easy to determine in community settings where services often go through just referral sent by GP which has very basic information I think it is a big ask to expect the PR team to be able to judge whether the patient has a comorbidity (respiratory or sometimes non-respiratory) that could affect survival. This can often be subjective to a degree and difficult to predict even for a medic (especially if outside of their specialty) is this just the 3 stated or are there others that would exclude the patient?	If significant other comorbidities should be taken into account. This tool is in the context of those in a PR programme. Downgrading of comorbidities to desirable rather than essential. Therefore, to flag other significant comorbidities, not to make a decision on appropriateness. Three suggested comorbidities to guide clinicians

5. Investigations	What are your cut offs for results or just a Y/N – what are you looking for? Prior investigations might not be available to wider community settings of pulmonary rehab. This might restrict your patient recruitment or roll out in community pulmonary rehab teams. As it is patient reported, I'm not sure that accurate responses will be achieved, and these tests can be subsequently reviewed by a clinician or arranged. CT scan, echo – patients often don't know what they have been for when they have investigations	Can either be yes/no or space for further information depending on information available to clinician/reported by patient.
6. Patient	Patients involved in the decision? Is there a patient specific info pack? Important, as some patients do not want any procedure and a referral therefore not warranted Flag to who? The patient or the LVR team?	Patient resources developed and suggestion to introduce to patient but no discussion around preferences recommended.

7.4 Discussion

7.4.1 **Summary of findings**

This chapter presents a decision-making support tool (the LVR-PR tool) that has been developed with wide stakeholder input using an iterative modified Delphi approach. Findings show that the tool is valid in identifying individuals suitable for onward referral on the LVR patient pathway using four essential criteria and two additional desirable criteria. Feedback from various stakeholders suggested that implementation in busy PR programmes could be feasibly achieved without a significant increase in workload for clinicians.

7.4.2 **Significance of findings**

The final items included in the tool (diagnosis, exercise capacity, breathlessness, patient, comorbidities and investigations) were all decided upon with broad consensus from contributing stakeholders. The first four of these items were unanimously considered to be essential when making an informed, standardised and appropriate decision around onward referral, whereas the decision to categories the latter two items as 'desirable' was essential in not making the tool too burdensome. Having to dedicate time to search for historical records relating to patient's medical history or prior investigations would have proved too timely for oversubscribed and time-constrained services and would probably have impacted uptake of the tool.

The patient category was also subject to much deliberation during the development process. Firstly, some clinicians were undecided on when would be the most suited time to discuss LVR as a concept and possible treatment with a patient, feeling that step two in the pathway (respiratory review) would be more appropriate. This was because at this point there would be more clarity around whether LVR may be an option for the particular individual. They

believed that this would make these conversations more meaningful allowing consequent decisions to be made on informed choice. The concept of informed choice in healthcare decisions has been previously studied in a lung cancer setting (Powell 2017; Hopmans 2016), but there is limited literature within the context of LVR. Findings from lung cancer patients showed that patient preferences were only selectively taken into consideration and while recommendations were made for more joint decisions making, some patients actually preferred a more direct approach from a professional with in depth knowledge to help weight up the risks and benefits involved. This requires greater attention in LVR decision making, particularly as this research largely focusses on different types of treatments rather than if a patient chose to undergo a treatment or not, which of course is a different situation. The findings presented in the CELEB trial (chapter 4) will be vital in contributing to these clinician-patient discussions. By providing comparative data on two similar treatments and aspects of treatment that may be important for the individual, for example hospital length of stay or complication rates joint decision making can be facilitated.

In consideration of this, and for the purpose of this tool it was jointly decided that as part of this initial step the clinician should only be expected to briefly introduce LVR and then provide educational resources for the individual to go away and read at their leisure and will. The educational resources would also provide information to sign post patients to further accurate resources if more information was desired. Engaging in more in-depth discussion around patient understanding and preference that could raise complex questions would not be expected at this time and should be addressed further down the line with a specialist respiratory physician following the review of necessary investigations showing that LVR criteria have been met and the individual is likely to be a suitable candidate.

This decision was helpful in reassuring clinicians concerns over professional knowledge in delivering LVR information/education to potential candidates. Particularly in the scenario of

having to answer difficult questions posed to them, or around delivering a sensitive topic to patients in the education sessions. There was apprehension that presenting a generic session to all members of a PR group, on a potentially 'life-altering treatment' the majority of whom would not go on to have an LVR intervention would probably cause some issues. To address this as stated above, the role of the PR clinician in broaching the topic of LVR was clarified and educational resources were also developed and well received by clinicians and the public.

Interestingly, the patients in the PPIE session were less concerned over the idea of discussing a sensitive topic and voiced greater concern over having information withheld. Members of the group were keen for an improvement in the volume, quality and accessibility of educational resources that are available to them and can be relied upon to provide correct information. Comments that were provided by the group suggested that they would prefer to be introduced to all existing and new therapies and this would be most useful early in the disease process. It was felt that this would help them to feel more educated and empower them to explore all options that may be available to them. This approach aligns with the self-management and patient empowerment style that is well documented in COPD care (Stoilkova-Hartmann 2018; Sigurgeirsdottir 2019).

7.4.3 **Methodological considerations**

This study had several strengths relating to its design. First, the strategic framework used provided a systematic approach to the development process. This helped me ensure that I didn't overlook any aspect of the process and that each important step was considered.

The modified Delphi approach, combining survey, focus group and informal discussion was selected to avoid missing individual views that is associated with social pressures in groups causing participants to conform to the most dominant voice or what is seen as the 'expert

view'. Additionally, the iterative approach used in this study allowed reflection at each step of the development process, an aspect that I valued greatly and was crucial in re-evaluating of the tool based on stakeholder input (Braun 2006). Consensus methods have been recognised as important practice in identifying and addressing uncertainty in healthcare settings whilst also evaluating validity (Eubank 2016; Shi 2012; Powell 2003). Although the final tool did not differ considerably from the first iteration the small adjustments that were made based on stakeholder input were, I believe crucial in enhancing the tool's usability. For example, in simplifying what was included in the final tool and adding direct information to the tool to describe how it should be used.

The strengths of the final working tool is that it has been designed based on the viewpoints of a range of key stakeholders and whilst being valid in addressing the objective of systematically considering patients for onward referral, it does not require particularly higher than average baseline knowledge in the specialist field of LVR and so could be generalised to most clinicians working in PR programmes.

There are also some weaknesses that should be addressed relating to the methodologies used. Although the importance of general reflexivity during the iterative process has been discussed as a strength, the lack of personal reflexivity, that is strongly advocated in research involving qualitative data and particularly thematic analysis (Dodgson 2019) should be highlighted as a shortcoming. My personal experiences and beliefs in this specialist area would undoubtedly have had influence on the tone of the focus groups and so on reflection it may have been more suitable for me to have a less central role in guiding these meetings.

Furthermore, as some members of the clinician group had previous or current professional relationships with those conducting the research this may also have had introduced bias through Influencing views or causing them to feel unable to speak up with opposing views.

Reliability of qualitative analysis including researcher bias have been recognised as of great importance (Morse 2002). In this study, to try to address potential bias both groups involved a statement on the researcher's involvement and previous experience in the field during the introductions. This was intended to promote transparency and is recommended in the CORE-Q guidelines for qualitative research (Tong 2007).

To further tackle this type of bias, in future research peer debriefs could be used (Noble 2015). For example, following the clinician focus group a debrief with participants could have been carried out to gauge whether there was a feeling that the researchers prior experiences or ideas were influencing the direction of the meeting and if so a further meeting using more open questioning or perhaps an alternative moderator may have been constructive.

It could also be argued that the sample size for the PPIE group (Deeks JJ) was limited and the purposive sampling method may have introduced bias. By recruiting a group of individuals who have all completed a course of PR the sample may not be representative of those who for example did not attend a PR assessment or did not complete their course perhaps because they have more severe disease, or they have accessibility issues. According to (Patton 2014) this method of sampling does not intend to isolate one common opinion and encourages variation but in this instance would allow consideration of what may be a typical response, from individuals with prior experience to the use of a tool in this context and the educational interactions and resource suggested.

The lack of pilot data due to the changes caused by the pandemic is an obvious weakness in the study proceedings but may also indicate that the tool is too burdensome for current services. As the comments collected from clinical services did not suggest this,

implementations of the tool as services resume usual practice and get on top of waiting lists in the future will provide further understanding of this.

Finally, the tool was considered to be valid based on results from the content validity index. In its purest form the concept of validity referred to tests measuring what it claims to measure However, to truly asses the validity of a tool such as this several forms of validity must be assessed. There is debate around which types of validity are necessary in deeming a tool valid. For example, generally four types of validity are considered valuable (face, concurrent, predictive and construct). Yet a strong argument is made as to why face validity should not be employed as a type of validity (Royal 2016). An important point related to the validity of this tool is the limitation of using cut points to make clinical decisions regarding suitability for treatment, or onward referral. For example, the LVR PR tool includes exercise capacity as one criteria to asses an individual's eligibility for referral and cut offs are suggested. This is included to ensure the individual is robust enough to undergo a procedure safely. However, previous research shows us that in fact, those with a lower exercise capacity are likely to see greatest benefit from LVR intervention in terms of both clinical outcomes and survival. And so, excluding those who are unable to walk a certain distance due to severe exertional breathlessness secondary to hyperinflation, which the procedures are designed to target, may be considered inappropriate and unfair. Considering this it may be that a measure of frailty could provide a better indication of whether a procedure can be safely undertaken. However, more work is required to explore this concept and identify a suitable measure of frailty for this purpose.

Reflecting on all limitations, suggests that future work will be important in validating this tool in a clinical setting.

7.4.4 **Conclusion**

The LVR-PR tool that has been developed and discussed in this chapter provides a simple mechanism to facilitate the consideration of people with COPD for LVR referral in a systematic manner, as recommended in NICE guidelines. This feasibility study found the tool to be valid and practical to embed into busy PR services across the UK. It does however, require clear and accurate educational resources for both patient and clinician that are kept up to-date to support its implementation.

8 Conclusion and future research directions

This chapter summaries the work that has been presented in the main body of this thesis and then goes on to discusses the findings in relation to the pre-defined hypothesis and aims. Suggestions for future research opportunities are also proposed in continuing the work towards improving patient access and outcomes in LVR management.

8.1 Summary of research findings

The main novel findings of this thesis are;

1. The number of patients that receive LVR treatment is disproportionate to the number who may be eligible due to problems with current patient pathways and clarity of referral criteria.
2. LVRS cannot be considered a superior treatment option to BLVR, for those with severe emphysema who have equipoise for either treatment.
3. Daily step count and gait speed can be measured digitally and are associated with survival and other important clinical outcomes in COPD and so may have utility as digital prognostic biomarkers.
4. LVR procedures are being carried out according to quality standards with only a small proportion of high risk cases being performed. Long term survival following LVRS and BLVR is similar.
5. The LVR-PR decision making tool appears to be feasible to implement to allow PR teams to identify and communicate back to referrers about who should have a further respiratory review to establish whether they may benefit from a lung volume reduction procedure.

8.2 Implications for clinical practice

Conclusions drawn from the work presented in this thesis, in the context of the pre-defined hypotheses offer important implications for future clinical practice that should be noted. Chapter three clearly demonstrated the need for a more organised pathway for LVR identification and referral. This should include the routine and systematic early consideration of patients in an appropriate setting using clear decision-making criteria. The work from this chapter substantiated PR as an ideal setting for the first step in the referral pathway to facilitate timely referral of those who may benefit from LVR interventions. This process should ideally be initiated at PR assessment to ensure fair consideration of all potentially eligible candidates. The LVR PR tool presented in chapter seven has been developed to implement this process and aid the integration of PR services in the LVR pathway. The tool suggests a well-defined criterion for consideration including clarity around those measures that were vague (MRC/exercise capacity) and practical instructions for completing the tool and the onward referral process. Supplementary resources have also been developed for ensuring PR clinicians are suitably knowledgeable to lead this process and discuss and signpost patients to clear information regarding LVR therapies. The success of integrating this tool will rely on sound communication between PR services and primary and secondary care services and therefore a decision should be made at each individual centre regarding the flow of onward referral from step one in the LVR pathway. Ideally this tool should relieve the burden of patient identification and referral from primary care and so output of this tool is intended to be kept within specialist respiratory services.

Work was presented in chapter three that highlighted the large quantity of missing exercise capacity data for LVR consideration. This can cause delays for those on the pathway and obtaining a formal exercise capacity test in a busy clinical environment can be problematic.

Therefore, greater interest in monitoring and measuring daily activity may be of value. In investigating the utility of digitally collected walking activity and gait parameters (chapter seven) as prognostic indicators I was able to explore the outcomes that have been proven to be associated with mortality in COPD as well as other prognostic indicators. These findings may be used to provide evidence that DMOs can be utilised in not only research trials but also clinical practice. For example, in establishing a baseline, for considering suitability for intervention, or for monitoring over a longer term to identify deterioration or following an exacerbation. These applications would provide a remote and more practical way of measuring an individual's ability in a real-world setting capturing what they actually do in daily life, which puts them at an advantage to exercise capacity tests. However, the literature base was small with some limitations including heterogeneous methods, which means the conclusions drawn from pooling these studies should be interpreted with some caution when considering implications for future practice.

Chapter four showed that LVRS is not significantly superior to BLVR in health outcomes that were recorded at 12 months post procedure. Therefore, in those patients considered to have equipoise for treatment, either intervention can be considered an appropriate choice and patient preference should be paramount. These findings should provide evidence and guidance to the LVR MDT in framing treatment options for patients and guiding discussions for shared decision making between patient and clinician. For example, for one patient a longer initial hospital stay, but fewer subsequent admissions (LVRS) would be a more appealing option whereas another may not be concerned about future admissions and prefer a less invasive procedure that is associated with a shorter initial length of stay.

Being able to discuss these decisions with patients in a more informed manner is a positive step in providing COPD care that is more patient centric.

8.3 Concluding remarks and future research directions

Lung volume reduction procedures are an important part of COPD management for carefully selected individuals, and there is an ever- increasing body of research that demonstrates their efficacy. The findings from this thesis contributes to this work but also highlight the work that still needs to be done in improving outcomes and access to these important treatments for people with COPD.

Chapter 3 highlighted the need for clearer referral criteria and a more systematic process in identifying those for consideration for LVR. Future research in this area should focus on the development and refining of LVR referral pathways that can be practically implemented at an appropriate time point and setting, and this will involve communication and engagement with all key stakeholders in LVR and PR services. As part of this work, and in planning a postdoctoral research project, the utility of assessing exercise capacity as part of the decision-making criteria for LVR consideration is an area I believe requires greater exploration. Currently, suggested criteria include an individual to be able to walk a minimum distance to be considered for the next step on the LVR patient pathway. However, LVR interventions are for those with severe emphysema, a condition that is characterised by debilitating exertional breathlessness and furthermore, we know from previous research that these procedures are best suited to those with lower exercise capacity. Therefore, excluding people that cannot manage to walk a certain distance on a field walking test may be futile. Nevertheless, these criteria do serve a purpose, to ensure the patient is well enough or robust enough to undergo an intervention. Thus, an alternative method of assessing this would be necessary and a more appropriate suggestion could be a fragility measure and further work is justified in exploring this. Additionally, the role of PR in the work up for LVR intervention is another area that needs greater consideration. As an already over stretched and poorly funded resource this should include identifying which patients benefit from it the most, where exceptions should

be made for its requirement (e.g. in patients that continue to work or remain physically active) and the length of time considered acceptable between completion of a course and referral for LVR evaluation.

Chapter four demonstrated the comparative value of LVRS and BLVR but to fully understand this I believe an economic evaluation of these interventions is a crucial piece of work. Planning this study will require health economist input to understand the economic burden in terms of healthcare utilisation versus the health outcomes achieved from both interventions.

The shortcomings of the study described in chapter four, namely the high attrition rate, emphasised the need for a larger RCT comparing LVRS and EBVs. Fortunately, such a study is already underway, in Switzerland and is due to be published in 2025. This will provide important contribution to the findings presented in this thesis. Future work should also be carried out that explores alternative outcomes in LVR trials. For example, quality of life outcomes or PA outcomes. This may involve qualitative work to look at which outcomes the patient values most following intervention and the development of a core outcomes dataset.

Additionally, future work in the field of physical activity and digital mobility outcomes should focus on validating the use of commonly used outcomes such as gait speed, as digital measures as well as identifying other walking activity and gait parameters that could be developed as digital outcomes. This will involve the setting up of larger prospective trials using standardised research designs.

In relation to contribution to a post-doctoral application the value of physical activity management in COPD care could also be explored. This may be best placed in a study involving an early COPD cohort that qualitatively explores what current practice is in discussing the importance of physical activity at diagnosis, and then designing a brief

intervention to target this. A longitudinal cluster analysis that looks at physical activity outcomes alongside other important confounders from diagnosis and over a longer trajectory may also contribute to how, and at what time point, treatments are targeted. And which individuals would benefit greatest.

From my experience of conducting research in this severe emphysema population I believe more work is needed to develop training techniques that can be feasibly implemented to augment exercise training and how rehabilitation is delivered prior and post LVR intervention. There is a growing body of evidence looking at prehabilitation for those undergoing surgery for lung cancer and I am interested in exploring this concept further for those on the LVR pathway. Bot pre-procedure and post procedure rehabilitation have the potential to improve outcomes of these important treatments. However, more work is required to determine how this can be delivered. Research that explores the adjuncts and techniques discussed in the introductory chapter of this thesis, specifically within a select population of those undergoing or being considered for LVR intervention would contribute to this field.

Finally, further directions for research in the LVR field should focus on streamlining and standardising the LVR pathway, in particular the interface with pulmonary rehabilitation, restructuring MDT process and implementing routine data collection. Delays in the patient pathway, exacerbated by the pandemic, have indicated the need to ensure equity of access to a proven intervention and in working towards addressing these future directions will ensure the effective identification and treatment of those who will benefit the most from LVR therapies.

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10. Appendices

10.1 Appendix 1: Instructions provided to patients in the CELEB trial for using MoveMonitor activity monitors

(Manual Activity Monitors)

MoveMonitor/ Actigraph

PRO active

General Information

Thank you for participating in this study! For the success of the study we would like to ask you to pay attention to the following points:

IMPORTANT:

- Wear the activity monitor at all times. Even in bed if able.
- Pretend you are not wearing the device.
- Only take off the monitor when you take a bath/shower or when you go for a swim.

DO NOT FORGET TO:

- Write down when you took off the devices unexpectedly.
- Fill in the diary **after the 7 days**.

IF YOU EXPERIENCE ANY PROBLEMS PLEASE CONTACT YOUR STUDY TEAM AT THE FOLLOWING NUMBER: 0207 3518029

Positioning the devices

Position the devices as shown on the figures on the following pages.

1. MoveMonitor
   - Positioning of the device

2



Position of the MoveMonitor on the middle of the back. The belt will close at the front, just above your pants. You are able to adjust the velcro to your size.

- Points of Attention
  - When you go to sleep: Place the band, in which the MoveMonitor is located horizontal on a (night) table with the flashing light up. This allows us to identify periods of non-wearing.

3

10.2 Appendix 2: Clinical Visit PROactive Physical Activity in COPD (C-PPAC) instrument



CLINICAL PROactive QUESTIONNAIRE

Patients with chronic lung disease, as you, often report that they have problems during physical activity. By physical activity, we mean all activities that require movement of your body. Examples are household activities, walking, going to work, or getting dressed. However, please consider all activities you do, and not only these examples.

We would like to know how you experienced your physical activity IN THE PAST 7 DAYS.

Please choose the answer that best applies to you IN THE PAST 7 DAYS.
There are no wrong answers. We very much value your response.

1) In the past 7 days, how much walking did you do outside?

- ☐ None at all
- ☐ A little (about 10 minutes every day)
- ☐ Some (about 30 minutes every day)
- ☐ A lot (about 1 hour every day)
- ☐ A great deal (more than 1 hour every day)

2) In the past 7 days, how many chores did you do outside the house? Some examples are gardening, taking out the garbage, or doing small errands.

- ☐ None at all
- ☐ A few
- ☐ Some
- ☐ A lot
- ☐ A large amount

3) In the past 7 days, how much difficulty did you have getting dressed?

- ☐ None at all
- ☐ A little
- ☐ Some
- ☐ A lot
- ☐ A great deal

4) In the past 7 days, how much difficulty did you have getting out and about?

- ☐ None at all
- ☐ A little
- ☐ Some
- ☐ A lot
- ☐ A great deal

5) In the past 7 days, how often did you avoid doing activities because of your lung problems?

- ☐ None at all
- ☐ Rarely
- ☐ Sometimes
- ☐ Frequently
- ☐ All the time

6) In the past 7 days, how breathless were you in general during your activities?

- ☐ None at all
- ☐ A little
- ☐ Moderately
- ☐ Very
- ☐ Extremely

7) In the past 7 days, how often did you lack physical strength to do things because of your lung problems?

- ☐ None at all
- ☐ Rarely
- ☐ Sometimes
- ☐ Frequently
- ☐ All the time

8) In the past 7 days, how tired were you in general during your activities?

- ☐ None at all
- ☐ A little
- ☐ Moderately
- ☐ Very
- ☐ Extremely

9) In the past 7 days, how often did you need to take breaks during your physical activities?

- ☐ None at all
- ☐ Rarely
- ☐ Sometimes
- ☐ Frequently
- ☐ All the time

10) In the past 7 days, how breathless were you when walking on level ground indoors and outdoors?

- ☐ None at all
- ☐ A little
- ☐ Moderately
- ☐ Very
- ☐ Extremely

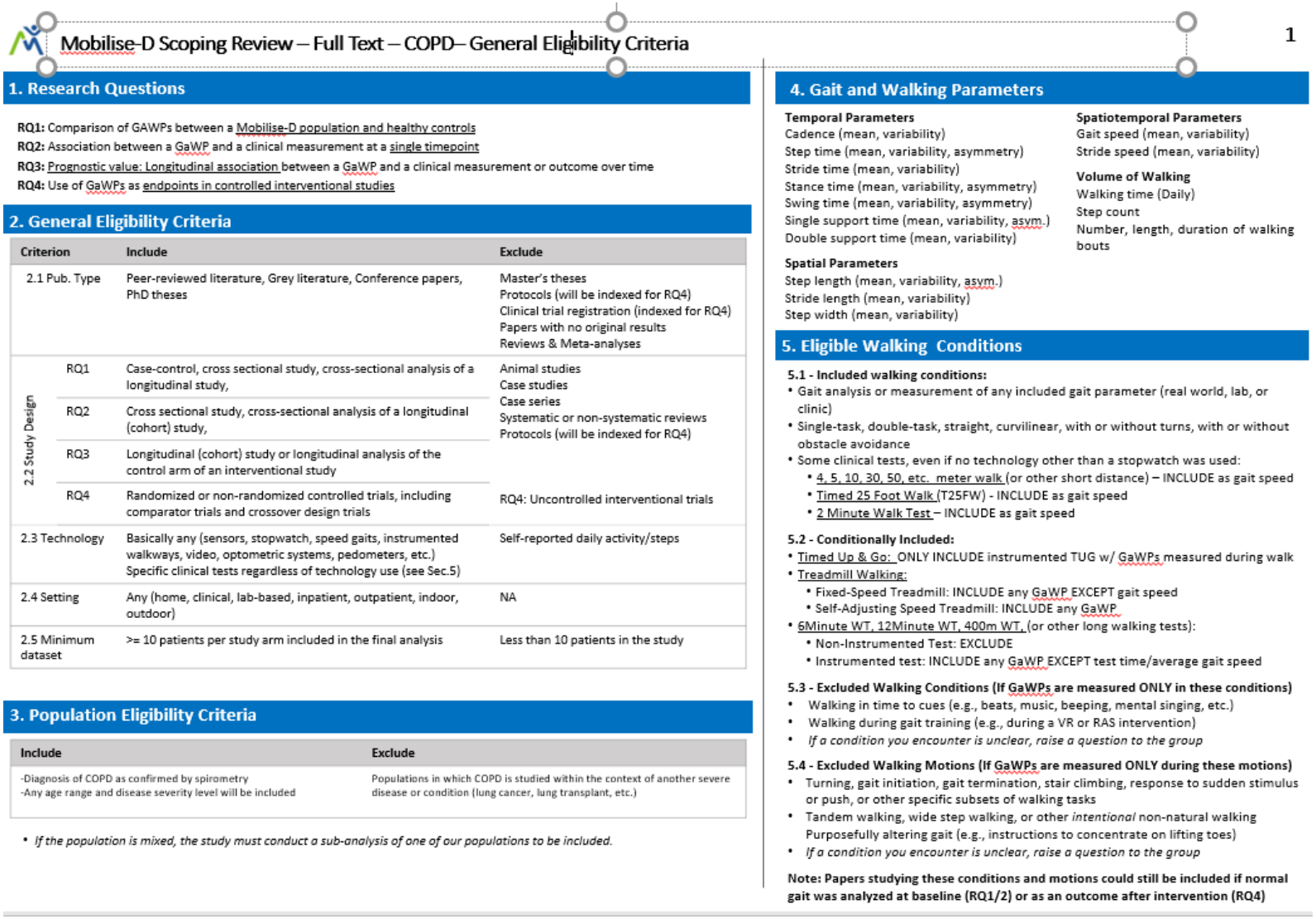
11) In the past 7 days, how much time did you need to recover from your physical activities?

- ☐ None at all
- ☐ A little
- ☐ Some
- ☐ A lot
- ☐ A great deal

12) In the past 7 days, did you need to consider your lung problems when you planned your activities? Examples are going out on a trip, keeping an appointment or expecting visitors.

- ☐ No
- ☐ A little
- ☐ Sometimes
- ☐ A lot
- ☐ A great deal

10.3 Appendix 3: Initial scoping review inclusion and exclusion criteria



Mobilise-D Scoping Review – Full Text – COPD– General Eligibility Criteria

1

1. Research Questions

RQ1: Comparison of GAWPs between a Mobilise-D population and healthy controls
RQ2: Association between a GaWP and a clinical measurement at a single timepoint
RQ3: Prognostic value: Longitudinal association between a GaWP and a clinical measurement or outcome over time
RQ4: Use of GaWPs as endpoints in controlled interventional studies

2. General Eligibility Criteria

Criterion		Include	Exclude
2.1 Pub. Type		Peer-reviewed literature, Grey literature, Conference papers, PhD theses	Master's theses Protocols (will be indexed for RQ4) Clinical trial registration (indexed for RQ4) Papers with no original results Reviews & Meta-analyses
2.2 Study Design	RQ1	Case-control, cross sectional study, cross-sectional analysis of a longitudinal study,	Animal studies Case studies Case series Systematic or non-systematic reviews Protocols (will be indexed for RQ4)
	RQ2	Cross sectional study, cross-sectional analysis of a longitudinal (cohort) study,	
	RQ3	Longitudinal (cohort) study or longitudinal analysis of the control arm of an interventional study	
	RQ4	Randomized or non-randomized controlled trials, including comparator trials and crossover design trials	RQ4: Uncontrolled interventional trials
2.3 Technology		Basically any (sensors, stopwatch, speed gaits, instrumented walkways, video, optometric systems, pedometers, etc.) Specific clinical tests regardless of technology use (see Sec.5)	Self-reported daily activity/steps
2.4 Setting		Any (home, clinical, lab-based, inpatient, outpatient, indoor, outdoor)	NA
2.5 Minimum dataset		>= 10 patients per study arm included in the final analysis	Less than 10 patients in the study

3. Population Eligibility Criteria

Include	Exclude
-Diagnosis of COPD as confirmed by spirometry -Any age range and disease severity level will be included	Populations in which COPD is studied within the context of another severe disease or condition (lung cancer, lung transplant, etc.)

- *If the population is mixed, the study must conduct a sub-analysis of one of our populations to be included.*

4. Gait and Walking Parameters

Temporal Parameters
Cadence (mean, variability)
Step time (mean, variability, asymmetry)
Stride time (mean, variability)
Stance time (mean, variability, asymmetry)
Swing time (mean, variability, asymmetry)
Single support time (mean, variability, asym.)
Double support time (mean, variability)

Spatial Parameters
Step length (mean, variability, asym.)
Stride length (mean, variability)
Step width (mean, variability)

Spatiotemporal Parameters
Gait speed (mean, variability)
Stride speed (mean, variability)

Volume of Walking
Walking time (Daily)
Step count
Number, length, duration of walking bouts

5. Eligible Walking Conditions

5.1 - Included walking conditions:
- Gait analysis or measurement of any included gait parameter (real world, lab, or clinic)
- Single-task, double-task, straight, curvilinear, with or without turns, with or without obstacle avoidance
- Some clinical tests, even if no technology other than a stopwatch was used:
  - 4, 5, 10, 30, 50, etc. meter walk (or other short distance) – INCLUDE as gait speed
  - Timed 25 Foot Walk (T25FW) - INCLUDE as gait speed
  - 2 Minute Walk Test – INCLUDE as gait speed

5.2 - Conditionally Included:
- Timed Up & Go: ONLY INCLUDE instrumented TUG w/ GaWPs measured during walk
- Treadmill Walking:
  - Fixed-Speed Treadmill: INCLUDE any GaWP EXCEPT gait speed
  - Self-Adjusting Speed Treadmill: INCLUDE any GaWP
- 6Minute WT, 12Minute WT, 400m WT, (or other long walking tests):
  - Non-Instrumented Test: EXCLUDE
  - Instrumented test: INCLUDE any GaWP EXCEPT test time/average gait speed

5.3 - Excluded Walking Conditions (If GaWPs are measured ONLY in these conditions)
- Walking in time to cues (e.g., beats, music, beeping, mental singing, etc.)
- Walking during gait training (e.g., during a VR or RAS intervention)
- *If a condition you encounter is unclear, raise a question to the group*

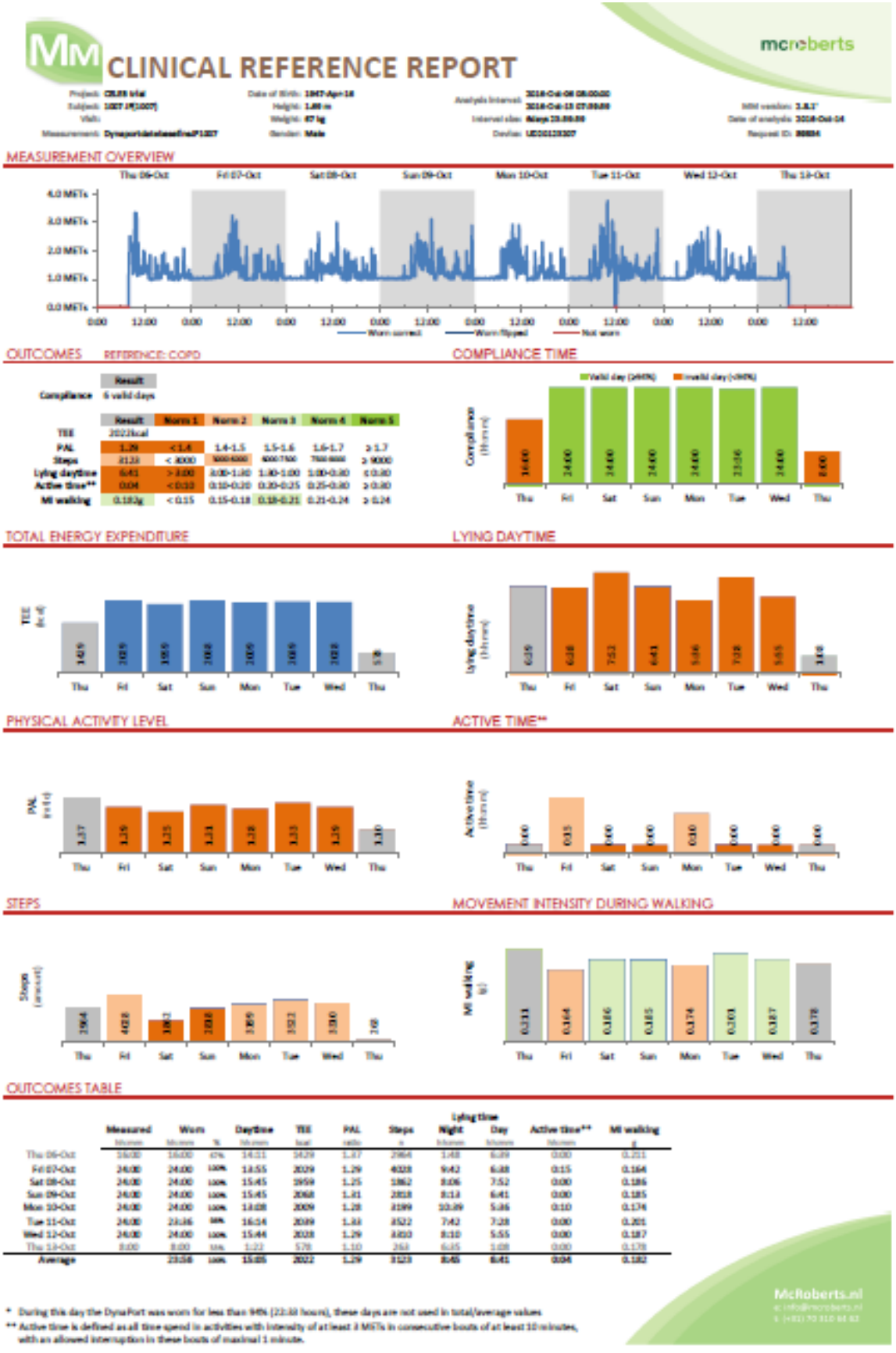
5.4 - Excluded Walking Motions (If GaWPs are measured ONLY during these motions)
- Turning, gait initiation, gait termination, stair climbing, response to sudden stimulus or push, or other specific subsets of walking tasks
- Tandem walking, wide step walking, or other *intentional* non-natural walking Purposefully altering gait (e.g., instructions to concentrate on lifting toes)
- *If a condition you encounter is unclear, raise a question to the group*

Note: Papers studying these conditions and motions could still be included if normal gait was analyzed at baseline (RQ1/2) or as an outcome after intervention (RQ4)

10.4 Appendix 4: Reasons for studies exclusion from meta-analysis

Study	Reasons for Exclusion
(Neumannova 2017; Kang 2018)	Did not report an effect estimate
(Fermont 2021; Cushen 2016; Sievi 2019; Fermont, Bolton, 2020; Medina-Mirapeix 2021; Witt 2021; Benzo 2013)	Unable to compare methodologies
(Pilsworth 2018; Jones 2019)	Research abstract lacking significant detail for comparison
(Walsh 2019)	Cross over with another cohort
(Walsh 2021)	Cohort used in another paper-statistical representation

10.5 Appendix 5: Physical activity MoveMonitor output report



10.6 Appendix 6: Integrating a Lung Volume Reduction pathway tool into Pulmonary Rehabilitation

Q1: Please indicate your professional role

Consultant Physician

Consultant Surgeon

Speciality trainee

Radiologist

Physiotherapist

Specialist Nurse

Q2: How would you describe your gender?

Male (including transgender males)

Female (including transgender females)

Prefer not to specify

Other not listed (please specify)

Q3: Please indicate which age bracket describes you?

18-24	45-54
25-34	55-64
35-44	65+

Q4: Are you involved in a Lung volume reduction (LVR) MDT?

Yes

No

Q5: Are you involved in Pulmonary rehabilitation (PR)?

Yes

No

Only in making referrals to PR

Q6: How confident do you feel in identifying patients that may be suitable for LVR? (0= not confident at all, 10= very confident)

0 10

Q7: We have split the tool into 6 key areas for consideration (listed below). Please indicate how important you consider each area to be for inclusion in a decision-making tool, used to identify potential candidates for LVR at the end of pulmonary rehabilitation

	Essential	Desirable	Unnecessary
Diagnosis			
Co-morbidities			
Breathlessness			
Exercise capacity			
Prior investigations			
Patient understanding/preference			

If you would like to suggest any other key areas, you feel are missing please specify

Q8: Do you have any comments or concerns about identifying people for possible work up towards LVR at the end of PR?

Thank you very much for you time and participation in this survey.

10.7 Appendix 7: PR centres involved in validating the LVR-PR tool

New Cross Hospital

Walsall General Hospital

Royal Stoke Hospital

Coventry & Warwickshire

Queen Elizabeth Birmingham

City & Sandwell, Birmingham

Worcester Royal Hospital

George Eliot Nuneaton

Heartlands Hospital, Birmingham

Midlands Partnership NHS

Northern General Hospital

The Rotherham NHS Foundation Trust

Barnsley Hospital NHS Foundation Trust

Doncaster and Bassetlaw Teaching Hospital NHS Foundation Trust

10.8 Appendix 8: Focus group questions

Focus group 1

Session overview

1) Introductions and overview of the session described as well as objectives of the project
2) Presentation of working draft of LVR decision making tool; SB
3) Pre-planned questions and discussion (moderated by SB)
4) Time for other questions from participants (SB and NH)
5) Closing of session and informing participants of next steps in project

Questions asked during focus group one

- Are you currently involved in recognising patients suitable for LVR and what is the process for this at your centre?
- Any barriers to recognising patients and making referrals? Why don't you make more referrals?
- Looking at the tool; does it make sense? Could all this information be collected relatively easily, or would it create an unmanageable amount of work?
- Would the tool work better in another format? E.g. flow diagram/ scoring system
- Would it be easier/better to complete a digital tool?
- Any barriers you foresee in implementing the tool into your programme?
- Any comments on the tool or questions?
- Do you currently talk to patients about LVR interventions and if so is this on an ad hoc basis? Or as part of your education programme?
- Do many patients bring up the topic of LVR/other interventions?
- Would more training be needed? More documentation/leaflets to give out to patients

Focus group 2

Session overview

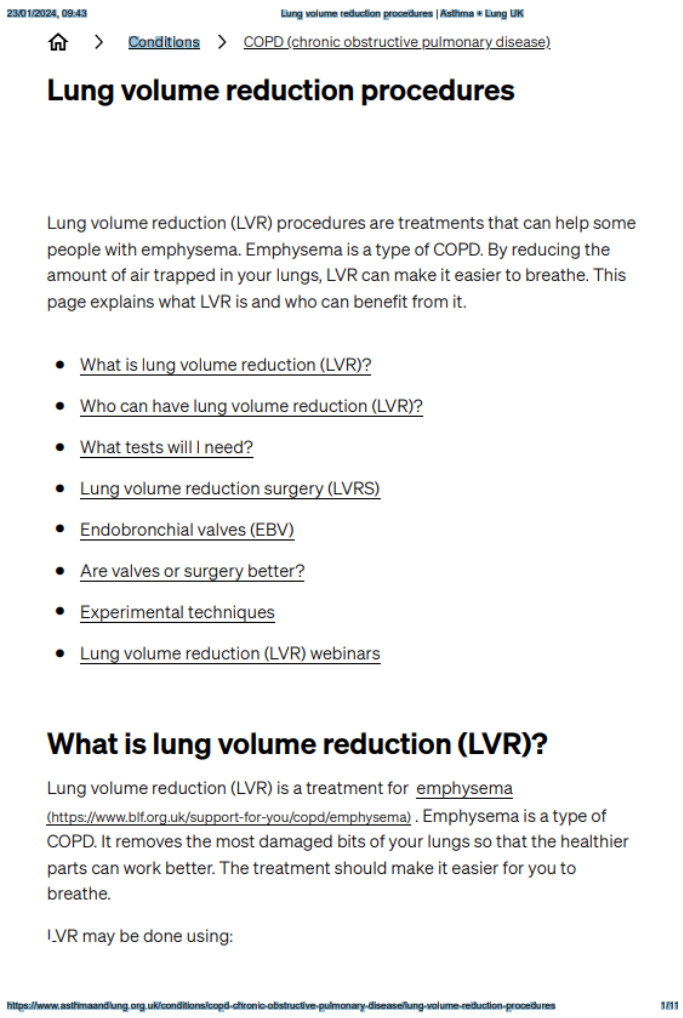
2) Introduction to session and reminder of ground rules; LB
3) Explanation of LVR project and expectations from focus group; SB.
4) **Video 1: LVR patient education video** discussion moderated by SB.
5) **Video 2: Explaining the surgery LVRS:** discussion moderated by SB
6) **Video 3: Explanation on the valves:** discussion moderated by SB
7) Specific questions around LVR decision making tool for group; SB (moderated by LB)
8) More general discussion and any questions that the group may have; SB, PW, LB.

Questions following each video used to facilitate discussion

- What are your thoughts on the contents of this video?
- Are there any things you thought were positive about the video?
- Are there any things that you thought were not so good?
- Is there any information you think could be added or questions that you would still want answered after watching the video?

10.9 Appendix 9: Link to online educational resources

https://www.asthmaandlung.org.uk/conditions/copd-chronic-obstructive-pulmonary-disease/lung-volume-reduction-procedures



23/01/2024, 09:43 Lung volume reduction procedures | Asthma + Lung UK

Conditions > COPD (chronic obstructive pulmonary disease)

Lung volume reduction procedures

Lung volume reduction (LVR) procedures are treatments that can help some people with emphysema. Emphysema is a type of COPD. By reducing the amount of air trapped in your lungs, LVR can make it easier to breathe. This page explains what LVR is and who can benefit from it.

- What is lung volume reduction (LVR)?
- Who can have lung volume reduction (LVR)?
- What tests will I need?
- Lung volume reduction surgery (LVRS)
- Endobronchial valves (EBV)
- Are valves or surgery better?
- Experimental techniques
- Lung volume reduction (LVR) webinars

What is lung volume reduction (LVR)?

Lung volume reduction (LVR) is a treatment for emphysema (https://www.blf.org.uk/support-for-you/copd/emphysema) . Emphysema is a type of COPD. It removes the most damaged bits of your lungs so that the healthier parts can work better. The treatment should make it easier for you to breathe.

LVR may be done using:

https://www.asthmaandlung.org.uk/conditions/copd-chronic-obstructive-pulmonary-disease/lung-volume-reduction-procedures 1/11