Oxford University Hospitals NHS Foundation Trust

Study Title: HypErpolarised Xenon PuLmonary MRI in the Evaluation for EndobronChial Lung Volume ReductIon Therapy

Internal Reference Number / Short title: EXPLICIT

Ethics Ref: Insert

IRAS Project ID: 346681

Date and Version No: 01 Jul 2025; V1.0

Chief Investigator:	Professor Fergus Gleeson, Consultant Radiologist[1]
Investigators:	Dr Rob Hallifax, Consultant Respiratory Physician[1]
	Dr Kher Lik Ng, Clinical Research Fellow[1]
	Dr James Grist, MRI Physicist[1]
	Dr Alastair Moore, Consultant Respiratory Physician[1]
	Miss Elizabeth Belcher, Consultant Thoracic Surgeon[1]
	Ms Avianna Laws, Clinical Research Operations Manager[1]
	[1] Oxford University Hospitals NHS Foundation Trust
Sponsor:	Oxford University Hospitals NHS Foundation Trust
Funder:	Medical Research Council (MRC)

There are no conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so

Oxford University Hospitals
NHS Foundation Trust

TABLE OF CONTENTS

Oxford University Hospitals NHS Foundation Trust

1. KEY CONTACTS

Chief Investigator	Professor Fergus Gleeson, Consultant Radiologist Fergus.Gleeson@ouh.nhs.uk
Sponsor	Oxford University Hospitals NHS Foundation Trust
Funder(s)	Medical Research Council (MRC)
Trial Manager	Avianna Laws, Clinical Research Operations Manager, Oxford Radiology Research Unit

2. LAY SUMMARY

One of the treatments to improve symptoms and life expectancy in patients with severe COPD is lung volume reduction therapy. Due to the high risks associated with surgical techniques, one-way expiratory endobronchial valves have been developed to reduce lung volume and these are inserted into the targeted airway(s) via bronchoscopy. When the airway supplying the targeted lung (which is typically severely damaged and working) is blocked with the valve(s), the targeted lung will deflate resulting in lung volume reduction. For this to work, the target lung should only have air flow coming from the main airway supplying it and no abnormal connection with other parts of the lung ("collateral ventilation"). Collateral ventilation would prevent the lung from deflating despite treatment.

Current practice to assess collateral ventilation is using a software to analyse CT images of the lungs and a bronchoscopy technique called Chartis to measure air flow in the airways. When collateral ventilation has been excluded following Chartis assessment, suitable patients could be offered valve treatment. However, these assessments are not perfect. This can result in either suitable patients not offered treatment due to technical limitations, or patients selected for treatment who do not benefit. Therefore, it is important to find other techniques that could improve the current assessment methods for better patient selection for treatment.

We believe that MRI scanning with a special gas (hyperpolarised xenon) breathed in during the scan could potentially identify patients for treatment. The xenon gas is harmless in the quantity we use. This technique shows the movement of xenon within the lungs and moving out of the lungs into the bloodstream, similar to how oxygen is absorbed. In COPD patients, we have found that xenon MRI scans has the potential to detect collateral ventilation.

We aim to study whether these patterns of collateral ventilation will predict the success of lung volume reduction therapy using endobronchial valves. We will study the pattern of collateral ventilation in those who have been directly selected to undergo valve treatment (Cohort A) and those who have been deemed not eligible for valve treatment (Cohort B). By doing so, we may be able to establish a pattern on xenon MRI that will help select those who are more likely to benefit

from valve treatment. The success of valve treatment is also dependent on the blood flow to the targeted lung

Our overall aim is to further our understanding into the factors such as air and blood flows that could affect the success rate of valve treatment. We also wish to evaluate the value of xenon MRI as a non-invasive method in the assessment of patients being considered for valve treatment. Learning the nature and pattern of these air flows through xenon MRI may help better select patients for valve treatment and include patients who would have been excluded through conventional assessments.

3. SYNOPSIS

In this study, we aim to identify and characterise the pattern of ventilation in 2 groups of patients with COPD using hyperpolarised xenon-129 MRI (HPX-MRI): A) patients who have been selected and subsequently undergone lung volume reduction therapy using endobronchial valves (EBV), B) those who have been identified as not eligible for endobronchial lung volume reduction therapy using current selection criteria. We also aim to assess and describe the physiological changes following endobronchial lung volume reduction therapy.

Study Title	HypErpolarised Xenon PuLmonary MRI in the Evaluation for EndobronChial Lung Volume ReductIon Therapy (EXPLICIT)		
Internal ref. no. / short title	EXPLICIT		
Study registration	This study will be registered on the ISRCTN		
Sponsor	Oxford University Hospitals NHS Foundation Trust First Floor, OUH Cowley, Unipart House Business Centre, Garsington Road Oxford OX4 2PG . Email: ouh.sponsorship@ouh.nhs.uk		
Funder	Medical Research Council (MRC)		
Study Design	Feasibility/pilot		
Study Participants	Up to 40 patients		
Sample Size	Cohort A – up to 20 patients Cohort B – up to 20 patients		
Planned Study Period	Up to 24 months		
Planned Recruitment period	Aug 2025 – Feb 2027		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To characterise the pattern of ventilation on HPX-MRI in those with confirmed CV	Quantitative and/or qualitative detection of differences in the pattern of ventilation in the two cohorts being investigated:	Baseline and follow-up

	and those treated with EBV	a) Those with and without confirmed CV; b) Those who were and weren't successfully treated with EBV.	
Secondary	To describe the physiological changes of the lungs seen on HPX-MRI post-EBV treatment	a) Quantitative and/or qualitative differences of HPX-MRI findings pre- and post-EBV therapy	Baseline and follow-up
Intervention(s)	Not applicable		
Comparator	Not applicable		

4. ABBREVIATIONS

6MWD	6-minute walk distance
6MWT	6-minute walk test
BD	Bronchodilator
CAT	COPD Assessment Test
CRF	Case report form
CT	Computed tomography
CV	Collateral ventilation
COPD	Chronic obstructive pulmonary disease
DALYs	Disability-adjusted life years
DV	Delayed ventilation
EBV	Endobronchial valves
FC	Fissure completeness
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HPX-MRI	Hyperpolarised ^{129}Xe MRI
HRCT	High resolution computed tomography
LH	Lung hyperinflation
LVR	Lung volume reduction
LVRS	Lung volume reduction surgery

mMRC	Modified Medical Research Council
MRI	Magnetic resonance imaging
PFTs	Pulmonary function tests
QCT	Quantitative CT
RV	Residual volume
SAE	Serious adverse event
SGRQ	St. George's Respiratory Questionnaire
TLC	Total lung capacity
TLVR	Total lung volume reduction
U.S.	United States
VDP	Ventilation defect percentage
V/Q	Ventilation/perfusion

5. BACKGROUND AND RATIONALE

Chronic obstructive pulmonary disease (COPD) has been defined as "*a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnoea, cough, expectoration) due to persistent abnormalities of the airways (bronchitis, bronchiolitis), and/or alveoli (emphysema), that often results in progressive airflow limitation.*"[1] With more than 3 million deaths annually, COPD is the third leading cause of global mortality and the seventh leading cause of global poor health.[2,3] COPD was the cause of 2.6% of global disability-adjusted life years (DALYs) in 2015.[3] In the UK, there were 1.26 million patients with COPD in 2021 with an overall annual cost of £2 billion spent on acute treatment of exacerbations and chronic management of the condition.[4] Of note, the annual cost is projected to increase to £2.6 billion and the cumulative total costs over 20 years are expected to exceed £46 billion with the bulk of the costs spent on patients with mild and moderate disease.[4]

Chronic inflammation in COPD results in structural damage of small airways and alveolar tissue leading to airway narrowing and chronic expiratory flow obstruction, increased mucous production and decreased lung elasticity.[5,6] Consequently, static lung hyperinflation (LH) occurs when there is increased lung volumes following parenchymal destruction and loss of elastic recoil.[7] Dynamic hyperinflation is distinct from static LH in which there is incomplete lung emptying due to airway obstruction which is then interrupted by the next inspiration leading to further air trapping.[7,8] Both static LH and further dynamic hyperinflation during exercise contributes to excessive loading to respiratory muscles resulting in functional weakness in respiration reducing exercise tolerance.[9] This vicious cycle of overloading and hyperinflation contributes to the neuromechanical dissociation of the respiratory system, one of the many factors causing the symptom of dyspnoea (or breathlessness) in COPD.[5,9]

Dyspnoea is the most frequently experienced symptom and is the major determinant of physical and mental health status in COPD.[10] Identification and management of LH is consequently

important in improving symptoms, exercise tolerance and quality of life.[8] Furthermore, treatment of LH has extrapulmonary benefits and impedes disease progression, rate of exacerbations and mortality. LH has been found to exert negative effects on cardiovascular function by reducing the heart size and left ventricular diastolic function.[11,12] LH is also a risk factor for recurrent infective exacerbations and is a predictor of mortality in COPD.[13,14] Pharmacological treatments such as inhaled bronchodilators and non-pharmacological strategies such as pulmonary rehabilitation have been extensively studied and reported to be effective in improving lung volumes.[8,15]

It has been shown that the mechanical reduction of lung volumes by eliminating the severely emphysematous parts of the lungs improves the dynamics of ventilation-to-perfusion matching and lung elastic recoil. Surgical methods of mechanical reduction include lung volume reduction surgery (LVRS) and bullectomy.[5,8] LVRS is unsuitable for high-risk patients because of its greater morbidity and mortality in these patients and can only be offered to highly selected patients.[16] As a result, non-surgical options of lung volume reduction (LVR) have been explored such as the bronchoscopic deployment of one-way expiratory endobronchial valves (EBV), airway bypass stents and coils, all of which aim to reduce LH.

Bronchoscopic deployment of EBV is the most extensively studied endobronchial LVR technique. The only two U.S. FDA-approved one-way valves currently in clinical use are the Zephyr (duckbill-shaped) and Spiration (umbrella-shaped) valve systems. A meta-analysis of all eligible clinical trials investigating the benefits of these two valve systems have found significant improvement in FEV1 (an objective measure of airway obstruction), lung residual volume (RV, an objective measure of lung hyperinflation), 6-minute walk distance (6MWD, an objective measure of exercise capacity) and St. George's Respiratory Questionnaire (SGRQ, a patient-reported measure of quality of life) for at least 6 months when compared with standard medical treatment.[17] The largest multi-centre randomised controlled trial with 190 participants and the longest follow-up period of 12 months to date is the LIBERATE study using the Zephyr valve system. The mean difference between groups in LIBERATE at 12-month follow-up for post-bronchodilator (post-BD) FEV1 in percent change was +17.96%, RV -522 mL, 6MWD +39.31m, SGRQ score -7.05 (lower score indicating better health) and modified Medical Research Council Dyspnoea scale -0.8 points (mMRC, lower score indicating less breathlessness).[18] Sustained benefits have been seen in FEV1, RV and 6MWD even after 3 years.[19] Pneumothorax, haemoptysis and post-procedural pneumonia were the most common complications, usually occurring within 6 months of EBV treatment. Endobronchial LVR treatment has also been reported to be an independent positive predictor of survival and reduces the number of COPD exacerbations.[20]

The greatest benefit of EBV therapy in terms of FEV_1 improvement is seen in those with heterogenous emphysematous disease and complete lobar fissure seen on quantitative CT (QCT) analysis.[21] Incomplete lobar fissure is associated with interlobar collateral ventilation (CV) which may prevent EBV treatment from working.[22] CV is the passage of air between alveoli through channels outside of the normal airways. Interlobar CV is more prevalent in COPD possibly due to the formation of new channels between lobes as a consequence of lung parenchymal destruction.[23] The presence of interlobar CV allows movement of air from an untreated lobe to the EBV-targeted lobe, subsequently preventing collapse and volume reduction.

To identify potential CV which would cause EBV treatment to fail, interlobar fissure completeness (FC) using QCT analysis and bronchoscopic assessment using a catheter-based system called Chartis is performed prior to treatment.[24,25] Chartis is performed using a catheter with an inflatable balloon at the distal tip to occlude the main lobar airway. This is connected to a console that measures airflow, pressure and resistance across the catheter.[26] Once the target bronchus is occluded, absence of flow after 5 minutes signifies the absence of CV. Chartis has a proven 75 - 90% accuracy prediction rate in EBV-treatment response when it determines there is no CV.[27-29] QCT analysis utilises specific automated software to measure FC based on high resolution CT (HRCT) images.[30] The Chartis system is recommended in those with partial FC (80 – 95%) to bolster the confidence of CV assessment but is optional in those with >95% of FC and EBV-treatment is not advocated in those with incomplete fissures (<80%).[24,31]

When treated with EBV, approximately 50% of patients achieved the target of ≥15% post-BD FEV_1 increase, 84% achieved the target total lung volume reduction (TLVR) of ≥350mL and 48% achieved the target mMRC dyspnoea score improvement.[18] As not all patients with confirmed negative CV will benefit from the EBV therapy, it is important to ensure that patients are carefully selected for the procedure. Table 1 summarises the current recommendations for patient selection.[24,25]

Table 1 – Current recommendations for suitability of EBV therapy[24,25]

Criterion	Details
Symptom limitation	mMRC ≥ 2, 6MWD between 100 – 500m.
Residual volume >175% predicted and RV/TLC >55%	Thresholds set in line with previous trials.
Post-BD FEV1 of 15 - 50% of predicted	Thresholds set in line with previous trials.
No evidence of significant coexistent pulmonary pathology on HRCT	Reversible pathologies should be treated pre-EBV treatment. Exclude in severe bronchiectasis and pulmonary fibrosis. High risk of pneumothorax if bulla present in or adjacent to the target lobe.
Heterogeneity of disease	Perfusion scan recommended in homogenous disease to target the lobe with low perfusion for EBV treatment.
Absence of CV in the EBV-targeted lobe	QCT measurement for FC +/- Chartis system.
Prior surgery	Exclude if prior surgery in ipsilateral lung
Hypercapnia	Exclude unless stable on NIV treatment for at least 3 months
Clinically stable disease	Exclude if >3 COPD exacerbations requiring hospitalisation despite optimal medical management in the past 12 months
Suitability for sedation or general anaesthesia and bronchoscopy	Exclude in untreated significant cardiovascular diseases or high risk of complications from general anaesthesia

Smoking cessation	To eliminate a contributing factor to disease progression
Undergone pulmonary rehabilitation and receiving guideline pharmacologic therapy	To optimise medical treatment prior to invasive therapy
Severe congestive heart failure (left ventricular ejection fraction <40%) or pulmonary hypertension (right ventricular systolic pressure >50 mmHg)	Exclude due to poor outcomes

Unfortunately, the modalities currently used to assess CV may fail. FC measurements can be under- or overestimated between software used in QCT analysis.[32] The Chartis system may also fail in about 20% of cases.[29] Failure has been attributed to low patient tolerance during bronchoscopy, inaccurate position or inadequate inflation of the balloon, the presence of secretions and false negative measurements.[30,33]

Because of its 20% failure rate, plus the need for bronchoscopy, a technique that reduces the failure rate and removes the need for bronchoscopy would clearly be of benefit. Hyperpolarised xenon-129 (Xe) is a state-of-the-art, non-invasive, ionising-radiation-free functional imaging modality that is reproducible, quantitative, safe and well-tolerated which involves minimal patient effort.[34,35] The inhalation of Xe gas imaged using MRI (HPX-MRI) enables direct visualisation of lung structure as it flows and fills the airways and alveoli, mirroring the passage of atmospheric gases.[36] Abnormalities in ventilation, due to airway narrowing or bullae formation for example, can be qualitatively and quantitatively measured.[37]

Proof of principle for the ability of hyperpolarised gas MRI to directly visualise CV was first described by Marshall *et al*.[38] Using a static imaging technique of a single breath-hold of up to 20 seconds, they were able to demonstrate delayed filling of ventilation defects thought to be due to collateral ventilation in four out of 10 COPD patients scanned. Delayed ventilation (DV) could be attributed to other factors such as air trapping and significant peripheral airway obstruction. However, in their cohort of patients, collateral ventilation was more plausible due to the peripheral to central pattern of delayed filling of ventilation defects. Chen *et al*. was able to assess DV using dynamic HPX-MRI in 13 out of 15 COPD scanned and suggested further research to establish dynamic HPX-MRI ability to assess CV.[39]

The aim of this study would be to assess the movement of Xe gas in the lungs using HPX-MRI to determine whether in patients with severe COPD it can reliably detect and measure collateral ventilation.

6. OBJECTIVES AND OUTCOME MEASURES

	Objectives	**Outcome Measures**	**Timepoints**
Primary	To characterise the pattern of ventilation on HPX-MRI in those with confirmed CV and those treated with EBV	Quantitative and/or qualitative detection of differences in the pattern of ventilation in the two cohorts being investigated:	Baseline and follow-up

		a) Those with and without confirmed CV; b) Those who were and weren't successfully treated with EBV.	
Secondary	To describe the physiological changes of the lungs seen on HPX-MRI post-EBV treatment	Quantitative and/or qualitative differences of HPX-MRI findings pre- and post-EBV therapy	Baseline and follow-up

7. STUDY DESIGN

This is a prospective, observational, cohort study comprising two patient cohorts – Cohort A – COPD patients, patients selected and planned for EBV treatment and Cohort B – COPD patients deemed unsuitable for EBV treatment due to presence of CV determined by the current gold standard assessments. The comparison of patterns of ventilation and/or physiological movement of gas using HPX-MRI will allow the assessment of collateral ventilation in the two cohorts of patients.

The study will recruit patients into the two cohorts through the local hospital-based COPD clinics. Participants who have been worked up for EBV therapy and their cases discussed at the local COPD multi-disciplinary team (MDT) meeting will be identified by the Clinician and informed of the study. COPD MDT comprises of respiratory physician(s), thoracic surgeon(s), thoracic radiologist(s), specialist nurse(s), respiratory physiotherapist(s) and occupational therapist(s).

The research team may participate in the MDT meetings where possible and may highlight potential patients suitable for the study to the clinicians. The clinicians involved in the MDT and the patients clinical care will inform the potential patients of the study and, if they agree, will provide them with the PIS and consent form, and ask their permission to be contacted by the research team to further discuss the study. If they agree to be contacted, a member of the research team will contact them, explain the study, assess eligibility and complete the informed consent form with the patient if they wish to participate. They will then invite them to undertake their baseline study visit locally at the Churchill Hospital, Oxford University Hospitals NHS Foundation Trust.

At the baseline visit, participants written consent (unless obtained prior to baseline visit), demographics, past medical history, alcohol and smoking history are collected, where possible. They may have their baseline heart rate, blood pressure, respiratory rate and oxygen saturations recorded. These and all trial data will be recorded in the EXPLICIT eCRF. As part of their clinical work-up for EBV therapy, a thin section volumetric CT chest (and its corresponding QCT analysis using StratX software) +/- Chartis assessment, full pulmonary function tests (PFTs), 6-minute walk test (6MWT), mMRC dyspnoea score and SGRQ should have been completed, where possible. If any of these (except PFTs, StratX and Chartis) were not completed as a part of their clinical

assessment before their baseline visit, they shall be carried out during their baseline visit, where possible.

HPX-MRI chest and/or perfusion MRI may be performed at the baseline visit. In the event of a new respiratory condition developed since the clinical CT chest as part of the EBV work-up before the baseline visit, a research low-dose CT may be performed to ensure the lung parenchyma has not changed. This will be justified by a research clinician, e.g. in the event of a new chest infection.

Following their baseline visit, participants who have had undergone EBV therapy may be invited to complete one additional follow-up visit after their first clinical post-procedure follow-up. This follow-up visit should happen at 6 months of their clinical follow-up. All the assessments carried out as part of their EBV clinical work-up (except StratX and Chartis) should have been repeated during their clinical follow-up. If any of these were not completed as part of their clinical assessment before their follow-up visit, they shall be carried out during their follow-up visit, where possible. HPX-MRI Chest and/or perfusion MRI may be repeated as part of their follow-up visit.

Participants who have not undergone EBV treatment will be invited at 6 months following their baseline visit to repeat all the assessments carried out during their baseline visit (except StratX and Chartis), where possible. HPX-MRI Chest and/or perfusion MRI may be repeated as part of their follow-up visit. In the event of a new respiratory condition developed since their baseline visit, a research low-dose CT may be performed to ensure the lung parenchyma has not changed. This will be justified by a research clinician, e.g. in the event of a new chest infection.

Each visit may comprise of one or more appointments to complete all the necessary assessments for the study. The research team will endeavour to coincide the research visits with pre-arranged clinical appointments at the hospital to reduce the burden of travel to the hospital site. Participants may be reimbursed up to £50 per visit if they have had to travel to the hospital site specifically for this research study.

All information will be recorded in a locally approved, secure, study database.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Study participants will be recruited to one of the cohorts as explained in the diagram below.

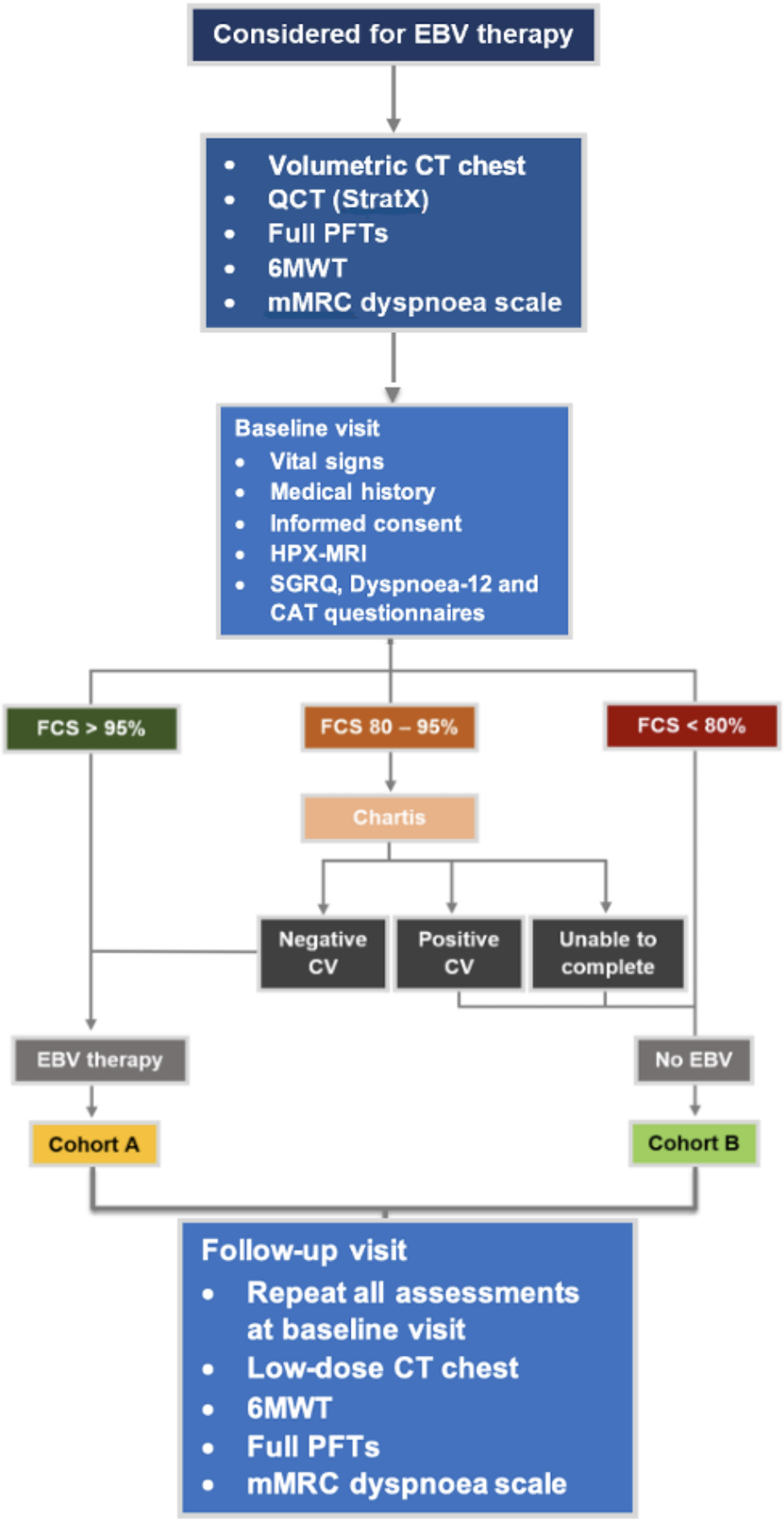
Considered for EBV therapy
Volumetric CT chest
QCT (StratX)
Full PFTs
6MWT
mMRC dyspnoea scale
Baseline visit
Vital signs
Medical history
Informed consent
HPX-MRI
SGRQ, Dyspnoea-12 and CAT questionnaires
FCS > 95%
FCS 80 – 95%
FCS < 80%
Chartis
Negative CV
Positive CV
Unable to complete
EBV therapy
No EBV
Cohort A
Cohort B
Follow-up visit
Repeat all assessments at baseline visit
Low-dose CT chest
6MWT
Full PFTs
mMRC dyspnoea scale

Figure 1 – EXPLICIT recruitment and study assessments flow chart.

Abbreviations: 6MWT – 6-minute walk test, CAT – COPD assessment test, CT – Computed tomography, CV – Collateral ventilation, EBV – Endobronchial valve, FCS – Fissure completeness score, HPX-MRI – Hyperpolarised xenon magnetic resonance imaging, mMRC – Modified Medical Research Council, PFTs – Pulmonary function tests, QCT – Quantitative CT, SGRQ – St. George's Respiratory Questionnaire

Cohort A (No evidence of CV and planned for EBV treatment)

- Data from this cohort will provide information on the patterns of ventilation when no CV has been established using QCT and/or Chartis assessment.
- Subgroup analysis will help identify if there are differences in the patterns of ventilation in those with confirmed successful treatment with EBV (radiologically confirmed atelectasis, and/or lung function and/or symptomatic improvement) and those who are deemed to not have successful treatment with EBV.
- Subgroup analysis will help identify if there were differences in the patterns of ventilation in those who have CV ruled out using QCT assessment only and those who have CV ruled out using both QCT and Chartis assessments.

Cohort B (Ineligible for EBV treatment following current gold standard assessments)

- Data from this cohort will provide information on the patterns of ventilation when CV has been established using current standard assessments and those deemed ineligible for EBV treatment due to inconclusive or incomplete Chartis assessment.

8.2. Inclusion Criteria

- Aged 18 years or over
- Willing and able to give informed consent
- Worked up for EBV therapy in the local COPD clinic

Cohort A – No evidence of CV and eligible for EBV treatment

- MDT and patient decision for EBV therapy

Cohort B – Ineligible for EBV treatment following current standard assessments

- MDT decision not for EBV therapy

8.3. Exclusion Criteria

- Pregnant, lactating or planning pregnancy during the course of the study
- Inability to lie flat for imaging

- Contraindications to MRI examinations as locally determined
- Any other reason, as determined by the study investigators, that renders the participant ineligible for the study

9. PROTOCOL PROCEDURES

9.1. Recruitment

Participants for all cohorts will be recruited from local COPD specialist clinics in Oxford University Hospitals NHS Foundation Trust once identified by a respiratory specialist.

9.2. Screening and Eligibility Assessment

Patients will be identified at the COPD MDT by clinicians with the guidance of the research team if they are present at the MDT meeting. Patients will be assessed by the clinical teams for eligibility against the inclusion and exclusion criteria. The clinicians involved in the MDT and the patients clinical care will inform the potential patients of the study and, if they agree, will provide them with the PIS and consent form, and ask their permission to be contacted by the research team to further discuss the study. If they agree to be contacted, a member of the research team will contact them, explain the study, assess eligibility and complete the informed consent form with the patient if they wish to participate. There will be no access to patient identifiable data outside of the direct care team prior to consent.

Participants must satisfy all the approved inclusion and exclusion criteria of the protocol. Participants will receive the Patient Information Sheet via email, in person or by post. They will then be invited to participate, and informed consent will be obtained prior to baseline visit, remotely..

9.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as needed to consider the information, and the opportunity to question the Investigator(s), their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the

signed Informed Consent will be given to the participant. Copies of the consent form will be retained at the study site and will be stored with the participant hospital record.

9.4. Randomisation

This study is not randomised. At registration, all participants will be assigned a unique study ID.

9.5. Blinding and code-breaking

There is no blinding in the study and no code breaking procedure.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

This is a prospective, cohort study of patients considered for EBV therapy as part of COPD treatment, using HPX-MRI as an additional imaging test. Please see Appendix A for the study schedule of procedures.

9.6.1. Description of study intervention(s)

Hyperpolarised Xenon gas HPX-MRI

HPX-MRI requires breathing in hyperpolarised Xenon, also known as 129Xe. Xenon is an inert gas that is present in the atmosphere in low concentrations, and has no smell or taste. Breathing Xenon or undergoing an MRI scan does not involve exposure to ionising radiation. The Xenon gas is manufactured and released in MHRA regulatory-approved facilities at Oxford. HPX-MR imaging will be performed using Xenon hyperpolarised by a Xenon hyperpolariser, which makes the xenon visible using MRI. The participant will be asked to inhale the gas and to breath-hold for a sufficient time (usually a few seconds) to allow for a successful attainment of images in the MRI scanner. The participant may undergo up to 4 hyperpolarized xenon breath-holds in a single scanning session.

Xenon has been found to be extremely safe and well tolerated, both during single breath-hold experiments. Common side effects include dizziness, drowsiness, deepening of the voice and a feeling of euphoria. They typically last a few seconds. Studies of over 1000 patients performed world-wide have shown no reported serious adverse events related to Xenon inhalation.

The patient will lie in an MR scanner and have conventional safety monitoring throughout the scan. Safety monitoring will consist of a combination of the following: direct visual observation, oxygen saturation and heart rate monitoring.

9.6.2. Description of comparator(s)

There is no comparator in this study.

9.6.3. Description of study procedure(s)

See Appendix A for Study Schedule for when study procedures are required.

Clinical information (10 mins)

Medical history including COPD GOLD stage, demographics, smoking and alcohol history, allergies, medications, mMRC dyspnoea scale and anthropometric measurements including height and weight, will be recorded during the study visit and entered directly into the study database.

Observations (5 mins)

Blood pressure, heart rate, respiratory rate and oxygen saturations

6-minute walk test (10 mins)

A six-minute walk test will be performed if not already performed as part of clinical assessment. The distance achieved (in metres) following 6 minutes of walking will be recorded alongside the pre and post oxygen saturations and mBORG score.

Questionnaires (10 mins)

Participant will complete questionnaires addressing dyspnoea and health quality if not already completed as part of clinical work-up (CAT, Dyspnoea-12 and SGRQ). Participants may complete questionnaires using a secure electronic system, either independently via an automated online link or in person with a member of the research team using a tablet device.

Other than recording the severity of physical experience of breathlessness, the Dyspnoea-12 scale also assesses emotional distress with relation to the patient's breathlessness. In cases where the participants score high in this section, the information will be sent further to the concerned clinician for appropriate management of any concerns.

MRI (approximately 30 mins)

Enrolled participants will be asked to inhale hyperpolarised xenon, on up to 4 occasions per visit (this will enable different sequence data to be acquired, and to allow scanning to be repeated if there is a technical failure).

Xenon is an inert gas that is present in the atmosphere in low concentrations. It has no smell or taste. Breathing xenon or undergoing an MRI scan does not involve exposure to ionising radiation. The xenon gas is manufactured and released in MHRA regulatory approved facilities in Oxford.

Side effects

Xenon has been found to be extremely safe and well tolerated. Common side effects include dizziness, drowsiness, deepening of the voice and a feeling of euphoria. They typically last less than a minute. In studies of over 1000 patients performed around the world; no serious adverse events (SAEs) have been reported related to xenon inhalation.

CT chest scan (5 mins) – *not necessarily performed at baseline visit*

An initial CT scan would be undertaken to clinically assess for the suitability of EBV and would ideally be used as the baseline scan. However, a research scan may be conducted, in case a new respiratory condition has developed before the baseline data collection. This will then be used as a baseline scan for the study. This is to ensure the lung parenchyma has not changed, for accurate correlation with HPX-MRI. This scan would be conducted only after the research clinician has justified it as necessary. Another research specific scan at visit 2 will be undertaken if not already done as a part of clinical reasons. The research scans would be done with a 1 litre bag of air (inspiration only).

Pulmonary Function Tests (PFTs) – *Required for eligibility assessment at baseline*

This will be performed as part of the clinical work-up and the results will be recorded for this study as part of research data collection. PFTs include: Spirometry (pre- and post-BD FEV1 and FVC), lung volumes (RV and TLC) and gas transfer (TLCO and KCO). This may be repeated at follow-up visit if not already performed as part of clinical follow-up.

QCT (StratX) – *not performed as part of research. Required for eligibility assessment.*

This will be performed as part of the clinical work-up. Thin section volumetric CT chest images will be uploaded onto StratX, and its automated analysis will provide data on lung voxel density and FCS. The results will be recorded for this study as part of research data collection.

Chartis – *not performed at baseline visit. Required for eligibility assessment.*

This will be performed as part of the clinical work-up. The endobronchial catheter-based system will measure the airflow and resistance of the occluded airway for at least 5 minutes to determine the presence of CV. The results will be recorded for this study as part of research data collection.

9.7. Baseline and follow up assessments

Initial patient approach

- Eligibility assessment by clinical team
- Study information provided to eligible patients

Visit 1 - Baseline

- Review of eligibility with participant
- Obtain written informed consent (unless obtained prior to baseline visit)

- All procedures will be performed as listed above

Visit 2 (6 months follow-up following EBV treatment (Cohort A) or the baseline visit (Cohort B))

Participants will be invited to attend for follow up where all assessments from visit 1 will be repeated.

Face to face visits will take approximately 2 hours.

9.8. Sample Handling

Samples for routine clinical care will be conducted as per local hospital practice.

9.9. Early Discontinuation/Withdrawal of Participants

During the course of the study, a participant may choose to withdraw early from the study treatment at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE
- Inability to comply with study procedures
- Participant decision

According to the design of the study, participants have the following options if they withdraw from the study:

1. Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.
2. Participants can withdraw from study scans but continue with data collection. Data already obtained will be retained for use in study analysis.
3. Participants are free to request all data to be withdrawn at any point and not used in data analysis unless already done so prior to patient's withdrawal

In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including, but not limited to:

1. Pregnancy
2. Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
3. Clinical decision

Participants that choose to withdraw from the study will not be replaced. The type of withdrawal and reason for withdrawal will be recorded in the case report form (CRF). If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

9.10. Definition of End of Study

The end of study will be defined as when all data has been entered and all queries resolved.

10. SAFETY REPORTING

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Reporting Procedures for Serious Adverse Events

A SAE occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). However, CT and Xenon MRI are widely used, and we have established data on safety, therefore SAEs or related AEs are not expected.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The plan for the statistical analysis of the study is outlined below. There is not a separate SAP document in use for the trial.

11.2. Description of the Statistical Methods

All baseline characteristics and measures will be summarised overall and by cohort and group, using appropriate summary statistics.

We will aim to describe the prevalence of DV in patients with COPD being worked up for EBV. We will aim to describe the patterns of ventilation seen on HPX-MRI in patients with COPD who have been successfully treated with EBV and compare these findings with those who have not been successfully treated with EBV and those who have not been treated with EBV.

We will aim to examine the relationship between the presence of DV on HPX-MRI and EBV treatment success. We will also aim to correlate the presence of DV seen on HPX-MRI to the presence of CV following Chartis assessment and FC <95% on StratX. Where possible, we aim to examine the relevance of MRI perfusion to the success of EBV treatment and presence of DV. We will also aim to describe the physiological changes observed on HPX-MRI in those who have undergone EBV treatment and whether these changes are different in those who have been treated successfully to those who have not.

Continuous data, including questionnaire outcomes, will be summarised by group and time point using mean and standard deviation (or median and interquartile range if non normally distributed). Effects on outcomes over time (baseline visit and follow up visit) will be analysed using appropriate statistical models.

11.3. Sample Size Determination

This is an exploratory study assessing the value of a novel imaging technique in the assessment of ventilation in those being considered for EBV treatment.

We plan to recruit 40 patients (20 in each Cohort) over a study period of 24 months. Approximately 20 – 30 patients undergo EBV treatment a year in OUH. As the only additional test required of the participants beyond their clinical investigations in this study is the HPX-MRI which could be done on the same day of their other clinical investigations, we could expect a reasonable (i.e. >50%) uptake to the study. Assuming a 50-60% recruitment rate per year, we estimate recruitment of 12-15 patients to Cohort A per year to a total of 20 patients in 18 months.

More patients will be expected to not meet the stringent criteria for EBV therapy. Recruitment of 20 patients to Cohort B will be achievable quicker than Cohort A given the greater number of patients deemed unsuitable post assessment.

This is a pilot study, and an accurate sample size calculation to determine the value of HPX-MRI is not possible. But from our prior studies, Chen et al., Doganay et al., and the Marshall et al. study, it appears that more than 50% of patients with severe COPD have delayed ventilation (DV) suggesting collateral ventilation(CV). This suggests that if HPX-MRI is to generate a useful signal related to DV/CV in comparison to Chartis and QCT may be detectable, as at least 20 of the 40 patients may have DV/CV.

11.4. Analysis populations

All participants who have completed HPX-MRI scans will be included in the analyses.

11.5. Stopping rules

Not applicable.

11.6. The Level of Statistical Significance

Statistical significance will be adapted depending on the novelty of results.[40]

11.7. Procedure for Accounting for Missing, Unused, and Spurious Data.

Complete case analysis will be performed at each time point. Missing data will be excluded.

11.8. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviations from the original statistical plan will be reported in the yearly trial report.

12. DATA MANAGEMENT

The plan for the data management of the study is outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.
Anonymised study data may be shared with approved third parties, including commercial organisations, to help improve imaging and treatment for people with COPD and other lung conditions. One example of this is that we may share anonymised Xenon MRI and CT scan data with researchers at the University of Oxford to support work on improving how the scans are analysed and matched together (a process called co-registration).

12.3. Data Recording and Record Keeping

All study data will be stored using one or more of: password protected hard drives and NHS servers in anonymised form.

All documents containing personal data (the linkage spreadsheet and informed consent forms) will be stored securely in lockable cabinets and are only accessible by study staff and authorised personnel. Personal data such as personal addresses, postcodes, emails or telephone numbers of participants will be recorded electronically on spreadsheets for screened and enrolled patients that are accessed via an access-restricted computer. Personal data such as contact details and information that could lead to the identification of a participant (except for those who have consented to be approached for future research) will be destroyed as soon as it is practical to do so and no later than 12 months after the end of the study.

The study investigators are responsible for keeping documents encrypted where possible and kept securely to ensure that in case of an emergency, participants can be identified and contacted. Study data, including all standard of care EBV work up and follow-up taken from the medical notes, will be recorded in a de-identified manner directly into the study database; participants would not be identifiable from this. All participants will be identified by a code number (unique study ID number) on case report forms and any electronic databases. All source documents will have all identifiers removed and replaced by only the unique study ID number. This also applies to control participants.

The consent forms which link the study ID with the name of the participant will be stored in the Trial Master File, separately to the study data, and will be archived for a minimum of 5 years after the end of the study.

Pseudonymised imaging and study data will be transferred and stored on secure OUH NHS FT and servers and/or encrypted hard drives. This transfer will be performed in line with the Trust's information security handling rules Information Protection Policy (ouh.nhs.uk).
Pseudonymised imaging and study data may be used for commercial purposes, but only with consent from a participant.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Data collected for the study may be reviewed for auditing and monitoring by authorised persons from the sponsor, regulatory authorities or their local host institutions to make sure that study is being carried out correctly. All investigators have a duty of confidentiality to research participants and nothing that could reveal their identity would be disclosed outside the research study team or site without specific consent from the research participant.

13.1. Risk assessment

A risk assessment and monitoring are not deemed necessary. Any risks associated with the study assessments or data management have been outlined in the protocol (sections 13 and 17.3) and mitigations outlined.

13.2. Study monitoring

No monitoring required for this study.

13.3. Study Committees

There are no oversight committees for this study as it is a small low-risk clinical research study.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file. A standard operating procedure will be in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event of a serious breach is suspected, the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval of the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

There will be no involvement of vulnerable participants or participants who are unable to consent for themselves. If a participant loses capacity during their participation in the study, they will be withdrawn from the study, study data collected to that point will be retained and they may be replaced by a new participant.

The scan sequences and their images will be reviewed for quality control, utility, and to determine how best they may be improved. The researchers on reviewing the research scans will not record or report any abnormalities identified unless it is considered to be clearly in the participant's clinical interest. In such a case, the participant will be informed that there is a potential abnormality that warrants a referral for further assessment. This is to avoid unnecessary anxiety and consequences for false positive clinically insignificant abnormalities that may be detected by scanning even in healthy individuals. The participants will be made aware of this before being asked to give informed consent.

16.5. Reporting

The CI shall submit an End of Study notification and final study report to the REC Committee (and any other parties as required).

16.6. Transparency in Research

Prior to the recruitment of the first participant, the study will have been registered on a publicly accessible database.

Where the study has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

16.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

The participants will not be paid for taking part; however, we will reimburse reasonable travel expenses where appropriate, and will provide refreshments throughout the visit.

17. FINANCE AND INSURANCE

17.1. Funding

This study is funded by the UKRI – OPP555 - Medical Research Council (MRC) July 2024.

17.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by UKRI MRC. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the OUH vests in OUH. The protection and exploitation of any new IP is managed by the IP and Research Contracts Team at OUH NHS FT.

20. ARCHIVING

At the end of the study, electronic files containing the anonymised data will be transferred to an encrypted hard drive and will be stored securely in an offsite archiving company which has been approved by the OUH NHSFT. This will be in line with local Record Retention Policy. The minimum retention period for research data and records is 5 years after publication or public release of the work of the research. After the archiving period has ended, the offsite commercial archiving company will confidentially and securely destroy the paper documents and electronic files.

21. REFERENCES

1. Celli B, Fabbri L, Criner G, Martinez FJ, Mannino D, Vogelmeier C, et al. Definition and Nomenclature of Chronic Obstructive Pulmonary Disease: Time for Its Revision. Am J Respir Crit Care Med. 2022 Dec; 206(11): 1317-1325.
2. World Health Organization (WHO). Chronic obstructive airways disease. 2016 Mar. https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd).
3. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017 Sep; 5(9): 691-706.
4. Nigris E, McEwan P, Marhsall J, Holmgren U, Foos V. POSB65 Economic Burden of COPD in the United Kingdom (2021–2040) Estimated with the COPD Health Outcome Policy and Intervention (CHOPIN) Model [abstract]. In: Drummond M, Mullins CD, editors. Virtual ISPOR Europe; 2021 Nov 30 – Dec 3. Value in Health; 2022 Jan; 25(1): S72-S73.
5. Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2023 GOLD Report. Feb 2023. https://goldcopd.org/wp-content/uploads/2023/03/GOLD-2023-ver-1.3-17Feb2023_WMV.pdf.
6. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med. 2011 Oct; 365(17): 1567-1575.

7. O'Donnell DE, Laveneziana P. Physiology and consequences of lung hyperinflation in COPD. Eur Res Rev. 2006; 15: 61 – 67.
8. Rossi A, Aisanov Z, Avdeev S, Di Maria G, Donner CF, Izquierdo JL, et al. Mechanisms, assessment and therapeutic implications of lung hyperinflation in COPD. Respir Med. 2015 Jul; 109(7): 785-802.
9. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006 Apr; 3(2): 180-184.
10. Miravitlles M, Worth H, Soler Cataluña JJ, Price D, De Benedetto F, Roche N, et al. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. Respir Res. 2014 Oct; 15(1): 122.
11. Watz H, Waschki B, Boehme C, Claussen M, Meyer T, Magnussen H. Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study. Am J Respir Crit Care Med. 2008 Apr; 177(7): 743-751.
12. Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, et al. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. Chest. 2010 Jul; 138(1): 32-38.
13. Zaman M, Mahmood S, Altayeh A. Low inspiratory capacity to total lung capacity ratio is a risk factor for chronic obstructive pulmonary disease exacerbation. Am J Med Sci. 2010 May; 339(5): 411-414.
14. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005 Mar; 171(6): 591-597.
15. Thomas M, Decramer M, O'Donnell DE. No room to breathe: the importance of lung hyperinflation in COPD. Prim Care Respir J. 2013 Mar; 22(1): 101-111.
16. Criner GJ, Cordova F, Sternberg AL, Martinez FJ. The National Emphysema Treatment Trial (NETT) Part II: Lessons learned about lung volume reduction surgery. Am J Respir Crit Care Med. 2011 Oct;184(8): 881-893.
17. Patel M, Chowdhury J, Zhao H, Lu X, Roth S, Giovacchini CX, et al. Meta-analysis and Systematic Review of Bronchoscopic Lung Volume Reduction Through Endobronchial Valves in Severe Emphysema. J Bronchology Interv Pulmonol. 2022 Jul; 29(3): 224-237.
18. Criner GJ, Sue R, Wright S, Dransfield M, Rivas-Perez H, Wiese T, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE). Am J Respir Crit Care Med. 2018 Nov; 198(9): 1151-1164.
19. Gompelmann D, Heinhold T, Rötting M, Bischoff E, Kontogianni K, Eberhardt R, et al. Long-term follow up after endoscopic valve therapy in patients with severe emphysema. Ther Adv Respir Dis. 2019 Jan-Dec; 13: 1753466619866101.
20. Hartman JE, Welling JBA, Klooster K, Carpaij OA, Augustijn SWS, Slebos DJ. Survival in COPD patients treated with bronchoscopic lung volume reduction. Respir Med. 2022 May; 196: 106825.
21. Sciurba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med. 2010 Sep; 363(13): 1233-1244.
22. Davey C, Zoumot Z, Jordan S, Carr DH, Polkey MI, Shah PL, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi trial): study design and rationale. Thorax. 2015 Mar; 70(3): 288-290.
23. Cetti EJ, Moore AJ, Geddes DM. Collateral ventilation. Thorax. 2006 May; 61(5): 371-373.

24. Slebos DJ, Shah PL, Herth FJ, Valipour A. Endobronchial Valves for Endoscopic Lung Volume Reduction: Best Practice Recommendations from Expert Panel on Endoscopic Lung Volume Reduction. Respiration. 2017; 93(2): 138-150.
25. Klooster K, Slebos DJ. Endobronchial Valves for the Treatment of Advanced Emphysema. Chest. 2021 May; 159(5): 1833-1842.
26. PulmonX. The Chartis® Tablet. Pulmonx, Redwood, 2018. https://pulmonx.com/chestv2021/chartis/
27. Herth FJ, Eberhardt R, Gompelmann D, Ficker JH, Wagner M, Ek L, et al. Radiological and clinical outcomes of using Chartis™ to plan endobronchial valve treatment. Eur Respir J. 2013 Feb; 41(2): 302-308.
28. Shah PL, Herth FJ. Current status of bronchoscopic lung volume reduction with endobronchial valves. Thorax. 2014 Mar; 69(3): 280-286.
29. Gompelmann D, Eberhardt R, Michaud G, Ernst A, Herth FJ. Predicting atelectasis by assessment of collateral ventilation prior to endobronchial lung volume reduction: a feasibility study. Respiration. 2010; 80(5):419-425.
30. Schuhmann M, Raffy P, Yin Y, Gompelmann D, Oguz I, Eberhardt R, et al. Computed tomography predictors of response to endobronchial valve lung reduction treatment. Comparison with Chartis. Am J Respir Crit Care Med. 2015 Apr; 191(7): 767-774.
31. Koster TD, van Rikxoort EM, Huebner RH, Doellinger F, Klooster K, Charbonnier JP, et al. Predicting Lung Volume Reduction after Endobronchial Valve Therapy Is Maximized Using a Combination of Diagnostic Tools. Respiration. 2016 ; 92(3): 150-157.
32. I Gyselinck, P Hoeben, H Geysen, F De Keyzer, C Dooms, D Van Raemdonck, et al. Comparing CT-based fissure completeness scores across software packages to predict interlobar collateral ventilation. Eur Respir J 2022; 60: Suppl. 66, 2840.
33. Gesierich W, Samitas K, Behr J. Determining collateral ventilation during bronchoscopy: unanswered questions. Thorax. 2014 Mar; 69(3): 289-290.
34. Roos JE, McAdams HP, Kaushik SS, Driehuys B. Hyperpolarized Gas MRI: Technique and Applications. Magn Reson Imaging Clin N Am. 2015; 23(2): 217-229.
35. Eddy RL, Parraga G. Pulmonary xenon-129 MRI: new opportunities to unravel enigmas in respiratory medicine. Eur Respir J. 2020; 55(2): 1901987.
36. Gefter WB, Lee KS, Schiebler ML, Parraga G, Seo JB, Ohno Y, et al. Pulmonary functional imaging: Part 2 – State-of-the-Art clinical applications and opportunities for improved patient care. Radiology. 2021; 299: 524-538.
37. Benjamin J, Altes TA, Lancaster L, de Lange EE, Goerner F, Hersman FW, et al. Comparison of Hyperpolarized Xenon-129 MR and Tc-99m DTPA Aerosol Lung Ventilation Imaging in Patients with COPD and Asthma. Poster session presented at: Joint ISMRM-ESMRMB; 2014 May 10-16; Milan, Italy.
38. Marshall H, Deppe MH, Parra-Robles J, Hillis S, Billings CG, Rajaram S, et al. Direct visualisation of collateral ventilation in COPD with hyperpolarised gas MRI. Thorax. 2012 Jul; 67(7): 613-617.
39. Chen M, Doganay O, Matin T, McIntyre A, Rahman N, Bulte D, et al. Delayed ventilation assessment using fast dynamic hyperpolarised Xenon-129 magnetic resonance imaging. Eur Radiol. 2020 Feb; 30(2): 1145-1155.
40. Lakens D, Adolfi FG, Albers CJ, Anvari F, Apps MAJ, Argamon SE, et al. Justify your alpha. Nat Hum Behav 2018; 2.
41. Yorke, J., Swigris, J., Russell, A. M., Moosavi, S. H., Ng Man Kwong, G., Longshaw, M., & Jones, P. W. (2011). Dyspnea-12 is a valid and reliable measure of breathlessness in patients with interstitial lung disease. Chest, 139(1), 159–164. https://doi.org/10.1378/chest.10-0693

22. APPENDIX A: SCHEDULE OF STUDY PROCEDURES

Procedures	All Cohorts	
	Baseline Visit	Visit 2
	Day 0	6 month
Eligibility assessment	✓	
Informed consent	✓†	
Demographics	✓	✓
Medical history	✓	✓
Cardiorespiratory examination (incl. respiratory rate, heart rate, blood pressure and oxygen saturations)	✓	✓
6-minute walk test	✓*	✓*
Pulmonary function tests	✓	✓*
MRI Chest with 129-Xenon gas	✓	✓
CT chest	✓§	✓§
Questionnaires (Dyspnoea-12, SGRQ & CAT)	✓	✓

Abbreviations: SGRQ – St George's Respiratory Questionnaire, CAT – COPD Assessment Test

† Where appropriate, informed consent may take place prior to the baseline visit

*To be performed if not already performed as part of clinical follow-up

§Baseline CT only to be repeated in the event of a new respiratory condition developed since the clinical CT chest as part of the EBV work-up. Follow-up CT only to be performed at visit 2 if a CT has not already been performed as part of clinical follow-up.

Oxford University Hospitals
NHS Foundation Trust

23. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made