A study to determine regional lung function in patients undergoing radiotherapy using hyperpolarized xenon gas MR imaging

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Confidentiality Statement

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1. KEY TRIAL CONTACTS

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2. SYNOPSIS

Trial Title	**A study to determine regional lung function in patients undergoing radiotherapy using hyperpolarized xenon gas MR imaging**	
Short title	**Hyperpolarized Xenon gas MR Imaging in Radiotherapy HPX-2011-003**	
Clinical Phase	Phase II	
Trial Design	Cohort Study	
Trial Participants	Patients considered suitable for radiotherapy that will affect the lung.	
Planned Sample Size	30	
Treatment duration	Hyperpolarized xenon gas will be administered for completion of hyperpolarized Xe-129 MRI scans. Radiotherapy as per local departmental protocols	
Follow up duration	9 months	
Planned Trial Period	7 years	
	Objectives	Outcome Measures/Endpoints
Primary	To demonstrate that hyperpolarized Xe-129 is sensitive to change following pulmonary radiotherapy, and thus may be developed as an objective and quantifiable method of functional lung assessment in patients undergoing radiotherapy that affects the lung	Change in hyperpolarized Xe-129 MR imaging from baseline to other time points post radiotherapy initiation.
Secondary	To obtain preliminary data demonstrating if changes in hyperpolarized Xe-129 MR imaging correlate with subjective and objective responses following pulmonary radiotherapy. To obtain preliminary data demonstrating if baseline hyperpolarized Xe-129 MR	Change in hyperpolarized Xe-129 MR imaging parameters from baseline to other time points post radiotherapy initiation compared to subjective and objective measures of lung function. Comparison of hyperpolarized Xe-129 MR imaging and four-

	imaging is a more reliable clinical indicator of patient respiratory tolerance to pulmonary radiotherapy than conventional lung function testing by determining the relationship between hyperpolarized Xe-129 MR imaging indices and functional patient outcome measures (dyspnoea and radiation-induced lung toxicity assessment). To use functional lung information in virtual predictive and adaptive radiotherapy treatment planning.	dimensional CT (4D-CT) at baseline. Retrospective comparison of modified radiotherapy treatment planning incorporating functional lung information from hyperpolarized Xe-129 MR imaging with conventional radiotherapy treatment plans.
Investigational Medicinal Product(s)	Hyperpolarized xenon gas	
Formulation, Dose, Route of Administration	The xenon gas will be hyperpolarized in the Radiology department, Churchill Hospital. We will administer a maximum of 6 x 1 Litre doses of hyperpolarized xenon gas to each participant per hospital visit for Xe-129 lung MR imaging. If it is not essential to give 100% xenon for imaging, the gas may be diluted with ultrapure nitrogen. The ratio of xenon to nitrogen will vary from 10% to 100% but the volume provided to the patient will always be 1 L. The route of administration is inhalation.	

3. ABBREVIATIONS

ADC	Apparent diffusion co-efficient
AE	Adverse event
AR	Adverse reaction
BRC	Biomedical Research Centre
cm^2s^{-1}	Square centimetres per second (measure of ADC)
CI	Chief Investigator
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
CRT	Chemoradiotherapy
CT	Computed tomography
4D-CT	Four-dimensional computed tomography
CTCAE	Common terminology criteria for adverse events
CTA	Clinical Trials Authorisation
EBRT	External beam radiotherapy
EPI	Echo Planar Imaging
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
FiXe	Fraction of inhaled xenon
FXe	Fraction of xenon
GCP	Good Clinical Practice
GP	General Practitioner
He	Helium
IB	Investigators Brochure
IMP	Investigational Medicinal Product
L	Litre
LPV	Lobar perfusion Value
MAC	Maximum Alveolar Concentration
MHRA	Medicines and healthcare products regulatory agency
MLD	Mean lung dose
MR/MRI	Magnetic resonance imaging
NIHR	National Institute for Health Research
NSCLC	Non-small cell lung cancer
PO_2	Partial pressure of oxygen

PTV	Planning target volume
PV	Perfusion values
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RILT	Radiation induced lung toxicity
RT	Radical radiotherapy
SAE	Serious Adverse Event
SaO_2	Arterial oxygen saturation
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SPV	Segmental perfusion value
SUSAR	Suspected Unexpected Serious Adverse Reactions
S\V	Alveolar surface area per unit volume of gas
TMF	Trial Master File
TSG	Oxford Radcliffe Hospitals Trust / University of Oxford Trials Safety Group
VPV	Ventilation perfusion volume
VDV	Ventilation defect volume
Xe	Xenon
XTC	Xenon Transfer Contrast

4. BACKGROUND AND RATIONALE

Lung cancer is the second most common cancer in the UK, with approximately 39,000 new cases diagnosed each year (1). It is the most common cause of cancer death for both men and women in the UK, accounting for 22% of all cancer deaths, which equates to around 34,500 people. Survival rates for lung cancer are poor. One year survival rates in the UK for males is 27% and for females 30%, falling to less than 10% at five years (2). Prognosis for lung cancer is so poor because over two thirds of patients are diagnosed at a late stage when curative treatment is not possible. Early diagnosis and assessment of tolerance for curative treatment would make a significant difference to survival rates.

Histologically, approximately 80% of lung cancer is non-small cell lung cancer (NSCLC). The main curative treatments for NSCLC are surgery, radical radiotherapy (RT) and radical chemoradiotherapy (CRT).

4.1. Radiation induced lung toxicity (RILT)

Radiation induced lung toxicity (RILT) occurs when normal lung tissue is irradiated while treating tumours. RILT presents in two phases designated radiation pneumonitis (acute) and fibrosis (late). Radiation pneumonitis generally occurs between two and seven months after RT and may present clinically with cough, dyspnoea, fever and chest pain or with radiographic changes only. Acute pneumonitis is treated with steroids but can be life-threatening even with treatment, though with early identification and treatment most patients recover. If untreated, acute pneumonitis can progress to permanent fibrosis after more than six months. RILT has been shown to increase in frequency after increased radiation dose, increased volume of the lung irradiated, some combinations of chemotherapy and RT, previous radiation and steroid withdrawal.

The risk of developing RILT can be determined by assessment of the mean lung dose (MLD) and volume of lung receiving a dose of 5-20 Gy ($V_{5\text{-}20}$) over a course of radical RT (3-10)**.** By reducing set-up variability and tumour motion due to respiration, the planning target volume (PTV) margins can be reduced, thus reducing the amount of normal lung irradiated and potentially resulting in a lower risk of RILT.

4.2. Functional imaging can identify lung injury

Radiation planning using only computed tomography (CT) data has traditionally treated all regions of the lung equally. However, most gas exchange occurs in the inferior aspects of the lung and irradiation of this region is correlated with risk of RILT. By identifying functioning lung that is irradiated, ventilation and perfusion imaging may improve prediction and assessment of pulmonary toxicity following radiotherapy. Pulmonary perfusion-weighted treatment plan optimization may be useful in reducing radiation damage in patients with large perfusion defects.

External Beam RT (EBRT) planning has traditionally used anatomic imaging to aid localisation of the target structures and surrounding normal structures. The risk of RILT with radical RT is based on the assumption that lung function is spatially uniform. There is evidence, however, that the functional subunits that contribute to whole lung function are not uniformly distributed (11). This is confounded by potential variations in lung function due to tumour characteristics and patient co-morbidity. Functional imaging of the lung using SPECT ^{99m}Tc labelled macroaggregate albumin provides 3D information on the distribution of pulmonary blood flow and may equate to areas of normal lung function (12). Imaging with hyperpolarized xenon gas MRI has an added advantage, as it not only provides 3D information on lung ventilation but potentially also provides information on lung perfusion. By identifying functioning lung that is irradiated, ventilation and perfusion imaging may improve prediction and assessment of pulmonary toxicity following radiotherapy.

4.3. Current pulmonary functional imaging is limited

Currently assessment of patients for radiotherapy involves lung function measurements to provide a clinical indicator as to whether or not the patient would tolerate treatment and maintain sufficient functioning lung post-treatment to continue with activities of daily living without significant impairment. The current gold standard for assessment of lung function is spirometry and gas transfer. Spirometry and gas transfer reflect *global* lung function but provides no information about the different regions of the lung or regarding the support 'framework' of the lung, the parenchyma. Changes in lung function as measured by spirometry do not coherently correlate with symptom severity or reflect a decline in patient health (13). This weak relationship is probably because the lung is a complex regional organ where localized disturbances of a variety of factors including gas flow (ventilation), blood flow (perfusion) and gas transfer all combine to impair respiratory function.

Some imaging techniques can detect regional lung health, however each has limitations. Computed X-ray tomography (CT) provides structural, rather than functional readout and exposes patients to both radiation and contrast. FDG-PET provides an individualized estimate of radiation response, but not pulmonary function information. Scintigraphy (SPECT) with radioactive gas, can

detect regional lung function changes from irradiation. However, SPECT has low spatial resolution and exposes the patient to ionizing radiation. Both SPECT and PET also expose patients to ionizing radiation.

4.4. Rationale for Hyperpolarized Xe-129 MR Imaging in Radiotherapy

Hyperpolarized Xe-129 MR imaging will provide regional functional information about the lung that may be useful in predicting RILT post radiotherapy. It is feasible to co-register hyperpolarized Xe-129 MRI with RT planning scans. Incorporating information from hyperpolarized Xe-129 MR imaging into radiotherapy planning has the potential to minimise and predict RILT.

Hyperpolarized Xe-129 MR imaging offers the potential to inform the radiotherapy planning process so that parts of the lung demonstrated to function well are spared at the expense of less functional/diseased parts. This may reduce radiotherapy side effects and enable individuals who would otherwise be unsuitable for radical treatment to receive potentially curative therapy.

4.5. Hyperpolarized noble gas MR Imaging

The first hyperpolarized gas MR images were obtained using Xe-129 in a mouse heart lung preparation by Albert et al. (14), followed shortly by hyperpolarized He-3 images of human lungs by MacFall et al. (15). In subsequent years, hyperpolarized He-3 MR imaging became the focus of investigation due to inherent advantageous physical properties. He-3 has a larger magnetic moment than Xe-129 giving an increased signal to noise ratio. Also, until recently polarization methods were capable of achieving 30-50% polarization levels for He-3 but only 10 % for Xe-129 (16, 17). Both of these factors contributed to a stronger MR signal for He-3 compared with Xe-129. In contrast, Patz et al. has described a modified polarization method, which enables 55% polarization levels of Xe-129 to be achieved at a production rate of 5.5 litres/hour (18). These levels of polarization are comparable to those previously published for He-3, making Xe-129 an increasingly attractive agent given its large natural abundance and wide availability.

4.6. Methods of Hyperpolarization

In their natural form, noble gases (Xe-129 and He-3) have low magnetic moments generating a

weak MR signal. Compared to protons, which are abundant throughout the body, there is a limit to the amount of noble gas that can be administered into the lungs. Laser optical pumping is a technique employed to enhance the nuclear polarization of noble gases via a process called hyperpolarization. This technique was developed over 50 years ago and has been extensively applied within the field of physics research (19, 20). Hyperpolarization results in the polarization of noble gases 100, 000 times greater than the polarization of hydrogen nuclei in conventional MRI. This large net polarization gives rise to a large MR signal. In this way hyperpolarization compensates for the low physical density of noble gases introduced to the lungs permitting good visualization of the airspaces. The MR signal is generated by the hyperpolarization of He-3/Xe-129 and is completely independent of the field strength, unlike conventional MRI (21-24). It is therefore possible to perform hyperpolarized Xe-129 MR imaging in a lower field strength with the benefit of reduced susceptibility artefacts. However most studies to date have been undertaken with 1.5T systems due to availability.

Comprehensive details of hyperpolarization methods have been previously published (20, 25-29). There are two methods of laser optical pumping including alkali-metal spin exchange (30) and metastability exchange (19). Hyperpolarization of Xe-129 can only be performed by the spin exchange technique. Both methods employ circularly polarized light at different wavelengths. In brief, the spin exchange technique (*Figure 1.*) involves heating a glass cell containing He-3 or Xe-129 and rubidium metal to produce rubidium vapour. The rubidium atoms absorb circularly polarized laser light illuminating the cell, resulting in high polarization of rubidium by "optical pumping". Collision between the polarized rubidium atoms and noble gas atoms transfers the polarization by "spin exchange". The product is hyperpolarized He-3 or Xe-129 atoms.

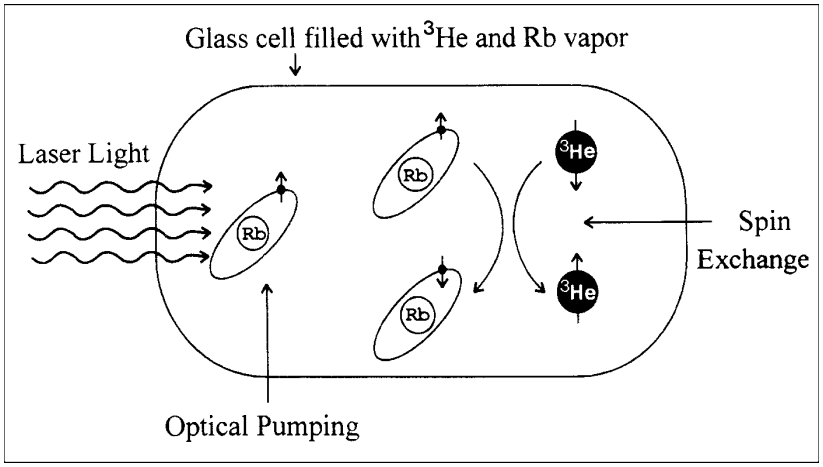


Figure 1. from (16).

Challenges faced when imaging hyperpolarized noble gases include the following: -

1. The hyperpolarization generating the MR signal is "non-renewable". Some polarization will be consumed during image acquisition and may only be replenished by the introduction of additional hyperpolarized gas.

2. The paramagnetic properties of oxygen within the lungs leads to a loss of polarization and decay of MR signal. However, this characteristic can be utilized beneficially to measure intrapulmonary PO_2.
3. He-3 is highly diffusive resulting in MR signal loss.

MR pulse sequences have been developed to account for these factors and enable regional imaging of lung structure and function down to the level of the secondary pulmonary lobule.

4.7. Hyperpolarized Helium (He-3) MR Imaging

To date, hyperpolarized helium (He-3) gas MRI has been the focus of ventilation imaging research. However He-3 is expensive and limited in world supply necessitating further investigation into other suitable gases, namely Xe-129. The techniques and findings from previous research with hyperpolarized He-3 MR imaging form the basis of the current study. A summary of the current literature has been therefore been included.

In normal individuals, the inhaled hyperpolarized He-3 gas is distributed homogenously throughout the lung airspaces. In contrast, localized regions deficient in hyperpolarized gas and therefore MR signal represent ventilation defects. These have been shown in a range of lung pathologies e.g. asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (31) and bronchiolitis obliterans (32, 33). The size and extent of ventilation defects demonstrated with hyperpolarized gas MR correlate with spirometry (16, 31). Furthermore, hyperpolarized gas MRI has shown increased sensitivity in detecting ventilation abnormalities compared with spirometry and lung ventilation scintigraphy (16, 34).

“Dynamic ventilation images” may be obtained with hyperpolarized gas MRI by employing ultrafast pulse sequences (35-38). Dynamic ventilation imaging allows the distribution and severity of air trapping to be assessed directly (37, 38) and has been performed to evaluate air trapping in patients with bronchial asthma (37) and cystic fibrosis (38).

Several methods for the quantitative measurement of regional lung ventilation using hyperpolarized He-3 MRI have been suggested in experimental animal studies (39-41). In a rat model of emphysema, the ventilation abnormalities detected preceded the histological changes seen in lung alveoli (42). This study, demonstrated detectable lung functional changes before structural abnormalities and further supports hyperpolarized gas MR functional imaging for earlier diagnosis in pathological disease processes.

The diffusion coefficient of a particular gas determines the average distance its atoms move in a given period of time. The lung microstructure acts to restrict the diffusion of hyperpolarized noble gas atoms enabling the average short time diffusion coefficient, (apparent diffusion coefficient, ADC) to be measured with MRI (43). Increased ADC values have been reported with

hyperpolarized He-3 MR imaging in emphysema, reflecting the increased free movement of He-3 gas atoms permitted by alveolar tissue destruction (43-46). In this way, regional ADC values can be used as a surrogate measure of alveolar airspace size. Precise correlations between hyperpolarized gas MRI ADC measurements and histological measurements of alveolar size have been reported (47-49). ADC values with hyperpolarized He-3 MR imaging have proven highly reproducible (50, 51), and been shown to correlate strongly with lung function tests (44).

Another potential application of ADC measurements is the assessment of radiation induced lung injury. Post radiation therapy, lower hyperpolarized He-3 ADC values may represent reduced alveolar volumes associated with fibrosis of the interstitium (52).

In the presence of oxygen within the lung, hyperpolarized noble gases undergo hastened loss of polarization resulting in a predicted reduced MR signal (53). This known paramagnetic effect of oxygen on He-3 gas may therefore be utilized to quantitatively measure intrapulmonary PO_2 (54, 55). Reproducibility of intrapulmonary PO_2 measurements has been confirmed.

4.8. Hyperpolarized Xenon (Xe-129) MR Imaging

Xenon (Xe) is an inert, non-toxic noble gas. Atmospheric air contains approximately 0.04 mol% of xenon. The xenon isotope Xe-129 is employed for hyperpolarized xenon MR imaging. The natural abundance of Xe-129 in atmospheric Xe is 26%, and can be extracted relatively easily.

Previous applications of xenon include use as an anaesthetic at high concentrations (at > 3 times the concentration to be used in this study and with ongoing delivery rather than a single breath), in scintigraphic and CT brain perfusion studies and as an inhaled contrast agent in CT (56, 57). Xe-129 is ten times more soluble than He-3 in water and one hundred times more soluble in lipid-rich tissue. Xenon's vastly increased solubility in blood and lipid-rich tissue demonstrates a partition coefficient of approx 0.1 (58). This property of Xe-129 may be exploited to evaluate gas exchange between alveoli and capillaries, and to provide information regarding the diffusion capacity (18, 59-65). In addition to assessment of ventilation and ADC in the gas spaces possible with He-3, Xe-129 allows for dissolved-phase imaging (14).

Following inhalation, approximately only 2% of Xe-129 is dissolved into the lung parenchyma or blood. The blood circulation distributes dissolved Xe-129 throughout the body enabling perfusion imaging in different organs. The MR signal characteristics of Xe-129 are strongly influenced by its environment such that the signal from dissolved-phase Xe-129 is significantly different to that of the gas-phase. A chemical shift of signal in the dissolved-phase is seen of approximately 200 parts per million from that of the gas-phase. Chemical shifting imaging in the lungs and other body organs has been demonstrated in rat models (66, 67). Investigation of hyperpolarized Xe-129 MR signal characteristics has revealed different signals corresponding to Xe-129 compartmentalized within fat, tissue and red blood cells. Simultaneous ventilation perfusion studies of the lung are

possible through collection of gas and dissolved-phase signal within a single acquisition of images.

Initially Albert *et al* demonstrated imaging of the lung airspaces using hyperpolarized Xe-129 introduced into the trachea of a mouse heart-lung model (14). High signal intensity was achieved using 25ml (3atm) of Xe-129 polarized to approximately 25%. This was followed by a combined imaging and spectroscopic approach by Mugler et al. Comparison was made between hyperpolarized Xe-129 and conventional H^1 MR images in two human volunteers following inhalation of hyperpolarized Xe-129, polarized to 2%. Significant correlation was shown between the gas space signal absence in conventional MRI and the gas space signal in hyperpolarized Xe-129 images (62).

The dynamics of Xe-129 within the chest have been further studied in a dog (17). This study demonstrated a decay of the Xe-129 MR signal within the gas-phase. This was observed to provide a measure of Xe-129 absorption into the tissue. Time constants for saturation were determined as 61ms and 70ms for tissue and red blood cells respectively.

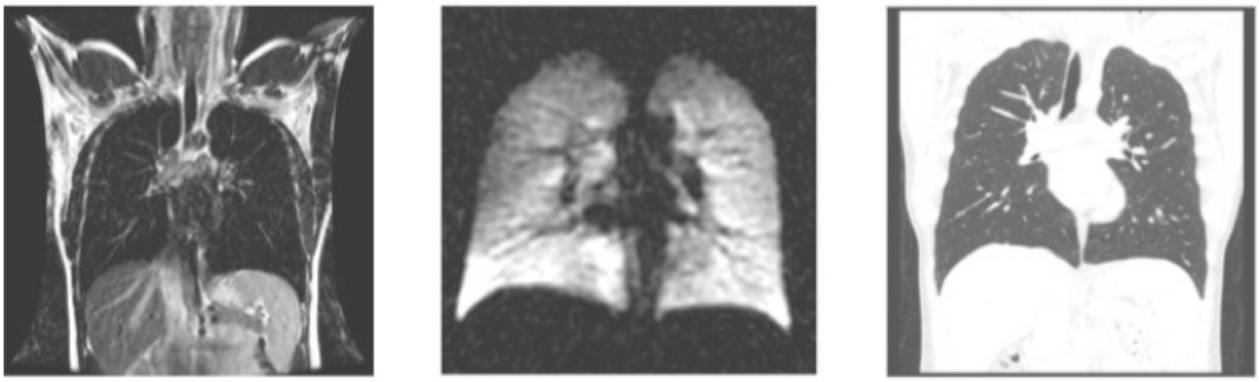
Hyperpolarized Xe-129 MR imaging may be applied as a non-invasive measure of lung function parameters specific to emphysema. The alveolar surface area per unit volume of gas (S/V) represents a primary measure of emphysema that may be evaluated using the chemical shift saturation recovery method (18, 59, 65). Another strategy using hyperpolarized Xe-129 MR is the xenon transfer contrast (XTC) method that may be adapted to derive values of S/V (18, 65). In addition, the XTC method has been used successfully to measure lung septal thickness in animals (63, 68) and humans (65) and evaluate the severity and progression of emphysema (47).

ADC values may also be determined with hyperpolarized Xe-129 MR imaging. However, Xe-129 has a much lower diffusivity than He-3 and demonstrates a lower diffusion coefficient. This offers an advantage over He-3 since measurement of alveolar and small airways dimensions is possible by applying diffusion weighted imaging (65, 69).

Hyperpolarized Xe-129 is also susceptible to the paramagnetic effect of oxygen within the pulmonary airspaces. The resultant loss of polarization and predicted decay in MR signal may be used to measure intrapulmonary PO_2. However, this is slightly more complex than when measuring with He-3 because additional signal loss due to diffusion of Xe-129 into alveolar tissue needs to be taken into account (18). An equivalent PO_2 is determined accounting for signal decay due to the presence of oxygen and Xe-129 diffusion.

At our Oxford centre, we have already commenced studies using hyperpolarized Xe-129 MR imaging in normal healthy volunteers and patients with chronic obstructive pulmonary disease (COPD). To date, we have administered 51 doses of 1L hyperpolarized xenon gas to 16 study participants for completion of hyperpolarized Xe-129 MR imaging. These have all been well tolerated with no serious adverse events. Preliminary results have shown that hyperpolarized Xe-129 MRI is a viable functional lung imaging modality. Images acquired from a normal healthy volunteer and patient with COPD using our scanner are shown below in *Figures 2, 3*.

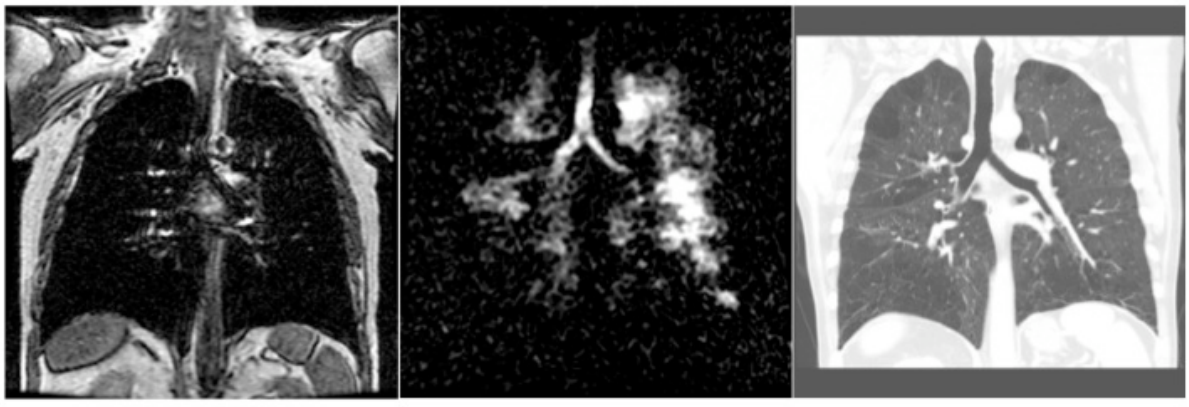
HEALTHY VOLUNTEER



A) Conventional MRI B) Xe-129 MRI C) Computed Tomography (CT) in lung windows

(Figure 2) Coronal images acquired from a healthy volunteer. A) Conventional MRI demonstrates no signal from the lung. B) Xe-129 MRI shows homogeneous ventilation signal throughout the lung. C) CT shows detailed lung structure.

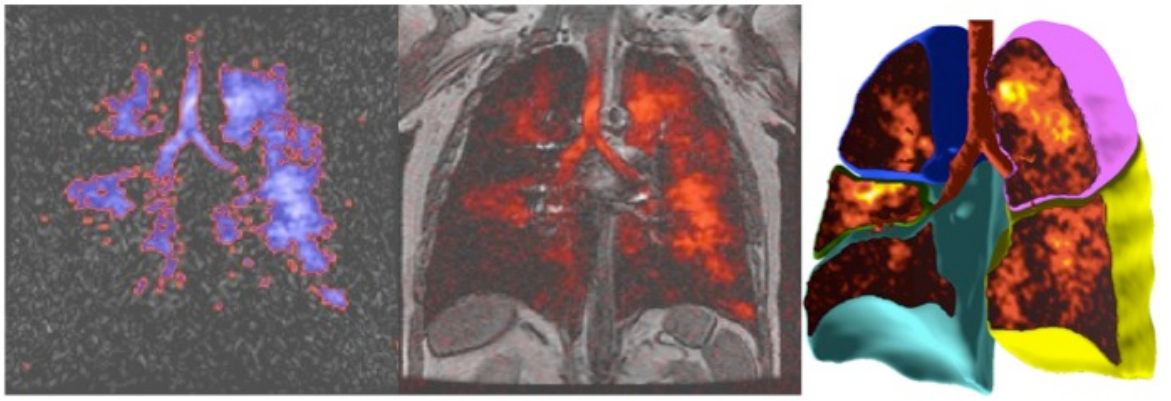
COPD



A) Conventional MRI B) Xe-129 MRI C) CT in lung windows

(Figure 3a) Coronal images acquired from a patient with COPD. A) Conventional MRI demonstrates no signal from the lung. B) Xe-129 MRI shows abnormal heterogeneous ventilation signal throughout the lung. C) CT shows severe paraseptal emphysema.

COPD



A) Xe-129 MRI

B) Xe-129 MRI and Conventional MRI

C) Xe-129 MRI, conventional MRI and volumetric CT

(Figure 3b) Post data processing of coronal images acquired from the same patient with COPD. A) Abstracted Xe-129 MRI ventilation image. B) Abstracted Xe-129 MRI mapped onto conventional MRI. C) Abstracted Xe-129 MRI mapped onto conventional MRI and then volumetric CT data to produce a 3-D image of the lungs.

5. PROPOSED RESEARCH

We aim to use hyperpolarized xenon gas (Xe-129) magnetic resonance imaging (MRI) and computed tomography (CT) imaging as a new technique capable of objectively and quantitatively, describing regional and structural lung abnormality in patients that will be undergoing radiotherapy affecting the lung. We will correlate this technique with baseline physiological and functional measures to determine if respiratory tolerance for radiotherapy is better predicted by hyperpolarized Xe-129 MR imaging. We will also evaluate changes in hyperpolarized-Xe-129 MR imaging before, during and after radiotherapy to determine if it provides improved assessment of radiation-induced lung injury.

MR imaging has an enhanced speed of image acquisition compared with CT and lung scintigraphy and offers the potential of ultra-fast sequences allowing dynamic assessment of lungs during respiration. In conventional MRI, the signal originates principally from the protons in water molecules of tissues. Therefore conventional MRI has limited use in respiratory disease because the lung has a very low density of protons, instead being largely composed of air spaces that do not generate MR signal. Hyperpolarized noble gases can resolve this problem. Helium (He-3) and Xenon (Xe-129) are unreactive or inert noble gases. The both have a nuclear spin of ½ enabling use in MR imaging to generate a signal.

The study will focus on hyperpolarized Xe-129 MR imaging as xenon is available in unlimited

supply in nature and has certain advantageous properties over He-3 including increased lipid solubility. Xe-129 is hyperpolarized, that is to say that nuclear spin within the atoms is increased. Hyperpolarization increases the MR signal enabling the Xe-129 gas to show up on the MR scan. In portions of the lung that have good airflow, the hyperpolarized Xe-129 gas will show up more and be seen more quickly. In addition Xe-129 readily dissolves in blood where it emits different MR signal characteristics. This property may be exploited to regionally quantify both ventilation and perfusion within the lung providing a comprehensive assessment of lung function.

The need for improved functional imaging to identify pre-existing lung disease and predict respiratory tolerance of patients undergoing radiotherapy affecting the lung is clear. Hyperpolarized Xe-129 MR imaging has the potential to inform individual suitability for radiotherapy schedules better than the investigations used currently. In addition improved functional imaging is required to monitor treatment response and enable treatment regimes to be tailored to the individual. Hyperpolarized Xe-129 MR imaging offers the potential of improved detection of radiation-induced lung injury, invaluable to treating patients with radiation induced injury. It may also provide information that would allow RT to be planned in such a way as to reduce the risk of patients developing RILT.

6. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

	Objectives	Outcome Measures/Endpoints
Primary	To demonstrate that hyperpolarized Xe-129 is sensitive to change following pulmonary radiotherapy, and thus may be developed as an objective and quantifiable method of functional lung assessment in patients undergoing radiotherapy that affects the lung	Change in hyperpolarized Xe-129 MR imaging from baseline to other time points post radiotherapy initiation.
Secondary	To obtain preliminary data demonstrating if changes in hyperpolarized Xe-129 MR imaging correlate with subjective and objective responses following pulmonary radiotherapy.	Change in hyperpolarized Xe-129 MR imaging parameters from baseline to other time points post radiotherapy initiation compared to subjective and objective measures of lung function.
	To obtain preliminary data demonstrating if baseline hyperpolarized Xe-129 MR imaging is a more reliable clinical	Comparison of hyperpolarized Xe-129 MR imaging and four-dimensional CT (4D-CT) at baseline.

	indicator of patient respiratory tolerance to pulmonary radiotherapy than conventional lung function testing by determining the relationship between hyperpolarized Xe-129 MR imaging indices and functional patient outcome measures (dyspnoea and radiation-induced lung toxicity assessment).	
	To use functional lung information in virtual predictive and adaptive radiotherapy treatment planning.	Retrospective comparison of modified radiotherapy treatment planning incorporating functional lung information from hyperpolarized Xe-129 MR imaging with conventional radiotherapy treatment plans.

7. TRIAL DESIGN

7.1. Summary of Study Design

This will be an open, single-centred study in the UK. The study group will include 30 patients who are considered suitable for radiotherapy that will affect the lung. Participants considered for radiotherapy that will affect the lung include those with a diagnosis of lung cancer and those with other diagnoses, for example, oesophageal cancer, chest wall tumours and lymphoma. All potential participants for this study undergo an *enrolment visit* (Visit 1). This is an opportunity to discuss the study in more detail, and for those choosing to take part to gain informed, written consent. Eligibility criteria will be checked. All female participants of child-bearing age will have had pregnancy excluded as part of their routine clinical care in Oncology prior to starting radiotherapy. Volunteers will be invited to undertake a 'dummy run' of Xe-129 lung MRI imaging, during which they lie on a couch similar to that used during the MRI, and practice the manoeuvre required when breathing in xenon from a 1L bag during subsequent lung imaging. During the dummy run this will simply be air or oxygen in the 1L bag.

The enrolment and baseline visits are compulsory for all participants. Participants will be required to complete at least one follow-up visit from the "half-way through" following commencement of radiotherapy, end of treatment and 3-months post-radiotherapy visits. The three follow-up visits will be offered to all patients, however completion of only one visit post-commencement of radiotherapy will be compulsory.

At the first baseline imaging visit (Visit 2), patients will be offered hyperpolarized xenon MR imaging, gadolinium-enhanced lung MRI and ventilation/perfusion nuclear medicine scan of the chest (optional) in addition to routine thoracic CT imaging. This enables co-registration between imaging modalities and correlation with physiological variables. Hyperpolarized xenon MR imaging involves acquisition of up to four MR sequences during one scanning session i.e. the participant will undergo up to four hyperpolarized xenon breath holds during each visit. The four inhalations may be different sequences or the same sequence may be repeated to assess reproducibility. Previous studies have shown that the signal from each xenon breath hold clears within seconds of exhalation. Participants will receive radiotherapy schedules according to departmental protocols. Patients will be offered hyperpolarized xenon MRI half-way through their radiotherapy schedule (Visit 3). At this time point no other imaging tests will be completed. In addition to routine thoracic CT, further hyperpolarized Xe-129 MRI and gadolinium-enhanced lung MRI will be offered on the final day of treatment and 3 months following completion of radiotherapy (Visits 4 & 5).

During each visit, patients are scheduled to undergo up to four hyperpolarized Xe-129 breath holds to complete MRI scanning. In the event that breathing and scanning are not entirely synchronised, one or two xenon breath holds may need to be repeated; so in total, each participant will undergo up to a maximum of 24 hyperpolarized Xe-129 breath holds during the four imaging visits over the 9 month study period.

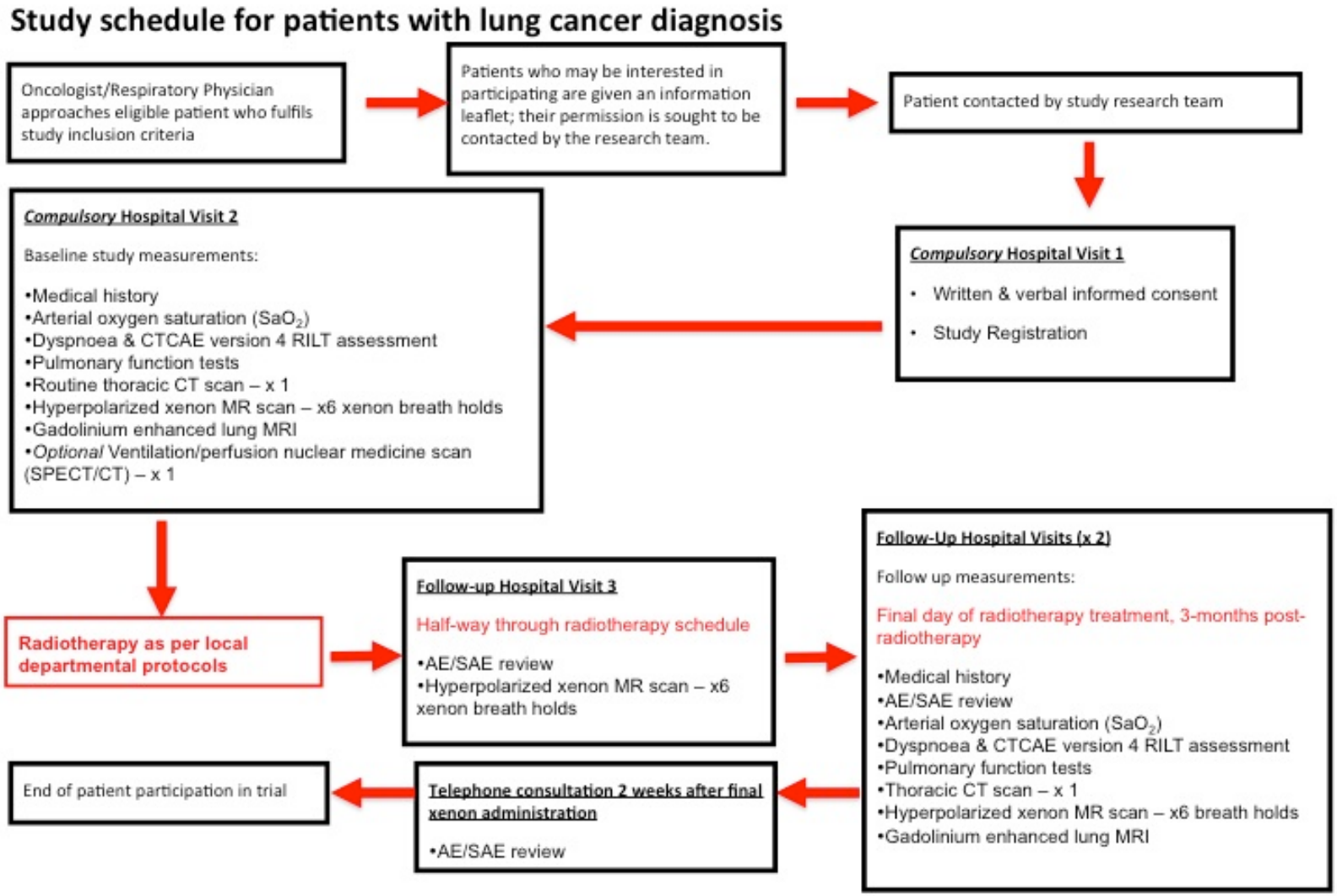
All patients enrolled with lung cancer will undergo clinical assessment involving objective physiological measures (pulmonary function testing and pulse oximetry) and patient orientated functional measures (dyspnoea scores, CTCAE version 4. Radiotherapy-induced lung toxicity assessment) at baseline, on the final day of radiotherapy treatment and 3 months post treatment. These assessments will not be completed at the two week following commencement of radiotherapy schedule visit.

Patients to be treated with radiotherapy affecting the lung that do not have lung cancer, such as oesophageal cancer, chest wall tumours, lymphoma affecting the mediastinum and others, will undergo clinical assessment (excluding full pulmonary function testing) and Xe-129 lung MRI imaging only at each visit.

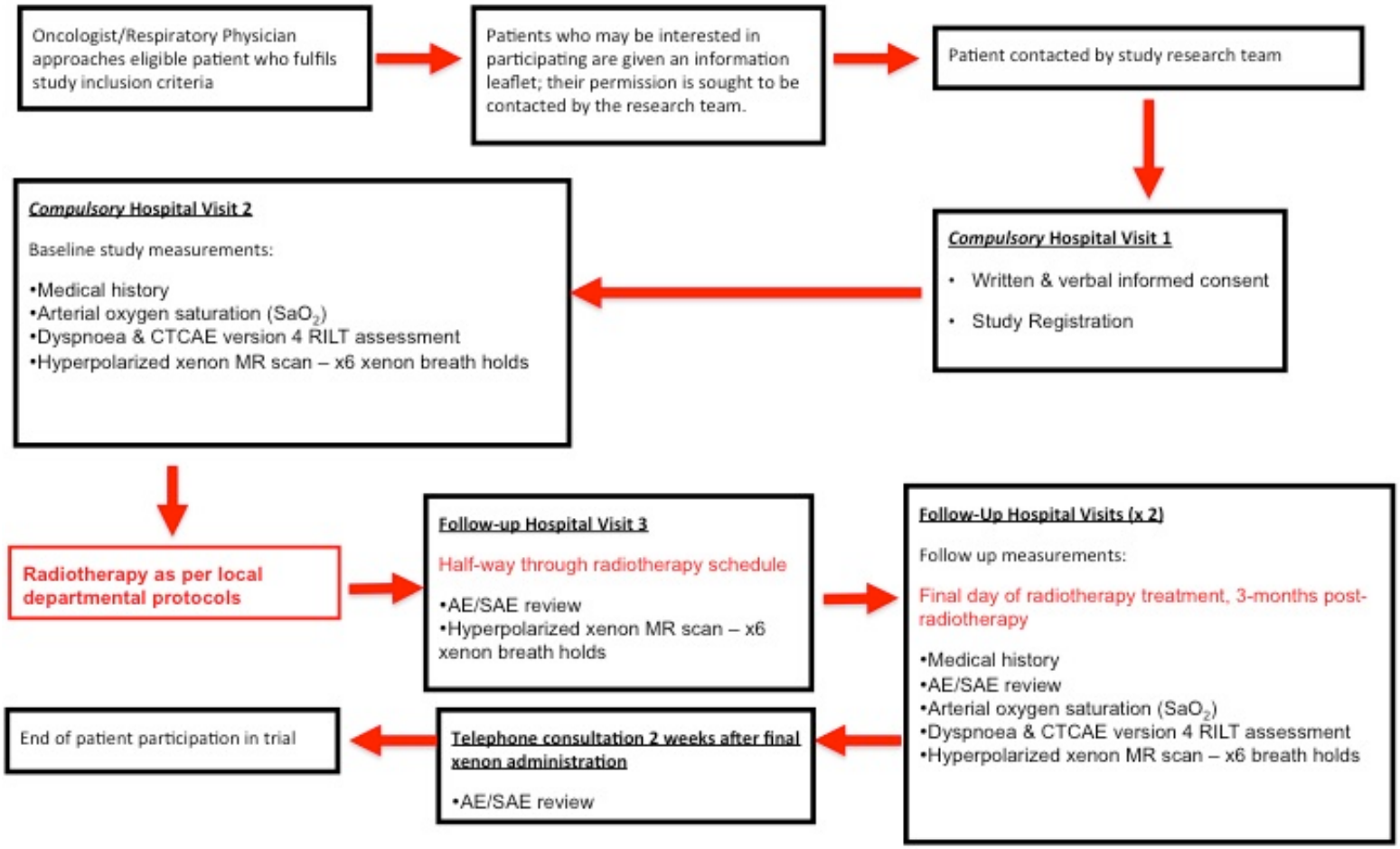
Participation in these full tests takes up to a day, allowing patients time to rest between tests. All participants will be monitored for at least 30 minutes after the final hyperpolarized xenon dose before they are discharged home. It is likely approximately 3 hours will have elapsed since administration of the first hyperpolarized xenon dose by this time. Participants will receive a telephone consultation 24 hours after completion of hyperpolarized Xe-129 MRI to review any AEs that have occurred in the interim following discharge. Furthermore, participants will attend hospital and see the Oncology clinical team on a daily basis during radiotherapy when they will have the opportunity to report any AEs relating to hyperpolarized Xe-129 gas. The study schedule includes follow-up by both the study team and Oncology clinical team in out-patient clinic at regular intervals throughout the 9 month trial duration. This will allow for review of possible AE/SAE two weeks after each hyperpolarized xenon scanning session.

Following the final xenon administration at the 3-month post-radiotherapy follow-up visit, participants will also receive a telephone consultation two weeks later to review AE/SAEs.

7.2. Summary Flow Chart of Study Design



Study schedule for patients with non-lung cancer diagnosis



8. PARTICIPANT IDENTIFICATION

8.1. Trial Participants

Study participants considered suitable for radiotherapy or chemoradiotherapy (concurrent or sequential schedule) affecting the lung will be recruited.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial.
- Male or Female, aged 18 years or above.
- Patients where radiotherapy or chemoradiotherapy (concurrent or sequential schedule) affecting the lung is considered appropriate by the treating clinical Oncologist.
- WHO performance status 0-2
- Able (in the Investigators opinion) and willing to comply with all study requirements.

8.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Inability to give written informed consent.
- Female participant who is pregnant, lactating or planning pregnancy during the course of the trial.
- Previous radiotherapy to the chest.
- The presence of another condition where the disease itself or treatment may interfere with the study endpoints.
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
- Inability to lie flat for imaging.
- Contraindications to MRI examination including indwelling pacemaker, non-MRI compatible metallic implant, severe claustrophobia, intra-ocular foreign body.
- Contraindications for gadolinium enhanced lung MRI scan – known hypersensitivity/allergy to the injection of MultiHance (contains gadobenate dimeglumine and small quantities of benzyl alcohol) that is given as part of this scanning or an adverse reaction to an injection given during previous MRI scanning, severe renal impairment.
- Epilepsy requiring on-going medical treatment, or a seizure within the past year.

9. TRIAL PROCEDURES

9.1. Recruitment

Potential participants will be identified from out-patient Lung cancer or Oncology clinic appointments. Potential participants will be approached by a member of their clinical team within the hospital setting. Any potential participant fulfilling the inclusion criteria will be informed of the trial by a member of their clinical team. If a patient expresses an interest in the study, they will be given a patient information leaflet and will be asked to give their permission to be contacted by the study team. The leaflet will also provide contact details for the study team should the patient wish to initiate contact.

A member of the study team will contact the participant to arrange an enrolment visit (Visit 1). This may be arranged to coincide with a scheduled out-patient clinic appointment for convenience. Enrolment will involve checking that the patient is eligible for the study, completion of informed consent and study registration. This will be an opportunity to discuss the study in detail, familiarise the participant with the Radiology department where the majority of study measures will take place and to complete a "dummy run" of Xe-129 lung MR imaging as previously described in section 7.1.

9.2. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed. This will be done in accordance with the national and local regulatory requirements.

Patients who express an interest in participating in the trial when a member of their clinical team, usually their Oncologist/Respiratory Physician, discusses it with them will be provided with an information leaflet and will be asked to give their permission to be contacted by the study team. The leaflet will also provide contact details for the study team should the patient wish to initiate this contact. Written and verbal versions of the participant information sheet and informed consent form will be presented detailing no less than: the exact nature of the study; 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, and with no obligation to give the reason for withdrawal.

Patients are given an MRI safety leaflet, and a contact number to discuss any aspect of the visit and scanning prior to giving consent.

The participant will be allowed as much time as wished to consider the information (at least 24 hours with written information to allow the patient to carefully consider participation but avoid any delay of radiotherapy treatment), and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. The informed consent procedure will conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representatives". A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site. A copy of the

signed Informed Consent will also be scanned onto the Radiology CRIS system and linked to the participant's Xe-129 MR imaging event.

The person who obtained the consent must be suitably qualified and experienced with up to date GCP/informed consent training, and have been authorised to do so by the Chief/Principal Investigator.

9.3. Screening and Eligibility Assessment

Potential participants will be approached by their Oncologist or Respiratory Physician within the hospital setting. Any potential participant fulfilling the inclusion criteria will be informed of the trial by a member of their clinical team. If a patient expresses an interest in the study, they will be given a patient information leaflet and will be asked to give their permission to be contacted by the study team. The leaflet will also provide contact details for the study team should the patient wish to initiate contact.

Prior to registration or any study measures being undertaken, documented informed consent will be completed as detailed in section 9.2.

All participants will undergo clinical assessment including medical history and baseline study measures (section 9.5) over 1 -2 hospital visits as outlined below: -

Demographics

The date of birth, gender and smoking habits will be recorded.

Medical History

This forms part of the patient's routine clinical care.

All female participants of child-bearing age will have had pregnancy excluded as part of their routine clinical care in Oncology prior to starting radiotherapy.

9.4. Randomisation, blinding and code-breaking

This study is not a randomised trial. All patients undergoing hyperpolarized MR imaging will breathe Xe-129.

9.5. Baseline Assessments for patients with a diagnosis of lung cancer

Arterial oxygen saturations (SaO_2) – measured after a period sitting quietly and resting. The average reading over a two-minute period is recorded.

Pulmonary Function Tests

Pulmonary function tests will be carried out, including spirometry, lung volumes and carbon monoxide transfer factor. Recordings will be compared to predicted values determined from standard published data.

Spirometry will involve the participant breathing out as fast as they can for as long as they can, at least three times. The maximal amount breathed out in one second (forced expiratory volume in one second, FEV_1) and total amount breathed out (forced vital capacity, FVC) will be recorded. Recorded values will be compared to predicted values determined from standard reference tables. Spirometry may be repeated following bronchodilator or steroid therapy to assess for reversibility as indicated by improvement FEV_1 if a clinical history of asthma or chronic obstructive pulmonary disease (COPD) is present.

Analysis will be based on change in % predicted values over time.

Dyspnoea

Dyspnoea (breathlessness) will be measured using the Dyspnoea-12 score (70), a seven-point Likert scale and a visual analogue score.

Analysis will be based on the change in score from the baseline over time.

Radiation-induced lung toxicity (RILT)

RILT will be assessed using the common terminology criteria for adverse events (CTCAE version 4). This is completed as part of standard routine care to enable assessment of functional impairment relating to radiotherapy-induced lung toxicity.

Analysis will be based on the change in score from the baseline over time.

Ventilation/perfusion nuclear medicine scan (SPECT/CT)

Ventilation/perfusion nuclear medicine scan will be completed at baseline only and is an optional study measure. This scan is performed using the 16-slice GE Discovery 670 scanner as per local protocol. The nuclear medicine scan involves three components: -

- Ventilation imaging – this involves the patient breathing in a gaseous tracer in aerosol form e.g. technetium-labeled diethylenetriamine pentaacetate (99mTc-DTPA) via a mouthpiece or mask.
- Perfusion imaging – this involves insertion of a cannula, and then an injection of a small volume, < 5 mL, of radioactive technetium labelled macro aggregates of albumin (99mTc-MAA). A gamma camera acquires images for both ventilation and perfusion components. Patients do not have to move to a different bed between the nuclear medicine and CT scans, so it is associated with minimum disruption.

Participants will be screened for contraindications to nuclear medicine scanning including known hypersensitivity to albumin or preference to avoid blood donation product. If a contraindication

to the nuclear medicine scan is identified, it will not be performed. This will not exclude the patient from participating in the study.

Computed Tomography (CT)

Thoracic CT will be performed at the Churchill Hospital. An injection of iodinated contrast will be administered through the same cannula that was inserted for the nuclear medicine scan. Scanning takes place 50-60 seconds post injection as per standard imaging protocol. CT images will be acquired during a single breath hold performed triggered to lung volume. The patient lies on their back, whilst scanning takes place.

Participants will be screened for contraindications to iodinated contrast prior to completion of this study measure. These include: -

- Marked renal failure not on dialysis
- Known allergy to contrast medium, history of anaphylaxis
- Known or suspected thyroid carcinoma
- Inability to gain intra-venous access

If contraindication to iodinated contrast is identified, all thoracic CT scans will be performed without contrast. This will not exclude the patient from participating in the study.

Software will be used to determine areas of lung attenuation, such as delineating areas < -950 HU validated by visual inspection by an experienced thoracic radiologists, and/ or other measures of local texture in CT imaging. Comparisons with manual region of interest performed on an image display software (OsiriX) will be made.

Hyperpolarized Xe-129 MR Imaging

The patient lies on their back in an MR scanner, and has conventional safety monitoring throughout the scan (direct visual observation, arterial oxygen saturations and heart rate monitoring). They wear a lightweight vest containing the imaging coils over their clothes that is necessary for acquiring images.

Before the first Xe-129 MR scan involving inhalation of up to 1L of xenon, patients will be asked to breath in a small volume of xenon of approximately 100mL mixed with medical grade nitrogen for a total volume of 1L. The patient will be instructed to perform a standard breath hold for a short period of time (approximately 2 seconds). This is a set-up procedure for the scan enabling optimization of Xe-129 MR parameters according to patient height and weight as well as a practice run for the patient. The output from calibration (flip angle measurement) enables the best quality Xe-129 MR images to be acquired for each individual and is not be used to evaluate the study endpoints.

For the actual Xe-129 MRI scan, the patient breathes out, and then breathes in from a bag containing up to 1L of xenon, balance nitrogen. The total volume of gas participants inhale for Xe-129 MRI scans is 1L, however this may consist of a mixture of 50-100% hyperpolarized xenon and up to 50% nitrogen i.e. 500 mL to 1L of hyperpolarized xenon is mixed with medical grade nitrogen to make up a total volume of 1L. Breathing in xenon is challenging for some people because it has a density 4.55 time greater than air, which increases airways resistance (72). Therefore patients are sometimes given assistance with the respiratory manoeuvre by physically compressing the bag during inhalation. The patient receives a bag full of air or oxygen to practice this breathing manoeuvre before breathing xenon. Scanning then takes place during a breath hold for approximately 20 seconds, or during an inhalation-exhalation manouevre. This manoeuvre with scanning will be repeated up to four times to enable acquisition of all Xe-129 MRI sequences. The four inhalations may be different sequences or the same sequence may be repeated to assess reproducibility. There are currently three confirmed sequences (ventilation, ADC and dissolved phase) with further sequences under technical development that will be introduced during the course of the study period.

If the patient fails to breathe in sufficient xenon at the required time, the investigator may suggest that the procedure is repeated once or twice. One patient will not exceed six inhalations of xenon in a single day. In the unlikely occurrence of an adverse event, a radiographer will be able to access the participant immediately. Participants are monitored for at least 30 minutes after the final hyperpolarized xenon dose before they are discharged home. It is likely approximately 3 hours will have elapsed since administration of the first hyperpolarized xenon dose by this time. Participants will receive a telephone consultation 24 hours after completion of hyperpolarized Xe-129 MRI to review any AEs that have occurred in the interim following discharge. Furthermore, participants will attend hospital and see the Oncology clinical team on a daily basis during radiotherapy when they will have the opportunity to report any AEs relating to hyperpolarized Xe-129 gas. The study schedule includes follow-up by both the study team and Oncology clinical team in out-patient clinic at regular intervals throughout the 9 month trial duration. This will allow for review of possible AE/SAE two weeks after each hyperpolarized xenon scanning session.

Following the final xenon administration at the 3-month post-radiotherapy follow-up visit, participants will also receive a telephone consultation two weeks later to review AE/SAEs.

Hyperpolarized Xe-129 MR imaging will be performed using xenon hyperpolarized by a xenon hyperpolarizer (Polarean 9880) and imaged on a 1.5T MRI scanner. A dedicated Xe-129 chest coil will be used. Images will be obtained in the coronal plane. During each scanning session, up to four hyperpolarized Xe-129 MR sequences will be acquired with the participant undergoing four separate xenon breath holds. Hyperpolarized Xe-129 MR will be repeated at baseline to assess reproducibility. Total scanning time will be approximately half a day during each visit. The participant will spend a total of approximately 1 ½ hour within the MRI scanner during each visit. Image acquisition strategy will include: -

- Short echo proton MRI for co-registration purposes.

- Static ventilation
- Dynamic ventilation.
- Diffusion Imaging (ADC).
- Intrapulmonary PO2
- Dissolved phase imaging.

If the study team fails to acquire all the required Xe-129 MRI sequences during a single scanning session as a result of technical difficulties or non-synchronisation of patient breathing and scanning, the patient may be requested to return within a few days to complete Xe-129 lung MRI scanning and ensure acquisition of all sequences for that study visit. This may take up to half a day and may involve repeating one or two Xe-129 MR sequences previously acquired since these cannot be analysed accurately if they have not all been performed at the same time point.

Analysis

All analyses will be performed by two experienced Thoracic Radiologists Fergus Gleeson (FG) and Rachel Benamore (RB) blinded to clinical data and all other investigation results to avoid bias.

1. Accurate co-registration of *global* and *regional* data from hyperpolarized Xe-129 MRI and CT chest, by correlating Xenon MRI Ventilation and ADC maps with CT identified areas of emphysema using CT density maps (measure in Hounsfield units).

   Multivariate analysis to correlate global ventilation and ACD data from hyperpolarized Xe-129 MRI with key patient-centred outcome measures – dyspnoea-12 score, RILT assessment.

Gadolinium enhanced lung MRI

This will be performed on a 1.5T MRI scanner according to local standard protocols. An injection containing gadolinium is given via the cannula (this will be the same one used for nuclear medicine and CT scans) and lung MRI carried out during a short breath hold. Since patients do not need to move from the bed following Xe-129 lung MRI there is minimal inconvenience and disruption for the patient.

Description of MultiHance (gadolinium injection)

MultiHance contains gadolinium, which is a rare earth metal that improves images of pulmonary arteries during lung MRI. Gadolinium is given in the form of gadobenate dimeglumine. The dose of MultiHance is around 0.2 ml/ kg body weight. There is no interaction or interference between MultiHance and inhalation of hyperpolarized Xe-129 gas, allowing this study measure to be performed straight after the hyperpolarized Xe-129 MRI scan safely.

Safety considerations for MultiHance

MultiHance is commonly used in clinical practice for perfusion imaging during MRI where it is safe and well tolerated. Common side effects (more than 1/100 but fewer than 1/10) are headache,

nausea, feeling hot and local reactions such as swelling or pain at the injection site. Rarely (more than 1/ 10,000 but fewer than 1/ 1,000) allergic reactions can arise leading to shock, itching, skin rashes, urticarial, fainting, a swollen face and neck and wheezing, or other serious effects including tinnitus, pancreatitis, pulmonary oedema, intracranial hypertensions or hemiparesis.

9.6. Baseline assessment for patients with diagnoses other than lung cancer

Patients with diagnoses other than lung cancer, for example, oesophageal cancer, chest wall tumours and lymphoma will undergo the following baseline assessments only: -

- Arterial oxygen saturations (SaO_2)
- Dyspnoea
- Radiation-induced lung toxicity (RILT)
- Hyperpolarized Xe-129 MR Imaging

Full details about each of the study measures has been provided above in Section 9.5.

9.7. Radiotherapy

Radiotherapy treatment will be CT planned and delivered as per local departmental radiotherapy protocols. The treating Oncologist will not have access and be blinded to the baseline Xe-129 MRI images whilst planning radiotherapy. Entry into this study will not delay patients commencing radiotherapy, and their treatment will not be altered as a result of their enrolment into this study.

The appropriate beam energy will be selected to optimize the RT dose distribution in the target volume and minimize dose to non-target tissues.

9.8. Subsequent Visits for patients with a diagnosis of lung cancer

At each hospital visit, study patients will be asked whether they have had any:

- Hospitalisations
- Consultations with other medical practitioners
- Disability or incapacity or other adverse event that has occurred since their last visit

All study measures will be performed and analysed as detailed previously in sections 9. and 12. of this document.

Although all three follow-up visits will be offered to participants, only one visit post-commencement of radiotherapy will be compulsory.

<u>Half-way through radiotherapy schedules</u>

The only study measure to be completed will be hyperpolarized Xe-129 MR imaging involving up to a maximum of six xenon breath holds. Adverse events and serious adverse events will be reviewed.

Final day of treatment and 3-months following completion of radiotherapy: -

- AE/SAE review
- Arterial oxygen saturation
- Dyspnoea & CTCAE version 4 RILT assessment
- Full pulmonary function tests
- Thoracic CT
- Hyperpolarized Xe-129 MR imaging involving up to a maximum of six xenon breath holds
- Gadolinium enhanced lung MRI

Two weeks after final xenon administration at 3-month post-radiotherapy

- AE/SAE review via telephone consultation

9.9. Subsequent Visits for patients with a diagnosis other than lung cancer

At each hospital visit, study patients will be asked whether they have had any:

- Hospitalisations
- Consultations with other medical practitioners
- Disability or incapacity or other adverse event that has occurred since their last visit

All study measures will be performed and analysed as detailed previously in sections 9. and 12. of this document.

Although all three follow-up visits will be offered to participants, only one visit post-commencement of radiotherapy will be compulsory.

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Final day of treatment and 3-months following completion of radiotherapy: -

- AE/SAE review
- Arterial oxygen saturation
- Dyspnoea & CTCAE version 4 RILT assessment
- Hyperpolarized Xe-129 MR imaging involving up to a maximum of six xenon breath holds

Two weeks after final xenon administration at 3-month post-radiotherapy

- AE/SAE review via telephone consultation

9.10. Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Withdrawal of Consent
- Loss to follow up

Withdrawal from the study will not result in exclusion of the data for that participant from analysis provided all baseline study measures have been completed.

The reason for withdrawal will be recorded in the 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.

9.11. Definition of End of Trial

The end of trial is the date of the last hospital visit of the last participant.

10. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

10.1. IMP Description

No treatments are given as a part of the proposed study since the appropriate radiotherapy schedule is taking place as part of patients' routine clinical care.

Hyperpolarized Xe-129 lung MRI requires breathing in an investigational medical product, hyperpolarized xenon gas, Xe-129, which is described in detail below.

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. We will administer a maximum of 6 x 1 Litre doses of hyperpolarized xenon gas to each participant per hospital visit for Xe-129 lung MR imaging. If it is not essential to give 100% xenon for imaging, the gas may be diluted with ultrapure nitrogen. The ratio of xenon to nitrogen will vary from 10% to 100% but the volume provided to the patient will always be 1 L.

The route of administration is inhalation. All female participants of child-bearing age will have had pregnancy excluded as part of their routine clinical care in Oncology prior to starting radiotherapy.

<u>Physiological effects</u>

At low concentrations such as those that will be used in this study, Xenon has effects similar to nitrous oxide (laughing gas). Nine out of 10 patients experience light headedness, paraesthesia, euphoria or a mild 'drunk' feeling, which in short lived and resolves within 2-3 minutes of breathing the gas (73-75).

<u>Side effects</u>

Xenon has been found to be extremely safe and well tolerated, both during single breath-hold experiments such as ours (n=26 (76)and n=44 (72)) and during 4 minute 20 second continuous breathing (n=1,830) (74). In a prospective study examining safety and tolerability of xenon, 32% of 44 volunteers experienced mild gastrointestinal symptoms (72). One volunteer experienced drowsiness, sleepiness and numbness, which resolved in about 7 minutes (72). She had considerable co-morbidity, including multiple sclerosis, B12 deficiency and Graves' disease. In a large retrospective study involving breathing xenon for cerebrovascular imaging during a 4 minutes 20 seconds period (in contrast to our single breath exposure), the incidence of pauses in breathing for >15 seconds was 0.6%, headache (usually mild) 0.4%, nausea or vomiting 0.2%, change in sensorium 0.1% and 0.05% hallucinations (74). 0.2% of patients had a seizure, but 3 of 4 of these patients were being investigated for unexplained seizures, and diagnostic information was not available for the fourth patient. Patients with multiple sclerosis had increased emotional lability. These side effects nearly all occurred towards the end of the exposure period. Pauses in breathing almost invariably were terminated by an instruction to take a breath.

<u>Safety considerations</u>

At high concentrations xenon has anaesthetic properties. The minimum alveolar concentration (MAC) of xenon at sea level is 70% (77). Our patients will breathe a fraction of inhaled xenon (FiXe) considerably lower than this, and will inhale a single breath and therefore not approach the gas equilibrium that is required when defining MAC. Our patients will inhale 1L from residual volume, resulting in an approximate fraction of xenon (FXe) of 10-30%. The alveolar FXe would tend to be marginally lowered due to Xe in the anatomical deadspace of the large airways, and marginally raised due to Xe not entering non- or slowly communicating air spaces within the lungs. Thus the FXe that our patients will be exposed to is considerably below the dose required to induce anaesthesia, and well within safe limits. It is not possible for patients to breathe more than 1 L of xenon, since they are given a single bag of the gas. This procedure may be repeated up to four times during one imaging session. In the event that breathing and scanning are not entirely synchronised, one or two xenon breath holds may need to be repeated; so in total, each participant will undergo a maximum of 24 hyperpolarized Xe-129 breath holds during the four imaging visits over the 9-month study period.

A further safety consideration is patients' oxygenation, since they will be inhaling 1 L of anoxic gas, followed by a breath hold. However, participants will only be exposed to this low oxygen fraction for a single breath hold. The breath hold is approximately 30 seconds, although patients are free to take another breath sooner if they cannot manage this long. The amount of oxygen available in 3.5 L of 11% oxygen is 385 mL, which is considerably more than the oxygen requirement for the duration of the breath hold (assuming oxygen use is 250 mL/ min). These calculations assume all gas within the lungs is in communication with inhaled gas, which is often not the case in respiratory disease, however the safety margins are extremely large. Reassuringly, studies in chronic obstructive pulmonary disease (COPD) patients using this breathing technique observed a mean fall in oxygen saturations of only 1.2 % of baseline during observation at 2 minute intervals for 10 minutes (72). In the unlikely event that a patient desaturates by more than 10% immediately following Xe inhalation, this manoeuvre will not be repeated.

Our patients will be carefully observed and monitored throughout the study, including direct visual observation, heart rate, respiratory rate and arterial oxygen saturations. The minimum number of people in attendance during a scan is two. This includes a doctor or allied health care professional such as a nurse or radiographer, who is solely responsible for patient monitoring, safety and well-being. They will be aware of potential risks of Xe, and appropriately trained in how to respond to any adverse sequelae arising. It also includes a technician/ radiologist who is responsible for acquiring images. In the event of any untoward medical event occurring mid-scan, staff can reach the patient immediately. As in all clinical areas throughout the Oxford Hospital Trust, emergency drugs and equipment are readily available and staff are trained in their use. This includes supplementary oxygen and resuscitation equipment.

All participants will be monitored for at least 30 minutes after the final hyperpolarized xenon dose before they are discharged home. It is likely approximately 3 hours will have elapsed since administration of the first hyperpolarized xenon dose by this time. Participants will receive a telephone consultation 24 hours after completion of hyperpolarized Xe-129 MRI to review any

AEs that have occurred in the interim following discharge. Furthermore, participants will attend hospital and see the Oncology clinical team on a daily basis during radiotherapy when they will have the opportunity to report any AEs relating to hyperpolarized Xe-129 gas. The study schedule includes follow-up by both the study team and Oncology clinical team in out-patient clinic at regular intervals throughout the 9-month trial duration. This will allow for review of possible AE/SAE two weeks after each hyperpolarized xenon scanning session.

Following the final xenon administration at the 3-month post-radiotherapy follow-up visit, participants will also receive a telephone consultation two weeks later to review AE/SAEs.

A 'Physician information sheet' documenting possible effects of Xe and appropriate medical responses has been drawn up, and will be provided to all those involved in Xe imaging.

10.2. Production, Storage and Dispensing of IMP

Xe-129 will be isolated from a gas mixture of 1.0% xenon, 10% nitrogen and 89% helium, manufactured in the USA and supplied by Spectra Gases Ltd, Littleport Cambridgeshire. It will be polarised via spin exchange optical pumping by laser, using the Polarean 9800 hyperpolarisation system. Xe-129 will then be frozen to isolate it from other gases and sublimated into Tedlar plastic bags for administration to participants via inhalation. The gas is labelled in accordance with EU trial directive requirements.

Each batch of Xe-129 will be tested using a Polarean 2881 polarization measurement system to ensure sufficient xenon gas is hyperpolarized to enable lung imaging. All staff involved in the process of Xe-129 manufacture will be trained to ensure that the manufacture is conducted safely to the correct technical specification. The manufacturing facility is licensed by the MHRA and each batch is manufactured to GMP standard and certified for release to the investigator by a Qualified Person according to the approved Standard Operating Procedures.

Calibration

Calibration involves the patient breathing a small volume of xenon of approximately 100mL mixed with medical grade nitrogen for a total volume of 1L. The patient will be instructed to perform a standard breath hold for a short period of time (approximately 2 seconds). This is a set-up procedure for the scan enabling optimization of Xe-129 MR parameters according to patient height and weight as well as a practice run for the patient. The output from calibration (flip angle measurement) enables the best quality Xe-129 MR images to be acquired for each individual and is not be used to evaluate the study endpoints.

For calibration, hyperpolarization will take up to 10 minutes. The same manufacturing process as clearly described by SOPs to produce up to 1L of hyperpolarized Xe-129 will be adhered to. The only difference is the length of hyperpolarization time resulting in a much smaller volume (100mL) of hyperpolarized xenon gas being produced. Xe-129 will be isolated from other gases and

sublimated into Tedlar plastic bags in Radiology for administration to participants via inhalation in the MR suite. To make a total volume of 1L, medical grade nitrogen is added. These small calibration doses are not considered to be IMPs and do not require QP release.

10.3. Compliance with Trial Treatment

Compliance auditing is not relevant to use of hyperpolarized xenon: a dose is only given by radiographers/ radiologists during the MR regional lung imaging itself. However, the volume of Xe-129 inhaled will be recorded on the CRF.

10.4. Accountability of the Trial Treatment

Medical grade xenon and nitrogen will be supplied by Spectra Gases Ltd, Littleport Cambridgeshire to Oxford Thoracic Imaging Centre where the gas will be polarized. The duration of hyperpolarization will be up to 70 minutes. Hyperpolarized xenon may be kept frozen for a short time (less than 30 minutes) before thawing. After thawing, bags of hyperpolarized xenon will be labeled with the patient's ID and the expiry date and time. Hyperpolarized xenon will be used within 30 minutes of thawing.

10.5. Concomitant Medication

Patients' medications will be recorded at baseline and at each follow-up visit.

10.6. Post-trial Treatment

The proposed study is an interventional study. As such all participants will receive best standard care throughout and this will continue without interference following study completion.

11.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	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 serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".

11.2. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

11.3. Procedures for Recording Adverse Events

All AEs observed by the investigator or reported by the patient during and for 24 hours after Xe-129 lung MRI are reported on the case report forms. A member of the research team will contact the participant by telephone 24 hours after completion of hyperpolarized Xe-129 MR imaging to record any AEs that may have occurred after leaving the hospital. These will be clearly documented on the patient CRFs. Thereafter only adverse events where there is a reasonable possibility of a relationship to inhaled xenon (adverse reactions) as judged by the chief investigator, and any adverse event considered by the chief investigator to be of medical interest/ importance are reported. These events will be reported on the case report forms.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

AEs considered related to inhaled xenon as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the investigator's clinical judgment whether or not an AE/ AR is of sufficient severity to require the patient's removal from Xe-129 MRI scanning. A patient may also voluntarily withdraw from study procedures if they tolerate it poorly. Further details of withdrawal are presented in Section 9.8.

In the event of symptoms arising, patients will be given appropriate care and medical supervision until symptoms resolve, or the condition becomes stable. Every effort will be made to gather outcome data on patients through study follow-up, or general practitioner/ hospital staff unless the patient is specifically withdrawn consent to such efforts.

11.4. Reporting Procedures for Serious Adverse Events

All SAEs (other than those defined in the protocol as not requiring reporting) following Xe-129 lung MRI scanning must be reported on the SAE reporting form to R&D within 24 hours of the Site Study Team becoming aware of the event. R&D will perform an initial check of the report, request any additional information, and ensure it is reviewed by the Medical Monitor on a weekly basis. It will also be reviewed at the next Trial Safety Group meeting. All SAE information must be recorded on an SAE form and faxed, or scanned and emailed, to R&D. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and faxed/emailed to R&D.

11.5. Expectedness

Expectedness will be determined according to the Investigators' Brochure.

After breathing gas containing xenon, feelings of light-headedness, paraesthesia, euphoria or mild 'drunk' feeling are common, occurring in 9 out of 10 people. These symptoms last for just a few minutes, just like breathing 'laughing gas'. The expected adverse reactions are described in the Investigators' Brochure.

11.6. SUSAR Reporting

All SUSARs will be reported by the CI to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Treatment codes will be un-blinded for specific participants.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current study.

11.7. Safety Monitoring Committee

The Oxford University Hospitals Trust / University of Oxford Trials Safety Group (TSG) will conduct a review of all SAEs for the trial reported during the quarter and cumulatively. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

11.8. Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor.

12. STATISTICS

12.1. Description of Statistical Methods

Early studies (73, 78), including work from our own group (79), using Xe-129 lung MRI have demonstrated that this technique provides valuable information regarding *global* pulmonary parenchymal apparent diffusion coefficients (ADCs – measures of increased air spaces) in COPD, demonstrating important differences compared to age matched controls or young, healthy volunteers. Our scanner has excellent anatomical resolution compared to those used in most previous work, enabling us to perform *regional* analysis, down to the level of the secondary pulmonary lobule and to determine bronchial wall thickness.

The primary outcome measure for determining Xe-129 lung MRI changes following radiotherapy will be evaluating the change in Xe-129 lung MRI imaging from baseline to other time points post-radiotherapy initiation.

We will also compare *global* Xe-129 lung MRI ADC measures between patients from other diagnostic groups (initially patients with NSCLC considered suitable for surgery, patients with COPD and patients with normal lungs who are well, but who are having chest CT imaging due to a prior testicular malignancy: these studies are covered by separate consent). We will carry out the following completely novel analyses: -

<u>Technique development</u>

- Assessments of detailed regional data, with regional ADC and bronchial wall thickness measurements.
- Accurate co-registration of *global* and *regional* data from Xe-129 lung MRI and chest CT, by correlating lung masks obtained from CT and proton MRI scans. Analysis of the correlation of MRI ADCs with CT lung tissue density (measured in Hounsfield units).
- Development of perfusion data (blood flow through the lungs) obtained using dissolved phase Xe-129 lung MRI, and validation against the current gold standard – ventilation/perfusion nuclear medicine scanning.
- Development of novel and automated analysis methods, based on computational models of lung function and combined anatomical and functional information from CT and MRI scans, following current work at the Computational Biology Group.
- Comparison of hyperpolarized Xe-129 MR imaging and four-dimensional CT (4D-CT) at baseline.

<u>Demonstration of superiority over standard lung function assessment tools</u>

- Multivariate analysis to correlate global and regional (lobar) data from Xe-129 lung MRI with key patient-centred outcome measures – dyspnoea assessment using the Dyspnoea-

12 score (70) and MRC breathlessness score. We will test the hypothesis that Xe-129 lung MRI has a closer correlation with these measures than FEV_1 or gas transfer.

12.2. The Number of Participants

The total sample size will be 30.

It is not possible to perform a detailed power calculation regarding sample size because this is the first time regional lung hyperpolarized Xe-129 MR indices have been correlated with physiological and functional outcomes in patients considered suitable for radiotherapy affecting the lung. We have taken the number of potential participants who are referred to our Oxford centre and considered suitable for radiotherapy affecting the lung over the last year into careful consideration and are confident that this sample size is feasible.

In our development work with this technology using He-3 gas, we have shown in 24 patients with COPD that hyperpolarized gas MR imaging identifies more lung regions affected by emphysema (defined from ADC values >0.34 cm^2/s) than does the severity of emphysema quantified by thoracic CT (defined from lung attenuation <960HU, a standard CT index).

To date most studies employing hyperpolarized Xe-129 have been on animal models and healthy volunteers and have reported it as a viable functional lung imaging modality (18, 65). The sample size proposed for this trial will be sufficient to be informative in our planned analyses and direct future investigation.

12.3. The Level of Statistical Significance

The level of significance will be set at $p<0.05$.

12.4. Criteria for the Termination of the Trial

The study will terminate following recruitment and completion of follow-up of at least 30 patients, or should a significant safety concern emerge.

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

Efforts to measure all data as outlined in the trial protocol will be made. If a patient provides data from only one Xe-129 MRI scan, this will be included in analysis for mapping, but not for reproducibility. The data will be reviewed by Fergus Gleeson, to confirm that it is robust, and any deviation from expected results will be reviewed to determine if this is due to scanning error, or other artefact.

12.6. Inclusion in Analysis

All evaluable participants will be included in the analysis. Participants will be deemed not to be evaluable for reproducibility if either or both baseline Xe-129 MRI scans are not assessable.

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

This is an interventional study; exploratory analyses in addition to those above may be conducted to further the development of the technique. These will be described in full in the final study report. Patient observations will cease at the time of termination of the trial.

13. DATA MANAGEMENT

13.1. 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). In this study the CRF will be used as the source document for initial clinical assessment, dyspnoea scores, RILT assessment and follow-up assessment. Safety assessment forms completed during hyperpolarized Xe-129 MRI scans to monitor patients' vital observations will also be source data. All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

13.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

13.3. Data Recording and Record Keeping

Trial records will be kept in accordance with the Radiology Department SOPs. All trial data excluding imaging data will be entered onto a password secured database (OpenClinica). The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file. The Data Protection Act will be adhered to at all times. Paper records concerning the trial subjects will be kept in locked filing cabinets in the Radiology Department.

Imaging data will be stored on a dedicated research server in the Radiology Department, Churchill hospital for a minimum of 5 years.

All data will be checked for missing or unusual values (range checks) and for consistency within participants over time. If any such problems are identified, a photocopy of the problematic CRF(s) will be reviewed for checking and confirmation or correction, as appropriate. Any data, which are changed, will be crossed through with a single line, initialed and dated.

14. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to ICH GCP by the sponsor. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

15. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

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

(b) The scientific value of the trial”.

In the event that 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 REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

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

16.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

16.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) 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. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

16.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

16.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts or a mileage allowance provided as appropriate. Refreshments and newspapers will be provided during each visit.

16.7. Other Ethical Considerations

This type of imaging research raises several ethical issues. The proposed hyperpolarized Xe-129 MR, gadolinium-enhanced lung MRI and optional ventilation/perfusion nuclear medicine scan will be provided in addition to any routine scans. Additional imaging may or may not add any information that will benefit the individual patient. Nuclear medicine and CT examinations involve ionizing radiation and there is a small but quantifiable risk associated with administration of iodinated contrast. These issues will be addressed as follows:

- Baseline and follow-up CT scans form part of standard routine patient care. Nuclear medicine scans are considered negligible exposure in comparison to doses from radiotherapy itself. However, any additional exposure will be formally justified.

- Patient Information Sheets will be provided describing the study and what it involves in non−technical language, as far as possible. Patients and patient's carers will be involved in development of the leaflet.
- Written informed consent will be obtained in an appropriate setting. The study will be introduced to the patient by a member of staff already known to the patient although consent will be performed by one of the study investigators.
- Potential hazards of hyperpolarized Xe-129, optional ventilation/perfusion nuclear medicine scan and CT will be explained to the patient. The potential reactions to iodinated contrast or gadolinium will be explained to the patient. If the patient has experienced a contrast reaction before then contrast will not be used.
- Patient inconvenience will be minimised by scheduling study investigations on the same day as routine clinic appointments, as far as possible. If a separate visit is necessary the patient will be compensated for any travel expenses.
- Patients will be informed that findings from the study may not benefit them directly but will be used to improve future assessment of lung function and monitoring of treatment response.
- Findings from imaging, e.g. incidental finding of distant metastasis which may influence patient management will be communicated to the referring clinician who will then advise the patient appropriately.

17. FINANCE AND INSURANCE

17.1. Funding

The trial sponsor will be the Oxford University Hospitals NHS Foundation Trust.

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The funder for this study will be the Oxford Biomedical Research Centre. Polarean has provided support for the trial by servicing the Xenon hyperpolarizer and GE Healthcare provided modifications to the Churchill Hospital MRI scanner to enable reading of the hyperpolarized xenon signal.

The chief investigator is responsible for applying for local Trust management approval to conduct the trial in accordance with local arrangements and policies. Trust approval and indemnity must be confirmed in writing before patient recruitment commences on the Investigator site.

The Oxford University Hospitals NHS Foundation Trust will authorise trial commencement once satisfied that all arrangements and approvals for the proper conduct of the trial are in place.

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 trial as a result of negligence on the part of a member of the trial team this liability cover would apply.

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

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

18. PUBLICATION POLICY

The final results of the trial will be submitted to a peer-reviewed journal for publication. Authors will be the Principal Investigator, the Co-Investigator, the Statistician and other members of the research team. No data on individual patients will be published without the permission of the Principal Investigator. Authors shall acknowledge that the study was performed with the support of the NIHR Oxford Biomedical Research Centre and Oxford Cancer Imaging Centre.

19. REFERENCES

1. The burden of lung disease 2nd Edition, A statistics report from the British Thoracic Society 2006.
2. ; Available from: http://info.cancerresearchuk.org/cancerstats/.
3. Graham MV. Predicting radiation response. Int J Radiat Oncol Biol Phys. 1997 Oct 1;39(3):561-2.
4. Graham MV. Hypofractionated radiation therapy in the modern era. Rays. 1999 Jul-Sep;24(3):400-5.
5. Kwa SL, Lebesque JV, Theuws JC, Marks LB, Munley MT, Bentel G, et al. Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys. 1998 Aug 1;42(1):1-9.
6. Seppenwoolde Y, Lebesque JV. Partial irradiation of the lung. Semin Radiat Oncol. 2001 Jul;11(3):247-58.
7. Seppenwoolde Y, Lebesque JV, de Jaeger K, Belderbos JS, Boersma LJ, Schilstra C, et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. Normal tissue complication probability. Int J Radiat Oncol Biol Phys. 2003 Mar 1;55(3):724-35.
8. Seppenwoolde Y, Muller SH, Theuws JC, Baas P, Belderbos JS, Boersma LJ, et al. Radiation dose-effect relations and local recovery in perfusion for patients with non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2000 Jun 1;47(3):681-90.
9. Gopal R, Tucker SL, Komaki R, Liao Z, Forster KM, Stevens C, et al. The relationship between local dose and loss of function for irradiated lung. Int J Radiat Oncol Biol Phys. 2003 May 1;56(1):106-13.
10. Guckenberger M, Baier K, Polat B, Richter A, Krieger T, Wilbert J, et al. Dose-response relationship for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. Radiother Oncol. 2010 Jun 2.
11. Marks LB, Munley MT, Bentel GC, Zhou SM, Hollis D, Scarfone C, et al. Physical and biological predictors of changes in whole-lung function following thoracic irradiation. Int J Radiat Oncol Biol Phys. 1997 Oct 1;39(3):563-70.
12. Marks LB, Spencer DP, Bentel GC, Ray SK, Sherouse GW, Sontag MR, et al. The utility of SPECT lung perfusion scans in minimizing and assessing the physiologic consequences of thoracic irradiation. Int J Radiat Oncol Biol Phys. 1993 Jul 15;26(4):659-68.
13. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004 Mar 4;350(10):1005-12.
14. Albert MS, Cates GD, Driehuys B, Happer W, Saam B, Springer CS, Jr., et al. Biological magnetic resonance imaging using laser-polarized 129Xe. Nature. 1994 Jul 21;370(6486):199-201.
15. MacFall JR, Charles HC, Black RD, Middleton H, Swartz JC, Saam B, et al. Human lung air spaces: potential for MR imaging with hyperpolarized He-3. Radiology. 1996 Aug;200(2):553-8.
16. de Lange EE, Mugler JP, 3rd, Brookeman JR, Knight-Scott J, Truwit JD, Teates CD, et al. Lung air spaces: MR imaging evaluation with hyperpolarized 3He gas. Radiology. 1999 Mar;210(3):851-7.
17. Ruppert K, Brookeman JR, Hagspiel KD, Driehuys B, Mugler JP, 3rd. NMR of hyperpolarized (129)Xe in the canine chest: spectral dynamics during a breath-hold. NMR Biomed. 2000 Jun;13(4):220-8.
18. Patz S, Hersman FW, Muradian I, Hrovat MI, Ruset IC, Ketel S, et al. Hyperpolarized (129)Xe MRI: a viable functional lung imaging modality? Eur J Radiol. 2007 Dec;64(3):335-44.
19. Colegrove FD SL, Walters GK. Polarisation of He3 gas by optical pumping. Phys Rev A. 1963;132:2561-72.
20. Happer W ME, Schaefer S, Schreiber D, van Wijngaarden WA, Zeng X. . Polarization of the nuclear spins of noble-gas atoms by spin exchange with optically pumped alkali-metal atoms. Phys Rev A. 1984;29:3092-110.
21. Tseng CH, Wong GP, Pomeroy VR, Mair RW, Hinton DP, Hoffmann D, et al. Low-field MRI of laser polarized noble gas. Phys Rev Lett. 1998 Oct 26;81(17):3785-8.
22. Wong GP, Tseng CH, Pomeroy VR, Mair RW, Hinton DP, Hoffmann D, et al. A system for low field imaging of laser-polarized noble gas. J Magn Reson. 1999 Dec;141(2):217-27.

23. Durand E, Guillot G, Darrasse L, Tastevin G, Nacher PJ, Vignaud A, et al. CPMG measurements and ultrafast imaging in human lungs with hyperpolarized helium-3 at low field (0.1 T). Magn Reson Med. 2002 Jan;47(1):75-81.
24. Bidinosti CP, Choukeife J, Nacher PJ, Tastevin G. In vivo NMR of hyperpolarized 3He in the human lung at very low magnetic fields. J Magn Reson. 2003 May;162(1):122-32.
25. Goodson BM. Nuclear magnetic resonance of laser-polarized noble gases in molecules, materials, and organisms. J Magn Reson. 2002 Apr;155(2):157-216.
26. Kauczor H, Surkau R, Roberts T. MRI using hyperpolarized noble gases. Eur Radiol. 1998;8(5):820-7.
27. Guenther D, Hanisch G, Kauczor HU. Functional MR imaging of pulmonary ventilation using hyperpolarized noble gases. Acta Radiol. 2000 Nov;41(6):519-28.
28. Kauczor HU, Chen XJ, van Beek EJ, Schreiber WG. Pulmonary ventilation imaged by magnetic resonance: at the doorstep of clinical application. Eur Respir J. 2001 May;17(5):1008-23.
29. Moller HE, Chen XJ, Saam B, Hagspiel KD, Johnson GA, Altes TA, et al. MRI of the lungs using hyperpolarized noble gases. Magn Reson Med. 2002 Jun;47(6):1029-51.
30. Bouchiat MA CT, Varnum CM. Nuclear polarisation in 3He gas induced by optical pumping and dipolar exchange. Phys Rev Lett. 1960;5:373-5.
31. McMahon CJ, Dodd JD, Hill C, Woodhouse N, Wild JM, Fichele S, et al. Hyperpolarized 3helium magnetic resonance ventilation imaging of the lung in cystic fibrosis: comparison with high resolution CT and spirometry. Eur Radiol. 2006 Nov;16(11):2483-90.
32. Gast KK, Viallon M, Eberle B, Lill J, Puderbach MU, Hanke AT, et al. MRI in lung transplant recipients using hyperpolarized 3He: comparison with CT. J Magn Reson Imaging. 2002 Mar;15(3):268-74.
33. Zaporozhan J, Ley S, Gast KK, Schmiedeskamp J, Biedermann A, Eberle B, et al. Functional analysis in single-lung transplant recipients: a comparative study of high-resolution CT, 3He-MRI, and pulmonary function tests. Chest. 2004 Jan;125(1):173-81.
34. Samee S, Altes T, Powers P, de Lange EE, Knight-Scott J, Rakes G, et al. Imaging the lungs in asthmatic patients by using hyperpolarized helium-3 magnetic resonance: assessment of response to methacholine and exercise challenge. J Allergy Clin Immunol. 2003 Jun;111(6):1205-11.
35. Salerno M, Altes TA, Brookeman JR, de Lange EE, Mugler JP, 3rd. Dynamic spiral MRI of pulmonary gas flow using hyperpolarized (3)He: preliminary studies in healthy and diseased lungs. Magn Reson Med. 2001 Oct;46(4):667-77.
36. Wild JM, Paley MN, Kasuboski L, Swift A, Fichele S, Woodhouse N, et al. Dynamic radial projection MRI of inhaled hyperpolarized 3He gas. Magn Reson Med. 2003 Jun;49(6):991-7.
37. Holmes JH, Korosec FR, Du J, O'Halloran RL, Sorkness RL, Grist TM, et al. Imaging of lung ventilation and respiratory dynamics in a single ventilation cycle using hyperpolarized He-3 MRI. J Magn Reson Imaging. 2007 Sep;26(3):630-6.
38. Koumellis P, van Beek EJ, Woodhouse N, Fichele S, Swift AJ, Paley MN, et al. Quantitative analysis of regional airways obstruction using dynamic hyperpolarized 3He MRI-preliminary results in children with cystic fibrosis. J Magn Reson Imaging. 2005 Sep;22(3):420-6.
39. Deninger AJ, Mansson S, Petersson JS, Pettersson G, Magnusson P, Svensson J, et al. Quantitative measurement of regional lung ventilation using 3He MRI. Magn Reson Med. 2002 Aug;48(2):223-32.
40. Mansson S, Deninger AJ, Magnusson P, Pettersson G, Olsson LE, Hansson G, et al. 3He MRI-based assessment of posture-dependent regional ventilation gradients in rats. J Appl Physiol. 2005 Jun;98(6):2259-67.
41. Spector ZZ, Emami K, Fischer MC, Zhu J, Ishii M, Vahdat V, et al. Quantitative assessment of emphysema using hyperpolarized 3He magnetic resonance imaging. Magn Reson Med. 2005 Jun;53(6):1341-6.
42. Emami K, Cadman RV, Woodburn JM, Fischer MC, Kadlecek SJ, Zhu J, et al. Early changes of lung function and structure in an elastase model of emphysema--a hyperpolarized 3He MRI study. J Appl Physiol. 2008 Mar;104(3):773-86.
43. Saam BT, Yablonskiy DA, Kodibagkar VD, Leawoods JC, Gierada DS, Cooper JD, et al. MR imaging of diffusion of (3)He gas in healthy and diseased lungs. Magn Reson Med. 2000 Aug;44(2):174-9.

44. Salerno M, de Lange EE, Altes TA, Truwit JD, Brookeman JR, Mugler JP, 3rd. Emphysema: hyperpolarized helium 3 diffusion MR imaging of the lungs compared with spirometric indexes--initial experience. Radiology. 2002 Jan;222(1):252-60.
45. Swift AJ, Wild JM, Fichele S, Woodhouse N, Fleming S, Waterhouse J, et al. Emphysematous changes and normal variation in smokers and COPD patients using diffusion 3He MRI. Eur J Radiol. 2005 Jun;54(3):352-8.
46. Woods JC, Yablonskiy DA, Choong CK, Chino K, Pierce JA, Hogg JC, et al. Long-range diffusion of hyperpolarized 3He in explanted normal and emphysematous human lungs via magnetization tagging. J Appl Physiol. 2005 Nov;99(5):1992-7.
47. Mata JF, Altes TA, Cai J, Ruppert K, Mitzner W, Hagspiel KD, et al. Evaluation of emphysema severity and progression in a rabbit model: comparison of hyperpolarized 3He and 129Xe diffusion MRI with lung morphometry. J Appl Physiol. 2007 Mar;102(3):1273-80.
48. Peces-Barba G, Ruiz-Cabello J, Cremillieux Y, Rodriguez I, Dupuich D, Callot V, et al. Helium-3 MRI diffusion coefficient: correlation to morphometry in a model of mild emphysema. Eur Respir J. 2003 Jul;22(1):14-9.
49. Chen XJ, Hedlund LW, Moller HE, Chawla MS, Maronpot RR, Johnson GA. Detection of emphysema in rat lungs by using magnetic resonance measurements of 3He diffusion. Proc Natl Acad Sci U S A. 2000 Oct 10;97(21):11478-81.
50. Morbach AE, Gast KK, Schmiedeskamp J, Dahmen A, Herweling A, Heussel CP, et al. Diffusion-weighted MRI of the lung with hyperpolarized helium-3: a study of reproducibility. J Magn Reson Imaging. 2005 Jun;21(6):765-74.
51. Diaz S, Casselbrant I, Piitulainen E, Pettersson G, Magnusson P, Peterson B, et al. Hyperpolarized 3He apparent diffusion coefficient MRI of the lung: reproducibility and volume dependency in healthy volunteers and patients with emphysema. J Magn Reson Imaging. 2008 Apr;27(4):763-70.
52. Ward ER, Hedlund LW, Kurylo WC, Wheeler CT, Cofer GP, Dewhirst MW, et al. Proton and hyperpolarized helium magnetic resonance imaging of radiation-induced lung injury in rats. Int J Radiat Oncol Biol Phys. 2004 Apr 1;58(5):1562-9.
53. Saam B, Happer W, Middleton H. Nuclear relaxation of 3He in the presence of O2. Phys Rev A. 1995 Jul;52(1):862-5.
54. Eberle B, Weiler N, Markstaller K, Kauczor H, Deninger A, Ebert M, et al. Analysis of intrapulmonary O(2) concentration by MR imaging of inhaled hyperpolarized helium-3. J Appl Physiol. 1999 Dec;87(6):2043-52.
55. Deninger AJ, Eberle B, Bermuth J, Escat B, Markstaller K, Schmiedeskamp J, et al. Assessment of a single-acquisition imaging sequence for oxygen-sensitive (3)He-MRI. Magn Reson Med. 2002 Jan;47(1):105-14.
56. Nambu K, Suzuki R, Hirakawa K. Cerebral blood flow: measurement with xenon-enhanced dynamic helical CT. Radiology. 1995 Apr;195(1):53-7.
57. Suga K, Nishigauchi K, Kume N, Takano K, Koike S, Shimizu K, et al. Ventilation abnormalities in obstructive airways disorder: detection with pulmonary dynamic densitometry by means of spiral CT versus dynamic Xe-133 SPECT. Radiology. 1997 Mar;202(3):855-62.
58. Eger EI, 2nd, Larson CP, Jr. Anaesthetic Solubility in Blood and Tissues: Values and Significance. Br J Anaesth. 1964 Mar;36:140-4.
59. Butler JP, Mair RW, Hoffmann D, Hrovat MI, Rogers RA, Topulos GP, et al. Measuring surface-area-to-volume ratios in soft porous materials using laser-polarized xenon interphase exchange nuclear magnetic resonance. J Phys Condens Matter. 2002 Apr 8;14(13):L297-304.
60. Ruppert K, Brookeman JR, Hagspiel KD, Mugler JP, 3rd. Probing lung physiology with xenon polarization transfer contrast (XTC). Magn Reson Med. 2000 Sep;44(3):349-57.
61. Ruppert K, Mata JF, Brookeman JR, Hagspiel KD, Mugler JP, 3rd. Exploring lung function with hyperpolarized (129)Xe nuclear magnetic resonance. Magn Reson Med. 2004 Apr;51(4):676-87.
62. Mugler JP, 3rd, Driehuys B, Brookeman JR, Cates GD, Berr SS, Bryant RG, et al. MR imaging and spectroscopy using hyperpolarized 129Xe gas: preliminary human results. Magn Reson Med. 1997 Jun;37(6):809-15.

63. Mansson S, Wolber J, Driehuys B, Wollmer P, Golman K. Characterization of diffusing capacity and perfusion of the rat lung in a lipopolysaccaride disease model using hyperpolarized 129Xe. Magn Reson Med. 2003 Dec;50(6):1170-9.
64. Abdeen N, Cross A, Cron G, White S, Rand T, Miller D, et al. Measurement of xenon diffusing capacity in the rat lung by hyperpolarized 129Xe MRI and dynamic spectroscopy in a single breath-hold. Magn Reson Med. 2006 Aug;56(2):255-64.
65. Patz S, Muradian I, Hrovat MI, Ruset IC, Topulos G, Covrig SD, et al. Human pulmonary imaging and spectroscopy with hyperpolarized 129Xe at 0.2T. Acad Radiol. 2008 Jun;15(6):713-27.
66. Swanson SD, Rosen MS, Coulter KP, Welsh RC, Chupp TE. Distribution and dynamics of laser-polarized (129)Xe magnetization in vivo. Magn Reson Med. 1999 Dec;42(6):1137-45.
67. Swanson SD, Rosen MS, Agranoff BW, Coulter KP, Welsh RC, Chupp TE. Brain MRI with laser-polarized 129Xe. Magn Reson Med. 1997 Nov;38(5):695-8.
68. Driehuys B, Cofer GP, Pollaro J, Mackel JB, Hedlund LW, Johnson GA. Imaging alveolar-capillary gas transfer using hyperpolarized 129Xe MRI. Proc Natl Acad Sci U S A. 2006 Nov 28;103(48):18278-83.
69. Chen XJ, Moller HE, Chawla MS, Cofer GP, Driehuys B, Hedlund LW, et al. Spatially resolved measurements of hyperpolarized gas properties in the lung in vivo. Part II: T *(2). Magn Reson Med. 1999 Oct;42(4):729-37.
70. Yorke J, Moosavi SH, Shuldham C, Jones PW. Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12. Thorax. [Research Support, Non-U.S. Gov't Validation Studies]. 2010 Jan;65(1):21-6.
71. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002 Jul 1;166(1):111-7.
72. Driehuys B. Safety, tolerability, and feasibility of hyperpolarized 129Xe magnetic resonance imaging of pulmonary ventilation in healthy volunteers and subjects with chronic obstructive pulmonary disease. Radiology. 2011;accepted for publication, pending minor ammendments.
73. Kaushik SS, Cleveland ZI, COfer GP, Metz G, Beaver D, Nouls J, et al. Diffusion-weighted hyperpolarized 129-Xe MRI in healthy volunteers and subjects with chronic obstructive pulmonary disease. Magn Reson Med. 2010 Dec 16.
74. Latchaw RE, Yonas H, Pentheny SL, Gur D. Adverse reactions to xenon-enhanced CT cerebral blood flow determination. Radiology. 1987;163(1):251-4.
75. al BDe. Safety, tolerability, and feasibility of hyperpolarized 129Xe magnetic resonance imaging of pulmonary ventilation in healthy volunteers and subjects with chronic obstructive pulmonary disease. Radiology. 2011;accepted for publication, pending minor ammendments.
76. Patz S, Hersmanc FW, Muradian I, Hrovat MI, Ruset IC, Ketel S, et al. Hyperpolarized 129Xe MRI: A viable functional lung imaging modality? Europ J Radiol. 2007;64:335-44.
77. Kennedy R, Stokes J, Downing P. Anaesthesia and the 'inert' gases with special reference to xenon. Anaesth Intensive Care. 1992;20(1):66-70.
78. Patakas D, Louridas G, Argyropoulou P, Stavropoulos C. Respiratory drive in patients with chronic obstructive pulmonary disease. Respir. 1978;36:194-200.
79. Plotkowiak M, Burrowes K, Wolber J, Buckley C, Davies R, Gleeson F, et al. Relationship between structural changes and hyperpolarized gas magnetic resonance imaging in chronic obstructive pulmonary disease using computational simulations with realistic alveolar geometry. Phil Trans R Soc. 2009;367(1896):2347-69.

20. APPENDICES

Appendix	Appendix code
Patient information sheet	A
Patient consent form	B
Physician's information sheet	C

21. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1	06/01/2014	TM	1. Clarified exclusion of pregnancy in female participants of child-bearing age by Oncology prior to radiotherapy and therefore hyperpolarized Xe-129 lung MRI. 2. Follow-up of participants after hyperpolarized Xe-129 MRI scan clarified including monitoring for at least 30 minutes each visit. 3. Clarification of AE/SAE review including telephone consultation two weeks after final xenon administration at 1-year post-radiotherapy visit.
2	2	11/08/2016	TM/FVG	1. The number of participants has been reduced to 30 in total. 2. The number of study visits have been reduced to a maximum of five: - a) Visit 1 – enrolment (compulsory) b) Visit 2 – Baseline (compulsory) c) Visit 3 – Half-way through radiotherapy schedule d) Visit 4 - Final day of radiotherapy treatment e) Visit 5 – 3-months post-radiotherapy. Participants will be required to complete at least one follow-up visit, the others are optional.

				3. Study measures have been reduced: - a) Ventilation/perfusion nuclear medicine scan is only to be completed at baseline and is optional b) Exercise tests have been removed from the protocol 4. Clarification of study measures to be completed by patients with and without a diagnosis of lung cancer 5. The study duration has been reduced to nine months to account for the reduced follow-up period 6. The planned trial period has been increased to 5 years 7. The primary objective has been amended to account for the reduced number of study visits/follow-up period. The change in hyperpolarised Xe-129 MRI will now be determined between baseline and time points post-radiotherapy initiation. 8. The inclusion criteria have been amended to include any patient considered for radiotherapy or chemotherapy affecting the lung. 9. The name of the xenon hyperpolariser model and manufacturer (Polarean) has been amended. 10. Clarification that thoracic CT will be performed at the Churchill hospital 11. The maximum total number of xenon inhalations has been reduced to 24 to account for the reduced number of study visits. 12. Clarification of type of Xe-129 MR sequences to be acquired.
1	3	27/03/2019	MC	1. Updated list of investigators and main contact 2. The planned trial period has been increased to 7 years.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.

