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Early View

Study protocol

Functional imaging in asthma and COPD: design of the NOVELTY ADPro substudy

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Functional imaging in asthma and COPD: design of the NOVELTY ADPro substudy

Helen Marshall[1], Jim M. Wild[1], Laurie J. Smith[1], Latife Hardaker[2], Titti Fihn-Wikander[3], Hana Müllerová[4] and Rod Hughes[5], for the NOVELTY study investigators

[1]POLARIS, Dept of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK; [2]Priory Medical Group, York, UK; [3]Evidence Delivery, BioPharmaceuticals Medical, AstraZeneca, Gothenburg, Sweden; [4]Respiratory & Immunology, Medical and Payer Evidence Strategy, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK; [5]External Scientific Engagement, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK.

Correspondence: Helen Marshall, POLARIS, Dept of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK.

E-mail: h.marshall@sheffield.ac.uk

Take home message

The NOVELTY ADPro substudy will use functional imaging and physiological and metabolic measures to examine patterns of ventilation, gas transfer, acinar dimensions and small airways dysfunction to more precisely phenotype patients with asthma and/or COPD.

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Abstract

The NOVEL observational longiTudinal studY (NOVELTY; ClinicalTrials.gov identifier: NCT02760329) is a global, prospective, observational study of ~12 000 patients with a diagnosis of asthma and/or chronic obstructive pulmonary disease (COPD). Here we describe the design of the Advanced Diagnostic Profiling (ADPro) substudy of NOVELTY being conducted in a subset of ~180 patients recruited from two primary care sites in York, UK. ADPro is employing a combination of novel functional imaging and physiological and metabolic modalities to explore structural and functional changes in the lungs, and their association with different phenotypes and endotypes.

Patients participating in the ADPro substudy will attend two visits at the University of Sheffield, UK, 12±2 months apart, at which they will undergo imaging and physiological lung function testing. The primary endpoints are the distributions of whole lung functional and morphological measurements assessed with Xenon-129 magnetic resonance imaging, including ventilation, gas transfer and airway microstructural indices. Physiological assessments of pulmonary function include spirometry, bronchodilator reversibility, static lung volumes via body plethysmography, transfer factor of the lung for carbon monoxide, multiple-breath nitrogen washout and airway oscillometry. Fractional exhaled nitric oxide will be measured as a marker of Type-2 airways inflammation.

Regional and global assessment of lung function using these techniques will enable more precise phenotyping of patients with physician-assigned asthma and/or COPD. These techniques will be assessed for their sensitivity to markers of early disease progression.

Keywords: asthma, chronic obstructive pulmonary disease, magnetic resonance imaging, small airways dysfunction, ventilation heterogeneity, Xenon-129

Introduction

Background

Asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent lung diseases, affecting >600 million individuals globally [1]. They are often regarded as separate clinical disorders; however, they are heterogenous diseases with similar symptoms and patients may have features of both [2, 3]. There is also significant overlap in the diagnostic criteria and clinical presentation for asthma and COPD, including symptoms, airflow obstruction, increased expiratory time, hyperinflation and response to bronchodilators [2, 3].

Spirometry is an important method of pulmonary function testing for diagnosing and stratifying obstructive lung disease; however, it is largely insensitive to changes involving the small airways and substantial small airways disease often exists before spirometry appears to be abnormal [4]. Patients with normal spirometry can also exhibit other characteristics of disease, such as ventilation heterogeneity, gas trapping and impaired gas exchange [4, 5].

There is therefore a need for additional diagnostic procedures to gain a better understanding of the nature of the structural and functional changes in the airways and alveoli that may be associated with different clinical phenotypes, endotypes, exposure to tobacco smoke or other harmful particles, and inflammatory patterns seen in patients with asthma and/or COPD.

Hyperpolarised Xenon-129 (^{129}Xe) magnetic resonance imaging (MRI) is a highly sensitive imaging technique that has gained traction in recent years for examining lung function and structure. Previous studies have used hyperpolarised Helium-3

(^{3}He) MRI to assess lung ventilation in patients with asthma and/or COPD [6-10], with some including measurements of longitudinal change [6, 7] and alveolar microstructure [6]. Due to the additional ability of ^{129}Xe to measure gas exchange, and a shortage of ^{3}He, recent studies have utilised ^{129}Xe MRI to assess lung ventilation [11-16], alveolar microstructure [11-13, 17] and gas exchange [18, 19] in patients with asthma and/or COPD. However, study protocols that use ^{129}Xe MRI to identify and characterise damage to the lungs in asthma and/or COPD, across the spectrum of disease stage, severity, and diagnosis, are lacking. Additionally, these studies have not used ^{129}Xe MRI to investigate ventilation, acinar microstructure, and gas exchange simultaneously or to assess longitudinal change.

Advanced Diagnostic Profiling (ADPro)

The NOVEL observational longiTudinal studY (NOVELTY; ClinicalTrials.gov identifier: NCT02760329) is a large, global, prospective, cohort study enrolling patients with a suspected or confirmed physician diagnosis of asthma and/or COPD [1]. Analyses have demonstrated heterogeneity within physician-assigned diagnosis groups and overlap between patients with asthma and/or COPD in the cohort [20].

The ADPro study is a substudy of NOVELTY recruiting patients from two primary care sites in York, UK. It is designed to examine patterns of ventilation, gas transfer, acinar dimensions and small airways dysfunction in patients with asthma and/or COPD using novel imaging, advanced pulmonary function tests and metabolic modalities. Procedures include hyperpolarised gas MRI, multiple-breath nitrogen washout (MBW) and airwave oscillometry (AOS). The ADPro substudy will use these modalities to assess early markers and phenotypes of lung disease, with the aim of

understanding which techniques are most sensitive to initial changes in lung morphology during disease progression.

Ventilation patterns

Hyperpolarised Xenon-129 (^{129}Xe) MRI can provide detailed, three-dimensional (3D) imaging of ventilation patterns, which allows measurement of the proportion of unventilated lung (ventilation defect percentage) and ventilation heterogeneity [11]. MBW allows calculation of the lung clearance index (LCI), which quantifies the overall degree of global ventilation heterogeneity and is sensitive enough to assess small airways abnormalities [21, 22]. ^{129}Xe MRI treatment response mapping can provide regional information on ventilation changes between imaging timepoints [23].

Small airways disease and inflammation

Small airways obstruction frequently occurs during the earliest stages of disease for both asthma and COPD [4]. However, clinical assessment of the small airways is challenging due to their small size and inaccessibility [21], and finding new methods and markers to facilitate the earlier detection of small airways disease may enable the delivery of targeted therapy to slow or alter the course of disease [21, 24]. Small airways obstruction can be assessed using AOS, MBW and body plethysmography [22, 25, 26]. ^{129}Xe MRI can also be used to gain information about the alveolar and acinar size and microstructure, and potentially detect early emphysema [27, 28]. Additionally, fractional exhaled nitric oxide (FeNO) indicates the level of Type-2 airways inflammation [4]. Examining these measures of small airways disease may help to determine markers of early lung disease and identify patients at risk of rapid progression.

Mucous plugging and gas trapping

Mucous plugs in patients with obstructive pulmonary disease are thought to contribute to the pathophysiology of airflow obstruction and gas trapping in severe asthma and COPD [29, 30]. Body plethysmography can be used to identify gas trapping and lung hyperinflation [4]. Structural proton (^{1}H) MRI images can also be used to visualise air trapping and larger mucous plugs [31].

Gas exchange

Gas exchange can be impaired due to inflammatory thickening of the lung parenchyma, or breakdown of alveolar walls in emphysema [4, 32], which can cause large air-filled spaces to form in the lung parenchyma [4, 33]. ^{129}Xe MRI is uniquely capable of imaging the transfer of gas from the airspaces across the alveolar-capillary barrier and into the red blood cells (RBCs), enabling the assessment of all three of the components of gas exchange: airspace, alveolar-capillary membrane and RBCs. This allows impairments in gas transfer that can arise with disease to be identified [32, 34]. The transfer factor of the lungs for carbon monoxide (TL_{CO}) provides information about the surface area and integrity of the alveolar membrane, and impairments in gas exchange [35].

Aims

To describe the design and rationale of the ADPro substudy of NOVELTY, which will allow detailed assessments of exploratory and pre-defined phenotypes in patients with physician-assigned asthma and/or COPD. Phenotypes being assessed include small airways disease, emphysematous disease and inflammatory phenotypes, and these will be compared between asthma and COPD. The study also aims to identify

methods that will allow the earlier detection of asthma and COPD in the future, and to explore patients at risk of progression.

Materials and methods

Study design

The ADPro substudy aims to recruit approximately 180 patients enrolled in NOVELTY. NOVELTY is a global, prospective, observational study enrolling ~12,000 patients with asthma and/or COPD (suspected or confirmed); the study design and patient eligibility criteria have been described previously [1]. Given the observational nature of NOVELTY, patients will receive standard medical care as determined by their physician; no experimental intervention or treatment will be given as part of NOVELTY. All patients enrolled in NOVELTY will attend a baseline visit in which patient demographics, characteristics, risk factors for development of obstructive lung disease, and patient reported outcomes (including Chronic Airways Assessment Test [CAAT] and Respiratory Symptoms Questionnaire [RSQ]) will be recorded. Patients will complete CAAT and RSQ every 3 months after the baseline visit. Patients participating in the ADPro substudy will attend two additional visits accompanied by a study nurse for lung imaging and lung function assessments at the POLARIS lung imaging centre, University of Sheffield, UK (figure 1). Imaging will be performed at the Royal Hallamshire Hospital and Northern General Hospital sites, under the governance of Sheffield Teaching Hospitals National Health Trust.

ADPro substudy protocol-based objectives

The primary objective is to assess global and regional lung functional and morphological measurements with ^{129}Xe MRI, including ventilation, gas transfer and airway microstructural indices. The procedures and variables used to assess the primary, secondary and exploratory objectives are given in table 1.

Secondary and exploratory objectives are to:

1. Evaluate relationships between ^{129}Xe MRI measurements of ventilation and airway microstructural indices, and pulmonary function markers of small airways dysfunction.
2. Evaluate relationships between ^{129}Xe MRI gas transfer and airway microstructural indices, and pulmonary function markers of gas transfer and gas trapping.
3. Describe heterogeneity of regional ventilation, gas transfer and alveolar microstructure.
4. Describe the progression of ^{129}Xe MRI and pulmonary function indices between substudy visits 1 and 2 and compare the sensitivity of the measures to longitudinal change.
5. Assess bronchodilator reversibility using pulmonary function tests and ^{129}Xe MRI.
6. Assess MRI-derived mucous plugging and air trapping scores.
7. Describe associations between FeNO and markers of ventilation heterogeneity, small airways dysfunction and clinical descriptors.
8. Assess the relationship between the progression of ^{129}Xe MRI and pulmonary function indices between substudy visits 1 and 2 and disease progression (assessed by change in FEV_1 and CAAT scores).

Patients

Patients enrolled in NOVELTY will be recruited from two primary care sites in York, UK. Patients with physician-identified suspected or confirmed asthma and/or COPD (no specified diagnostic criteria) recruited to the ADPro substudy will be a representative spread across physician-assigned diagnostic groups and physician-assessed categories of severity. Patients will be aged ≥16 years and be enrolled

from an active clinical practice. Patients will not have participated in any respiratory interventional trial in the previous 12 months.

Substudy procedures

At each substudy visit, patient smoking activity and concomitant medication within the past 24 h, asthma or COPD exacerbations within the past 6 weeks, physiological data (*e.g.* height, weight and body mass index) and contraindications to MRI will be recorded by the study nurse using a designated electronic case report form (eCRF). At substudy visit 1, imaging and pulmonary function testing will be undertaken post bronchodilator (figure 1). At visit 2, ^{129}Xe ventilation MRI at end inspiratory tidal volume and ^{129}Xe gas exchange MRI will be obtained pre- and post-bronchodilator, and ^{129}Xe MRI microstructural imaging will be obtained post-bronchodilator. Post-bronchodilator imaging will be conducted ≥20 min after the administration of 400 µg of salbutamol. Post-bronchodilator, MRI will be performed before pulmonary function tests to avoid any changes in lung physiology that might be induced by performing the forced manoeuvres required for spirometry and plethysmography. Patients will be asked to withhold their bronchodilator medications for ≥24 h prior to visit 2, during which time any reliever medication use will be recorded. The imaging and pulmonary function tests that will be conducted at each visit, and their component measures, are shown in figures 1 and 2, and table 1, respectively.

Imaging

MRI is non-invasive and ionising radiation-free. ^{129}Xe MRI involves the inhalation of hyperpolarised ^{129}Xe and imaging during a short breath-hold. Patients will be scanned supine using a whole body 1.5T MRI scanner equipped with a ^{129}Xe

transmit/receive vest coil (GE Signa HDx, Milwaukee, USA). The ^{129}Xe gas will be generated onsite [36] under the Medicines and Healthcare products Regulatory Agency regulatory specials license and administered via inhalation from a Tedlar® plastic bag.

We are assessing markers of ventilation heterogeneity to investigate whether they may explain some of the variability of symptoms in patients with similar levels of airflow impairment. We will compare the regional ventilation imaging patterns and LCI with patient-reported outcomes to determine if these measures can predict symptoms such as breathlessness. ^{129}Xe breath-hold ventilation imaging of the lung will be performed at end inspiratory tidal volume and at TLC using a 3D steady-state free precession sequence, with co-registered ^{1}H anatomical imaging [11]. ^{129}Xe 3D dissolved phase imaging will be used to assess gas exchange by assessing ^{129}Xe in the capillary RBCs, lung tissue and also gaseous ^{129}Xe in the alveolar compartments [37]. ^{129}Xe 3D diffusion-weighted MRI will be used to assess alveolar microstructure [27]. Structural proton (^{1}H) MRI of the lung using a 3D gradient echo sequence, at approximate lung volumes of end inspiratory tidal volume, RV and TLC, and also an ultra-short echo time sequence [38] will be used to qualitatively assess air trapping. Mucous plugging will be assessed by radiological review of the images; structural proton (^{1}H) MRI will be co-registered with larger ventilation defects to determine to what extent the ventilation defects are due to mucous plugs or bronchial tapering. ^{129}Xe MRI treatment response mapping will enable the evaluation of regional lung ventilation longitudinally over the 12-month period, and between pre-bronchodilator and post-bronchodilator imaging. Longitudinal relaxation time (T_1) and proton spin density mapping (M_0) will be performed using 3D gradient echo sequences with variable flip angles [39, 40].

Pulmonary function tests

Spirometry to calculate forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, peak expiratory flow, forced expiratory flow at 25–75% of the forced vital capacity, and inspiratory capacity will be performed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria [41]. Static lung volumes (to calculate TLC, RV, functional residual capacity (FRC), RV/TLC and FRC/TLC) will be measured via body plethysmography according to international guidelines [42] using a Vyaire PFT Pro (Vyaire Medical, Inc., Basingstoke, UK). TL_{CO} will also be performed on a Vyaire PFT Pro and according to international guidelines [43]. Spirometry, static lung volume and gas transfer measurements will be expressed as both z-scores and % predicted. Measurements will be converted to z-scores using recommended reference equations [41, 44, 45]; a z-score of <-1.64 will be defined as the lower limit of normal.

MBW to calculate the LCI will be performed using an Eco Medics Exhalyzer® D and according to international guidelines at visit 1 only [22]. AOS will be performed using a Thorasys TremoFlo® C-100, according to manufacturer guidelines and in keeping with international guidance [46], to calculate the resistance at 5 Hz (R5) and the difference between the resistance at 5 and 20 Hz (R5–20), the reactance at 5 Hz (X5), the resonance frequency (f_{res}) and the area of the reactance curve (AX). The results will be expressed as % predicted and z-scores [47]. Reversibility of airway obstruction will be assessed at visit 2 only. At visit 2, patients will withhold their short-acting bronchodilator medication for ≥6 h prior to reversibility testing and their long-acting bronchodilators, with or without inhaled corticosteroids, for 12–24 h, depending on whether the patient is using twice- or once-daily therapy.

Metabolic measures

FeNO will be performed using a Niox Vero® according to the equipment manufacturer recommendations and ATS/ERS guidelines [48]. All FeNO data will be entered into the eCRF.

Statistical analysis

The sample size calculation used in NOVELTY has been described previously [1]; given the observational nature of the ADPro substudy, no formal size calculation was performed. However, we aimed to recruit ~30 patients within each disease severity for patients with a clinical primary diagnosis of asthma or COPD (with or without features of the other diagnosis). This projected sample size was selected based on previous MRI studies that have identified clinically meaningful correlations [12, 13, 15, 16]. Disease progression will be defined by relative changes to FEV_1 and CAAT between visits 1 and 2. Spearman's correlations will be performed to assess relationships between imaging, pulmonary function test and clinical metrics. Data will be divided into three groups based on physician-assigned diagnosis: asthma, asthma and COPD, and COPD. For each metric, differences between groups will be assessed using either a one-way ANOVA test with Tukey correction for multiple comparisons (for normally distributed data), or a Kruskal–Wallis test with Dunn's correction for multiple comparisons (for non-normally distributed data). To assess change in metrics between visit 1 and visit 2, and change in metrics in response to bronchodilator administration, paired t-tests (for normally distributed data) or Wilcoxon matched pairs tests (for non-normally distributed data) will be performed. A p-value <0.05 will be considered statistically significant. Treatment changes will be

considered as a co-variant when assessing imaging or physiological changes between visit 1 and visit 2.

Ethics approval and consent

The ADPro substudy will be conducted following the principles of the Declaration of Helsinki, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practices, Good Pharmacoepidemiology Practices and applicable legislation for observational studies. The ADPro substudy has been approved by the Leicester Central Research Ethics Committee (reference no. 16/EM/0439). Written informed consent will be obtained by trained study staff from all patients who wish to participate in the ADPro substudy prior to any procedure being performed.

Discussion

By examining a range of functional, morphological, physiological and metabolic markers, the ADPro substudy will allow evaluation of the varying patterns of ventilation heterogeneity, gas exchange, acinar dimensions and small airways dysfunction in patients with asthma and/or COPD, as well as their relationship to important clinical features. These evaluations could allow us to profile patients based on the presence of small airways disease, airways inflammation, lung parenchymal distortion and disease progression. We hope that by more precisely phenotyping and endotyping patients with physician-diagnosed asthma and/or COPD, we will identify clinically meaningful profiles that may help to inform a precision medicine-based approach to asthma and COPD care in future. In addition, this comprehensive approach within a single cohort may highlight where differences exist between patients with guideline-determined diagnoses of asthma or COPD and patients with physician-diagnosed asthma and/or COPD in the real-world, and where they overlap. Furthermore, given the broad inclusion criteria, patients included will be representative of both early and late disease stages. Analysing the longitudinal changes in patients with preserved spirometry will be of particular importance when determining which methods are the most sensitive to early changes to the lungs in disease and which may enable the earlier detection of disease in future.

Until recently, phenotyping of patients with obstructive lung disease has been reliant on non-specific clinical risk factors and exposures, poorly differentiating symptoms and overlapping lung function measures [2, 3]. The addition of functional imaging, such as ^{129}Xe MRI, may facilitate more specific and earlier detection of significant airways and lung parenchymal disease. Compared with FEV_1, ^{129}Xe MRI has

increased sensitivity to lung abnormalities and bronchodilator response, and can depict regional heterogeneity of ventilation, as opposed to providing a whole-lung average. It is also more effective than computed tomography (CT) in evaluating the alveolar microstructure and distinguishing patients with COPD from healthy controls [28]. The high sensitivity of ^{129}Xe MRI provides a means to detect and characterise early emphysematous and obstructive lung disease, and to identify patients suitable for early interventions. ^{129}Xe MRI can provide information to aid the identification of structural and functional phenotypes, particularly in regions of air trapping and mucous plugging [28]. Therefore, the clinical use of ^{129}Xe MRI in future may allow us to identify more discrete phenotypes across diagnostic categories and predict those at risk of more rapidly progressive disease.

Given the observational design of the NOVELTY study, patients will receive standard medical care. The ADPro substudy will analyse markers of disease progression irrespective of treatment changes, however, changes to treatment will be considered as a co-variant for when assessing any imaging or physiological changes.

The strengths of the ADPro substudy reflect those of the NOVELTY study [1]; patients with asthma and/or COPD have been recruited from primary care and are not limited by many of the eligibility criteria restrictions associated with randomised controlled trials. Containing a diverse patient population within the same study protocol will enable comparisons between patients across the spectrum of asthma and COPD, including those with features of both diagnoses and those with early disease. Furthermore, this study will evaluate ^{129}Xe MRI ventilation, microstructural and gas exchange indices in this patient population, whereas previous studies using

^{129}Xe in patients with asthma or COPD have only reported on one or two aspects of lung function and have not assessed longitudinal change [11-19].

One limitation of the ADPro substudy may be that recruitment through clinical practice could bias the study population towards those with more frequent healthcare utilisation. The substudy population are recruited from one area of the UK, so may not be representative of patients in other parts of the world. Travelling to the study site and receiving the tests required at both study visits is likely to be time-consuming and could constitute a substantial burden for the patient. It is possible that patients who are willing to travel and undergo extensive imaging procedures, particularly during the COVID-19 pandemic, may have mild disease. In order to reduce the time burden of each visit, not all tests are conducted at both visits. Finally, the 12-month time-period between visit 1 and visit 2 will not be long enough to capture all patients with disease progression; a longer trial would be needed to explore long-term disease progression.

As the primary purpose of this study was to evaluate functional ventilatory assessment, clinical and physiological measurements, it was not deemed necessary to include detailed anatomical structure. Given the sensitivity of MRI ventilation imaging, CT imaging is unlikely to have added to the understanding of these relationships, and the utilisation of ionising radiation would add risk and inconvenience to participants. In future, larger studies comparing the relative utility of MRI and CT for the assessment of functional markers in specific disease areas may be necessary.

Overall, this longitudinal study is employing novel imaging techniques, as well as physiological and metabolic testing to more precisely phenotype patients with

asthma and COPD by identifying small airways disease, emphysematous disease and inflammation. These techniques will be assessed for their sensitivity to changes in lung function and morphology during disease progression, and in response to bronchodilator administration. This study is being conducted during the COVID-19 pandemic despite the associated challenges. These findings should increase our understanding of the phenotypes and endotypes of patients with asthma and COPD, and help to inform a precision-based medicine approach to patient care in future.

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Support statement

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Conflict of interest

H. Marshall, J. Wild and L. Smith are employees of University of Sheffield, who received funding to conduct the study. H. Marshall has received support for attending meetings from AstraZeneca. T. Fihn-Wikander and H. Müllerová are employees of AstraZeneca. R. Hughes has received personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Novartis outside of the submitted work, and is an employee of AstraZeneca. L. Hardaker has no conflicts to disclose.

Data availability

Not applicable.

TABLE 1 Overview of ADPro substudy assessments

Procedure	Variable	What is being measured?	What information about lung disease is obtained?
^{129}Xe ventilation magnetic resonance imaging (MRI)	Ventilation defect percentage (VDP) [49]	The ratio of unventilated lung volume to total lung volume	These measures tell us about the extent of lung ventilation abnormalities
	Coefficient of variation of ventilation signal intensity (CV) [50]	Ventilation heterogeneity	
	Regional treatment response (∆R) [23]	The difference in regional gas distribution between two timepoints	∆R can assess the effect of treatments (*e.g.* before and after bronchodilator) or change over time (*e.g.* from visit 1 to visit 2) on ventilation in the different regions of the lung
^{129}Xe gas transfer MRI [34, 37]	Red blood cell to membrane ratio (RBC/M) Red blood cell to gas ratio (RBC/gas)	The amount of ^{129}Xe dissolved in RBCs, ^{129}Xe dissolved in lung tissue and gaseous ^{129}Xe in the airspaces	Measures of gas exchange and the alveolar membrane can be used to gauge regional gas-transfer defects and lung function

	Membrane to gas ratio (M/gas)		
^{129}Xe diffusion MRI [27, 28]	Apparent diffusion coefficient (ADC)	A measure of the ability of gas within the airspaces to diffuse by random Brownian motion, sensitive to the underlying alveolar dimensions	Information about the size of the alveoli, and airspace enlargement
	Mean diffusive length scale (Lm_D)	Mean acinar airway dimensions, analogous to mean linear intercept length (L_K) from histology	Detection of early emphysema before it can be detected using spirometry
^{1}H MRI T_1 mapping [39, 40]	Longitudinal relaxation time (T_1)	An intrinsic MRI property affected by water content and interactions between water molecules and macromolecules	T_1 measurements are affected by lung perfusion, inflammation, emphysema and regional partial pressure of oxygen in the alveolar airspaces
	Proton spin density (M_0)	Water content	M_0 is reduced in emphysema and air trapping
Structural proton	Radiological score	Qualitative assessment of air trapping	Air trapping and hyperinflation indicate lung

^{1}H MRI [31]			function impairment and proximal airway remodelling [51]
Static lung volumes using body plethysmography [26, 42, 51]	Total lung capacity (TLC)	Total lung volume at maximal inspiration	
	Residual volume (RV)	Volume of the lungs at maximal expiration	
	Functional residual capacity (FRC)	Volume of the lungs after a normal exhalation	
	RV/TLC	Gas trapping	
	FRC/TLC	Hyperinflation	
Transfer factor of the lung for carbon monoxide (TL_{CO}) [35]	TL_{CO}	The overall gas exchange ability of the whole lung	The efficiency of gas transfer indicates the function of alveoli and the microvasculature
	Transfer coefficient for carbon monoxide (K_{CO})	The rate of uptake of carbon monoxide across the alveolar-capillary membrane	
Multiple-breath nitrogen washout (MBW) [21, 22]	Lung clearance index (LCI)	The degree of ventilation heterogeneity present within the lung	Sensitive to small airways disease

Airwave oscillometry (AOS) [25]	Resistance at 5 Hz (R5)	Total airways resistance	Thought to reflect changes in the more distal small airways and to indicate long-term asthma control, exacerbations and disease severity
	Resistance between 5 and 20 Hz (R5–20)	Difference in resistance between 5 and 20 Hz reflects peripheral lung resistance	
	Airway reactance (AX)	Compliance or stiffness of the small airways	
	Resonance frequency (f_{res})		
Fractional exhaled nitric oxide (FeNO) [4, 52]	FeNO	Nitric oxide levels in exhaled breath	Degree of inflammation in the lungs A marker of Type-2 airways inflammation

^{1}H: proton; ^{129}Xe: Xenon-129; ADPro: Advanced Diagnostic Profiling; COPD: chronic obstructive pulmonary disease.

FIGURE 1 ADPro substudy design

^{1}H: proton; ADPro: Advanced Diagnostic Profiling; AOS: airwave oscillometry; BD: bronchodilator; BMI: body mass index; COPD: chronic obstructive pulmonary disease; FeNO: fractional exhaled nitric oxide; MBW: multiple-breath nitrogen washout; MRI: magnetic resonance imaging; NOVELTY: NOVEL observational longiTudinal studY; R5–R20: resistance between 5 and 20 Hz; TL_{CO}: transfer factor of the lung for carbon monoxide; ^{129}Xe: Xenon-129.

FIGURE 2 Lung structure and variables assessed in the ADPro substudy

ADPro: Advanced Diagnostic Profiling; ADC: apparent diffusion coefficient; AX: airway reactance; CV: coefficient of variation of signal intensity; ΔR: regional treatment response; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of the forced vital capacity; FeNO: fractional exhaled nitric oxide; f_{res}: resonance frequency; FEV_1: forced expiratory volume in 1 s; FRC: functional residual capacity; FVC: forced vital capacity; IC: inspiratory capacity; K_{CO}: transfer coefficient for carbon monoxide; LCI: lung clearance index; Lm_D: diffusive length scale; M_0: proton spin density mapping; M: membrane; PEF: peak expiratory flow; R5: resistance at 5 Hz; R5–20: resistance between 5 and 20 Hz; RBC: red blood cell; RV: residual volume; TLC: total lung capacity; T_1: longitudinal relaxation time; TL_{CO}: transfer factor of the lung for carbon monoxide; VDP: ventilation defect percentage.

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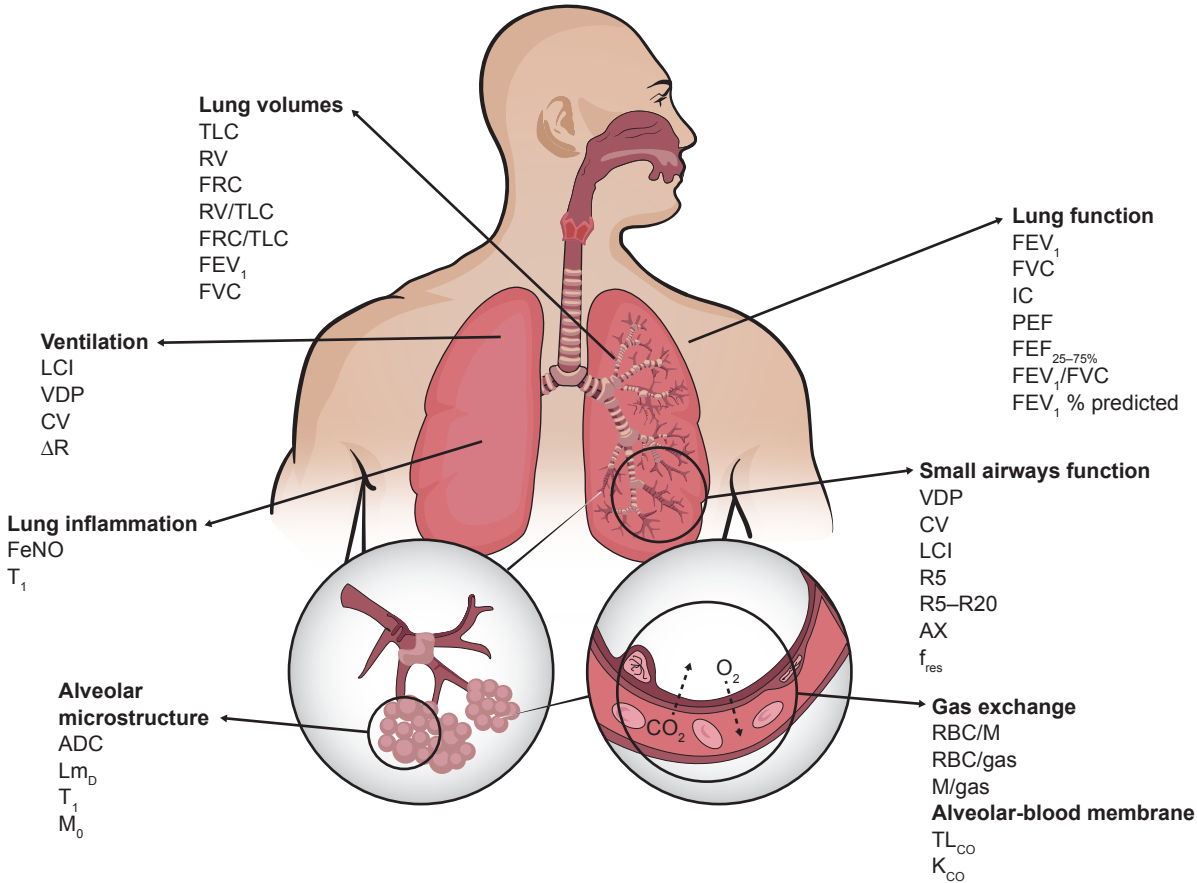
Lung volumes
TLC
RV
FRC
RV/TLC
FRC/TLC
FEV_1
FVC
Ventilation
LCI
VDP
CV
ΔR
Lung inflammation
FeNO
T_1
Alveolar microstructure
ADC
Lm_D
T_1
M_0
Lung function
FEV_1
FVC
IC
PEF
$FEF_{25–75\%}$
FEV_1/FVC
FEV_1 % predicted
Small airways function
VDP
CV
LCI
R5
R5–R20
AX
f_{res}
Gas exchange
RBC/M
RBC/gas
M/gas
Alveolar-blood membrane
TL_{CO}
K_{CO}
O_2
CO_2

NOVELTY: a NOVEL observational longiTudinal studY
~12 000 patients ≥12 years of age, from primary and specialist clinical practices in 19 countries
Diagnosis or suspected diagnosis of asthma and/or COPD

ADPro: Advanced Diagnostic Profiling substudy
~180 patients already enrolled in NOVELTY to be recruited from two primary care sites in York, UK
Representative spread of physician-assigned diagnosis and severity

Imaging and physiological tests will be performed at the POLARIS lung imaging centre at the University of Sheffield, UK
Patients will travel ~1 h by car from York to the imaging centre for visit 1 and visit 2

Visit 1 (Day 0) — **Visit 2 (12±2 months)**

Visits 1 and 2			
Physiological data	• Height • Weight	• Calculated BMI • Waist circumference	• Heart rate • Pregnancy status
Risk factor assessments	• Smoking status and history • Occupational exposure to pollutants		• Allergens
Study questionnaire	• Asthma/COPD treatments (duration and posology) in last 12 months • Concomitant inhaled corticosteroid and bronchodilator medications in previous 24 h • Smoking activity in previous 24 h • Prior exacerbations in previous 6 weeks		

Visit 1 All imaging and physiological testing performed **post-BD**
Imaging (^{129}Xe MRI and ^{1}H MRI)
MBW
AOS (R5–R20)
TL_{CO}
Body plethysmography
Spirometry

Visit 2 Imaging and physiological tests performed **pre- and post-BD**
AOS (R5–R20)
FeNO
TL_{CO}
Body plethysmography
Spirometry
Imaging (^{129}Xe MRI and ^{1}H MRI)
Administration of 400 µcg of salbutamol
After ≥20 min, all imaging and physiological tests (except FeNO) will be repeated **post-BD**

Primary substudy objectives
Determine the distributions of whole lung functional and morphological measurements assessed with MRI (ventilation, gas transfer, airway microstructural indices)

Functional imaging in asthma and COPD:
Design of the NOVELTY ADPro substudy

NOVELTY: a global, prospective, observational study of
~12,000 patients with asthma and/or COPD

Advanced Diagnostic Profiling (ADPro)
~180 patients from two primary care sites in the UK

2 visits **12 ±2** months apart

Physiological
Pulmonary and airways function assessments

^{129}Xe MRI
Ventilation
Gas transfer
Microstructure

Biomarkers
FeNO

Aims

Precise patient phenotyping
- Small airways disease
- Emphysema
- Inflammation

Evaluation of ADPro methods
- Detection of earlier disease
- Sensitivity to markers of progression