Assessing the effects of personalised airway clearance techniques in children and young people with Primary Ciliary Dyskinesia

by

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POLARIS

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Abstract

Primary ciliary dyskinesia (PCD) is a rare inherited condition in which mucociliary clearance is impaired from birth. Ineffective mucus clearance poses a risk of repeated infections, inflammation, and bronchiectasis in PCD. As such, physiotherapists advise people with PCD to complete airway clearance techniques (ACT) twice daily at home to facilitate mucus clearance from the lungs. ACT regimens are personalised to the needs of the individual but current tools available clinically to assess the effects of ACT regimens clinically are limited.

In a population of children and young people with PCD, this study aimed to establish how current literature tells us ACT regimens should be personalised, and how they currently are personalised in practice. It also aimed to quantify lung health and short-term response to a personalised ACT regimen (compared to no-ACT) and to understand the circumstances under which personalisation of ACT regimens is altered with the introduction of functional lung imaging. Using a mixed methods approach, this exploratory study has employed cognitive task analysis methods (critical decision method and think aloud problem solving) to make the decision-making of clinicians explicit, and ^{129}Xe ventilation MRI to accurately assess lung health and treatment response.

This research has found that the personalisation of ACT regimens is complex; physiotherapists often encounter and manage uncertainty when personalising regimens. It has confirmed ventilation distribution is heterogeneous in children with PCD, that ^{129}Xe metric VDP is more sensitive to detect ventilation abnormalities than the widely used spirometry metric, $FEV_{1.}$ It has shown that the response to a personalised ACT regimen was varied, with some individuals improving and others worsening immediately post-ACT. It has discovered that functional lung imaging informed ACT regimen modification in most cases, but that in individuals with more severe disease, physiotherapists planned to reassess the individual in light of the MRI data prior to proposing ACT regimen changes. ^{129}Xe MRI can assess change in ventilation distribution following an ACT regimen; as an exploratory study, these findings can inform future research.

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Abbreviations

^{1}H MRI	Proton magnetic resonance imaging
^{1}H VDP	Ventilation defect percentage derived from ^{1}H (PREFUL) MRI
^{3}He	Helium-3
^{3}He MRI	Hyperpolarised Helium-3 ventilation magnetic resonance imaging
^{129}Xe	Xenon-129
^{129}Xe MRI	Hyperpolarised Xenon-129 ventilation magnetic resonance imaging
^{129}Xe VDP	Ventilation defect percentage derived from ^{1129}Xe MRI
ACBT	Active cycle of breathing technique
ACT	Airway clearance technique
AD	Autogenic drainage
BTHFT	Bradford Teaching Hospitals Foundation Trust
CDM	Critical decision method
CF	Cystic Fibrosis
CoV	Coefficient of variance
CSLD	Chronic Suppurative Lung Disease
CSM	Case study method
CTA	Cognitive task analysis
CT	Computerised tomography
EITV	End-inspiratory tidal volume
EPP	Equal pressure point
FEV_1	Forced expiratory volume in the first second
FET	Forced expiratory technique
FOV	Field of view
FRC	Functional residual capacity
FVC	Forced vital capacity
HASTE	Half-Fourier-Acquired Single-shot Turbo Spin Echo
HFCWO	High frequency chest wall oscillation
HRQoL	Health related quality of life
HSVMA	High speed video microscopy analysis
IDA	Inner dynein arms
IPPB	Intermittent positive pressure breathing
IPV	Intermittent percussive ventilation
IV	Intravenous
IQR	Interquartile range
IS	Incentive spirometry
L	Left
LCI	Lung clearance index

LL	Lower limit
LLN	Lower limit of normal
LOA	Limits of agreement
LRT	Lower respiratory tract
LTHT	Leeds Teaching Hospitals Trust
LVP	Low ventilation percentage
MBW	Multiple breath washout
MIE	Mechanical insufflation exsufflation
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MTD	Microtubular disarrangement
N_2	Nitrogen
NaCl	Sodium chloride
NIV	Non-invasive ventilation
NNO	Nasal nitric oxide
ODA	Outer dynein arms
OPEP	Oscillatory positive expiratory pressure
PCD	Primary Ciliary Dyskinesia
PEFR	Peak expiratory flow rate
PEP	Positive expiratory pressure
PIFR	Peak inspiratory flow rate
PPI	Patient and public involvement
PREFUL	Phase resolved functional lung
Prn	Prone
PsA	Pseudomonas aeruginosa
%P-LV	Percentage of persistent of low ventilation
%P-VD	Percentage persistent ventilation defect
PVPD	Percussions, vibrations, and postural drainage
QOL-PCD	Quality of life primary ciliary dyskinesia outcome measure
R	Right
RCT	Randomised controlled trial
RF	Radio frequency
RMCH	Royal Manchester Children’s Hospital
RPDM	Recogniton-primed decision model
RV	Residual volume
RVI	Reversible volume index
SCH	Sheffield Children’s Hospital
SI	Situs inversus

Sit	Sitting up
SPGR	3D Spoiler gradient echo
SS	Situs solitus
SSFP	Steady state free precision
STRM	Signal treatment response map
Sup	Supine
TAPS	Think aloud problem solving
TCV	Thoracic cavity volume
TLC	Total lung capacity
TRM	Treatment response map
UL	Upper limit
ULN	Upper limit of normal
UoS	University of Sheffield
URT	Upper respiratory tract
UTE	Ultra-short echo
VDP	Ventilation defect percentage
VHI	Ventilation heterogeneity index
VTRM	Volume treatment response map
VV	Ventilated volume

Chapter 1: Introduction

1.1 Thesis structure

This thesis approaches four general scientific classes of problem: how we ***should*** personalise clinical care given different patient needs; how we actually ***do*** so; what the ***effects*** of personalised care are; and whether we ***might*** personalise care differently, given access to novel imaging techniques. The specific case material involves a practical inquiry into how we should, do, and might manage a lung disease called Primary Ciliary Dyskinesia (PCD), taking a pragmatic approach to a clinical problem. Due to a lack of evidence and guidance on how to treat this rare condition, the thesis will sometimes refer to a broader category of Chronic Suppurative Lung Diseases (CSLDs) which includes PCD, but also more common conditions such as Cystic Fibrosis (CF).

This chapter will explain why impaired mucus clearance is a problem for individuals with PCD, (Section 1.2), introduce Airway Clearance Techniques (ACTs) which are the mainstay of treating and managing PCD, and explain why the personalisation of ACTs though complex is necessary, due to the heterogenous population and numerous options available to achieve the desired goal of effective mucus clearance (Section 1.3). However, it is imperative that we understand the effects of the interventions we advise patients to complete, previously this has not been easy with the lung health markers available clinically (Section 1.4). Therefore, more research is needed to assure patients how their ACT regimens are personalised and how well they are working (Section 1.5). The programme theory (Section 1.6) provides structure throughout this thesis, which investigates a complex problem in a real-world context with a pragmatic approach (Section 1.7). The specific aims and objectives of the thesis are to understand how we currently should (and do) personalise ACTs regimens, what the effects of these regimens are, and if clinicians change how they personalise ACT regimens with access to an accurate marker of lung health (Section 1.5.1).

Chapter 2 presents a scoping review that concludes that personalising ACTs regimens in CSLDs involves consideration of a wide number of factors and there is a lack of clarity of how clinicians navigate these factors.

Chapter 3: presents a cognitive task analysis of ACT personalisation as reported by expert paediatric PCD physiotherapists, concluding that uncertainties commonly arise, and ACT regimens are piloted to test if they will work, allowing regimen modifications prior to implementation.

Chapter 4: presents a cross-sectional study assessing lung health in children and young people with PCD using functional magnetic resonance imaging (MRI), concluding there is heterogeneity in the extent of ventilation abnormalities in this population.

Chapter 5: presents a before and after study assessing the effects of personalised ACT regimens in children and young people with PCD using functional imaging, concluding that response to personalised ACT regimens is variable with some individuals improving and others worsening.

Chapter 6: presents a cognitive task analysis of how clinicians use functional imaging when reviewing personalised ACT regimens, concluding functional MRI informs modifications to ACT regimens in some cases, however in cases where MRI findings diverge from the clinical picture sometimes clinicians are uncertain how to modify regimens.

Chapter 7:, the discussion, summarises the key messages and limitations of the thesis, as well as making recommendations for clinical practice and further research.

1.2 PCD is an impactful, chronic respiratory condition.

1.1.1 PCD is a rare condition, but the incidence is hard to quantify.

The reported prevalence of PCD within the literature varies; the largest pan-European cohort data shows a prevalence of between 1:10,000 and 1:20,000 live births (1), with other literature in the field reporting prevalence between 1:2,200 and 1:40,000 (2). It is anticipated that true variance is seen within different populations, as illustrated by the Bradford Pakistani population where PCD is more common than CF (2). Additionally, spurious variance in prevalence is likely to arise from the challenges relating to the diagnosis of PCD which will be discussed in Section 1.2.4. PCD is currently estimated to effect over 5000 people in England although it is unknown if this figure will increase with increasing awareness of this rare condition.

1.2.1 PCD causes impaired mucociliary clearance.

PCD is predominantly an autosomal-recessive inherited condition in which ciliary function is impaired (3). Cilia are microscopic hair-like structures, which project from cells. In the healthy respiratory tract, motile cilia line the epithelium throughout the conducting airway to the terminal bronchioles (4) (Figure 1). They beat continuously in a co-ordinated wave like motion at a high frequency (8-11 Hz) to propel mucus from the peripheral to central airways where it can be cleared into the gastrointestinal tract to be

swallowed or expectorated (5). Cilia are complex structures, and in PCD a range of ultrastructural defects are seen (Figure 2); in the outer and, /or inner dynein arms, radial spokes, nexin link, and location of the microtubules. Rarely cilia aplasia can also be seen (6).

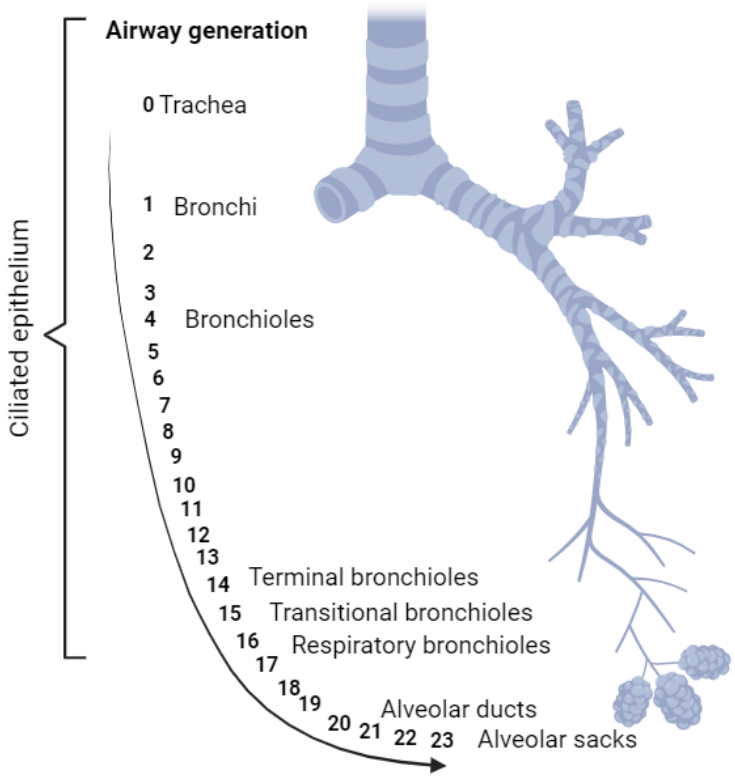


Figure 1: Depicts a representation of the bronchial tree, adapted from Weibel (7). Cilia line the conducting zone, from the nose to the respiratory bronchioles. Created in BioRender. Schofield, L. (2025) https://BioRender.com/k95f478

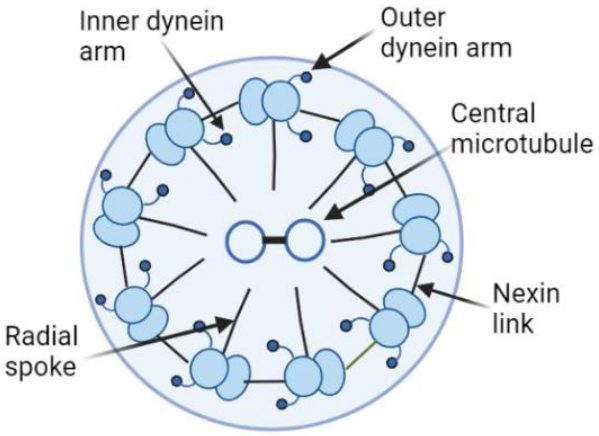


Figure 2: Illustration of the cross-section of a motile cilia. Created in BioRender. Schofield, L. (2025) https://BioRender.com/ a79y534

These defects cause impaired cilial function; abnormalities can be seen in the cilia beat pattern and frequency, some individuals have completely static cilia, progress is being made in understanding the association between the ultrastructural and functional

defects (6). In the respiratory tract, this absence of effective mucociliary clearance causes mucus to be retained in the airways, obstructing the small airways, and leading to a risk of lower respiratory tract infections (8). Over time repeated chest infections can cause a vicious vortex of impaired mucociliary clearance, infection, inflammation and lung damage (9), a process seen across CSLDs as depicted in Figure 3.

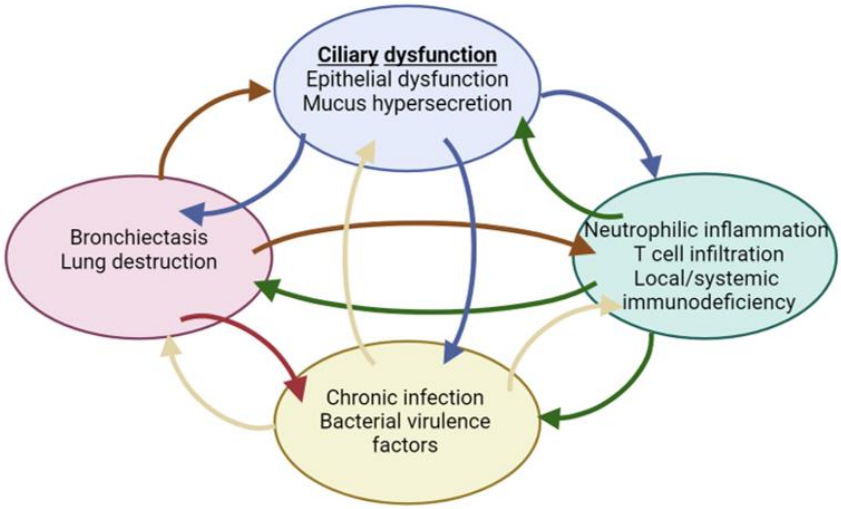


Figure 3: A schematic representation of the vicious vortex of bronchiectasis, adapted from Flume et al. (9). Created in BioRender. Schofield, L. (2025) https://BioRender.com/ p39o096.

1.2.2 Persistent, productive cough is a hallmark of PCD.

Within children, typical PCD symptoms include a persistent productive cough, rhinorrhoea, nasal congestion, recurrent otitis media and hearing impairment, commonly with a background of neonatal respiratory distress (10). Organ laterality defects (situs inversus or heterotaxy) are seen in around 50% of individuals with PCD (11). Over time, repeated chest infections are seen and as adults, individuals with PCD commonly present with established bronchiectasis (12). Respiratory exacerbations can be difficult to identify; symptoms such as a wet cough and rhinorrhoea are continuous, and changes in symptoms can be subtle (13). As retained secretions can cause an audible respiratory wheeze, people with PCD may previously have been diagnosed with difficult or atypical asthma (14). As a rare condition with symptoms in common with many other childhood illnesses, diagnosing PCD can be difficult (10).

1.2.3 Diagnosing PCD is complex.

Diagnostic testing in PCD is highly specialised, complex, and expensive (10). There are a range of diagnostic tests available; reviewing cilial beat frequency and patten using high-speed video analysis (HSVA); examination of cilial ultrastructure using transmission electron microscopy (TEM), measuring nasal nitric oxide (NNO) levels, and testing for known PCD genetic variants. However, none of these tests are reliable

enough to exclude a positive PCD diagnosis; ciliary ultrastructure can appear normal on TEM in the presence of known PCD genetic variants; NNO is commonly very low for unknown reasons in PCD, but NNO can also be normal in PCD (15). International differences are seen in the diagnostic pathways for individuals with suspected PCD, as illustrated by the American Thoracic Society (ATS) (16) and European Respiratory Society (ERS) (15) guidelines. In North America, NNO is a central component of PCD testing and two NNO results can be sufficient to diagnose or exclude PCD, whereas in Europe, while the reference ranges and standard protocols for NNO testing are established, NNO is used only used alongside other diagnostic tests (15). Similarly, HSVA is a core component of the ERS guideline but is not recommended by the ATS. This variation may arise from international differences in access to diagnostic facilities and as the diagnostic techniques used are highly specialist, there is international agreement on the importance of referrals to diagnostic facilities with appropriate expertise (17). The differences in the diagnostic algorithms may cause a 15% discordance in diagnosis (18) and as such it is noted that the ERS guidelines are used as the diagnostic standard within this research. In England, the age of diagnosis has reduced to a median age of 2.6 years in specialist paediatric centres, which is thought to be associated with the arrival of a National paediatric PCD service, improving awareness of PCD and access to diagnostic facilities (11). Contrastingly, in an adult specialist centre age of diagnosis can be higher and more variable (median 23.5 years, range 1–72 years (19).

1.2.4 PCD has a heterogeneous prognosis.

PCD is a heterogeneous condition in terms of clinical manifestation, severity, and disease trajectory (20-22). International variance in lung health in PCD is seen and projected lung health in children with PCD at age 6 (assessed by FEV_1) was worse in UK than many other European countries (22). The disease trajectory in children and young adults with PCD can vary, with some individuals improving, some deteriorating and other remaining stable, deterioration in lung function over time was seen in 30% of children and young adults in the UK (22). In the absence of UK based longitudinal data for individuals over the age of 24, the prognosis of PCD is understood from other international populations whilst being mindful of the differences in both diagnosis and health care systems. As assessed by high resolution computerised tomography (HRCT) scan, a range of abnormalities are seen in PCD including bronchiectasis, bronchial wall thickening, air trapping, atelectasis and mucus plugging (23). 70-73% of children (24, 25) and 80% of adults with PCD have bronchiectasis and 25% of adults are in respiratory failure; defined either by the requirement for long-term oxygen or

being listed for lung transplant (26). A high-resolution computerised tomography (CT) scan depicting bronchiectasis in a person with PCD is shown in Figure 4.

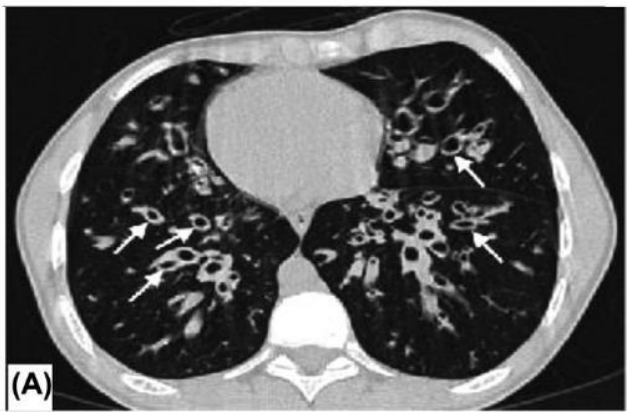


Figure 4: High resolution CT scan showing bronchiectasis and dextrocardia in person with PCD. Image reproduced from Tadd et al. (27 p.475) with permission from the publisher (license no. 5925280458149).

Understanding of PCD phenotypes is growing. Recent research has shown disease severity can vary according to cilial ultrastructural defect type. Individuals with inner dynein arm or microtubular disorganisation defects have been found to have more severe disease than those with isolated outer dynein arm defects with: higher CT structural abnormality scores, predominantly due to mucus plugging (28); lower lung function (FEV_1) and a greater rate of decline in lung function (29). While the PCD specific knowledge base is building, PCD is often compared to CF, with common symptoms of retained secretions, repeated lower respiratory tract infections and development of bronchiectasis over time (30). Whilst the two conditions both feature impaired mucociliary clearance, the underlying pathophysiology differs (31), and therefore specific treatments are seen especially in CF where significant changes have been in CF clinical practice with the arrival of CF transmembrane conductor regulator (CFTR) modulators. In studies performed pre-CFTR modulators, lung function, as assessed by $FEV_{1,}$ has been found to be in better in people with PCD than people with pancreatic insufficient CF and comparable with people with pancreatic sufficient CF (32), but in children under 15 years old lung function can be worse in PCD than CF (11). Life expectancy data for PCD has yet to be published but what we know from looking to the wider CSLD population, is that such conditions are associated with premature death (33, 34).

1.2.5 The impact of living with PCD is significant.

People living with PCD experience a greater impact on their quality of life with increasing age (35, 36). Symptoms onset from birth, people with PCD often have a history of neonatal respiratory distress, and lobar collapse is also seen neonatally (37).

Lung function is impaired from childhood, becoming more abnormal with advancing age (21). It is not uncommon for people with PCD to require intravenous antibiotics to manage their disease, and as reported by Rubbo *et al.* (11), 30% of children with PCD required at least one course of intravenous antibiotics within a 12 month period. Aerobic exercise capacity is also frequently reduced (38). The symptoms of PCD, such as cough and rhinorrhoea, can be very visible and stigmatising, leading individuals to conceal their symptoms and treatments (39). As a rare condition people with PCD may have had poor healthcare experiences and have developed mistrust of medical professionals (39). The treatments to manage PCD can be time-consuming, a burdensome reminder of the disease (40), make people feel worse and cause feelings of loss of freedom (41). Barriers to completing regimens include time, forgetting, and wider family needs (41). With similar barriers found in people with CF, (42) it is suspected that adherence to treatments in PCD may be low. Looking towards our youngest individuals, treatments also impact on parents who recognise the importance and benefits of undertaking preventative treatments but can find completing them to be stressful and can cause feelings of guilt, doubt and pressure (43). Exacerbations can also cause significant increases in emotional worry and concern for care-givers (44).

In the absence of accurate healthcare costs of PCD, estimates are taken from the broader comparable bronchiectasis population and the CF population. Data from 1999 shows us that people with bronchiectasis have high rates of hospital admissions, which at the time resulted in annual costs of $5681 (45). CF data from 2012 shows annual UK health care costs of €48,603 (46). Whilst the relevance of this data is limited by its age and the impact of inflation, the introduction of costly CFTR modulators in CF, and the population care differences, it does illustrate the economic burden of CSLDs. Living with a CSLD impacts on schooling, with adolescents missing on average 23.6 school days per year (47) and whilst the impact on work attendance is yet to be quantified, clinical practice tells us this is a problem for our patients (48). Additionally, exacerbations result in absenteeism for caregivers (44).

To summarise, PCD is one of a number of incurable, life limiting CSLDs which from birth affects the ability of young people to clear their lungs. Some important contextual factors for understanding its management are that PCD is a heterogeneous condition, and the complications which arise from it are an important public health problem, with a burden that affects patients, carers, health systems and society.

1.2.6 Patients want to be sure their treatments are optimised.

Appropriate engagement of *stakeholders*, specifically patient and public involvement (PPI) is vital in research (49) and as such PPI has been employed throughout this

project from the initial setting of research priorities through to dissemination. Aware of the paucity of evidence pertaining to ACTs in PCD (Section 1.3.4) PCD Support UK (PCDS-UK), a UK-based charitable organisation who aim to support people with PCD of all ages and their families, were approached as an initial step. They were involved as partners; planning, funding, and facilitating an initial focus group in 2017. Attended by young people, aged 6-19, with PCD people aged and their parents, this session aimed to identify the groups physiotherapy research priorities, using child friendly tasks (50) to elicit and prioritise ideas through voting (51). As stakeholders, this group's research priority; understanding and optimising the effects of ACTs in PCD, provided warrant to explore the uncertainties surrounding ACTs further. A study PPI group has been more formally established, comprising of five young people with PCD aged 8-20, four parents, two of who link with the PCDS-UK committee. The PPI group met every 2-4 months during the project, with additional contact with members as needed. The role of PPI members in the study will be highlighted in the methods sections of further chapters.

1.3 Personalised airway clearance techniques (ACTs) are a key part of managing PCD despite a paucity of evidence.

1.3.1 ACTs are a core component of managing PCD.

Effective management of PCD is key to maintaining lung health. With abnormal lung function seen from a young age, the early instigation of standardised care is recommended (21). As a rare disease, the management of PCD through a specialist centre can result in improved access to health professionals, improvement in lung function and reduced emergency health care utilisation (52). Within Europe, people with PCD are commonly managed in multidisciplinary clinics, with clinical reviews as frequently as every 2-3 months. With no curative treatment currently available, PCD management focuses on the regular surveillance and timely management of respiratory infections and the features of sinonasal and ontological disease whilst maintaining well-being (20). Lung health is monitored clinically with spirometry providing details of air flow limitation (global lung ventilation), and standard-of-care imaging, most commonly chest radiographs and CT scans, used to assess structural lung changes such as bronchiectasis or significant mucus accumulation. Regular sputum or cough swab samples are used to screen for respiratory tract infections, and infections are promptly managed with antibiotics. In terms of prevention, evidence to support the use of prophylactic oral antibiotics within PCD, specifically prophylactic Azithromycin is now emerging (53). However as impaired mucociliary clearance is the key underlying functional problem in PCD, the central component of PCD management are techniques

to facilitate clearance of mucus from the airways, commonly known as airway clearance techniques (ACTs). ACTs are a range of interventions which aim to augment the body's natural mucociliary clearance from the respiratory tract. As in PCD impaired cilia line the conducting airways but the cough mechanism remains intact, ACTs regimens aspire to effectively mobilise mucus from small, peripheral airways up the bronchial tree to larger, central airways where it can be coughed and expectorated (Figure 5A and B). Through effective ACTs the goal is to prevent the vicious cycle of inflammatory tissue damage illustrated in Figure 6.

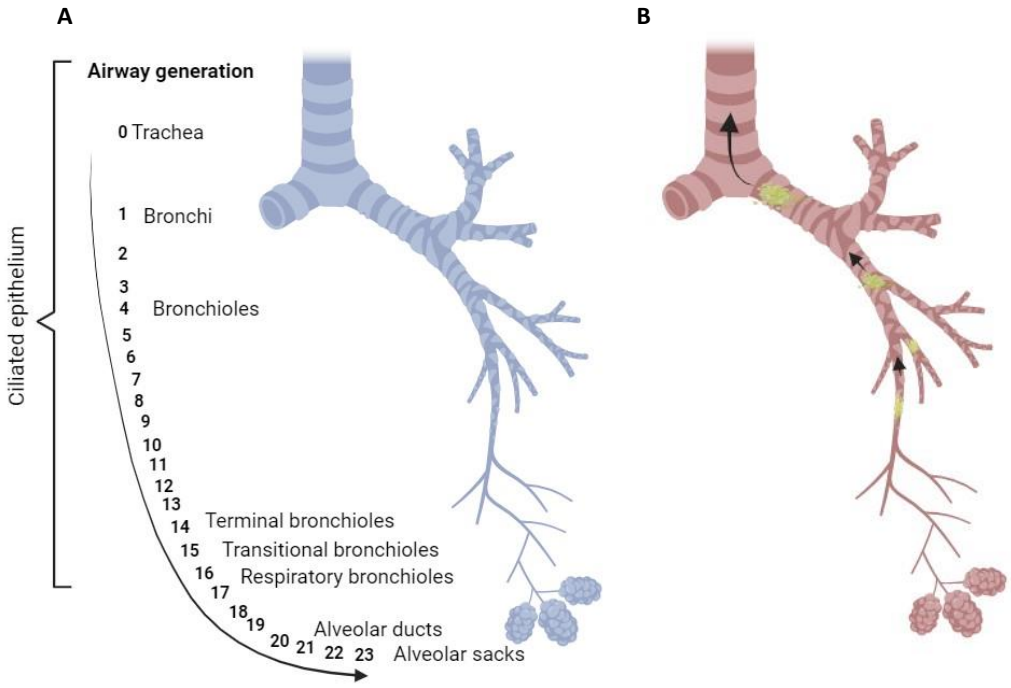


Figure 5: A depicts a representation of the bronchial tree, adapted from Weibel (7). B depicts an illustration of mucus clearance from the lower respiratory tract. Created in BioRender. Schofield, L. (2025) https://BioRender.com/ k29z371

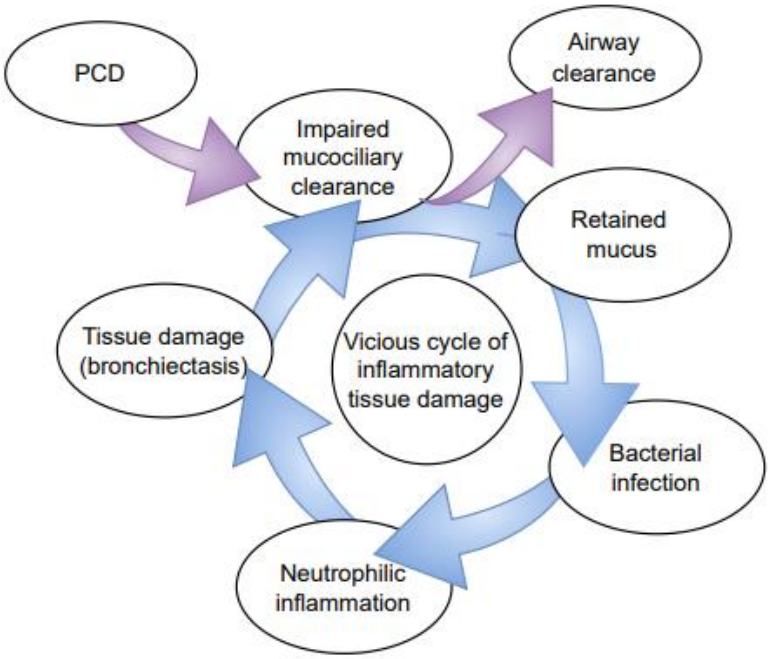


Figure 6: The role of PCD and airway clearance on the vicious cycle of inflammatory tissue damage. Figure adapted from Cole (54)..

In PCD, regular ACTs are recommended from the point at which a diagnosis is suspected (20). In UK clinical practice, ACTs are most commonly advised by physiotherapists. In settings where children with PCD are managed, the physiotherapists commonly work within a broader multidisciplinary team comprising commonly of a medical doctor and nurse specialist, with support from a dietitian and psychologists in some cases.

1.3.2 ACTs are underpinned by physiological reasoning.

ACTs are underpinned by known physiological principles of ventilation in healthy lungs, and the impact of disease on the airways. In PCD, lung units can become obstructed with mucus which narrows the airways, in turn increasing resistance to airflow. As airflow takes the path of least resistance, this causes lung units to ventilate in an asynchronous pattern (55). The physiological principles upon which ACTs are based include; *interdependence, collateral ventilation, pendelluft, ventilation distribution* and *2-phase gas-liquid flow* have been well described by McIlwaine *et al.* (56). Lung units are nestled together, forming a support structure between adjacent acinar units, this is known as *interdependence* (55). With an increased tidal volume, this *interdependence* can support the re-expansion of lung units (56). In addition to the normal paths of ventilation through the airways, ventilation can take place through channels between adjacent alveoli, a process known as *collateral ventilation* which is thought to be more significant in abnormal airways (57). Air can move into obstructed areas as adjacent

lung units begin to empty; a process called *pendelluft* which is exploited during airway clearance by breath holding for three seconds (56). *Ventilation* varies within different areas of the lung; in adults' ventilation is greatest where there is a greater negative pleural pressure in the dependent regions of the lung, this is altered with position change, being greatest in the mid to lower lobes in sitting and in the lower most lung in side-lying (56). In children, usually up until around the age of 12, the mechanics of the chest wall are different, and whilst it is widely accepted that the distribution of ventilation is greater in the non-dependent lung areas (56, 58), ventilation distribution has been shown to vary between individuals using electrical impendence tomography (59). *2-phase gas-liquid flow* modelling provides understanding that the movement of mucus from distal to central airways can be facilitated by ensuring airflow bias in favour of expiratory flow, so that PEFR is greater than PIFR by at least 10% (56). Mucus in PCD can be difficult to clear, it is similar to mucus in CF in terms of the biophysical and transport properties, and also contains higher volumes of the inflammatory marker Interleukine-8 (60). Oscillation frequencies which are similar to cilia beat frequency have been shown to improve both the rigidity of mucus and tracheal mucociliary clearance (56).

1.3.3 A range of ACTs are used in clinical practice.

There are a range of ACTs available to physiotherapists for use in the *real-world context of* clinical practice which employ the physiological principles described to augment airway clearance which will be described here. These include breathing techniques, manual techniques, airway clearance devices, and adjuncts to airway clearance techniques for which an overview is provided below. As there is still insufficient evidence to support the use of physical activity specifically as an ACT (61) and current clinical practice does not routinely recommend exercise as an alternative to more formal ACTs (62), exercise for airway clearance will not be included within this thesis.

Cough is a natural reaction which can be used to clear mucus from the larger airways resulting from a deep inspiration and glottic closure, followed by high extra-thoracic pressure resulting in rapid and explosive expiratory flow. In PCD, airways can be more prone to dynamic collapse and repeated coughing can cause airway closure resulting in ineffective airway clearance (56). Forced Expiratory Technique (FET) or "huffing" is a technique which uses increased tidal volumes and an increased Peak Expiratory Flow Rate (PEFR) with an open glottis. By moderating extra-thoracic pressures, the point in

the airways at which dynamic compression occurs, known as the Equal Pressure Point (EPP), can be manipulated to increase expiratory flow and mobilise secretions (56).

Active Cycle Breathing Technique (ACBT) is a cyclical breathing technique, with components of relaxed diaphragmatic breathing, deeper inspirations with inspiratory holds, known as thoracic expansion exercises, and FETs. Autogenic Drainage (AD) is also a breathing technique, it involves using the EPP to target secretions by varying the depth of breathing within the vital capacity, whilst moderating the inspiratory and expiratory flow. Both ACBT and AD have PEFR ≥ Peak Inspiratory Flow Rate (PIFR), and aim to ventilate lung units, mobilise, and evacuate secretions (56).

Manual techniques (percussion and vibrations) used in isolation are passive techniques being delivered by another person; in the community this may be a family member or carer. Percussion involves using a cupped hand or a percussor cup to percuss over to the chest wall. Expiratory vibrations are a compressive vibratory force applied to the chest wall during exhalation. Both percussion and vibrations aim to increase airway turbulence, and vibrations also increase PEFR (56).

During airway clearance, the patient can occupy different positions such as sitting or side lying. Historically the use of varied positioning was an approach called postural drainage, involving 12 positions, and aiming to increase mucociliary clearance with gravity from different regions of the lungs. Positional changes are still used within ACT regimens, but instead of draining lung units, the aim of positioning is to influence regional ventilation and lung volumes during ACT regimens (63).

Positive Expiratory Pressure (PEP) devices (Figure 7A and D) have an exhalation valve to restrict expiratory flow, causing positive pressure within the airways throughout exhalation and a temporary increase in Functional Residual Capacity (FRC). This allows air to access the channels of collateral ventilation and moves the EPP proximally. Commonly, when using PEP, the technique involves using a slightly active expiration which usually achieves pressures of 10-20cmH2O, but can also be with a FVC manoeuvre, a technique known as “HiPEP” which typically achieves higher pressures of 40-100cmH2O (64, 65). Oscillatory PEP (OPEP) devices (Figure 7B and C) similarly provide PEP within the airways, but also provide an additional fluctuating pressure or oscillation which is thought to increase airway turbulence and potentially increase ciliary beat (66). A range of devices for both PEP and OPEP are available which differ in their resources and performance, for example, some devices require the patient to have a higher expiratory flow rate or are gravity dependent, different devices produce different oscillation frequencies, amplitudes, and wave patterns and oscillation can be seen at different expiratory flow rates (66). The interfaces available can vary in

size and shape, but commonly PEP can be delivered via a mouthpiece or face mask and OPEP by mouthpiece. Other PEP variations include Bottle or Bubble PEP a set up in which patients blow exhale through tubing inserted into a bottle of water of a specific depth to create the PEP and Baby PEP, a more passive technique administered by health professionals or parents holding the mask on an infant (65).

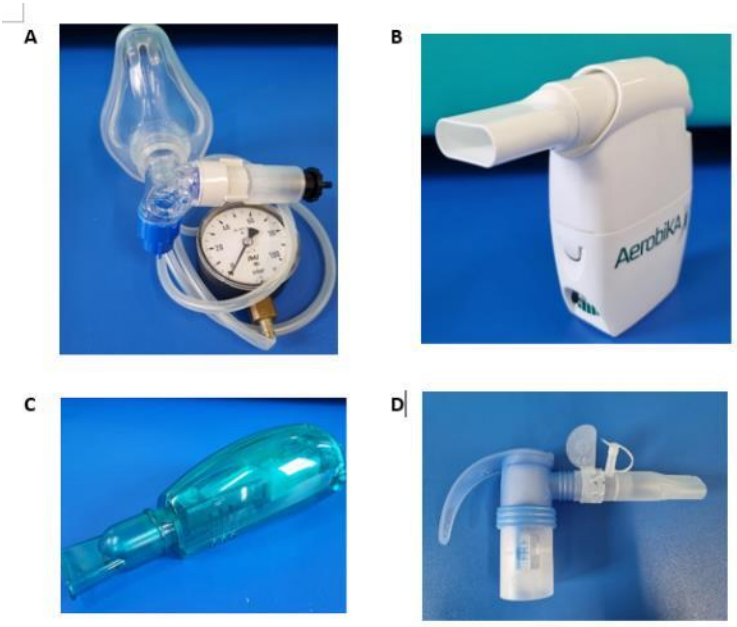


Figure 7: Examples of ACT devices: A= A PEP mask system with manometer; B= An Aerobika® OPEP device; C= An Acapella choice® OPEP device; D= A combined PARI PEP S device and PARI LC sprint nebuliser system.

High Frequency Chest Wall Oscillation (HFCWO) is a device consisting of a jacket inflated with air which is then pulsated to provide compression and oscillation to the chest wall. Used in isolation, this is a passive technique which increases PEFR as well as accessing the physiological benefits of oscillation, however, it does not have a mechanism to increase volume and access obstructed lung units (56) and as such is not recommended as a first line intervention in PCD (62). Other ACTs not commonly used in daily home PCD management include Intermittent Positive Pressure Breathing and continuous high-frequency oscillation as they both require high flow oxygen, and incentive spirometry as people with PCD do not commonly have restricted inspiration.

There are also a small number of nebulised medications used as adjuncts to airway clearance within PCD. Hypertonic saline is a mucokinetic, thought to improve clearance by drawing water to the airway surfaces, increasing ciliary beat and potentially stimulating a cough reflex (67). DNase, is an enzyme which denatures DNA within sputum, reducing the concentration of highly polymerised DNA within sputum and therefore reducing sputum viscosity (67).

Whilst the interventions described above can be used in isolation, they are often employed in combination (68) to allow integration of the different physiological components. For example, PEP and OPEP devices in themselves do not provide an expiratory flow bias of at least 10%, so they can be combined with breathing techniques such as ACBT or FETs which bring the expiratory airflow bias. Nebulised medications are traditionally administered before or after airway clearance, with timing depending on their method of action. However, it is possible for nebulisers to be attached to some PEP and OPEP devices (Figure 7D), mostly commonly seen when nebulising hypertonic saline, yet this is a practice which has caused some controversy. Concerns have been raised that the drug delivery is lower when using combined nebuliser and ACT device compared to the nebuliser alone (69, 70). However, improved patient outcomes have been seen with combined nebuliser and ACT devices including volume of sputum expectorated, reduced sputum symptoms, improved tolerance (70) and improved lung function (71). Such improvements despite a lower delivered dose is proposed to be due to the improved peripheral deposition with PEP (69) with further research needed.

1.3.4 Current evidence tells us no single ACT is superior.

As PCD is a rare condition, only a handful of studies have assessed the effects of ACTs in PCD (72-74). In each of these studies FEV_1 was used as the primary outcome measure to: assess the effects of a single standardised 20 minute session using the PEP mask for cycles of 30 breaths, FETs and cough, supervised by a physiotherapist who applied overpressure to aid clearance as indicated (72); to compare the effects of five days of twice daily inpatient physiotherapist administered percussion and vibrations in 12 postural drainage positions (PVPD) to 5 days of twice daily home based HFCWO (73); to compare the effects of twice daily OPEP (Acapella) versus twice daily parent/carer administered PVPD over three months (74). Significant improvements in FEV_1 were found following OPEP, HFCWO and physiotherapist administered PVPD, and a non-significant improvement following parent/carer administered PVPD, but no significant difference was seen between the ACT types (73, 74). No significant change was seen following a single session of the PEP mask (72), there are a number of potential causes for this difference in outcome: use of a single ACT session; their study population appear to have a milder disease severity indicated by difference (baseline FEV_1 mean 91.9% versus 72.9% and 75.9%); different ACT components including the inclusion versus exclusion of inhaled medications. Inhaled medications are an important component of ACT regimens to consider; a recent randomised controlled trial explored the use hypertonic saline within ACT regimens in people with PCD (75). No significant change was seen in their primary outcome of quality of life measured by

total score on the non-disease specific St George Respiratory Questionnaire, highlighting the importance of using sensitive specific tools to measure outcome.

With this paucity of evidence in PCD, it is appropriate to consider ACTs in the wider context of CSLDs. The short-term benefits of completing airway clearance has been demonstrated in two Cochrane reviews of studies comparing any ACT type to no-ACT (76, 77). A considerable number of comparative studies have been published, assessing the effects of one ACT device or intervention versus another, this body of literature has been appraised by 6 Cochrane reviews. These studies have collectively shown that no single ACT is universally superior over a 6 month period, in terms of FEV_1 (78), QoL and breathlessness (79).

The quality of ACT comparative trials has suffered, due to inconsistencies in the reporting of outcome measures, and insufficient washout periods in cross-over trials (78). Whilst the value of high quality randomised controlled trials is appreciated, a major problem of this approach in this field is that completing an ACT is not like taking a drug. ACT regimens are time consuming and require active participation of patients. Consequently ACT research has faced difficulties, with blinding and strong patient preferences causing high drop-out rates in randomised studies (80). Additionally, there are flaws in adopting a standardised approach to a heterogeneous population, and instead, empirical research using study designs that more closely reflect the *context* in which they are used are needed (78). A recent study which used remote pressure sensor technology to assess the completion of ACT regimens using PEP and OPEP in children with CF over 16 months found the pressures achieved during ACT sessions are usually sub-optimal and the individuals had their own consistent way of exhaling though the device almost like a expiratory signature (81). This study is an important step in understanding highly personalised regimens in a real-world context. ACT research needs to do better at collecting data which is both clinically meaningful and has used appropriate outcome measures.

In summary, a range of ACTs, with different mechanisms of action, are used either alone or in combination, in the clinical management of PCD. There is little evidence for the clinical effectiveness of one-size-fits-all or standardised ACT regimens. Patient's engagement with components of their home ACT regimen may vary, depending on their preferences and perceived efficacy. As there are mechanistically plausible reasons why ACTs should improve lung health compared to the absence of ACTs (Sections 1.2.2 and 1.3.2), the key *uncertainty* is around how can we *refine* ACTs to improve their efficacy? The MRC framework, for developing and evaluating complex interventions, recognises that their efficacy is often dependent on a multi-dimensional and dynamic '*context* '(49), generally defined as "setting…roles, interactions and

relationships" (82, p.7). The framework demands that '*programme theory*' should be developed with diverse '*stakeholders*' - those delivering, receiving, or otherwise affected by the intervention - describing how its proposed mechanisms of action interact with context. Interventions can then be '*refined*' with key stakeholders, guided by programme theory, and addressing remaining *uncertainty*, given existing knowledge and our values or purposes.

The philosophical literature recognises that population heterogeneity, the presence of equally good pathways to particular goals, and change over time make standardised interventions undesirable (83). The scientific literature on heterogeneity of treatment effects suggests that different harm-benefit trade-offs apply to individuals who differ from each other in determinants of intervention efficacy (84, 85). For this reason, correctly defined, Evidence-Based Medicine (EBM) is "the integration of best research evidence with clinical expertise and patient values" (86, p.1) – clinical expertise means tailoring research evidence to clinical status, circumstances, patient preferences and actions (87). At a national level, the NHS Constitution makes this an ethical imperative: "*The patient will be at the heart of everything the NHS does… NHS services must reflect, and should be coordinated around and tailored to, the needs and preferences of patients, their families and their carers*" (88), and health has seen an increasing concentration on personalised and responsive care over the last fifteen years (90).

At this point we have established that CSLDs, including PCD, represent a substantial humanistic and societal burden, but there is no evidence yet that the key management strategy, ACTs, have important population average treatment effects when delivered in a standardised, or one-size-fits-all fashion. The scientific literature on heterogeneity of treatment effects, suggests uncertainty about how to *refine* ACTs is part of a wider set of scientific or intellectual problems about personalisation. The policy literature confirms stakeholders – the EBM movement globally, the UK Government and the NHS locally – make the need for personalisation an ethical problem. With this in mind, the next section explores the practical problem of how to personalise ACTs.

1.3.5 ACT regimens are commonly personalised in clinical practice, but *key uncertainties* exist.

Overview/reviews

In the UK, it is recommended that people with PCD have an ACTs review with a respiratory physiotherapist, every three months (62). These reviews provides an opportunity to assess and advise individuals on their ACT regimens. This section will explore the current guidance around how physiotherapists personalise ACT regimens

within these reviews. Within this thesis personalisation of ACT regimens is used to describe the tailoring of ACT recommendations for an individual with PCD or other CSLD.

Methods of personalisation

It is clear from key documents in the field that a personalised approach to ACT regimens is recommended both within PCD (20, 62) and more broadly in CSLDs (78, 91). The evidence base indicates that some interventions are used more widely than others and that formal ACTs are more commonly used than exercise as disease severity increases (92). What is less certain, is how specific ACT regimens are selected and tailored or *refined* for individuals. As discussed in Section 1.3.3, ACT intervention choice may be based upon physiological principles and mechanistic theories and the importance of physiotherapists to understand these has been highlighted (56). However, this physiological based reasoning is positioned amongst other factors which must be considered when choosing a regimen for an individual including patient preference, device availability, social and environmental factors (56). Other approaches presented within the literature include considering ACT devices in terms of the age of the patient and the ability to deliver nebulisers concurrently (93), its advantages and disadvantages (94), or choosing an intervention based on disease severity (95). As home based interventions, there are also recommendations to prioritise regimens which allow independence and that the patient prefers (95). Patient's value having their ACT regimens tailored to their needs and identify the importance of their considering their preferences and lifestyle during consultations (96). An individual's ability to complete a regimen effectively and their needs may change over time, therefore regular re-evaluation of ACT regimens is important (94).

Management of mucociliary clearance often requires the physiotherapist to consider and manage factors beyond the lungs. In PCD, mucociliary clearance is also impaired in the URT. Consideration of the upper airway may be needed when selecting delivery devices, specifically the patient interface (62). Incontinence is common in CSLDs and with cough the most commonly reported cause of incontinence, this is another factor which must be considered when looking at airway clearance (65). Similarly musculoskeletal restrictions and abnormalities such as pain and reduced movement can impact on airway clearance and must also be screened for and managed (65). In this regard, adaptive interventions are personalised based on specific needs of individuals, in response to their changing performance and requirements (97). Therapeutic decisions are patient-centred, collaborative and iterative (98), requiring optimisation under multiple criteria (99).

Whilst there is guidance that outcomes should be assessed using appropriate measures and that patients should be provided with a written plan and support for adherence (65), so far, there is no clear guidance on how physiotherapists navigate their way through the many ACT options to choose an ACT for an individual. The tacit knowledge in this area is yet to be made explicit and will be the subject of Chapter 3. In addition to the physiological principles discussed, consideration will now be given to holistic assessment, the impact of ACTs and how their effects can be assessed.

1.4 The tools currently available to assess the effects of ACTs are limited.

Personalisation assumes that clinicians and patients understand the effects of interventions to make appropriate clinical judgement. Mechanistically, there are plausible reasons why ACTs *should* aid secretion clearance (Sections 1.3.2 and 1.3.3), but we need to know if ACTs *do* improve the impaired airway clearance in PCD (Section 1.2.2). In PCD, chronic symptoms can make the identification of change in symptoms difficult (Section 1.2.3), therefore, assessing the effects of ACTs requires validated markers of lung health. A range of tools claim to measure markers of concepts, such as 'respiratory function' or 'lung health', markers which, in theory, ACTs should affect. A recent scoping review has summarised outcome measures used to assess the lower airways within PCD including spirometry, imaging, health related quality of life (HRQoL) and exacerbation frequency (100). These tools, in addition to other commonly used clinical assessment tools, will be discussed in the context of ACT research to provide context for the uncertainties clinicians face (Chapter 3). There is ongoing concern that ACT research does not have a gold-standard outcome measure and has such been limited by using a collection of non-ideal measures (101). Whilst a current randomised cross-over trial is seeking the most useful ACT outcome measure in adults with CF (102), as lung disease is often milder in children it is important to ensure that outcome measures are sensitive enough to detect change in the paediatric population (103).

1.4.1 Lung function tests only provide information on global lung function.

Spirometry is the most widely available clinical test to assess function of the whole lungs through measuring lung volume and airflow at the mouth, with the most commonly used indices: forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). It is also the most widely used outcome in both ACT (78, 103) and PCD research (100). However, there are concerns about its limitations, firstly to assess lung health in children with PCD, and secondly, to assess the effects of ACT regimens.

Whilst in CF, FEV_1 correlates with QoL (104) and is a predictor of mortality (105), the evidence in PCD is less clear. In PCD there are conflicting reports of the correlation between spirometry and structural abnormalities on high resolution computerised tomography (HRCT), and the sensitivity of FEV_1 is felt to be poor: 73% of individuals with structural lung abnormalities have normal FEV_1 (106); and it less sensitive than the multiple breath washout (MBW) metric, the lung clearance index (LCI) (107). In PCD heterogeneity in FEV_1 which cannot be explained by known factors is seen (108), and even during periods of disease stability, large variability in FEV_1 is seen (109). Whilst standardised spirometry processes should be followed (110), it is unclear whether clinically obtained spirometry data meets technical standards which may influence the reliability of results. A recent review of the use of outcome measures to assess the effects of ACTs in children with CSLD's reported a statistically significant difference was only found in two out of 17 studies that employed FEV_1 to assess the short-term effects of ACTs (103). A greater proportion of studies (11 out of 18) that assessed the longer-term effects of ACTs found a statistically significant improvement in spirometry metrics ,and whilst this may be due to the true effect of ACTs, other factors could influence the findings, especially considering the variance in FEV_1 in PCD previously described (103). So, while FEV_1 is widely used it is unsuitable to assess the effects of ACTs.

Multiple breath washout (MBW) is a breathing test which assesses homogeneity of ventilation by measuring the clearance of an inert tracer gas (usually N_2 or SF_6) from the airways (111). Lung clearance index (LCI) is the most commonly used measure derived from the MBW test and represents the number of total breaths needed to clear the tracer gas (111). As a tidal breathing test, MBW is easy to perform and therefore has a role in assessing lung function in children, although it still not used routinely in clinical practice (111). Whilst LCI has been shown to be more sensitive to assess lung health than FEV_1 in people with PCD (106, 112), the correlation of LCI with other outcomes remains unclear (100). With good reproducibility (113) LCI may have a role in the assessment of global lung disease severity, however like spirometry MBW metrics are unable to assess regional abnormalities. At present there is no evidence to support the role of LCI to assess change following an ACT in children with PCD. No significant change was seen following an ACT in children with CF (114) or adults with bronchiectasis (113). It is recognised that MBW tracer gas will be unable to pass into areas of lung which are completely obstructed with mucus, allowing some ventilation defects to be undetected (115), and if an ACT causes opening of previously obstructed lung units that continue to have poor ventilation, a worsening in LCI may be seen (114).

1.4.2 Imaging can provide information on regional lung health.

High resolution CT is the current gold standard for measuring structural lung disease progression (100) and a review of CT images as part of physiotherapy assessment when personalising ACT regimens has been recommended (116). CT offers information on regional structural changes in the lungs, however its ability to provide information on the function of the lungs is limited (106). Whilst CT is used to assess lung health in PCD (117), scoring systems such as the Brody score which was developed for use in people with CF may overlook disease specific changes (118). Structural abnormalities in PCD can differ from CF, for example the location of abnormalities, therefore a PCD specific CT scoring system (the SPEC score) has recently been developed to permit a more accurate assessment for individuals with PCD (23). The SPEC score may provide a tool to assess longitudinal changes on CT but the role of CT to assess the effects of shorter term interventions continues to be limited due to the ionising radiation exposure involved (119), especially when working with children.

Proton MRI (^{1}H MRI) offers a radiation free alternative to CT that can provide structural information, and with dynamic scanning using non-contrast techniques developed over the last 10-15 years proton MRI now offers and some functional information from the lungs (120). Structurally, ^{1}H MRI has been shown to have performance outcomes similar to current clinical gold standard CT (106, 121) and a study of adolescents with PCD found all had structural abnormalities (106). ^{1}H MRI can also identify mucus plugging (122): with a high protein density and longer T2 weighting, mucus is bright and easy to visualise. Proton MRI has the ability over CT, to differentiate mucus from the bronchial walls (123). However, this is limited to the larger airways, for example MRI sequences with a spatial resolution of 3mm, mucus obstruction in airways with a diameter less than 6mm are unlikely to be resolved.

Functionally, Hyperpolarised gas Ventilation MRI (HP VMRI) is a novel tool which can assess regional areas of ventilation. Inhaling hyperpolarised gas, previously hyperpolarised Helium-3 (He^{3}) but more recently hyperpolarised Xenon-129 (^{129}Xe), immediately prior to imaging permits visualisation of the distribution of gas within the lung cavity, providing global and regional functional information. As a radiation free imaging method, sequential scans can be safely performed to allow the dynamic review of changes in regional lung function in response to treatment. ^{129}Xe MRI is safe and well tolerated, even in younger age groups (124), for these reasons PPI stakeholders involved in the development of this study design are especially supportive of exploring its role in this context. ^{129}Xe MRI derived metric ventilation defect percentage (VDP) is

the proportion of the thoracic cavity with no signal from the hyperpolarised gas which is seen where there is no ventilation.

A review by Mallallah *et al.* (125) summarised the clinimetric properties of HV MRI, including studies that employed ^{3}He MRI or ^{129}Xe MRI. As ^{129}Xe MRI is now more commonly used and will be used within this thesis, the properties of ^{129}Xe VDP specifically in CSLDs is summarised in Table 1. Whilst test-retest data is currently only available from one person with PCD (126), high test-retest reliability of ^{129}Xe VDP has been demonstrated in three independent studies of people with CF (127-129). The validity of ^{129}Xe VDP has been assessed through correlation with established markers of lung health; FEV_1 and LCI. In the CF population the correlation between ^{129}Xe VDP and FEV_1 has ranged from strong (130), to moderate (131), and weak .A strong correlation between ^{129}Xe VDP and LCI people with CF has also been demonstrated (130, 132). Differences in the clinimetric properties reported between studies may arise from different MRI acquisition and processing methods (including the magnetic field strength of the MRI scanner) (129), and from variance in using actual, percent predicted or z-score spirometry values.

Table 1: Summary of studies reporting sensitivity of ^{129}Xe VDP in CSLD. ICC= intraclass correlation coefficient, BA= Bland Altmann, LOA= 95% limits of agreement.

Paper	Population	Design	Findings
Wee *et al.* (126)	PCD, (n=1)	Two scans in one day. Assessment with ^{129}Xe MRI at 3T, spirometry and MBW.	Single subject so summary data not available.
Couch *et al.* (127)	Children with CF (n=18), aged 10-17 years	Test-retest: two scans in one session. Assessment with ^{129}Xe MRI at 3T, spirometry and MBW.	Test-retest reliability: ICC=0.99
Smith *et al.* (128)	Adults and children with CF (n=29).	Test-retest: two scans in one session (n=11); baseline and 16 months (n=29). Assessment with ^{129}Xe MRI at 1.5T, spirometry and MBW.	Single session: ICC= 0.99, BA bias 0.2% LoA −1.4 to 1.8%. Baseline to 16 months: ICC= 0.97, BA bias = 0.8% LoA −7.0 to 8.5% No correlation seen between (absolute or relative) change over time in ^{129}Xe VDP and FEV_1 or MBW
Walkup *et al.* (129)	Children with CF (n=38)	Test-retest: two scans in the same day (mean interval =33 mins) (n=38); baseline and follow-up (median interval =28 days) (n=36). Assessment with ^{129}Xe MRI at 3T, spirometry and MBW.	Single session: BA bias 0.12% LoA −3.2 to 3.4%. No relationship between same-day difference in ^{129}Xe VDP and FEV_1 or LCI At 28 days, no significant change in ^{129}Xe VDP (no group repeatability metrics provided).
Marshall *et al.* (130)	Adults and children with CF (n=31).	Two centres (C): C1 (n=24), C2 (n=7). Single assessment with ^{129}Xe MRI at 1.5T, spirometry and MBW.	Strong and significant correlation between ^{129}Xe VDP and FEV_1 (z-score): C1: r= 0.83, ($p<0.001$), C2: 0.7 ($p<0.001$). Significant correlation between ^{129}Xe VDP and LCI : 0.91, $p<0.001$
Thomen *et al.* (131)	Children with CF (n=11)	Single assessment with ^{129}Xe MRI at 3T and spirometry.	Moderate but non-significant correlation between ^{129}Xe VDP and FEV_1: r=−0.54 ($p<0.09$)
Kanhere *et al.* (132)	Children with CF (n=8) and healthy (n=10)	Single assessment with ^{129}Xe MRI at 3T, spirometry and MBW.	Weak correlation of ^{129}Xe VDP and FEV_1: r=0.31 (p= 0.03). Strong and significant correlation of ^{129}Xe VDP and LCI r=0.88 (p= 0.0001).

^{129}Xe MRI VDP has shown discriminatory power to detect disease and disease progression over time prior to routinely clinically used measures (133, 134) and is an appropriate marker of lung health (125). ^{129}Xe MRI is highly sensitive; it can identify

ventilation defects in PCD patients with normal MBW and spirometry parameters (135). The ventilation defects seen in children with PCD are not seen in healthy adults or children (135), an example of images from a child with PCD are shown in Figure 8. Additionally the types of defects are heterogeneous, with some individuals showing numerous ventilation defects and others showing large defects (135).

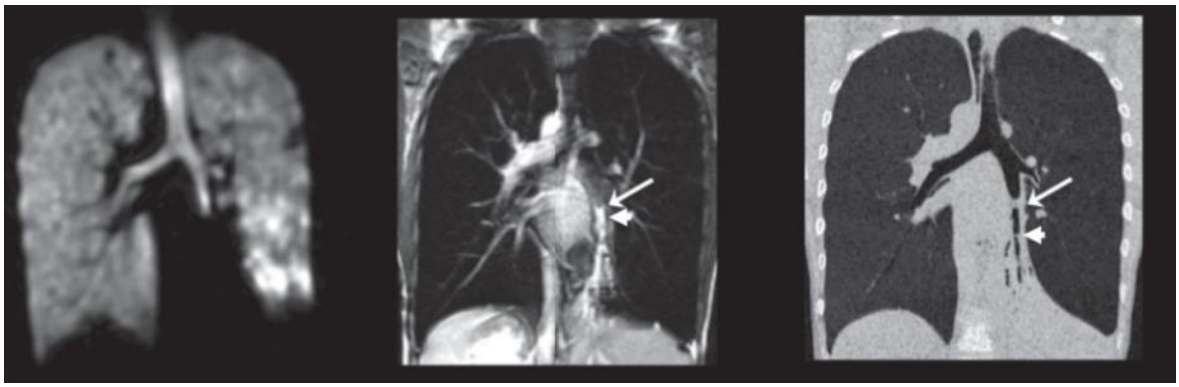


Figure 8: Imaging of a child with PCD using ^{129}Xe MRI, Proton MRI and CT. Reprinted with permission of the American Thoracic Society. Copyright © 2024 American Thoracic Society. All rights reserved. 7 Smith LJ, West N, Hughes D, Marshall H, Johns CS, Stewart NJ, et al. Imaging Lung Function Abnormalities in Primary Ciliary Dyskinesia Using Hyperpolarized Gas Ventilation MRI. Annals of the American Thoracic Society. 2018;15(12):1487-90. (135) Annals of the American Thoracic Society is an official journal of the American Thoracic Society.

The responsiveness of ^{129}Xe VDP to detect change following intervention has been seen in a number of studies. On average, a 42% improvement in ^{129}Xe VDP was seen children with CF treated with intravenous antibiotics due to a pulmonary exacerbation (136). Smith *et al.* (137) assessed 11 individuals with CF pre and post sub-maximal exercise testing and found varied response with significant improvement seen in four, significant worsening in one, visible re-distribution of ventilation without a significant change in VDP in four and no notable change in two. This study illustrates the potential for varied individual responses to standardised interventions.

As we established that ACTs aim to manipulate the physiological principles of ventilation to mobilise secretions (Section 1.3.2), as a tool which measures ventilation, ^{129}Xe MRI holds potential to provide valuable insight into the effects of ACTs. HP VMRI (^{3}He/^{129}Xe MRI) has also been shown to be sensitive to change following a single, standardised ACT regimen in conditions similar to PCD (138, 139). However, all previous studies assessing response to ACTs have utilised ^{3}He MRI as opposed to ^{129}Xe MRI (138-142). HP VMRI is a relatively specialist tool in its infancy currently in use in less than 20 centres worldwide. As such, it is not yet known how highly sensitive ^{129}Xe MRI may be used in the clinical context to inform the management patients with PCD; if information from a highly sensitive novel tool aligns with the broader clinical picture of individuals with PCD and how clinicians may use this information in clinical

care. Additionally, while HP VMRI (^{3}He/^{129}Xe MRI) repeatability data is available in the CF population (133, 134) repeatability data is not available for the PCD population. As we have established there are differences between CF and PCD, this project includes a work-package on same-day repeatability of ^{129}Xe MRI in PCD to assess for natural variation without an ACT.

Unlike specialist HP VMRI, proton MRI is a potentially widely available tool. Novel proton free-breathing techniques (Phase resolved functional lung (PREFUL) MRI) provide an estimation of ventilation and show promise to assess the response to interventions; correlation has been seen between PREFUL metric ^{1}H VDP and ^{129}Xe MRI VDP in children with CF (143). Currently no studies assessing people with PCD using PREFUL imaging techniques have been published, so further work to explore its sensitivity both in PCD, and to the effects of ACTs, is needed.

1.4.3 Other markers commonly used in clinical practice are flawed.

The goal of ACTs is to facilitate sputum clearance, yet sputum volume and weight can be an unreliable measure of clearance especially in children, as secretions can also be swallowed rather than expectorated and clearance does not necessarily occur during or immediately after the ACT (101, 103). Auscultation by stethoscope is a tool commonly used in practice, it requires interpretation of the sounds heard by the operator and studies of the concordance between physiotherapists has ranged from poor to moderate (144, 145). Computed aided lung sound analysis has been proposed as a method to overcome the subjectivity of auscultation (101) but is yet to be widely adopted in clinical practice. As a home based intervention, patients and parents perception of ACTs is probably clinically useful, however there is no validated tool to assess this and it can be unclear how this has been evaluated in published literature (78). Health related quality of life and exacerbation frequency are used in PCD trials (100), but are not discussed here as they are not appropriate for measuring short term outcomes.

1.5 There is a need to understand the effects of personalised ACT regimens used by people with PCD.

We have established the burden of living with PCD on individuals and society (Section 1.2.6) and the importance to PPI stakeholders of optimising ACTs, a key component of PCD management (Section 1.3.4). There is uncertainty when physiotherapists are advising patients on personalised ACT regimens; the theory of how ACTs work is established (Section 1.3.2), but the theory of how regimens are personalised is less

clear (Section 1.3.4). To refine ACT interventions, we need to be able to tell if ACTs are maintaining and improving lung health empirically, and to understand why certain regimens are effective for certain individuals. However, changes in PCD symptoms can be nebulous (Section 1.2.3) and the standard markers of lung health available clinically to assess the effects of ACTs are insensitive to change and global measures fail to provide the sophisticated regional detail required in this context (Sections 1.5.1, 1.5.2 and 1.5.4). We hypothesise that that ^{129}Xe-MRI is a better marker of lung health than FEV_1 in this context; being safe, radiation free and sensitive both to mild lung disease and changes following ACTs (Sections 1.4.2 and 1.5.3). In order to understand the role of functional imaging in assessing personalised ACTs in PCD we need to undertake an empirical study. Mindful of real-world access to HP VMRI, as a more widely available but possibly less sensitive tool than ^{129}Xe MRI (Section 1.5.3), it is logical to also explore the parallel and complementary role of Proton MRI within this context.

1.5.1 More research is needed to assure patients how, and how well, their ACT regimens are being optimised.

PCD creates a significant burden for patients, carers, health systems and society (Section 1.2.6) and now is the right time to move from a state of habit to one of enquiry in terms of personalising ACTs. There are mechanistically plausible reasons for thinking ACTs, as a central component of PCD care, should alleviate symptoms and slow disease progression (Section 1.3.2) but there is little evidence that standardised, one-size-fits all approach for ACT interventions does so (Section 1.3.4). Patients and parents want to better understand the effects of the ACT regimens that are the current mainstay of their treatment (Section 1.2.7). Policy imperatives, including the NHS Constitution, the evidence-based medicine agenda, and the MRC Framework, warrant the development and evaluation of personalised approaches, as we have good scientific reasons to believe they will provide greater efficacy (Section 1.3.4). However as current tools to assess lung health and the effects of intervention are limited, clinicians' ability to tailor interventions based on physical cues and modify based on response is limited (1.4.1 and 1.4.3). ^{129}Xe MRI offers a highly sensitive, specialised tool to assess lung health and treatment response, ^{1}H MRI offers a less established but potentially more accessible tool as a surrogate for ^{129}Xe MRI (1.4.2). Whilst highly sensitive MRI methods present an opportunity for novel information, it is not known how MRI data may inform clinicians who are currently personalising ACT regimens in clinical practice.

1.6 Thesis summary

While the broader literature offers some clues, there is no clear overview of how we should or how we do personalise ACTs (Section 1.4). For this reason, **Chapter 2** presents a scoping review of the personalisation of ACTs in CSLDs that will summarise the current evidence for how ACTs should be personalised. A scoping review is an appropriate approach for this broad question, it will identify the breadth and characteristics of the literature and identify any knowledge gaps (146). Secondly, there is no clear insight into how physiotherapists do personalise ACTs (Section 1.4). To clarify this, **Chapter 3** presents a cognitive task analysis (CTA) of how expert physiotherapists currently personalise ACT regimens. As clinical decision-making by physiotherapists is a recurrent, multifaceted and contextual process which incorporates biomedical and psychosocial elements (147), CTA is an appropriate tool to uncover how experts, in this case physiotherapists, make decisions in complex situations (148). The prognosis of PCD is heterogeneous, and as the assessment tools that are currently available have recognised limitations, assessing lung function in individuals with PCD is challenging. To establish a more informed picture of lung health in PCD, **Chapter 4** is a cross-sectional study, conducted to assess if ^{129}Xe MRI, and free breathing ^{1}H MRI (PREFUL) methods can assess lung health in children with PCD. Assessing change in PCD is difficult and physiotherapists currently have limited tools to assess if the regimens they advise patients to complete are effective (Sections 1.2.2 and 1.5), so we need an inquiry to understand if the current clinical approaches for personalising ACTs are effective with an appropriate marker of lung health. For this reason, **Chapter 5** will carry out a before and after study exploring the effects of personalised ACT regimens using functional imaging, specifically ^{129}Xe MRI and free breathing ^{1}H MRI (PREFUL) methods. ^{129}Xe MRI repeatability work has not been done before in PCD, as such, with a work-package on same-day repeatability of ^{129}Xe MRI in PCD to assess for natural variation without an ACT, this is an appropriate study design. It is not known if and how treatment recommendations would be changed if clinicians have access to accurate information on the effects of ACT regimens. As such, **Chapter 6** will perform cognitive task analysis (CTA) of clinicians' decisions about ACT regimens before and after the introduction of the information from functional imaging pre- and post-ACT. CTA methods are used within health research to understand how clinicians make clinical decisions, an appropriate method for exploring how novel imaging may influence decision-making in the real-world context of ACT personalisation. Chapter 6 also draws upon multiple case-study method to integrate the MRI findings with clinical decision-making to explore under what circumstances MRI data influences clinical decision-making. Multiple case-study method is a perfect fit for this heterogenous population with personalised interventions, providing insights which

would not have been possible from either the quantitative or qualitative data in isolation. In finally understanding how ACT regimens should be and are personalised, what the effects of personalised ACT regimens are and how this information may influence clinicians' decision-making, we will then have an explicit knowledge base for future research understanding how we formally optimise ACT regimens for individuals in future research and practice.

1.6.1 Thesis programme theory

A schematic representation of the programme theory for this thesis is provided in Figure 9. Our programme theory is: if we recognise the limitations of current markers of lung health (Section 1.4.1 and 1.4.3); we can use functional MRI to accurately assess lung health (Section 1.4.2); we can accurately assess impaired lung function in individuals (H3, chapter 4); then we can employ personalised ACTs (Section 1.3.5); guided by current literature on how to personalise (H1, chapter 2); tailored by expert physiotherapists for individuals (H2, chapter 3); then we can use functional MRI to assess individual response to personalised ACTs (H4, chapter 5); clinicians, informed by functional MRI can modify regimens (H5, chapter 6); optimal regimens can be implemented for individuals; so that respiratory infections and bronchiectasis can be prevented or minimised; long term lung health and quality of life can be improved for people with PCD and the burden of PCD on society can be reduced.

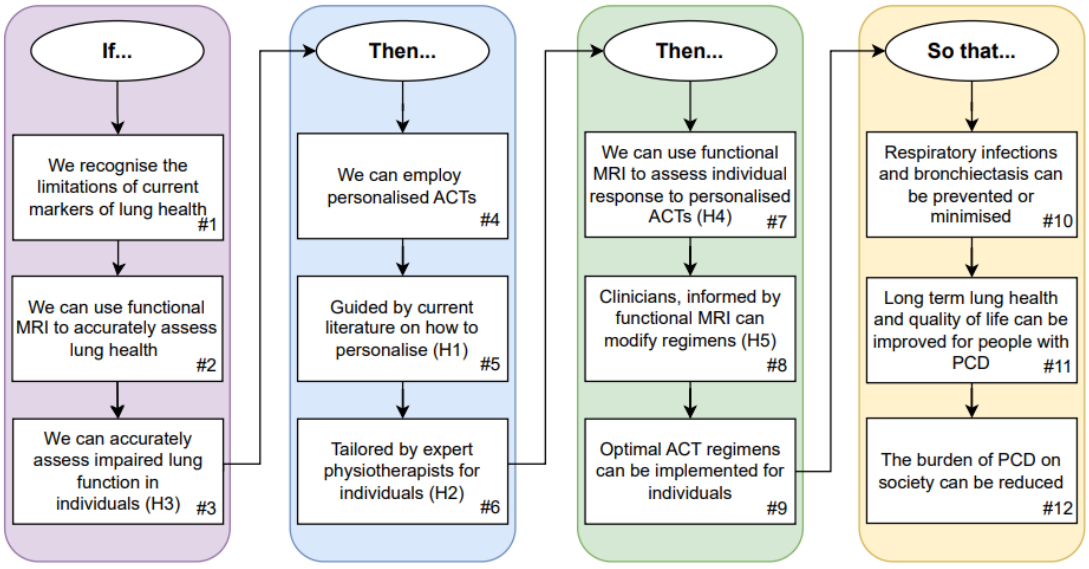


Figure 9: Schematic representation of the thesis programme theory.

This programme theory considers stratification of the population (purple), personalisation of the intervention (blue), use of a valid outcome to assess effectiveness (green), and the wider context of this thesis (yellow).

1.7 Philosophical *pragmatism* is an appropriate world view through which to explore the personalisation of ACTs.

Personalising care for a rare but heterogeneous population, in the presence of multiple treatment options with uncertainty arising from insensitive outcome assessments, is a complex matter (49). The practical problem, and *key uncertainty*, for physiotherapists is how to achieve consistent outcomes given that outcomes are affected by *context* (149), where context can be defined as settings, roles, relationships, interactions. Physiotherapists are asked to personalise ACT regimens with little clarity about how this should be done. The opportunity for this thesis is to inquire how evidence says we *should*, and how clinicians currently *do* personalise care, and to explore whether functional imaging can improve the precision of or reduce uncertainties in ACT personalisation.

Physiotherapy practice involves: the translation of evidence to the individual patient's context; drawing together quantitative findings, such as those from outcome measures, with qualitative findings, for example patient preference and lifestyle; making clinical recommendations that would not be possible without consideration of a diverse range of information (149). With the aim of conducting clinically relevant research, pragmatism is a highly appropriate paradigm for physiotherapy research (149), and is the philosophical approach that this thesis adopts. Pragmatism facilitates enquiry into the outcomes of different courses of action, with the ultimate aim of resolving uncertainty (150) and warrants the use of the most appropriate research methods to answer the relevant questions. Within this thesis it is recognised that personalised care is complex, and difficult to evaluate. This warrants the use of CTA methods, which are used to explore decision-making, specifically managing real-world complex circumstances (148). Formal mixed methods study designs allow for the combining data of different types (e.g. qualitative and quantitative) taking advantage of the strengths of different approaches, to show convergences and divergences in findings (150) and to provide insights which would not have been possible with a single approach.

This thesis will use a sequential mixed methods approach, building and integrating the findings from earlier work packages into the analysis of subsequent work packages (150, 151). In line with Dewey's step-wise approach to inquiry, as explicated by Morgan (152), this thesis will: recognise a problem, (Sections 1.2.6, 1.2.7, 1.3.4, 1.4 and 1.5.1); explore the impact of defining the problem in a different way (Sections 1.2.6, 1.2.7, 1.3.4, 1.4 and 1.5.1); develop and evaluate the impact of a possible solution (Sections 1.4.2, Chapters 5 and 6); outline potential future actions (Chapter 7).

1.7.1 Mixed methods integration

Throughout this thesis, the most appropriate methods are used to answer the research question, including both quantitative and qualitative methods. Employing multiple methods provides strength to the research findings, offering a unique understanding of the personalisation of ACTs which would not have been possible using one method in isolation (153). As mixed methods research integrates the data to permit further understanding (154), at times in this thesis, methods, data or analysis from multiple research methods are combined at points of integration (155). Whilst the specific methods are described as they arise in each of the chapters, a schematic overview of the points of integration in this thesis are provided in Figure 10. Within this thesis, the five purposes for mixed methods research as defined by Greene *et al.* (156, p. 259)are employed:

1. Expansion: extending the breadth of the inquiry to both quantitatively assess the effects of ACT regimens with ^{129}Xe MRI (Chapter 5) and qualitatively through the clinician data reviews (Chapter 6).
2. Complementarity: elaborating on the quantitative assessment of ACT regimens with ^{129}Xe MRI in Chapter 5, to explore how the data may influence the personalisation of ACT regimens in clinical practice (Chapter 6), increasing the meaningfulness of the ^{129}Xe MRI findings to the real world of ACT personalisation.
3. Triangulation: Seeking corroboration of how current literature tells us ACT regimens should be personalised with PPI experiences of ACT personalisation (Chapter 2) and clinicians decision-making when personalising ACT regimens (Chapter 3); assessing the potential to use [1]
4. Development: of the ACT personalisation model, initially derived current literature, this was revised with further data from PPI feedback (Chapter 2), the recognition primed decision model (RPDM) (Chapter 3), think aloud problem solving (TAPS) interviews (Chapter 6); of the clinical data collection form, from current literature and current ACT personalisation by clinicians (data collected during Chapter 5, provided to clinicians in Chapter 6).
5. Initiation: using the patient participant baseline demographics acquired from the cross-sectional study (from Chapter 4), and quantitative assessment of the effects of ACT regimens (Chapter 5) to discover the circumstances under which MRI informs ACT personalisation (Chapter 6).

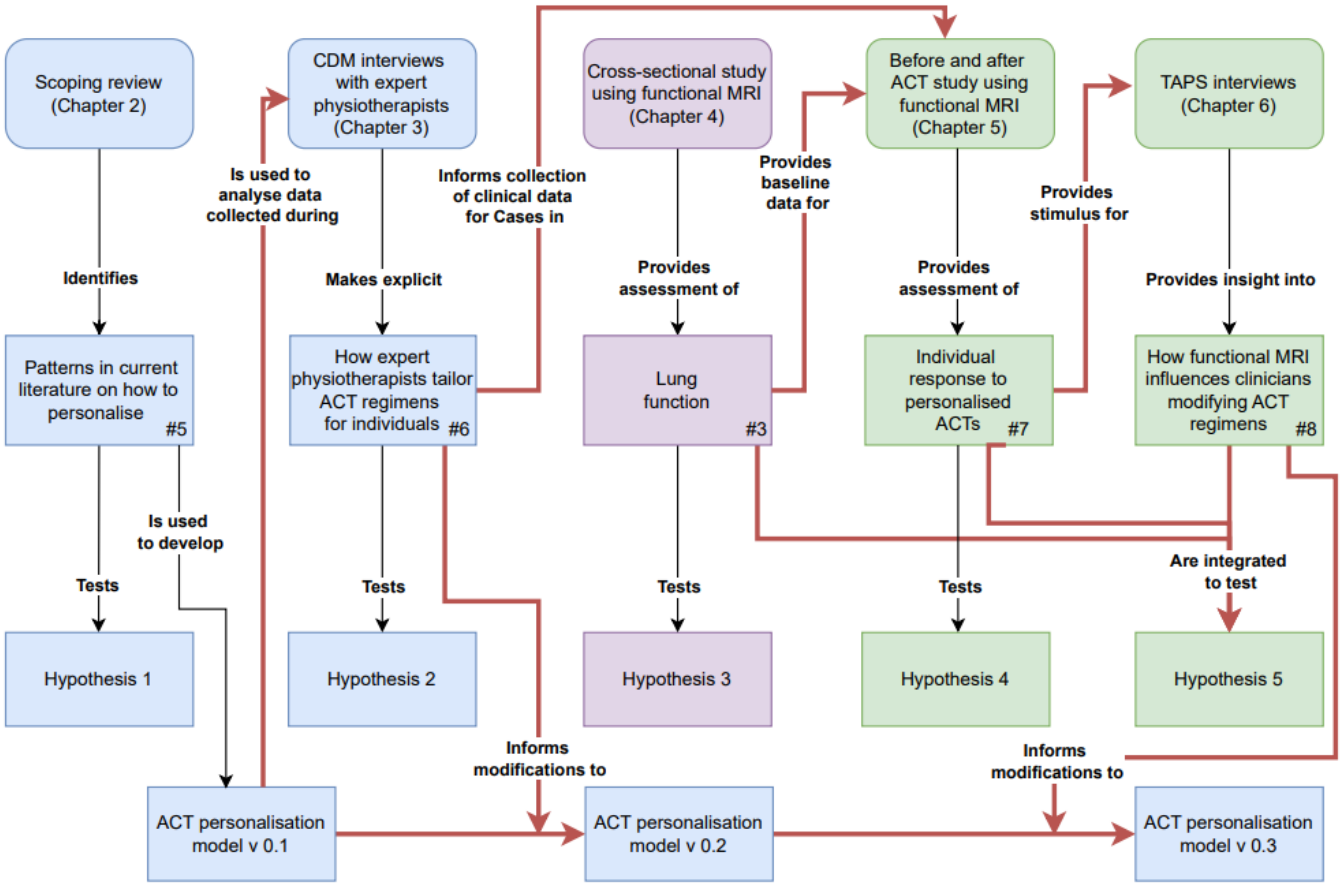


Figure 10: A schematic overview of the integration of data throughout the thesis. The black arrows show analysis with a single method, the red arrows show integration of more than one methods. Cross reference to the study programme theory is indicated with # numbers.

1.8 Research questions, hypothesises, aims, and objectives.

1.8.1 Research Questions

1. What does current literature tell us about how ACT regimens should be personalised?
2. How do clinicians personalise ACT regimens?
3. Can the primary outcome measure, ^{129}Xe VDP, assess lung health in children with PCD?
4. What are the short-term effects of personalised ACT regimens on lung health in children and young people with PCD?
5. What are the circumstances under which the personalisation of ACT regimens is altered by the introduction of functional imaging?

1.8.2 Hypothesises

H1: There will be identifiable patterns in the literature on how to personalise ACTs for CSLDs (Chapter 2).

H2: There will be identifiable patterns in how expert physiotherapists personalise ACTs for children and young people in practice (Chapter 3).

H3: The primary outcome measure, ^{129}Xe MRI-derived VDP, can be used to assess lung health in children with PCD (Chapter 4).

H4: There will be improvement in visual indicators of lung health, as measured, pre- and post-, by ^{129}Xe VDP, after personalised ACTs are completed (Chapter 5).

H5: Functional imaging will inform expert physiotherapists in the personalisation of ACTs for children with PCD (Chapter 6).

A summary of the chapter content according to the thesis hypotheses is provided in Table 2.

Table 2: summarises the chapter content according to the thesis hypothesis.

		Chapter				
Hypothesis		2	3	4	5	6
H1	There will be identifiable patterns in the literature on how to personalise ACTs for CSLDs	√				
H2	There will be identifiable patterns in how expert physiotherapists personalise ACTs for children and young people in practice		√			
H3	The primary outcome measure, ^{129}Xe MRI-derived VDP, can be used to assess lung health in children with PCD (Chapter 4).			√		√
H4	There will improvement in visual indicators of lung health, as measured, pre- and post-, by ^{129}Xe VDP,, after personalised ACTs are completed				√	
H5	Functional imaging will inform expert physiotherapists in the personalisation of ACTs for children with PCD					√

1.8.3 Broad aims

1. To understand what current literature tells us about how ACTs should be personalised.
2. To understand how physiotherapists personalise airway clearance regimens.
3. To explore if ^{129}Xe MRI can quantify lung health in children and young people with PCD.
4. To quantify response to a personalised ACT regimen (compared to no-ACT) in children and young people with PCD.
5. To understand the circumstances under which personalisation of airway clearance regimens is altered with the introduction of functional lung imaging.

1.8.4 Specific objectives

Chapter 2:: A scoping review of the literature, to summarise positions on how ACT regimens *should be* personalised in CSLDs and to identify research gaps.

Chapter 3: A knowledge elicitation exercise with physiotherapists using semi-structured interviews and the critical decision method to understand how ACT regimens *are* personalised and assessed in practice.

Chapter 4: A cross-sectional assessment of regional lung health in children and young people with PCD using ^{129}Xe and ^{1}H MRI.

Chapter 5: A controlled before-and-after study to assess the short-term effects of an individualised airway clearance regimen on regional lung function versus no

intervention over 4-hours using ^{129}Xe ventilation MRI and ^{1}H MRI in children and young people with PCD.

Chapter 6: A mixed methods multiple-case study:

- Using 'think aloud' methods to show how clinicians make decisions about ACT personalisation with the introduction of MR images.
- Integrating quantitative MRI data and qualitative interview data in order to delineate the clinical scenarios where imaging led to divergent changes in ACT recommendations.

1.9 Ethical conduct

With the exception of the scoping review, NHS ethical approval was sought for all components of this mixed methods study within a single application. Specific consideration was given to particular areas of the study which are summarised here.

As a small group of specialist clinicians working in a rare disease, it was important to ensure anonymity of the clinician participants (Chapters 3 and 6) to provide them with confidence to speak honestly and openly during their interviews. Data was anonymised, with care taken to ensure clinicians could not be identified through transcript excerpts. As clinical reasoning is a central component of physiotherapy practice, it was not anticipated that clinicians would be challenged by the critical decision method interviews in Chapter 3 or think aloud methods used in Chapter 6. Clinicians were able to discuss their participation with colleagues with the exception of specific cases in Chapter 6 which were to be reviewed by other members of the MDT as part of the study, clinicians were asked to refrain from discussing data from the study with colleagues until all data collection pertaining to the case was completed.

In the absence of data to inform same-day variability of lung health in PCD, it was warranted to include a group of patient participants who did not complete an ACT (Chapter 5). As completion of an ACT twice daily is widely recommended in PCD, early planning informed the feasibility of this: advice was sought from PCD medical consultants to establish the perceived risks of this; PPI members were consulted at an early stage to explore the acceptability of this to potential participants and their parents. Based on PPI feedback: arrangements were made to allow participants of the no-ACT group to complete their ACT regimen after the final MRI scan which would allow participants to delay their first ACT session of the day rather than omit it, completing a second ACT session pre-bed; participation in the no-ACT group was by invitation and participants or parents for those under 16 were able to request to participate instead in the ACT group. Based on medical consultant feedback, the risks of delaying a single

ACT session were felt to be low, as many people with PCD struggle with adherence to their ACT regimens. As an exploratory study, the wider project advisory group members advised to have a small number of participants in the no-ACT group.

As research involving children, the young participants were central to the success of the project. A PPI group which included children and young people with PCD was established prior to the start of the project. Young PPI members were involved throughout the study, key elements which had ethical considerations included: the development of age-appropriate participant information sheets; review of the participant assent form; conceptualisation, content development and production of a video blog to provide additional information for young potential participants; consultation on the study schedule. Both assent and consent were required for individuals under 16 years of age to participate and time was taken to discuss the study and answer any questions both prior to taking consent and throughout the study to ensure the young person was willing to participate and were aware of their ability to withdraw from the study at any time. In response to feedback from a funding panel, all participants were approached initially by a member of their direct care team, rather than the lead researcher. PPI members were consulted on how and when to contact potential participants following the initial approach.

NHS research ethics committee approval was received prior to set up of the study (Appendix 2) and local site approval was obtained for the research activities at each individual site. The initial application included four research sites: Leeds Teaching Hospitals, Bradford Teaching Hospitals, Sheffield Children's Hospitals, and the University of Sheffield. When opening of an additional site was indicated due to lower recruitment than anticipated, an ethics amendment was submitted for this.

1.10 Conclusion

Impaired mucociliary clearance is the physiological problem in PCD, which makes people with PCD at risk of repeated infections and bronchiectasis. ACTs are a core component of PCD management aiming to augment mucus clearance. Personalised ACT regimens are recommended, tailored based on the assessment of patient characteristics and preferences. However, clinicians may face uncertainty in optimising regimens for individuals as current markers of lung health used clinically to assess response are limited. Functional lung imaging techniques offer an opportunity to assess regional lung ventilation, which has potential to provide accurate information to clinicians and reduce uncertainty in ACT personalisation. If we can effectively optimise ACT regimens for individuals with PCD, we have an opportunity to improve their long-

term lung health and quality of life and reduce the burden of PCD on both individuals and society.

Chapter 2: Current literature advises ACT regimens should be personalised, scoping review.

2.1 Introduction and objectives

We have identified that PCD causes impaired mucociliary clearance, and retained secretions pose a risk of repeated infections and bronchiectasis. To minimise this risk, ACTs are a core component of managing PCD and whilst personalised ACT regimens are recommended, it is unknown what current literature tells us about how ACTs should be personalised based on the assessment of patient characteristics and preferences. This chapter aims to address the first hypotheses generated in Chapter 1: *H1: There will be identifiable patterns in the literature on how to personalise ACTs for chronic suppurative lung diseases (CSLDs)* (Table 2)

To test this hypothesis, we conducted a scoping review of peer-reviewed publications, to establish what current literature tells us about how clinicians *should* personalise ACT regimens. As PCD is a rare condition with a very limited evidence base, the population for this scoping review has been broadened to CSLD.

Objectives

1. To examine the extent and range of research on personalisation of ACT regimens in CSLD.
2. To summarise key findings of the literature and identify research gaps.

CSLD is a clinical syndrome, with respiratory signs or symptoms of a persistent productive cough, which can present alongside other symptoms including dyspnoea, airway reactivity and recurrent chest infections (91). The term “Chronic suppurative lung disease” has been used interchangeably, both in the literature and clinical practice, with Bronchiectasis, a radiological diagnosis and feature of CSLD, in which irreversible dilation of the bronchi is identified by CT (91).

CSLD has a wide a range of causes and is often associated with underlying diseases including PCD and CF, but can also be of unknown cause (157). Heterogeneity in the underlying courses, the interchangeable use of terms and misdiagnosis in CSLD has led to variation in estimates of incidence and prevalence (157). The reported prevalence of CSLD in the UK varies between 0.2/100,000 in children and 566.1/100,000 in adult females (158, 159), and globally prevalence varies, with higher rates seen in more deprived populations, for example, the Indigenous population of central Australia (160).

This scoping review has recently been published in ERJ open:

Schofield, L.M., Singh, S.J., Yousaf, Z., Wild, J.M. and Hind, D., 2023. Personalising airway clearance in chronic suppurative lung diseases: a scoping review. ERJ Open Research, 9(3).

2.2 Methods

2.2.1 Design

A scoping review was undertaken to capture sources and types of evidence, identify key concepts, knowledge gaps and research priorities (146). It was not possible to undertake a systematic review as this is a complex and broad area in which a comprehensive review had not been previously undertaken. Scoping reviews aim to comprehensively capture the research in the field, including all types of study design, with iterative and methodical processes to analytically describe and interpret the literature without critically appraising the quality of the individual pieces found (146).

2.2.2 Identification of relevant literature

A highly relevant article of interest in the field was used as the primary manuscript for a pearl growing exercise (161). From this article, citation searching, and reference list checking were used to identify further key articles of known interest. The index terms from this collection of articles of interest were used in addition to key search terms for the three facets (CSLD and ACT and personalisation) to form a more extensive search strategy (see Appendix 3). The search was run initially through Medline and then converted for other major health databases in this field (Embase, Cinhal, Pedro, Cochrane, and Web of Science). Citations and hand searching the index list of known highly relevant journals identified further items.

Selection of items for inclusion

The documents were managed initially using Endnote™ to allow for removal of duplicates and subsequently transferred into the online collaborative research management tool Rayyan© (Rayyan.ai) for screening. Screening was completed by two reviewers, a highly specialist clinician in the field and a patient and public involvement group member who received bespoke training to ensure appropriate knowledge and understanding of the review scope and process. This approach provided topic experts with diverse experiences. Screening criteria (see Table 3) were developed and refined by the lead reviewer and supervisory team. Screening against the set criteria was done in isolation with reviewers' blind to each other's decisions. Conflict of decisions was managed initially by discussion between the two reviewers

with a final decision made by a third reviewer, a clinical academic physiotherapist. The outcomes of this process are shown in Figure 11.

Table 3: Inclusion and exclusion screening criteria for the scoping review.

Category	Inclusion	Exclusion
Publication types	Published in last 25 years. Full text available. English language	Published at least 25 years ago. Posters, conference abstracts. Non-English
Study type	Human	Animal, basic science
Condition	CSLD PCD Cystic Fibrosis (CF) Bronchiectasis	Chronic obstructive pulmonary disease Acute illness, pre/post-surgery Obesity Neonates Chest infections in otherwise well people
Intervention	Airway clearance techniques (ACT) Breathing techniques (ACBT, AD, FETs) Devices (Aerobika®, Cornet®, Acapella®, PEP, high frequency chest wall oscillation) Manual techniques (percussion, vibration) Non-invasive ventilation *if used for airway clearance. Physical activity/exercise if aim is airway clearance	Pulmonary rehab or exercise (unless the focus/aim is for airway clearance) Percussive ventilation- for ventilation not ACT Non-invasive ventilation (NIV) if not specifically for airway clearance Inspiratory muscle training (unless used for ACT) Forced oscillation technique (used to measure lung function)
Focus	Individualised approach Choice of treatment Timing of treatments Frequency of treatments	Comparing ACT modalities without any personalisation component

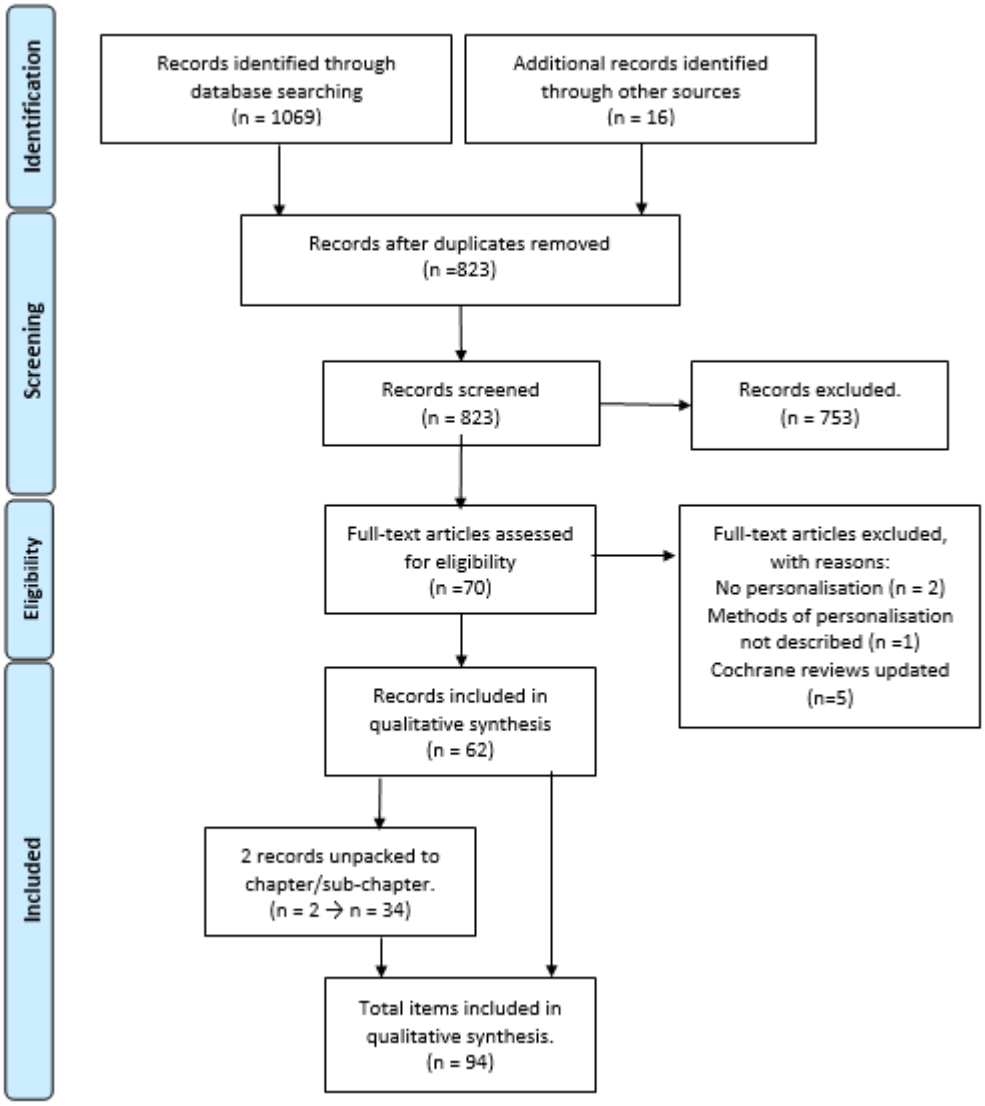


Figure 11: PRISMA flowchart with literature identification and screening details.

2.2.3 Data extraction

Details of the factors used or considered when personalising ACTs were extracted from all records and the TIDier checklist (162) was initially used as a framework for this. Due to the large volume and variety of data falling in “procedure”, adaptions were made, with the addition of sub-fields on a best-fit approach to ensure the clarity in the result reporting. A total of 7 fields were used to categorise the personalisation factors: Physical patient factors, non-physical patient factors, intervention factors, procedure, dosage, response, and provider location. Multiple passes through the data were completed to ensure all items were extracted and categorised appropriately. Articles were ordered alphabetically by the first author throughout the data analysis, analysis according to date of publication or population is beyond the scope of this thesis.

2.2.4 Patient and public involvement

Young people with PCD and their parents are experts in this field and as such were actively involved as PPI members. As previously described, one PPI member was involved in screening articles for inclusion. Following data extraction and categorisation, preliminary results were also fed back to a PPI group. Members felt the factors identified were generally comprehensive and reflected their experiences of ACT personalisation but advised that the time between appointments was an additional factor which may influence ACT regimen personalisation. An additional pass through the data was undertaken following this feedback to ensure any data relating to this factor was captured.

2.2.5 Chapter acknowledgements

The contributions for this chapter from the lead researcher, Lynne Schofield, are as detailed below:

- Study design
- Development of search strategy, inclusion and exclusion criteria
- Conducting literature searches
- Screening articles for inclusion
- Data extraction,
- Collation of findings
- PPI work
- Development of the ACT personalisation model.

Acknowledgments for specific contributions are also given to:

- Prof Dan Hind verification of data extraction and co-development of the ACT personalisation model. For guidance throughout planning, data collection and analysis.
- PPI member Zarah Yousaf, in screening articles for inclusion.
- Professor Sally Singh, who acted as the third reviewer where a conflict of decision arose around inclusion of articles.
- PPI members for their feedback on the results and ACT personalisation model.

2.3 Results

2.3.1 Personalisation of ACTs is commonly discussed in current literature.

As summarised in Figure 11, one thousand and eighty-five abstracts were identified, of which 823 were reviewed after the removal of duplicates. Seventy publications were reviewed in full, of which 62 met the inclusion criteria and were included in the analysis As summarised in Table 4, the publications included; general reviews (n=29), randomised controlled trials (RCTs) (n=8), guidelines (n=5), Cochrane reviews (discussion and author conclusion sections) (n=4), case reports (n=3), surveys (n=4), expert panel or consensus reports (n=3), standards of care (n=2), qualitative interview (n=1), audit (n=1), a self-classified "booklet" (n=1) and a cohort study (n=1). Articles related specifically to CF (n=38), Bronchiectasis (n=10), PCD (n=1), or more than one condition (n=7). In terms of age, the publications pertained to both paediatrics and adults (n=14), paediatrics (n=14), adults (n=8), or did not specify this (n=15). By first author location, the publications mainly originated from three countries: UK (n=18), USA (n=14), Australia (n=15); and also included Canada (n=3) Italy (n=3), Netherlands (n=2) Sweden (n=2), Austria (n=1) New Zealand (n=1), Greece (n=1) Switzerland (n=1), Poland (n=1).

Table 4: Details of the publications included in the review.

Author (year)	**Location (first author)**	**Publication type**	**Population**
ACPCF (65)	UK	Standards of care	CF, paediatric and adult
Acton and Stark (163)	USA	Review	CF
Bishop *et al.* (164)	Australia	RCT	CF, adults
Butler and Sutherland (165)	New Zealand	Review	CF
Button *et al.* (166)	Australia	Cohort study	CF, paediatric
Button (167)	Australia	Guideline	CF, paediatric and adult
Chang *et al.* (168)	Australia	Task Force Report	Bronchiectasis, paediatric and adult
Currie *et al.* (169)	Australia	Survey	CF
Daniels (95)	UK	Review	CF, adults
Davidson (170)	USA	Review	CF, paediatrics
Dentice *et al.* (171)	Australia	RCT	CF, adults

Author (year)	Location (first author)	Publication type	Population
Dentice and Elkins (172)	Australia	Cochrane review	CF, paediatric and adult
Dwyer *et al.* (173)	Australia	RCT	CF, adults
Egan *et al.* (174)	USA	Review	Bronchiectasis
Elkins and Dentice (175)	Australia	Cochrane review	CF, paediatric and adult
Fitzgerald *et al.* (176)	Australia	RCT	CF, paediatric
Flume *et al.* (94)	USA	Guideline	CF
Flume (177)	USA	Review	CF
Franks *et al.* (178)	Australia	Qualitative interviews	Bronchiectasis
Hill *et al.* (179)	UK	Guideline	Bronchiectasis, adults
Hill *et al.* (180)	UK	Expert panel	CF, Bronchiectasis, paediatric and adult
Hill *et al.* (181)	UK	Review	CF, paediatric
Homnick (182)	USA	Mini symposium	CF, paediatric
Hoo *et al.* (183)	UK	Survey	CF, paediatric and adult
Hristara-Papadopoulou *et al.* (184)	Greece	Review	Various
IPGCF (185)	Switzerland	Booklet	CF, paediatric and adult
Lannefors *et al.* (186)	Sweden	Review	CF, paediatric
Lee *et al.* (187)	Australia	Mini review	CSLD, Bronchiectasis, paediatric, adult
Lee *et al.* (68)	Australia	Letter- audit	Bronchiectasis, adults
Lester and Flume (188)	USA	Review	CF
Main *et al.* (189)	UK	Cochrane review	CF, paediatric, adult
Main *et al.* (190)	UK	Review	CF, Bronchiectasis, paediatric, adult
Marks (191)	USA	Mini symposium	CF
McCool and Rosen (192)	USA	Guideline	Various
McIlwaine *et al.* (193)	Canada	Cochrane	CF, paediatric, adult
McIlwaine *et al.* (56)	Canada	Review	CLD, paediatric, adult
McIlwaine *et al.* (194)	Canada	Review	CF
Milla *et al.* (195)	USA	RCT	CF, paediatric, adult

Author (year)	Location (first author)	Publication type	Population
Myers (196)	USA	Review	Various
Oberwaldner (197)	Austria	Review	Various, paediatric
Olsen *et al.* (64)	Sweden	Review	unspecified
O'Neill *et al.* (198)	UK	Survey	Bronchiectasis
O'Neill *et al.* (199)	UK	RCT	CF, adults
O'Neill *et al.* (200)	USA	Review	Bronchiectasis, paediatric, adult
Palma *et al.* (201)	Italy	Case report	CF+ spinal muscular atrophy, paediatric
Pasteur *et al.* (116)	UK	Guideline	Bronchiectasis, paediatric, adult
Pembridge and Chalmers (202)	UK	Review	Bronchiectasis
Phillips *et al.* (203)	Australia	Survey	Bronchiectasis, paediatric, adult
Prasad and Main (204)	UK	Review	CF, paediatric, adult
Rowbotham and Daniels (205)	UK	Review	CF
Schechter (206)	USA	Review	Various, paediatric
Schofield *et al.* (62)	UK	Standards of care	PCD, paediatric
Southern *et al.* (207),	UK	Review	CF, paediatric, adult
Spinelli *et al.* (208)	Italy	Case Report	CF, paediatric
Spinou (209)	UK	Review	CF
Terlizzi *et al.* (210)	Italy	Review	CF
Treacy (211)	UK	Case Report	CF, adult
van der Giessen (212)	Netherlands	RCT	CF, paediatric
Van Der Schans (213)	Netherlands	Review	Various
Volsko (93)	USA	Review	Various, paediatric, adult
Walicka-Serzysko *et al.* (214)	Poland	Consensus	CF
Wilson *et al.* (215)	Australia	RCT	CF, paediatric, adult

As the European “Blue booklet” (185) and the CF Trust standards of care (65) are large, highly relevant publications they were segmented down to the level of the chapter and subchapter respectively with relevant sections included as individual items for data extraction. For the reader’s convenience from this point onwards, the included items will be referenced to as documents, and the data set updated to display the 62 publications as 94 documents.

2.3.2 A large number of factors which should be considered when personalising ACTs were identified.

Within the 7 fields used for extraction, 29 aspects of ACT personalisation were found in the 94 documents. For clarity, the type of interventions that feature in the documents are provided in Table 5, and the aspects of personalisation in Table 6.

Table 5: Summary of the ACT modalities discussed in the publications in the review.

Author (and subchapter no. when applicable)		FET	Directed cough	ACBT	AD	PEP	OPEP	Percussions /Vibrations	Postural drainage	Positioning	HFCWO	Physical activity	NIV	IPPB	MIE	IPV	Simeox	Inhaled medication
ACPCF (65)	5.1	-		✓		-	-	-	-	-	-	-	-	-	-	-	-	-
	5.2	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
	5.3	-	-	-	-	✓		-	-	✓		-	-	-	-	-	-	-
	5.4	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-
	5.5	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-
	5.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓	-	-
	5.7	-	-	-	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-
	5.8	-	-	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-
	7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
	9.1	-	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	
	11.2	-	-	-	-	-	-	-	-	✓		-	-	-	-	-	-	✓
	11.3	-	-	-	-	✓		-	-	✓		-	-	-	-	-	-	
	11.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	11.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	11.9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Ap1	-	-	-	✓	✓	✓	✓	✓	-	-	✓	-	-	-	-	-	-
Acton and Stark (163)		-	-	✓	✓	✓	✓	✓	✓	-	-	✓	-	-	-	✓	-	✓
Bishop *et al.* (164)		-	-	✓	-	✓	-	✓	-	-	-	-	-	-	-	-	-	✓

Author (and subchapter no. when applicable)	FET	Directed cough	ACBT	AD	PEP	OPEP	Percussions /Vibrations	Postural drainage	Positioning	HFCWO	Physical activity	NIV	IPPB	MIE	IPV	Simeox	Inhaled medication
Butler and Sutherland (165)	-	-	✓	-	✓	✓	✓	✓	✓	✓	✓	-	-	-	-	-	-
Button *et al.* (166)	-	-	✓	-	-	-	-	✓	-	-	✓	-	-	-	-	-	-
Button (167)	-	-	✓	✓	✓	✓	✓	✓	✓		✓	✓	-	-	-	-	✓
Chang *et al.* (216)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Currie *et al.* (169)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Daniels (95)	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	-	-
Davidson (170)	✓	-	✓	✓	✓	✓	✓	✓	-	✓	-	-	-	-	-	-	-
Dentice *et al.* (171)	-	-	-	-	✓	-	✓	-	-	-	-	-	-	-	-	-	✓
Dentice and Elkins (172)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Dwyer *et al.* (173)	-	-	-	✓	✓	✓	✓	-	-	-	-	✓	-	-	-	-	-
Egan *et al.* (174)	-	-	✓	✓			✓	✓	-	✓	✓		-	-	-	-	✓
Elkins and Dentice (175)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Fitzgerald *et al.* (176)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Flume *et al.* (94)	-	-	✓	-	✓	✓	✓	✓	-	✓	✓	-	-	-	-	-	-
Flume (177)	-	-	-	✓	✓	-	✓	-	-	✓	-	-	-	-	✓	-	✓
Franks *et al.* (178)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hill *et al.* (179)	-	-	✓	✓	✓	✓	✓	✓	-	✓	✓	-	✓	-	✓	-	✓
Hill *et al.* (180)	✓	✓	✓		✓	✓		✓	-	✓	✓	-	-	✓	✓	-	-

Author (and subchapter no. when applicable)		FET	Directed cough	ACBT	AD	PEP	OPEP	Percussions /Vibrations	Postural drainage	Positioning	HFCWO	Physical activity	NIV	IPPB	MIE	IPV	Simeox	Inhaled medication
Hill *et al.* (181)		✓	-	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	-	✓	-	✓
Homnick (182)		✓	-	✓	✓	✓	✓	✓	✓	-	✓	✓	-	-	-	✓	-	-
Hoo *et al.* (92)		✓	-	✓	✓	✓	✓	-	✓	-	✓	✓	-	-	-	-	-	✓
Hristara-Papadopoulou *et al.* (184)		-	-	-	-	✓	✓	-	-	-	✓	-	-	-	-	✓	-	-
IPGCF (185)	2.1	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	2.2	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
	2.3	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
	2.4	✓	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
	2.5	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-
	2.6	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
	2.7	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
	2.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓	-	-
	2.9	-	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	2.10	✓	-	-	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-
	2.11	✓	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
	4	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	-
	6	-	-	✓	-	-	-	-	-	-	-	-	✓	-	-	-	-	-

Author (and subchapter no. when applicable)		FET	Directed cough	ACBT	AD	PEP	OPEP	Percussions /Vibrations	Postural drainage	Positioning	HFCWO	Physical activity	NIV	IPPB	MIE	IPV	Simeox	Inhaled medication
	9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	13	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-
Lannefors *et al.* (186)		-	-	-	✓	✓	-	-	✓	-	-	✓	-	-	-	-	-	✓
Lee *et al.* (187)		-	-	✓	-	✓	✓	-	-	-	-	✓	-	-	-	-	-	✓
Lee *et al.* (68)		-	-	✓	✓	✓	-	✓	✓	-	✓	✓	-	-	-	-	-	✓
Lester and Flume (188)		-	✓	✓	✓	✓	✓	✓	✓	-	✓	✓	-	-	-	✓	-	-
Main *et al.* (189)		✓	✓	✓	✓	✓	✓	✓	✓	-	✓	-	-	-	-	-	-	-
Main *et al.* (190)		-	-	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	-	✓	-	-	✓
Marks (191)		-	-	-	-	✓	✓	-	-	-	-	-	-	-	-	✓	-	-
McCool and Rosen (192)		✓	-	-	✓	✓	✓	✓	✓	-	-	-	-	-	-	-	-	-
McIlwaine *et al.* (193)		-	-	-	-	✓	✓	✓	✓	-	✓	-	-	-	-	-	-	-
McIlwaine *et al.* (56)		-	-	-	-	✓	✓	✓	✓	-	✓	✓	-	-	-	-	-	-
McIlwaine *et al.* (194)		✓	✓	✓	✓	✓	✓	✓		-	✓	✓	-	-	-	-	-	-
Milla *et al.* (195)		-	-	-	-	-	-	-	-	-	✓		-	-	-	-	-	-
Myers (196)		-	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-
Oberwaldner (197)		-	-	-	-	✓	-	✓	✓	-	-	-	-	-	-	-	-	-

Author (and subchapter no. when applicable)	FET	Directed cough	ACBT	AD	PEP	OPEP	Percussions /Vibrations	Postural drainage	Positioning	HFCWO	Physical activity	NIV	IPPB	MIE	IPV	Simeox	Inhaled medication
Olsen *et al.* (64)	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
O'Neill *et al.* (198)	-	-	✓	✓	✓	✓	-	✓	-	-	✓	-	✓	-	-	-	✓
O'Neill *et al.* (199)	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	✓
O'Neill *et al.* (200)	-	-	✓	✓	✓	✓	-	-	-	✓	-	-	-	-	-	-	✓
Palma *et al.* (201)	-	-	-	-	-	-	-	-	-	-	-	-	-	✓	✓	-	--
Pasteur *et al.* (116)	-	-	✓	✓	✓	✓	✓	✓	-	✓		✓	✓	-	-	-	✓
Pembridge and Chalmers (202)	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	✓
Phillips *et al.* (203)	✓	-	✓	-	-	✓	-	-	✓	-	✓	-	-	-	-	-	-
Prasad and Main (204)	-	-	-	✓	✓	✓	✓	✓	-	✓	✓	-	-	-	✓	-	-
Rowbotham and Daniels (205)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Schechter (206)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Schofield *et al.* (62)	✓	-	✓	✓	✓	✓	✓	-	-	✓	✓	-	-	-	-	-	-
Southern *et al.* (207),	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Spinelli *et al.* (208)	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
Spinou (209)	-	-	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	-	-	-	-
Terlizzi *et al.* (210)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Treacy (211)	-	-	-	-	-	-	✓	✓	-	✓	-	✓	-	-	-	-	-
van der Giessen (212)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓

Author (and subchapter no. when applicable)	FET	Directed cough	ACBT	AD	PEP	OPEP	Percussions /Vibrations	Postural drainage	Positioning	HFCWO	Physical activity	NIV	IPPB	MIE	IPV	Simeox	Inhaled medication
Van Der Schans (213)	✓	-	-	✓	✓	-	✓	✓	-	✓	✓	-	-		-	-	-
Volsko (93)	-	-	✓	✓	✓	✓	✓	✓	-	✓	✓	-	-	✓	✓	-	-
Walicka-Serzysko *et al.* (214)	-	-	-	-	✓	✓	-	-	✓	-	-	-	-	-	-	-	✓
Wilson *et al.* (217)	-	-	✓	✓	✓	✓	✓	-	✓	-	✓	-	-	-	-	-	✓

Twenty-nine considerations for personalisation were grouped into seven broad categories: the patient's physical and psychosocial factors, the ACT type (Table 6), procedure and duration, the individual patient's response to the intervention, and the provider.

Patient factors

The consideration of patient's physical factors was discussed in a total of 87 documents: age (n=47), disease type (n=16), disease stage or severity (n=42), clinical respiratory signs, for example radiological appearances and lung function (n=72), clinical non-respiratory signs, for example gastroesophageal reflux (n=36), and other medications such as nebulised antibiotics (n=4).

Psychosocial factors were discussed in 72 documents; patient preference (n=52), treatment burden (n=47), the individual's ability to engage with treatments (n=33), adherence (n=32), and lifestyle (n=18).

Intervention factors

Personalisation of aspects of the ACT regimen featured in all documents. Most commonly, consideration was given to the type of ACT intervention used (n=91). Factors that may influence the type of ACT intervention chosen featured in 70 documents; the physical resources required for the intervention such as device cost (n=42), difficulty to perform (n=12), physiological properties of the intervention (n=24), specific device features for example the patient interface (n=28), environmental aspects relating to the appearance of the device such as the noise it produces (n=13), recognised contraindications or precautions of certain interventions (n=28).

Adapting elements of the procedure, or how the patient performs the ACT was also commonly advised (n=69); combining multiple ACT interventions within the same session (n=49); sequencing or timing of interventions (n=22); device settings, such as the resistance (n=25), number of repetitions of regimen components (n=15), and "patient technique" (n=24).

Titrating the frequency or duration of ACT regimens each featured in 32 documents. With some overlap between these elements, this "dosage" component of personalisation was identified in a total 41 documents. Additionally, one paper reported varying the dose of ACT adjunctive inhaled medications.

Response

The use of individual response to personalise ACT regimens featured in 53 documents; modifying the regimen during the initial set up or during a session (n=38), modification based on response

after multiple treatment sessions (n=27), assessing for adverse effects (n=13). Assessing how a patient responds involves assessing clinical respiratory signs amongst other things, but these have been included as a separate component of personalisation due to the temporal nature of tailoring based on outcome.

Provider

The influence of the provider on the ACT regimen was discussed in 23 documents, either in terms of the experience of the individual clinician (n=12); or the characteristics of the institution (n=18).

The factors influencing clinician treatment choice were reported in two survey-based documents. Clinical decision processes to guide ACT personalisation featured in two documents, presented as algorithms.

Table 6: Aspects of ACT personalisation which were identified within each of the included publications. The aspects are categorised into overarching ACT personalisation factors. Where a publication was assessed by subchapter, details are provided by subchapter within the author column.

Author		Patient factors		Intervention factors			Response	Provider
		Physical	**Psychosocial**	**ACT type**	**Procedure**	**Dosage**		
ACPCF (65)	5.1	Age Disease severity Resp. signs	Preference Engagement Lifestyle Burden	Difficulty Contraindication/ precaution	Unit repetition Technique Multi-intervention	Duration	-	-
	5.2	Age Resp. signs	Engagement Burden	Physiology Device features	Unit repetition Technique Sequencing Settings Multi-intervention	Duration	Mid-ACT session Adverse effects	-
	5.3	Age Resp. signs	Preference	Physiology Device features	Technique Settings Multi-intervention	Duration	Mid-ACT session	-
	5.4	Age Resp. signs	Preference Adherence	Physiology Device features	-	-	-	-
	5.5	Disease severity	Preference Adherence Engagement	Resources	Multi-intervention	-	Adverse effects	-
	5.6	Disease severity Resp. signs	-	Resources Device features	Settings Multi-intervention	-	Mid-ACT session	-
	5.7	Age Disease severity Resp. signs Non-resp. signs	Engagement Burden	Contraindication/ precaution	Multi-intervention	-	Mid-ACT session	-
	5.8	Disease severity Resp. signs	-	Resources	Multi-intervention	-	-	-
	7	Age	Preference	Resources	Sequencing	-	Mid-ACT	Individual

Author		Patient factors		Intervention factors			Response	Provider
		Physical	Psychosocial	ACT type	Procedure	Dosage		
		Disease severity Resp. signs	Engagement Burden	Environment Device features	Multi-intervention		session Post-ACT session(s) Adverse effects	clinician Institution
	9.1	Disease severity Resp. signs	Preference	Device features	-	-	Post-ACT session(s)	-
	11.2	Disease severity Resp. signs Non-resp. signs	Burden Lifestyle	Physiology	Multi-intervention	-	-	-
	11.3	Resp. signs Non-resp. signs	-	Contraindication/ precaution	Technique	-	Adverse effects	-
	11.4	Resp. signs	-	Contraindication/ precaution	-	-	Post-ACT session(s)	-
	11.5	Resp. signs	-	Physiology Contraindication/ precaution	-	-	-	Institution
	11.9	Disease severity Resp. signs	Burden	-	-	Duration Frequency	-	-
	Ap1	Age Disease severity Resp. signs Non-resp. signs	Preference Adherence Lifestyle	-	-	Duration Frequency	-	Individual clinician Institution
Acton and Stark (163)		Age Disease severity Resp. signs	Adherence Engagement Burden	Resources Difficulty Device feature Environment	Unit repetition Multi-intervention	Duration Frequency	Mid-ACT session Post-ACT session(s)	-

Author	Patient factors		Intervention factors			Response	Provider
	Physical	Psychosocial	ACT type	Procedure	Dosage		
Bishop *et al.* (164)	Medication	Preference Burden	-	Sequencing	-	Post-ACT session(s)	-
Butler and Sutherland (165)	Age Resp. signs. Non-resp. signs	Preference Adherence Engagement Burden	Resources Difficulty Physiology	Technique	Duration Frequency	Mid-ACT session Post-ACT session(s) Adverse events	Individual clinician Institution
Button *et al.* (166)	Disease severity Resp. signs Non-resp. signs	-	Contraindication/ precaution	Unit repetition Settings	Duration Frequency	Mid-ACT session	-
Button (167)	Age Disease severity Resp. signs Non-resp. signs	Preference Engagement Burden	Resources Device features	Sequencing	Frequency	-	-
Chang *et al.* (216)	Age Disease severity Resp. signs	-	Resources	-	Frequency	Adverse effects	-
Currie *et al.* (169)	Resp. signs	-	-	-	Frequency	-	Individual clinician
Daniels (95)	Disease severity	Preference Adherence Lifestyle Burden	Resources Environment Contraindication/ precaution Device features	Settings Unit repetition Sequencing Multi-intervention	-	Mid-ACT session Post-ACT session(s)	-
Davidson (170)	Age Disease severity Non-resp.	Preference Adherence Engagement Lifestyle	Resources Difficulty Environment Device features	Multi-intervention	-	Mid-ACT session Post-ACT session(s)	Institution

Author	Patient factors		Intervention factors			Response	Provider
	Physical	Psychosocial	ACT type	Procedure	Dosage		
	signs	Burden				Adverse events	
Dentice *et al.* (171)	-	Preference Burden	Device features	Sequencing	-	Mid-ACT session	-
Dentice and Elkins (172)	-	Preference	-	Sequencing Multi-intervention	-	-	-
Dwyer *et al.* (173)	Disease severity Resp. signs	Burden	-	Settings	Duration Frequency	Mid-ACT session Post-ACT session(s)	-
Egan *et al.* (174)	Age Disease severity Resp. signs Non-resp. signs Diagnosis	Adherence Engagement Burden	Resources	-	Frequency	-	-
Elkins and Dentice (175)	Resp. signs	Preference Adherence Burden	-	Sequencing	-	Mid-ACT session	-
Fitzgerald *et al.* (176)	Resp. signs	-	-	Sequencing	-	Post-ACT session(s) Adverse effects	-
Flume *et al.* (94)	Age Disease severity Resp. signs Non-resp. signs	Preference Engagement Burden	Resources Environment Contraindication/ precaution Device features	Settings Multi-intervention	Duration Frequency	Mid-ACT session Post-ACT session(s) Adverse effects	-
Flume (177)	Disease severity	Preference	Resources Contraindication/	-	-	-	-

Author	Patient factors		Intervention factors			Response	Provider
	Physical	Psychosocial	ACT type	Procedure	Dosage		
	Resp. signs		precaution				
Franks *et al.* (178)	Disease severity Resp. signs	Preference Adherence Engagement Lifestyle	Resources	Multi-intervention Sequencing	-	Post-ACT session(s)	Individual clinician Institution
Hill *et al.* (179)	Disease severity Resp. signs Non-resp. signs	Preference Adherence Burden	-	Multi-intervention	Duration Frequency	Mid-ACT session	-
Hill *et al.* (180)	Disease severity Resp. signs	-	Resources	-	Frequency	-	Institution
Hill *et al.* (181)	Age Disease severity Resp. signs Non-resp. signs	Preference Adherence Engagement Lifestyle Burden	Resources Difficulty Environment Device features	Setting Multi-intervention Sequencing	-	Mid-ACT session	Institution
Homnick (182)	Age Disease severity Resp. signs Non-resp. signs	Preference Adherence Engagement Lifestyle Burden	Resources Environment	Multi-intervention	-	Post-ACT session(s)	Individual clinician
Hoo *et al.* (92)	Disease severity Non-resp. signs	Preference	Resources	-	-	-	Institution
Hristara-Papadopoulou *et al.* (184)	Age Disease severity	Adherence Burden	Resources Environment Device features	Setting	Duration Frequency	Mid-ACT session	-
IPGCF (185) 2.1	Age Resp. signs	Burden Preference	Resources Physiology	Unit repetition Technique	Duration Frequency	Mid-ACT session	-

Author		Patient factors		Intervention factors			Response	Provider
		Physical	Psychosocial	ACT type	Procedure	Dosage		
					Multi-intervention			
	2.2	-	Engagement	-	Technique	Duration	Mid-ACT session	-
	2.3	Age Resp. signs	Engagement	Physiology Contraindication/ precaution	Technique Multi-intervention	-	Mid-ACT session	-
	2.4	Age Resp. signs Non-resp. signs	Preference Engagement	Device features	Unit repetition Technique Setting Multi-intervention	Duration Frequency	Mid-ACT session	-
	2.5	Resp. signs	Preference Adherence Burden	Resources Difficulty Physiology	Setting Multi-intervention	Frequency Duration	Mid-ACT session	-
	2.6	Age Resp. signs Non-resp. signs Diagnosis	-	-	Unit repetition Technique Multi-intervention	-	-	-
	2.7	Age Resp. signs Disease severity Non-resp. signs	Engagement	Physiology	Setting Technique	Duration	Mid-ACT session	Individual clinician
	2.8	Resp. signs Non-resp. signs	-	Device features	Setting Physiology	-	-	-
	2.9	Age	-	-	Unit repetition Technique Multi-intervention Sequencing	Duration	Mid-ACT session	-

Author		Patient factors		Intervention factors			Response	Provider
		Physical	Psychosocial	ACT type	Procedure	Dosage		
	2.10	Age Resp. signs	Adherence Burden	Resources Physiology Device features	Multi-intervention	Frequency	-	Institution
	2.11	Age Resp. signs	-	Physiology	Multi-intervention	-	-	-
	3	Age Disease severity Resp. signs	Adherence Engagement	Device features Combination	Technique Sequencing Multi-intervention	-	Mid-ACT session	-
	4	Age Resp. signs Non-resp. signs	Burden	Physiology	Multi-intervention	-	-	-
	6	Disease severity Resp. signs	Burden	Device features Physiology	Setting Multi-intervention	-	-	-
	9	Resp. signs	-	Contraindication/ precaution	-	Duration	-	-
	10	Disease severity Resp. signs	-	Contraindication/ precaution	Technique	-	-	-
	11	Non-resp. signs	-	Contraindication/ precaution	-	-	-	-
	13	Resp. signs Non-resp. signs	-	-	-	-	-	-
Lannefors *et al.* (186)		Age Disease severity Resp. signs Non-resp. signs Diagnosis	Preference Adherence Engagement Lifestyle Burden	Contraindication/ precaution Device features Physiology	Settings Multi-intervention Technique	Duration Frequency	Mid-ACT session Post-ACT sessions	Institution

Author	Patient factors		Intervention factors			Response	Provider
	Physical	Psychosocial	ACT type	Procedure	Dosage		
Lee *et al.* (187)	Age Resp. signs Non-resp. signs	Preference Adherence Engagement Burden	Resources Difficulty Environment Contraindication/ precaution Device features Physiology	Settings Unit repetition Technique Multi-intervention	-	Mid-ACT session	-
Lee *et al.* (68)	Resp. signs Non-resp. signs	Preference	-	Multi-intervention	-	-	-
Lester and Flume (188)	Age Disease severity Resp. signs Non-resp. signs	Preference Engagement Lifestyle Burden	Resources Difficulty Environment	Settings Unit repetition Technique Multi-intervention	Duration	Mid-ACT session	Individual clinician Institution
Main *et al.* (189)	Age	Preference Burden	Resources	-	-	Post-ACT session(s)	-
Main *et al.* (190)	Age Disease severity Resp. signs Non-resp. signs Diagnosis	Preference Engagement Adherence Lifestyle Burden	Resources Difficulty Environment Contraindication/ precaution Device features Physiology	Unit repetition Sequencing Multi-intervention	Duration Frequency	Mid-ACT session Post-ACT session(s) Adverse effects	Individual clinician Institution
Marks (191)	-	Preference Burden Lifestyle	Resources Device features Physiology	Setting Unit repetition Multi-intervention	Duration	Mid-ACT session	-
McCool and Rosen (192)	Diagnosis	Burden	Resources Difficulty	Multi-intervention	-	-	-
McIlwaine *et al.* (193)	Age Disease severity	Preference	-	-	-	-	-

Author	Patient factors		Intervention factors			Response	Provider
	Physical	Psychosocial	ACT type	Procedure	Dosage		
	Resp. signs						
McIlwaine *et al.* (56)	Age Disease severity Resp. signs Diagnosis	Preference Engagement Lifestyle	Resources Physiology Device features Difficulty Contraindication/ precaution	Technique Multi-intervention	-	-	-
McIlwaine *et al.* (194)	-	Preference Burden	-	-	-	-	-
Milla *et al.* (195)	-	-	Device features	Setting	-	Mid-ACT session	-
Myers (196)	Resp. signs Diagnosis	Preference	Resources	Setting Technique Multi-intervention	Duration Frequency	Mid-ACT session Post-ACT session (s)	-
Oberwaldner (197)	Age Resp. signs Diagnosis	Engagement Adherence	Resources Contraindication/ precaution	Multi-intervention	-	-	-
Olsen *et al.* (64)	Disease severity Resp. signs Diagnosis	Preference Adherence	Resources Contraindication/ precaution Physiology	Setting Unit repetition Technique Multi-intervention	Duration Frequency	Mid-ACT session	-
O'Neill *et al.* (198)	Resp. signs	-	-	-	-	-	Individual clinician Institution
O'Neill *et al.* (199)	-	Burden	-	Sequencing	-	-	-
O'Neill *et al.* (200)	Age Disease severity Resp. signs	Preference Adherence Engagement Burden	Environment Physiology Device features	Multi-intervention	-	Post-ACT session(s)	-

Author	Patient factors		Intervention factors			Response	Provider
	Physical	Psychosocial	ACT type	Procedure	Dosage		
Palma *et al.* (201)	Non-resp. signs Diagnosis	-	-	Setting Multi-intervention	Duration Frequency	-	-
Pasteur *et al.* (116)	Resp. signs Diagnosis	Preference Adherence Lifestyle Burden	Resources Contraindication/ precaution	Sequencing Multi-intervention	Duration Frequency	Mid-ACT session Post-ACT session(s)	Individual clinician
Pembridge and Chalmers (202)	Diagnosis Resp. signs	-	-	-	-	-	-
Phillips *et al.* (203)	Age Resp. signs Non-resp. signs	Preference Adherence Burden	Resources Contraindication/ precaution	-	Duration Frequency	-	Individual clinician Institution
Prasad and Main (204)	Age Disease severity Resp. signs Non-resp. signs	Adherence Lifestyle Burden	Resources Contraindication/ precaution Physiology	Setting Unit repetition Technique Multi-intervention	Duration Frequency	Mid-ACT session	Institution
Rowbotham and Daniels (205)	Age Resp. signs Non-resp. signs Diagnosis	Preference Adherence Engagement Burden	Resources	-	Duration Frequency	Post-ACT session(s)	Institution
Schechter (206)	Age Resp. signs Non-resp. signs Diagnosis	Preference Adherence Engagement Lifestyle	Resources Contraindication/ precaution	-	-	-	-
Schofield *et al.* (62)	Age Resp. signs Non-resp. signs Diagnosis	Preference Engagement Burden	Resources Contraindication/ precaution Device features	Sequencing	Frequency	Post-ACT session(s)	Institution

Author	Patient factors		Intervention factors			Response	Provider
	Physical	Psychosocial	ACT type	Procedure	Dosage		
Southern *et al.* (207)	Age Disease severity	Preference Adherence Burden Lifestyle	-	-	Frequency	Mid-ACT session Post-ACT session(s)	-
Spinelli *et al.* (208)	Age Non-resp. signs Diagnosis	Engagement	-	-	-	Post-ACT session(s) Adverse events	-
Spinou (209)	Age Disease severity Resp. signs Non-resp. signs	Preference Adherence Engagement	Resources Contraindication/ precaution	Multi-intervention	Duration Frequency	Post-ACT session(s)	-
Terlizzi *et al.* (210)	Age Resp. signs Medication	Preference Lifestyle Burden	Resources	Sequencing	Frequency	Post-ACT session(s)	-
Treacy (211)	Resp. signs	Preference Burden	Resources	Setting Sequencing	Duration Frequency	Mid-ACT session Post-ACT session(s) Adverse effects	-
van der Giessen (212)	-	Preference Burden	-	Sequencing	-	-	-
Van Der Schans (213)	Resp. signs Non-resp. signs	Preference	Contraindication/ precaution Physiology	-	-	Post-ACT session(s)	-
Volsko (93)	Age Disease severity Resp. signs Non-resp. signs	Preference Adherence Engagement Burden	Difficulty Contraindication/ precaution	Setting Multi-intervention	-	Mid-ACT session Post-ACT session(s) Adverse effects	-

Author	Patient factors		Intervention factors			Response	Provider
	Physical	Psychosocial	ACT type	Procedure	Dosage		
Walicka-Serzysko *et al.* (214)	Age Disease severity Resp. signs Medication	Preference Adherence Engagement Burden	Resources Device features Contraindication/ precaution Environment	Sequencing Multi-intervention Technique	Drug dosage	-	-
Wilson *et al.* (217)	-	Preference	-	Sequencing	-	-	-

Recommendations for future research specifically pertaining to personalisation of ACTs were expressed in 18 publications, as summarised in Table 7.

Table 7: Summary of recommendations for future research in all publications. RCT= Randomised controlled trial.

Personalisation factor	Recommendation
Provider	Studies to understand international variation in the use of different ACTs (92).
Patient, Physical	RCT subgroup analysis and cross-sectional studies to identify physical factors or situations which may indicate efficacy of different ACT regimens (186, 189, 193, 204, 213). Studies with recruitment targeting people who the interventions are intended for (200). RCTs to evaluate the effects of ACTs during exacerbations (179). Trials to explore the efficacy of NIV as an ACT in people with CF with more severe disease or those who have recently been discharged from hospital (173). Studies to evaluate the safety and efficacy of ACTs in children and young people (186). Trials to identify biomarkers for subgroups of children with bronchiectasis who may benefit from muco-actives (216).
Patient, Psychosocial	RCT subgroup analysis and cross-sectional studies to identify psychosocial factors which may indicate efficacy of different ACT regimens (186). Trials to assess the variation in adherence to different ACTs (65). Studies should report validated measures of patient preference, cost-effectiveness and adverse reactions to assist consumer decision-making (193).
Intervention	Multicentre studies to determine subgroup of children with bronchiectasis who may benefit from muco-actives (216). Trials to understand the impact of timing of DNase on adherence, clearance and lung function (171). Studies to ascertain the efficacy of combining nebulisers and ACT devices (175). Studies on of the effects of different ACTs on different aspects of the pathophysiology of CF (193). Studies exploring ACT personalisation (200). Trials should provide sufficient detail of ACTs undertaken (64, 94).
Response	RCTs using appropriate outcomes; quality of life, exacerbations, symptoms, hospitalisations, days of school/work lost, lung function indices and adverse events (216). Studies with outcomes appropriate for the population (186). Development of outcomes which will be sensitive to differentiate the effects of different ACTs in children (189). RCTs to understand appropriate outcome measures for assessing the effects of ACTs in patients with more severe disease (179).
Time to follow up	Studies assessing the shorter-term effects of ACTs during exacerbations, or longer term effects in stable patients (193).

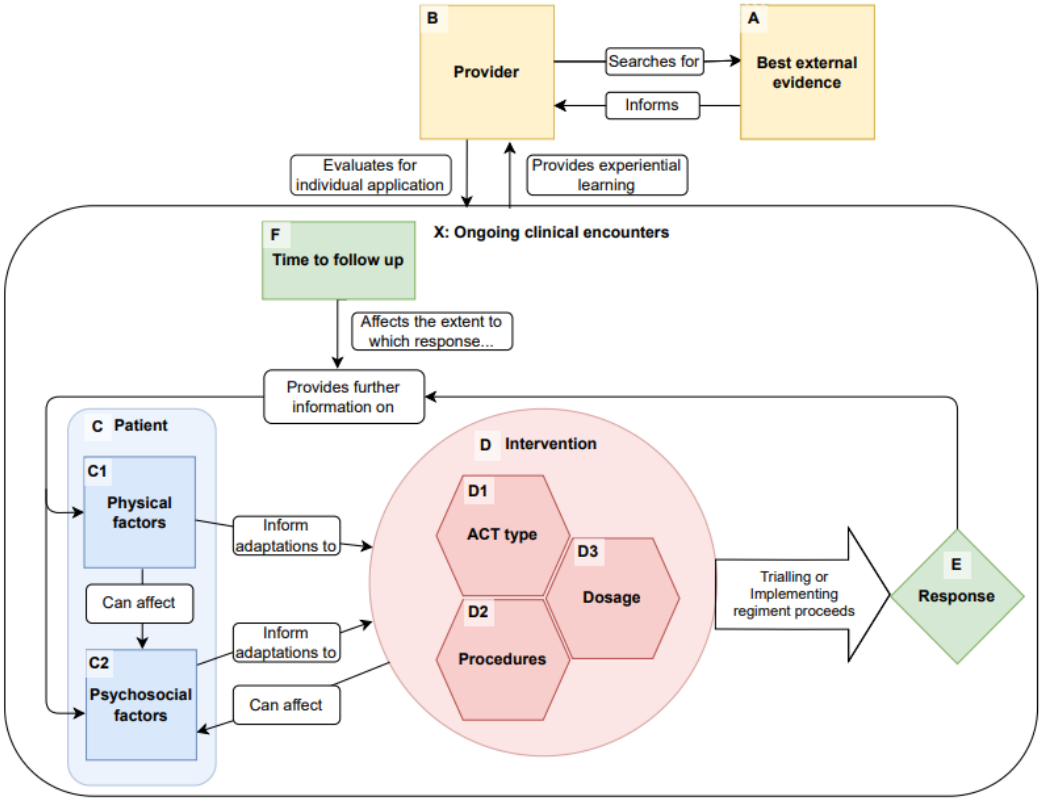
These results confirm the hypothesis, there are identifiable patterns in the literature on how to personalise ACTs for CSLDs (H1).

2.3.3 A model of *intervention refinement;* the ACT personalisation model.

The model developed from the findings is shown in Figure 12.

X . Ongoing clinical encounters

Everything in the rounded rectangle is a clinical encounter or a set of linked encounters concerning an individual patient. Klein's theory of naturalistic decision-making predicts that the expert perceives this as a *gestalt,* a complex whole which explores different types of relationships and interactions, using cues, actions, goals and expectancies as components of recognition (218).



A: Best external evidence = Published literature, Peer advice
B: Provider = Individual clinician, Institution
C1: Physical factors = Age, Diagnosis, Disease severity, Respiratory signs, Non-respiratory signs, Other medications.
C2: Psychosocial factors = Preference, Adherence, Engagement, Lifestyle, Burden.
D1: ACT type = Physiology, Device features, Resources, Difficulty, Environment, Contraindications/precautions.
D2: Procedures = Unit repetition, Technique, Settings, Multi-intervention, Sequencing.
D3: Dosage = Frequency, duration, medication dosage
E: Response = Mid-ACT, Post ACT(s), Adverse effects

Figure 12: ACT personalisation model version 0.1, derived from the findings of the scoping review and PPI feedback.

A. Evidence

Evidence based practice involves *"integrating individual clinical expertise with the best available external clinical evidence"* (219 p.71) (Relationship B>A). The clinician uses their expertise to assess the applicability of the evidence to the individual patient (219), linking evidence with known physiological properties of ACTs to meet individual patient needs (56) (Figure 12, Relationship A>B>X).

B. Provider

The provider encompasses the individual clinician working with the individual to devise a personalised ACT regimen, and the institution in which they are based (Figure 12).

This category incorporates the previous experience of the individual clinician and the institution which can influence ACT recommendations (203, 204). A provider may learn experientially from healthcare encounters (Figure 12, X>B) and carry forward that knowledge, as well as knowledge based on published research and guidelines (A>B) into future healthcare encounters (B>X). Working by analogy with studies on physiotherapist reasoning from outside of CSLDs, we can posit that clinician experience may influence the cues they distinguish as relevant when assessing a patient (X>B), either during the initial assessment or when reviewing their treatment response (220). Clinician experience and their institution may also influence the choice and method of application of ACT intervention (92, 203).

C. Patient

Patient has two key areas: physical and psychosocial factors.

1. Physical factors are a range of physical attributes of the patient, including their age, diagnosis, disease severity or stage, signs, and symptoms from both the respiratory system and other key multi-systems, and medications (Figure 12).

Physical factors provide the overall warrant for ACTs (93), and for selection of the components of ACT regimens (Figure 12, C1>D1 and D2) (56). A patients age can be an indicator of their ability to engage with treatments (C1>D) (221) and the physiological development of their lungs (56). Age, along with comorbidities such as pneumothorax or gastroesophageal reflux (GOR), may restrict the types of ACT interventions appropriate for use (C1>D1) (65), or the ways in which the interventions are completed (C1>D2). For example, the presence of GOR may affect the positions in which ACTs are completed (166). Physical factors may also moderate the frequency or duration of ACT required (C1>D3) (179) and ultimately, guide time to follow up (65). Medications which are not a component of the ACT

regimen, for example as inhaled antibiotics, can influence the timing of the ACT regimen (164).

2. Psychosocial factors

Psychosocial factors are a broad range of non-physical factors specific to the individual; patient preference, adherence, engagement, lifestyle (home environment, support structure, daily routine) and treatment burden (Figure 12).

These can prove to be facilitators or barriers to completion of ACTs, with patient preference and adherence being key components, potentially guiding ACT choice, procedures and timing (Figure 12, C2>D1 and D2), (95). An individual's ability to engage with treatment can also influence the ACT type, materials and procedures chosen (222) and the frequency or duration advised (65) (C2>D1 and D3).

Treatment burden, preference and adherence can all be impacted by components of the intervention (D>C2) such as the required duration (165) or the noise a device makes (95).

D. Intervention

Intervention has three key areas: ACT type, Procedure, Dosage.

1. ACT type

This encompasses the type of ACT intervention and any resources required to complete the regimen. It comprises the intervention’s physiological properties, features, the resources it requires, difficulty to complete, how it affects the immediate environment, and potential contraindications/precautions (Figure 12).

The ACT type may be selected for the underlying physiological properties it theorises to target, guided by physical factors (56) (Figure 12, C1>D1). Some ACT types can be more difficult to complete effectively and as such, elements of this may be influenced by cognitive or physical ability (65, 187) (C2>D1). Different ACT types have different equipment requirements, not limited to, cost, availability, cleaning and maintenance, electricity. ACTs may influence the environment around them as they may vary in size, appearance or make noise. This can affect patients preference and the choice of intervention may be influenced by how the ACT fits into a patient’s lifestyle (95) (D1>C2). Physical factors may also flag a contraindication or precaution to a certain intervention (203) (C1>D1).

2. Procedures

Procedures are the way in which the intervention is completed.

Personalisation here can involve; number of repetitions of certain components, the technique used, device settings, combining multiple ACT types within one session and the sequence of interventions (Figure 12).

The way in which a technique is employed can be varied; informed by physiological reasoning (64) (Figure 12, D1>D2), enabled by physical or cognitive ability (C>D2) and guided by response (223) (E>C >D2). Unit-repetition including number of breaths or FETs per cycle may be influenced by physical or psychosocial cues or response (185) (B/C>D2). Adjunct settings may be manipulated to target underlying physiological properties or a desired response. Different ACT types may be combined with the aim of incorporating their physiological strengths and the sequencing of these interventions may be based on known properties of the interventions, response, or patient preference (56, 222).

3. Dosage

Dosage relates to the frequency and duration of ACT completion (Figure 12). This may be influenced by physical or psychosocial factors/cues, such as disease severity (168) (Figure 12, C1>D3) or burden (65) (C2>D3), and could be modified based on treatment response (166) (E>C>D3). Different interventions may require different durations to achieve the goal of effective airway clearance which may affect patient preference and treatment burden (D3>C2). Prior knowledge of this may in turn influence ACT choice and procedures (187) (D3>D1/D2).

E. Response

Response is the outcome of trialling the intervention (Figure 12, D>E). This can be; immediate allowing for modifications to be made whilst the ACT session is in progress, at the end of a single intervention, or after the intervention has been completed numerous times (186) (Figure 12). Response also includes assessing for adverse effects (168)

F. Time to follow up.

The timing of the next review may be influenced by the context in which the review is taking place, for example, more frequent reviews usually occur during an inpatient admission compared to routine outpatient follow up. Knowledge of the time to the next review directly affects the time until the response is reassessed which in turn may influence the extent of changes made.

2.4 Discussion

This scoping review provides an overview of published approaches to personalisation of ACTs in CSLDs. Twenty-nine considerations for personalisation, grouped into seven broad areas, were extracted from 62 publications, mostly review papers, from 12 countries and presented in narrative, tabular form, and graphical form. These factors include: the individual's physical and psychosocial presentation; the intervention type, procedures completed with the intervention, frequency and duration of the intervention, the individuals' response, and the provider. The diversity of considerations involved in personalising ACT regimens illustrates the complexity of this field. As such, this review has provided an ACT personalisation model grounded in the published literature and feedback from people with CSLDs. These results confirm the hypothesis, there are identifiable patterns in the literature on how to personalise ACTs for CSLDs (H1).

2.4.1 The personalisation of ACTs regimens is complex.

The clinical presentation of people with CSLDs is changing in terms of the timing and specificity of diagnosis, exacerbation frequency, lung function (224) and survival rates (225). The impact of this upon clinical practice is already being seen, for example, there is debate over how asymptomatic infants with CF should be managed, following the introduction of new-born screening (226). As the needs of people with CSLD change, it is vital that physiotherapists can effectively navigate the personalisation of ACT regimens to allow them to be responsive clinical decision makers.

In his definition of evidence-based medicine as *"The conscientious, explicit and judicious use of current best-evidence in making decisions about the care of individual patients"* (p.71) Sackett *et al.* (219) implied that we should personalise care in the expectation of better outcomes. According to current literature, both a patient's physical condition including their disease severity, and an individual's response to their ACT regimen are important components of ACT regimen personalisation, with these two factors featuring in the majority of the documents. However, we know that the tools available to physiotherapists for assessing lung health and the effects of ACTs are currently limited (101). For example, routinely used lung function has poor agreement with structural changes assessed by CT scans (106). FEV_1 is also not is it likely to be sensitive enough to assess change brought about by modifications (101); previous research investigating the effects of a single ACT session on FEV_1 have shown either no response (103, 227), or a statistically, but not clinically significant response (113). Patient reported outcome measures such as the St George's Respiratory Questionnaire or Leicester Cough Questionnaire, may provide insight into the longer term outcomes of ACT regimens (227) but these questionnaires have all shown poor

sensitivity to change in PCD (228) and to date, the PCD specific quality of life score (229) has not yet been assessed in the context of ACT regimens. However, there may be a role for biomarkers, such as the percentage of ventilation defects within the lungs identified by hyperpolarised gas ventilation MRI which are more sensitive to detect abnormality than FEV_1 (133, 134) ,and have the potential to detect changes in lung health (125, 227). If patient's physical condition and their response to a regimen are key components of personalising a regimen, yet the available assessment tools available are inadequate, there is added complexity for clinicians advising patients on the optimal regimen. Thus, sensitive tools are needed to assess lung health (Chapters 4 and 6) and provide further certainty about whether ACT regimens are achieving the effects that physiotherapists expect (Chapters 5 and 6).

Some personalisation factors were found more commonly in the literature than others, raising the potential that some factors may carry more weight in clinical practice. During exacerbations, Phillips *et al.* (203) found clinical presentation and contraindications were ranked the most important by physiotherapists, but in the other contexts this may differ, for example Daniels (95) reports that adherence becomes the most prominent factor when choosing the timing of inhaled medicines. It is also likely that the factors are not discrete and that some factors may influence others. The most obvious example of this is adherence which is likely to be influenced by many other factors (95, 186).

In a complex field, this review imposed organisation on the data extracted by categorising the data into 29 factors (Section 2.3.2) and subsequently into an ACT personalisation model. Only two papers presented insight into possible ways to navigate ACT personalisation using algorithms. Van Der Schans (213) outlined a simplistic priority-based approach; first establish an effective regimen then address adherence. In contrast, Volsko (93) provided a more complex process, touring through treatment response, physical factors, assessing response, and finally adherence. As neither paper encompassed the breadth of factors that were identified in the initial article used in the pearl growing exercise (161), they were not used as the framework for data extraction. However, these papers highlighted that whilst organisation of factors may be beneficial to clinicians, the content and order of factors may be controversial.

Current guidance provided within CSLD literature on which factors should be prioritised is divergent: clinical presentation and contraindications (203); adherence in relation to the timing of inhaled medications (95); establishment of an effective regimen then address adherence (213); or, progression through previous response, physical factors, current response, then adherence (93). This review presents a model with ACT

personalisation as a cyclical process, which holistically incorporates all factors which may be relevant for an individual at the time, permitting the prioritisation of factors to be done by physiotherapists at a case-by-case level. This provides a key difference to previously published literature and facilitates the application of the model to all age groups.

2.4.2 Strengths and limitations

As a scoping review, formal assessment of the evidence quality was beyond the scope of this review (146). With many review papers in the field, it is likely that a systematic review with narrower inclusion criteria would have yielded fewer documents but allowed a greater review depth. Without appraisal of the quality of the evidence, it is not possible to establish if this may have influenced the personalisation model. Whilst testing the model in a clinical context is beyond the scope of this chapter, the model is stress tested in further chapters 3 and 6. This review did not attempt to explore the relative importance of individual factors, instead presenting them as inter-related components of a healthcare encounter or encounters.

Many of the aspects of personalisation could have been placed into different factors due to polysemy. One example of this is gastroesophageal reflux, which could either represent a co-morbidity, an intervention contraindication or precaution, or both. The levels of detail provided by authors to allow terms to be put into context varied, which has caused a risk of subjectivity and misinterpretation. Clear documentation of the factors influencing personalisation would aid clarity for readers of any future studies in this area.

The value of stakeholder involvement in complex situations (49), was realised here with the identification of an additional contextual component. The additional sweep confirmed that frequency of follow up was mentioned in the documents, but not specifically in the context of a factor to be considered when personalising regimens. As such, frequency of follow up does not feature as a formal factor within the scoping review but will be taken forwards as a contextual component for consideration within subsequent parts of this thesis. The data was reviewed by individuals with PCD and their parents, and therefore were not representative of the broader CSLD population. Further work with a more diverse PPI membership may facilitate further model refinements and strengthen the broader clinical application of the model.

Further primary research to understand *how* expert clinicians make clinical decisions on ACT regimens is needed as this is a complex field. In-depth interviews may demystify the how the factors identified in this review are prioritised in decision-making.

2.4.3 Further research is needed to understand how ACTs are currently personalised in clinical practice.

A number of recommendations for future research pertaining to ACT personalisation were found within the literature. There is a warrant for research to provide a better understanding of how to identify individuals who may respond well to certain ACTs regimen components (165, 186). ACT regimens are complex and there is a call for more transparent reporting of the regimens completed by study participants (64, 94), which the TIDieR checklist (162) would be well placed for. With known limitations of randomised controlled trials in airway clearance research (80), consideration should be given to trial designs which permit adaptation of interventions (230, 231) to facilitate exploration of personalised ACTs and research that is more reflective of physiotherapists' practice.

As a rapid review, the level of abstraction provided an overview of the factors involved in personalising ACT regimens. Further research could explore key areas in more detail, such as how clinicians assess the effectiveness of ACT regimens in the absence of sensitive outcome measures.

2.5 Conclusion

This scoping review has examined and summarised the current published literature pertaining to personalising ACT regimens in CSLD and has confirmed there are patterns in the literature on how to personalise ACTs for CSLDs, (Hypothesis 1), one component of our programme theory (Figure 13).

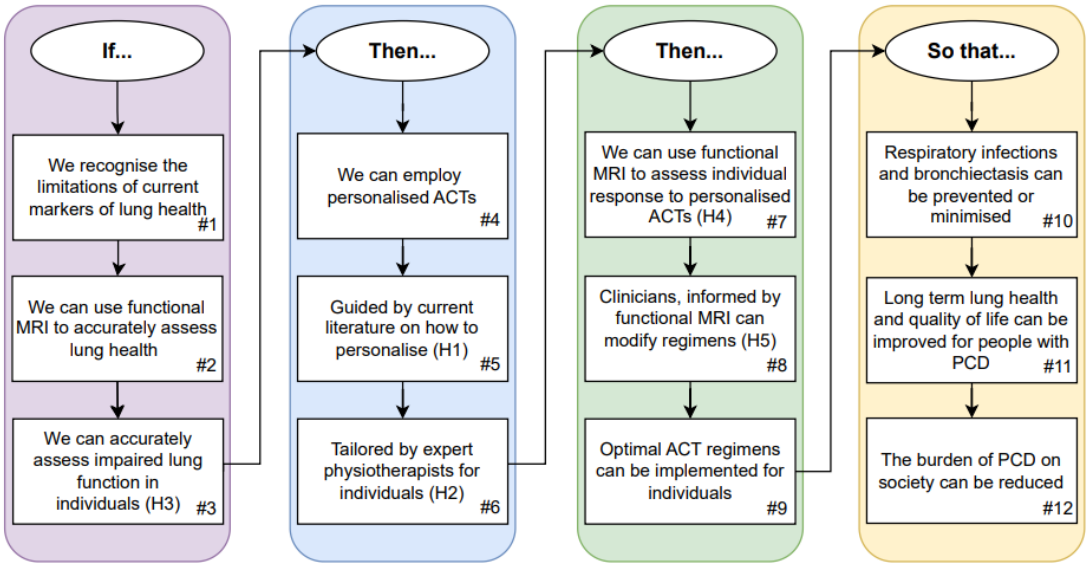


Figure 13: Programme theory for the thesis.

In this complex area, literature informs us that clinicians evaluate physical and psychosocial patient factors to select intervention components (ACT type, procedures, and dosage) which through their own experience allows them to recommend a personalised ACT regimen tailored to the individual patient's needs and circumstances; through monitoring of response, the regimen can be iteratively adapted through reassessment of the individual with the aim of recommending an optimal regimen. However, as current literature tells us, the tools to accurately assess lung health and the effects of regimens are limited (sections 1.4.1 and 1.4.3), clinicians may face uncertainty, trying to optimise effectiveness whilst managing treatment burden and patient preference. Whilst physiotherapists aim to improve patient's respiratory health and quality of life, key uncertainties remain:

- How do physiotherapist navigate personalisation? (Chapter 3)
- Is lung health in PCD heterogenous? (Chapter 4)
- Are personalised regimens having the desired effects? (Chapter 5)
- Would more accurate information on lung health from functional MRI aid physiotherapists' ACT regimen decision-making? (Chapter 6)

Chapter 3: The personalisation of ACTs in practice is a complex, iterative process; Cognitive Task Analysis (CTA) of semi-structured interviews.

3.1 Introduction and objective

Chapter 1 identified: with impaired mucociliary clearance in PCD, ACTs are a core component of PCD management; as there are numerous ACTs available and no one ACT is superior personalised ACTs are recommended; the tools available to assess the effects of ACTs in clinical practice are limited. Chapter 2 summarised the factors involved in ACT regimen personalisation: assessment of physical and psychosocial patient factors; selection of different components of potential interventions components (ACT type, procedures, and dosage); influence of the provider; time until the follow up review. The personalisation of ACTs is complex, and yet the tools to accurately assess the effects of regimens are limited, leaving uncertainty over whether ACT regimens are achieving their objective. It is unclear how physiotherapists proceed with implementing interventions and this thesis hypothesised: there will be identifiable patterns in how expert physiotherapists personalise ACTs for children and young people in practice (H2). We have confirmed that current literature tells us there are a range of factors which should be considered when personalising ACT regimens but that a knowledge gap exists (Chapter 2). This chapter aims to address a hypothesis, generated in Chapter 1:

H2: There will be identifiable patterns in how expert physiotherapists personalise ACTs for children and young people in practice (Table 2).

To test this hypotheses, we conducted a knowledge elicitation exercise with physiotherapists using cognitive task analysis to explicitly understand how ACT regimens are currently personalised.

Objective

1. To undertake a knowledge elicitation exercise with physiotherapists using semi-structured interviews and the critical decision method to understand how ACT regimens *are* personalised and assessed in practice.

3.2 Methods

Cognitive Task Analysis Methodology (CTA) is sometimes used in clinical settings (232, 233) to uncover how experts make decisions in complex situations. With various ACT interventions available and multiple personalisation factors found within the literature, this is an appropriate clinical context in which to employ CTA. Here, Critical Decision Method (CDM) which resides within the methodology of CTA is used to turn tacit knowledge into explicit knowledge (148).

3.2.1 Sample

Expert physiotherapists, with at least five years clinical experience, two of those in respiratory and who were working within the English paediatric PCD specialist centres were recruited for in-depth knowledge elicitation interviews. Potential participants were identified through the PCD physiotherapy professional network and invited to volunteer by an email distributed by LTHT's Research Governance Manager. A copy of the participant information sheet for clinicians is provided in Appendix 5.1. Theoretical data saturation is a point at which data analysis does not yield any new theoretical information (234). A target sample size of 6, an appropriate number for thematic saturation target in a homogenous group of experts (235) was achieved; six out of seven clinicians approached participated, one declined.

3.2.2 Interviews

Interviews were conducted by the lead researcher, who had both undertaken training on conducting interviews and prior experience of conducting qualitative interviews. An interview schedule (Appendix 4) based on the CTA four “sweep” approach depicted in Figure 14(148) was used to gain progressively more detailed information. Each physiotherapist was invited to suggest an appropriate example of where they made a complex decision regarding the personalisation of an ACT regimen for a child or young person with PCD. Participants were aware of this in advance, no specific guidance was given about preparing information for the interview, case notes were not accessed to verify the accuracy of the clinical case. Their example formed the basis of the rest of the interview, with the aim of eliciting information on how the clinician made this decision. The physiotherapists provided an overview of the case, which was used in the subsequent sweeps to drill down into further detail. The second sweep was used to provide a more detailed account to form a timeline and identify critical points within that timeline where the situation could have changed depending on the decision made at that time. The third sweep explored the physiotherapists’ perceptions, expectations, goals, judgments, and uncertainties about the case, particularly at the critical points identified in the second sweep. Interviewees were asked when making the decisions

what options were considered and what information was needed. The final sweep asked questions such as “what if.” This is an opportunity to take each point already discussed and allowed the interviewee to consider what they might have done differently, and if they had, what would have happened (148).

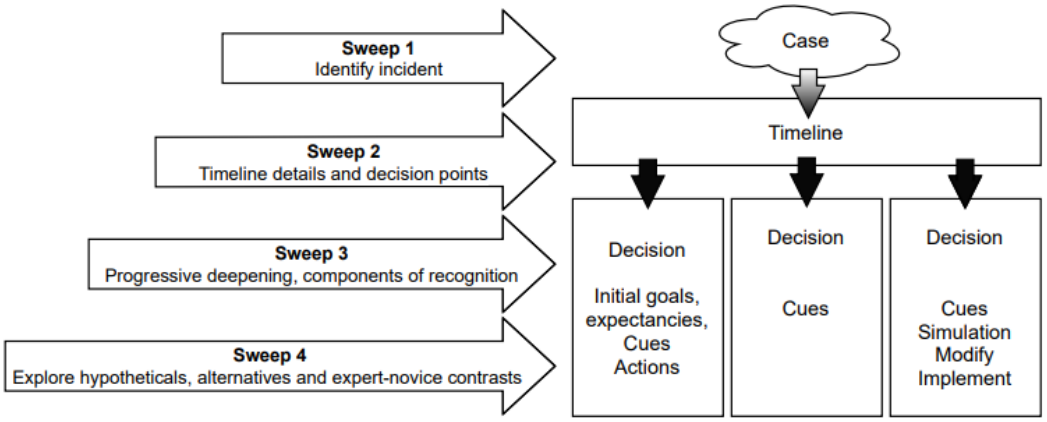


Figure 14 depicts a diagrammatic representation of the Critical decision method procedure, adapted from (148 p.74).

1:1 interviews were completed over Microsoft Teams and the audio recorded with an encrypted Dictaphone; interviews lasted between 55-100 minutes. Field notes were taken to assist with recounting the timeline back to the participant but did not form part of the analysis. Physiotherapists were assigned a unique ID number to maintain anonymity. As part of the consent process, participants were made aware that it may be possible to identify them from some of the information that they give as part of the interview, but that data would be reported anonymously, and no identifiable information would be reported. Basic demographic information collected comprised of; number of years of experience in respiratory care, number of PCD patients routinely under their care, subspecialty interest in PCD.

To increase rigour, member checking was used to assess if the timeline of the case reflected the experience of the research participant (236); following the interview, with prior agreement, participants were emailed and invited to review the initial timeline from their case and provide any feedback. Five of the six clinicians provided feedback to the lead researcher by email: three participants clarified details of the case and the timelines were adjusted accordingly; two felt no changes were needed.

3.2.3 Data analysis

Interviews were transcribed by the lead researcher and imported into NVivo for processing and identification of themes. Transcripts were coded to two highly relevant models: the recognition-primed decision model (RPDM) (218), an established model for exploring the decision-making of experts; the ACT personalisation model, a highly

relevant but novel model developed from the scoping review and PPI member feedback (Chapter 2). The RPDM (Figure 15) was initially selected as a highly relevant model, however during analysis it became apparent that the highly iterative nature of ACT personalisation resulted in a dense volume of data being coded to the “Will it work? Yes, but modify” loop of the RPDM. As using this model alone limited the analysis of excerpts arising from the highly iterative nature of ACT modifications, the ACT personalisation model (Figure 16) was used for secondary assessment.

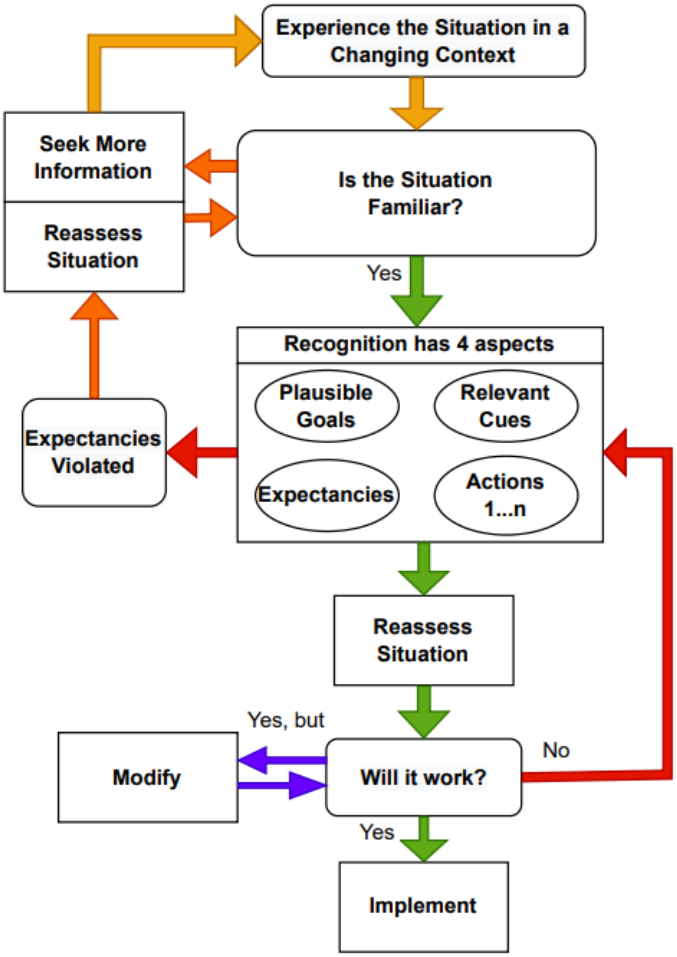
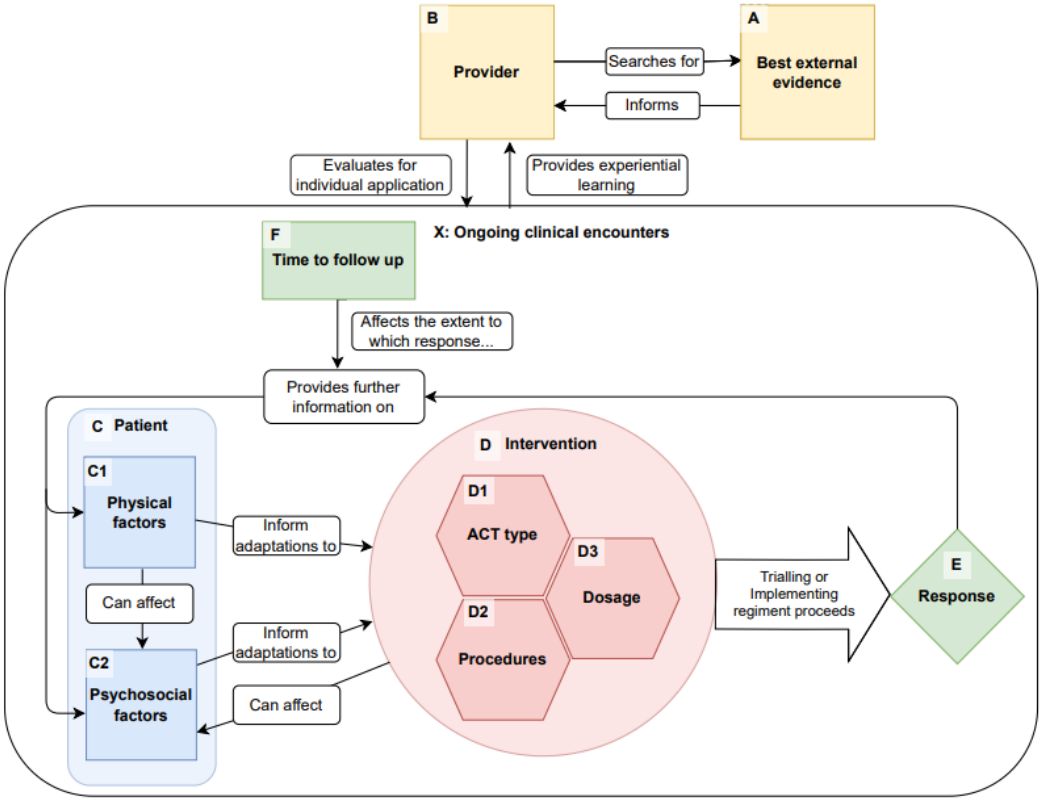


Figure 15: depicts Klein's recognition primed decision model (218).



A: Best external evidence = Published literature, Peer advice
B: Provider = Individual clinician, Institution
C1: Physical factors = Age, Diagnosis, Disease severity, Respiratory signs, Non-respiratory signs, Other medications.
C2: Psychosocial factors = Preference, Adherence, Engagement, Lifestyle, Burden.
D1: ACT type = Physiology, Device features, Resources, Difficulty, Environment, Contraindications/precautions.
D2: Procedures = Unit repetition, Technique, Settings, Multi-intervention, Sequencing.
D3: Dosage = Frequency, duration, medication dosage
E: Response = Mid-ACT, Post ACT(s), Adverse effects

Figure 16 The ACT personalisation model version 0.1 , developed in Chapter 2.

All coding and analysis, completed by the lead researcher and overseen by Professor Hind, followed the CTA phased analysis method (148):

- Preparation: review and complete data records, plan first data sweep.
- Structure data: data immersion, decomposition; coding, cataloguing, frequency counts and descriptive statistics.
- Discover meaning: identify central patterns, emergent threads of meaning and discrepancies using contrast and comparison of accounts.
- Represent key findings: communicate and display findings, using incident accounts, timelines.

For verification, PPI members were invited to provide feedback on a summary of the findings at a virtual PPI session. Findings were also triangulated with current literature within the discussion.

Following analysis of all transcripts, the ACT personalisation model and RPDM were integrated by:

- Using coding stripes in NVivo to identify sections of transcripts were coded to both models and sections which were only coded to one model at the level of the case.
- Identifying codes from both models which commonly occurred together across cases.
- Physical mapping of the RPDM stages to the ACT model in a workshop with Professor Hind.
- Testing of the revised model against the flow of decision-making in the interview transcripts.

3.2.4 Patient and publication involvement and engagement

The PPI group comprising young people with PCD, and their parents were consulted on the work in this chapter when the preliminary findings of the RPDM analysis were available. During an interactive session members were introduced to the RPDM through videos. Members suggested cues, actions, goals, and expectancies based on their experiences of ACT consultations, reviewed summaries of each of the cases and provided reflections on the findings. The cues, actions, goals, and expectancies they identified were used to verify the transcript coding. Their feedback on the case summaries provided an opportunity to triangulate the findings with real world experiences of ACT regimen consultations and physiotherapist decision-making from patient and parent perspectives. Their reflections offered alternative viewpoints that were explored during the discussion.

3.2.5 Chapter acknowledgements

The contributions for this chapter from the lead researcher, Lynne Schofield, are as detailed below:

- Study design conceptualisation,
- Development of participant information sheet,
- Securing NHS/HRA ethics approval and LTHT site approval,
- All data collection,
- All interview transcription,
- All coding and analysis,
- Integration of the RPDM and ACT model.

Acknowledgments for specific contributions are also given to:

- Anne Gowing, Research governance manager at LTHT for the initial approach of participants.

- Professor Dan Hind for guidance on study design conceptualisation, development of the study interview, overseeing of coding and analysis, and workshopping integration of the RPDM and ACT model. For guidance throughout planning, data collection and analysis.
- PPI members for data verification and providing feedback on results.

3.3 Results

3.3.1 Klein's Recognition Primed Decision Model helps describe clinician personalisation of ACT regimens, with reservations.

Timelines showing RPDM stages and decisional shifts for each case are shown in Figure 17**Error! Reference source not found.**. A cross-case analysis based on the RPDM is shown in Figure 18 and examples of transcript coding in Table 8.

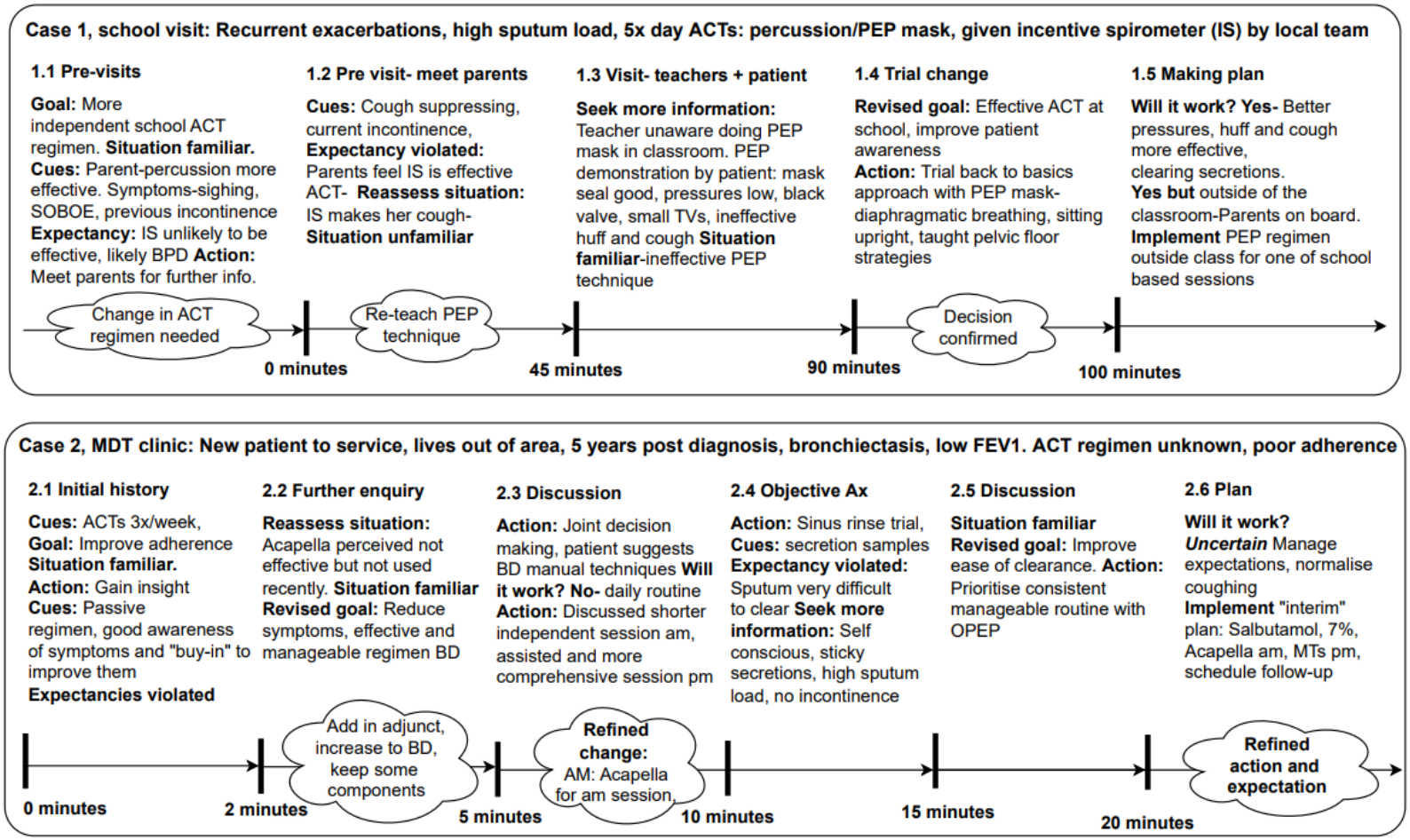


Figure 17: (part 1 of 3): Timelines illustrating an overview of RPDM stages (bold) and decisional shifts (clouds) for each case. BPD= breathing pattern disorder, IS= incentive spirometry, PEP= positive expiratory pressure, OPEP= oscillatory positive expiratory pressure, BD= twice daily, MTs= manual techniques, 7%= 7% nebulised sodium chloride, FEV_1= forced expiratory volume in one second, PCF= peak cough flow, FETs= forced expiratory techniques, I-time= inspiratory time, L=left, R= right.

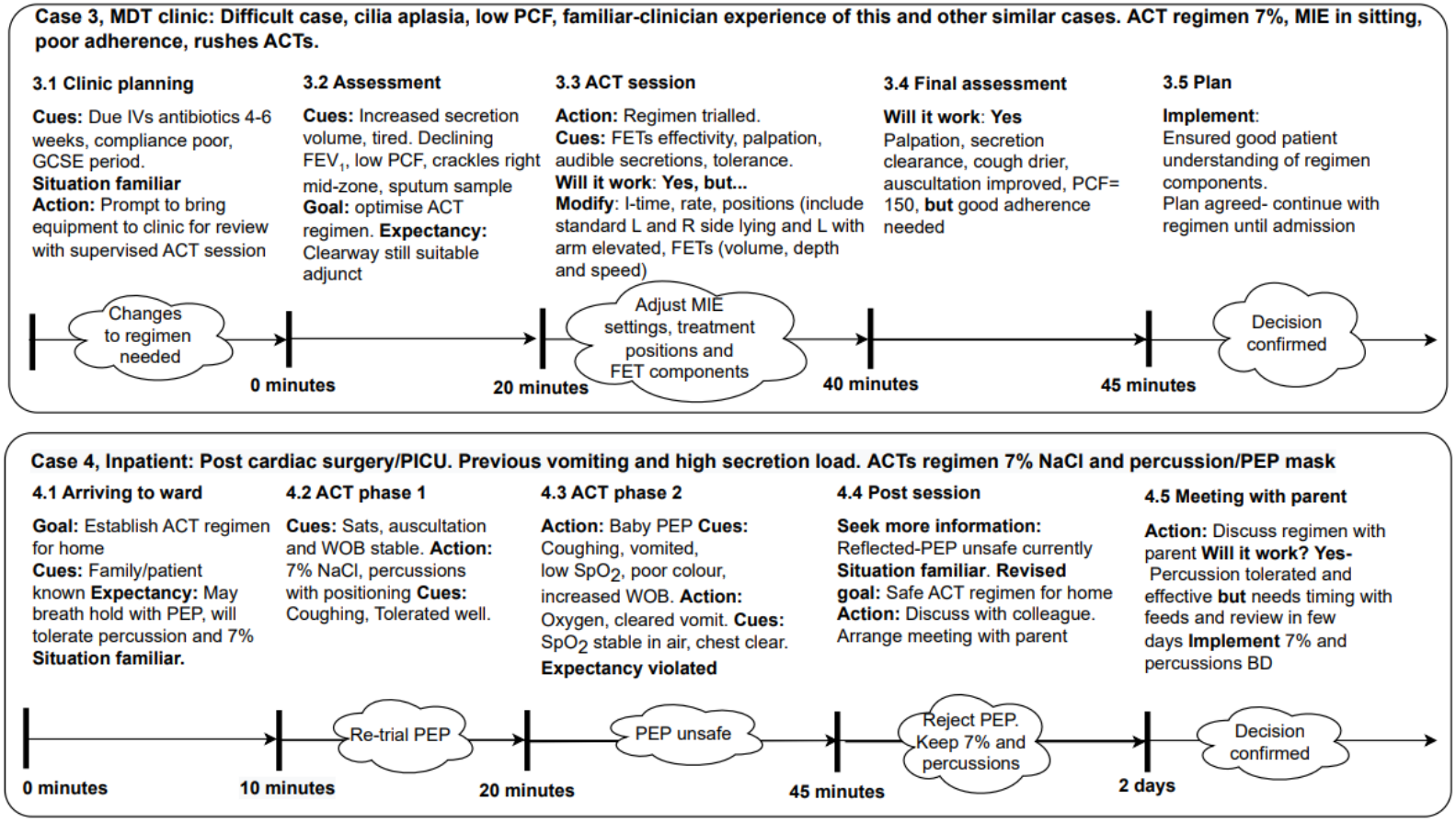


Figure 17 (part 2 of 3): Timelines illustrating an overview of RPDM stages (bold) and decisional shifts (clouds) for each case. MIE= manual insufflation-exsufflation, IVs= intravenous antibiotics, , PCF= peak cough flow, FET= forced expiratory technique, I-time= inspiratory time, PEP= positive expiratory pressure, WOB= work of breathing, SpO_2 = saturation of peripheral oxygen, BD= twice daily.

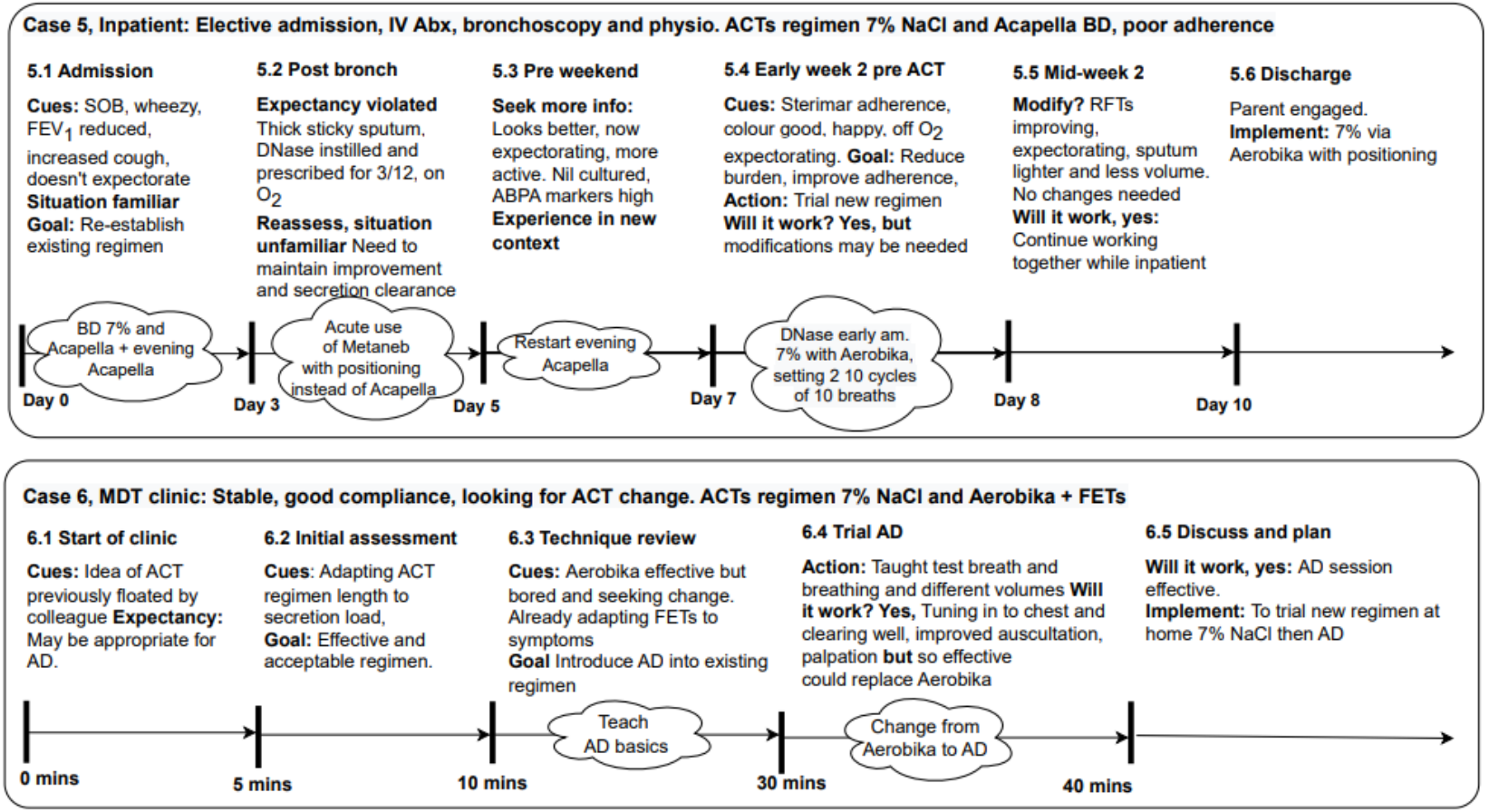


Figure 16 (part 3 for 3): Timelines illustrating an overview of RPDM stages (bold) and decisional shifts (clouds) for each case. SOB= shortness of breath, O_2= oxygen, ABPA= Allergic bronchopulmonary aspergillus. RFTs= respiratory function tests, AD= autogenic drainage, FETs= forced expiratory technique.

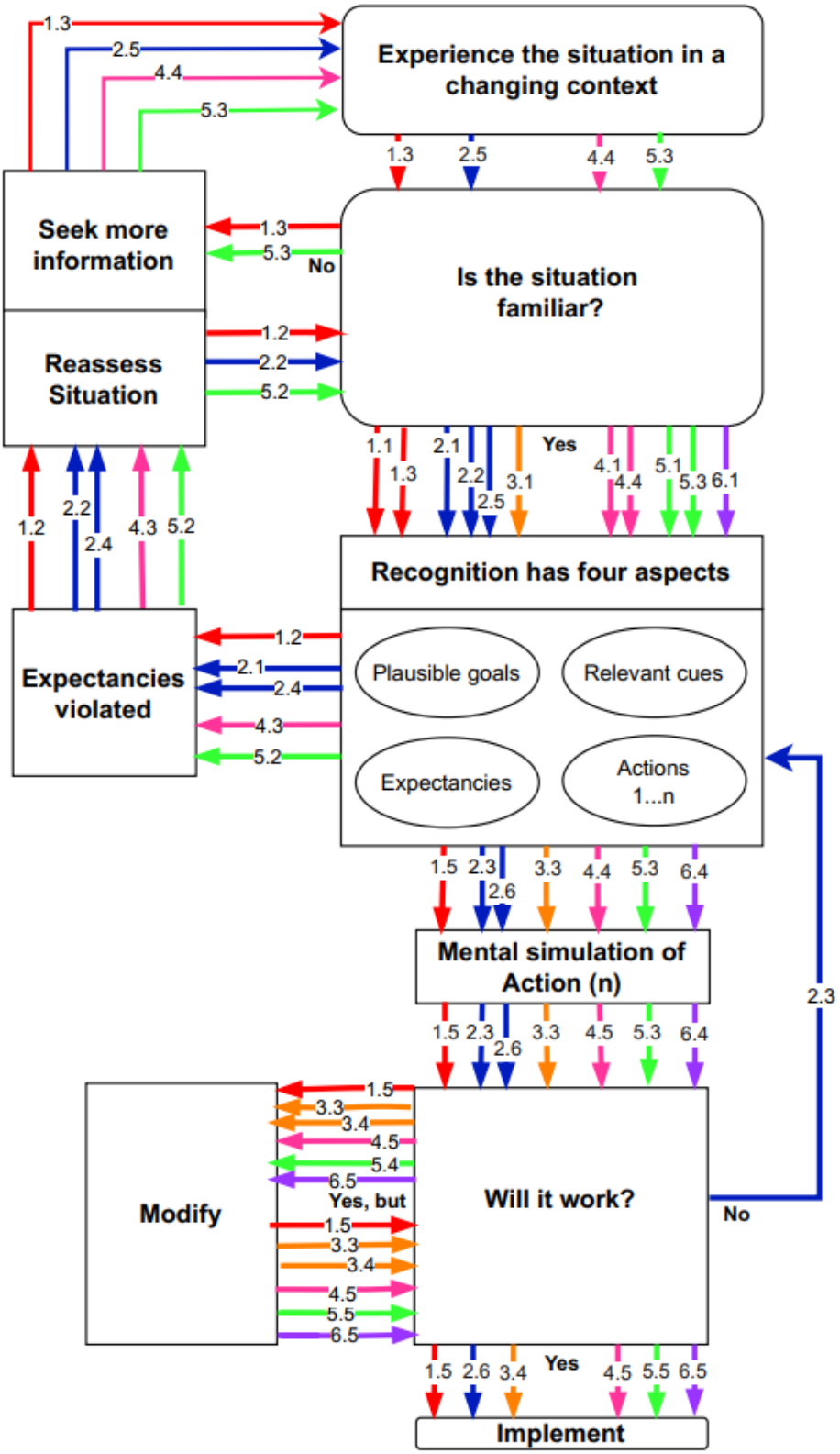


Figure 18: Cross-case analysis using Klein's recognition primed decision model (218).

Table 8: Recognition primed decision model codes with example excerpts from the interview transcripts.

Code	Excerpt
Cues (n=6)	*"He…struggles to complete treatments…as regularly as we would want him to… his lung function had dropped…he was quite crackly… in his…right mid zone on auscultation, he was clearing more sections, not discoloured or anything…* ***those key…assessment findings prompted me to kind of recognise that something needed to change"*** (Case 3.1).
Expectancies (n=6)	*"He had previously held his breath with it and hadn't tolerated having the (PEP) mask on so* ***I was more expecting him to not tolerate it."*** (Case 4.1)
Goals (n=6)	**"To get everybody into a nice routine** because this family were not doing what they were supposed to do." (Case 5.1)
Revised goal	***"I need to see that the Aerobika was going to be enough****…if it wasn't…then I would need to think; do I now need to go down the route of the Clearway®"* (Case 5.4)
Violation of expectancies (n=4)	*"I wouldn't normally give somebody an incentive spirometer for airway clearance, but Mum had…said that it was really helpful…so it was really interesting …to actually unpick that…****to actually work out what's going on."*** *(Case 1.2)*
Mental simulation (n=6)	*"The whole thing is great idea to wake up at half four in the morning and do physio, but* ***the reality is erm that's not going to happen"*** (Case 2.3)
Will it work? (n=6)	*"The volume of sputum that he was producing…his chest getting clearer…on palpation and auscultation…by the end of the session his chest was significantly clearer….****this form of airway clearance was effective"*** (Case 6.5)
Expert/novice contrast (n=6)	"***Often they'll miss that kind of need to act on something…they're just not attuned to*** *it…it takes…that level of experience"* (Case 3)
Tools/ Technologies (n=2)	*"What would be really great would be…(to)* ***image a patient****…(to)* ***actually see…what is actually happening with the airway clearance****…that would be ideal really just to be able to assess different airway clearance techniques"* (Case 6)

Consensus was seen across the cases in the early parts of the encounters. All clinicians found the situation familiar initially, even when the case was new to their service (Case 2). Pattern recognition was possible due to the identification of cues: frequent admissions despite a very high treatment burden, and shortness of breath (Case 1.1); late diagnosis of PCD, bronchiectasis, low FEV_1 and poor adherence (Case 2.1); cilia aplasia, regular IV antibiotics due, exam pressures and poor adherence (Case 3.1); an infant post cardiac surgery, prone to vomiting, with a sibling who struggles with adherence to PCD treatments (Case 4.1); minimal improvement with IV antibiotics at local hospital, for bronchoscopy due to deteriorating lung function, not expectorating secretions and poor adherence (Case 5.1); stable health, good compliance, good physical awareness in a patient who is already modifying their own ACT regimen (Case 6.1-6.2).

Plausible goals were based on initial cues: increase independence with airway clearance in school (Case 1.1); improve adherence (Case 2.1); optimise the home ACT regimen (Case 3.2); establish an ACT regimen for home pre-discharge (Case 4.1); re-establish the existing home ACT regimen (Case 5.1); implement an effective and acceptable home ACT regimen (Case 6.1)

Divergence between cases arose due to expectancies; they were upheld in two cases (Cases 3 and 6) but violated in four (Cases 1,2,4 and 5). When expectancies were violated, (Cases 1,2,4 and 5), initial courses of action were reconsidered : breathing patten dysfunction was initially suspected as the primary problem, but this was reconsidered when parents explained the incentive spirometer was effectively aiding their child's secretion clearance (Case 1.2); significant "buy-in" to improve symptoms was identified in a patient with poor adherence (Case 2.2); during the re-trial of a PEP mask the infant vomited and desaturated (Case 4.3); a bronchoscopy identified "cheese like sputum" and subsequently failed to culture any bacterial growth (Case 5.2-5.3).

When expectancies were violated, the situation was reassessed. In Cases 2 and 4, the violation of expectancies formed new cues, leading to refined goals and actions. An individual with good symptom awareness and motivation to improve symptoms changed the clinician's goal from improving adherence, to finding an effective regimen to reduce symptoms (Case 2.1). Reflection on the PEP mask session resulted in action to reject this component for the home ACT regimen (Case 4.4). Where further information was needed (Cases 1, 2 and 5), this information provided new cues, bringing familiarity to the situation. Information from a teacher and observing the PEP mask regimen provided insight that the patient was not completing their ACT effectively (Case 1.3). Asking the patient about barriers to sputum expectoration identified high volumes of sticky sputum and self-consciousness as limiting factors, rather than stress incontinence (Case 2.4). Although a bronchoscopy found very thick sputum, surprisingly nothing was cultured from the sample, so it was established that clearance of the thick sputum was very much reliant on an effective ACT regimen (Case 5.3)

Prior to implementing an ACT regimen, all specialist physiotherapists undertook mental or physical simulations of the proposed actions, satisfying themselves that the plan was sound. In most cases, this process led to modifications before the regimen was implemented (Cases 1, 2, 3, 4 and 6); the PEP mask remained the right adjunct to facilitate an independence, but refinements were needed, a "back-to-basics" approach focussing on technique, positioning to optimise pelvic floor control, and a private space for clearance (Case 1.4-1.5); Case 2 proposed her parent delivered manual techniques before school; the clinician recognised this was infeasible, and explored techniques

which could be completed independently (Case 2.3); the Clearway® was still an appropriate adjunct, but adjustments were made to the device settings, patient positioning, and FET depth and speed (Case 3.3); for a safe home regimen, communicating the importance of timing the ACTs around the infant's feeds to parents (Case 4.5); as Case 6's ability to utilise Autogenic Drainage (AD) surpassed expectations, instead of just adding AD concepts to their existing regimen, AD was to replace the Aerobika® in their home ACT regimen (Case 6.4).

Most expert physiotherapists felt novices would have taken a different path through the incident but the reasons for this varied: missing changes in symptoms or objective signs, as in PCD such changes can be subtle or have a gradual onset (Cases 1, 3, 4, 6); the "multisystem" approach of managing factors beyond the lungs may have been missed (Cases 2 and 4); not probing to acquire sufficiently detailed subjective information (Cases 1 and 3); not implementing changes to optimise regimens, in some cases due to confidence (Cases 1, 3, 5 and 6).

Clinicians were aware of the complex and iterative nature of personalising and optimising treatment regimens:

"If I change the way he's huffing, I'm going to have a different influence on secretions …that balance between…effort in a huff…and not kind of putting too much effort and closing…glottis or….airways …what it would sound like at a lower lung volume…what's secretions and what's airway collapse…that's treatment, but it's assessment as well isn't it, and I think that's quite complex" (Case 3).

"The goals…was to do something that was going to improve…her ease of clearance and…it's trying to work out what the cause was… during the course of an admission, you can sort of see that really clearly but it's sort of having a stab in the dark, but with I guess, with experience behind you" Case 2.

Clinicians had confidence in using their experience to guide their decisions. When asked hypothetically what additional information, tools or technologies could have helped, suggestions they highlighted the limitations of spirometry (Cases 1 and 3) and LCI (Case 3) and the potential role of MRI (Cases 3 and 6), and peer support was likely to be chosen over technologies (Case 5).

3.3.2 A literature derived ACT model describes much of the personalisation of ACTs.

The personalisation themes identified by the scoping review and PPI members featured within all interview transcripts (Table 9). Specific details of how the physiotherapists' modified regimens were isolated: the types of patient characteristics which were assessed; particular components of the intervention that were selected;

assessment of the individual's response to the ACT regimen; when the individual would be reviewed next; the influence of the physiotherapist as the provider of the recommendations. components provided greater detail on the nature of intervention modifications (all n=6)

The physiotherapists drew upon their assessment of a broad range physical characteristics: age, disease severity and pulmonary factors were described in all cases; consideration was given to PCD specific factors and other non-respiratory factors in most cases (both n=5); medications that were not used specifically for airway clearance in half of the cases. Physiotherapists also described taking the individuals' psychosocial factors into account during the ACT review: the individuals' lifestyle, adherence, and ability to engage with the ACT regimen was discussed in all cases; the burden of the ACT regimen on the individual and the patient's preference each featured in five of the six interviews.

All elements of the ACT regimen including ACT type, procedures and dosage were personalised to the individual in all cases. Physiotherapists selected or confirmed the ACT type was suitable for the case: considering how difficult the type of ACT intervention was to complete (n=4); whether the ACT was suitable for the environment where it would be completed (n=5); device features (n=4); mindfully assessing for any contraindications or precautions (n=4); working within available resources (n=5). The personalisation of intervention procedures included: combining multiple ACT types into one regimen (n=6) and ensuring the sequence of them was optimal (n=5); establishing the device settings (n=3); working to optimise the patient's technique (n=6); with either an individual set number of unit-repetition or working with the individual to teach them how to vary this depending on their symptoms (n=6). The dosage of the intervention was discussed in all cases, with the frequency and duration each in five interviews. The individual's response to the ACT regimen was assessed both during (n=5) and following the intervention (n=6), with specific awareness of an adverse response required during two reviews. In each case the physiotherapist considered when they would next have the opportunity or need to reassess the patient. The physiotherapists as the "provider" of the ACT recommendations described how their experience may influence their practice (n=6), and how location could also influence the regimen (n=4).

Table 9: Personalisation factors codes with example excerpts from the interview transcripts.

Factor/Sub-Factor (no of transcripts)	Excerpt
Patient	
Physical (n=6)	
Age (n=6)	*"Whether or not I…felt he was **the right age*** (Case 6)
Diagnosis (n=5)	***"In PCD you know that natural pattern** of the wet cough becoming more productive throughout the day* (Case 2)
Disease severity (n=6)	*"Most of our patients don't need to come into hospital you know **most are really well."*** (Case 3)
Extra-pulmonary (n=5)	*"He was…**struggling to maintain his weight** so that also fed into the discussion regarding timing."* (Case 4)
Other medications (n=3)	"How much of that was the ***steroids***, the prednisolone we don't know." (Case 5)
Pulmonary (n=6)	*"Our objective assessments is initially around….the lungs, so **auscultating, listening to the chest, looking at asking about sputum volume colour,** and things like that."* (Case 1)
Psychosocial (n=6)	
Adherence (n=6)	"*With this family the **compliance is a concern"*** (Case 4)
Burden (n=5)	*"It needs to be able to happen at home and they're already struggling so…. how am I going to make this **minimum effort** for them."* (Case 5)
Engagement (n=6)	*"If she's **anxious and…embarrassed** about coughing… I think that she's likely to have a much better technique somewhere private"* (Case 1)
Lifestyle (n=6)	*"The **social circumstances** surrounding the family and the difficulties that they have with airway clearance."* (Case 4)
Preference (n=5)	***"She actually prefers the…PEP mask** and so I you know I'd rather go with something that that she she's happy with as well."* (Case 1)
Intervention	
ACT type (n=6)	
Difficulty (n=4)	*"It is **a fairly complicated technique**…he might leave the consultation room and think "I don't know what she was going on about, I don't know how to do my physio." (Case 6)*
Environment (n=5)	*"What is and isn't appropriate for a parent to deal with **at home."*** (Case 4)
Features (n=4)	*"If we're combining, I normally do it with an Aerobika® because there's **less metal parts** in there."* (Case 2)
Physiology (n=4)	*"He needs something to…help him get a bigger breath and to kind of almost **augment that expiratory air flow."*** (Case 3)
Resources (n=5)	"*We're lucky that we have a set **equipment budget** for…PCD…sometimes you are constrained by what you have."* (Case 2)
Contraindication/ precaution (n=4)	*"With her increasing short of breath needing the inhaler a lot and I was wondering **whether the oscillatory bit was actually irritating** her…I did consider that beforehand, but…I thought if anything is irritating it's probably the 7%".* (Case 5)
Procedure (n=6)	
Multi-intervention (n=6)	"*An **AD approach to like huffing**… encouraging him to use his…**cough assist…in left side lying…and then some in***

Factor/Sub-Factor (no of transcripts)	Excerpt
	right side lying…with like his arm…elevated over his head." (Case 3)
Sequencing (n=5)	***"Manual techniques twice a day following his nebuliser***." (Case 4)
Settings (n=3)	*"With a* ***black resistor (PEP) valve."*** (Case 1)
Technique (n=6)	*"Thinking about* ***her shoulders, her position and where she is breathing from*** *while she's doing her physio*." (Case 1)
Unit repetition (n=6)	*"****Sets of ten breaths****."* (Case 6)
Dosage (n=6)	
Duration (n=5)	*"Some days...it would be clear in five sets of ten breaths, some days it would take* ***ten or 15 sets".*** (Case 6)
Frequency (n=5)	*"****Twice a day*** *to keep her airways clear."* (Case 2)
Response (n=6)	
Adverse effects (n=2)	*"****His colour had changed,*** *that* ***he was working a bit harder,*** *that he was gasping a little bit."* (Case 4)
Mid-ACT (n=5)	***"During his treatment*** *looking at how he's huffing and things, again I think that's quite a complex kind of you know thing to interpret you know whether you actually are achieving kind of the clearance that you're aiming to achieve"* (Case 3)
Post ACT (n=6)	***"If she's doing all of this airway clearance perfectly but she's still not clearing, can we add something else in"*** (Case 2)
Time to follow up (n=6)	When ***we might only see her once a year face to face***, it's trying to make those appointments meaningful (Case 2)
Provider (n=6)	
Experience (n=6)	"You naturally…grow up dealing with different cases and you take a bit from whatever you've done and take it forward, ***every experience good or bad you learn from it."*** (Case 5)
Location (n=4)	"*The incentive spirometer was given to her by a physio…during a fairly recent admission to* ***another hospital not by the team here"*** (Case 1)

Involving patients or their parents in decision-making or recognising the patient or parent as *stakeholders* featured as psychosocial factors in all cases; from choosing single components of the regimen, such as timing (Case 5), to patient-led regimen changes (Case 6). One additional *contextual* consideration; time, impacted on the decision-making process, but not the implemented regimen. Inpatient admissions provided more time (Cases 4 and 5): allowing further simulation prior to implementation (Case 5.4-5.5) and space for reflection, to re-evaluate existing information (Case 4.4). During clinics and visits, less time was available (Cases 1,2, 5 and 6). Regimen changes were still implemented, but clinicians used strategies to manage time pressures: during a double appointment for two siblings, a brief review of sibling A

allowed more time for the sibling B (Case 6); follow-up reviews were planned (Cases 1, 2 and 3).

These results confirm there are identifiable patterns in how expert physiotherapists personalise ACTs for children and young people in practice (H2).

3.3.3 Review of the RPDM and ACT personalisation models

The RPDM and ACT model provided detail on different elements of ACT personalisation. The RPDM permitted identification of how clinicians identified situations as familiar, when expectancies were violated and how these were managed, and formalised the steps of tacit decision-making prior to implementation. However, the complex nature of modifications made during the ACT review we more difficult to delineate. The ACT model provided a structure for more detailed analysis of the patient factors which were considered, the intervention components which were selected and the iterative process of response offering further information for the decision. The ACT model did not provide details of when expectancies were violated or how these instances were managed.

Mapping findings across the models by analysing the ACT model personalisation factors in the context of the RPDM, four factors were used by clinicians throughout all stages of the decision-making process: *physical, psychosocial, procedure and treatment response*. Personalisation factors were most commonly found within two stages of the RPDM: during recognition, both as cues and informing goals; and when considering “will it work?”. More divergence was seen for personalisation factors *procedure and intervention,* with different clinicians drawing on these factors at different stages of the decision-making process.

Analysing the components of the RPDM by mapping this to the ACT model as depicted in (Figure 19): patient physical and psychosocial factors were the *cues* obtained by the physiotherapist’s to identify *the situation as familiar*; *goals* were informed by individual patient factors (Box C), for example disease severity and adherence, and set in the context (Arrow B>X) of the “provider’s” *expectancies* (Box B); patient factors informed adaptations or prompted the physiotherapist to *modify* the intervention (Arrow C>D); trialling the regimen was the physiotherapist’s *action* (Arrows D>E and B>X); response provided further information on *will it work* (Arrow E>C); when *expectancies were violated*, it provided an opportunity for experiential learning (Arrow X>B).

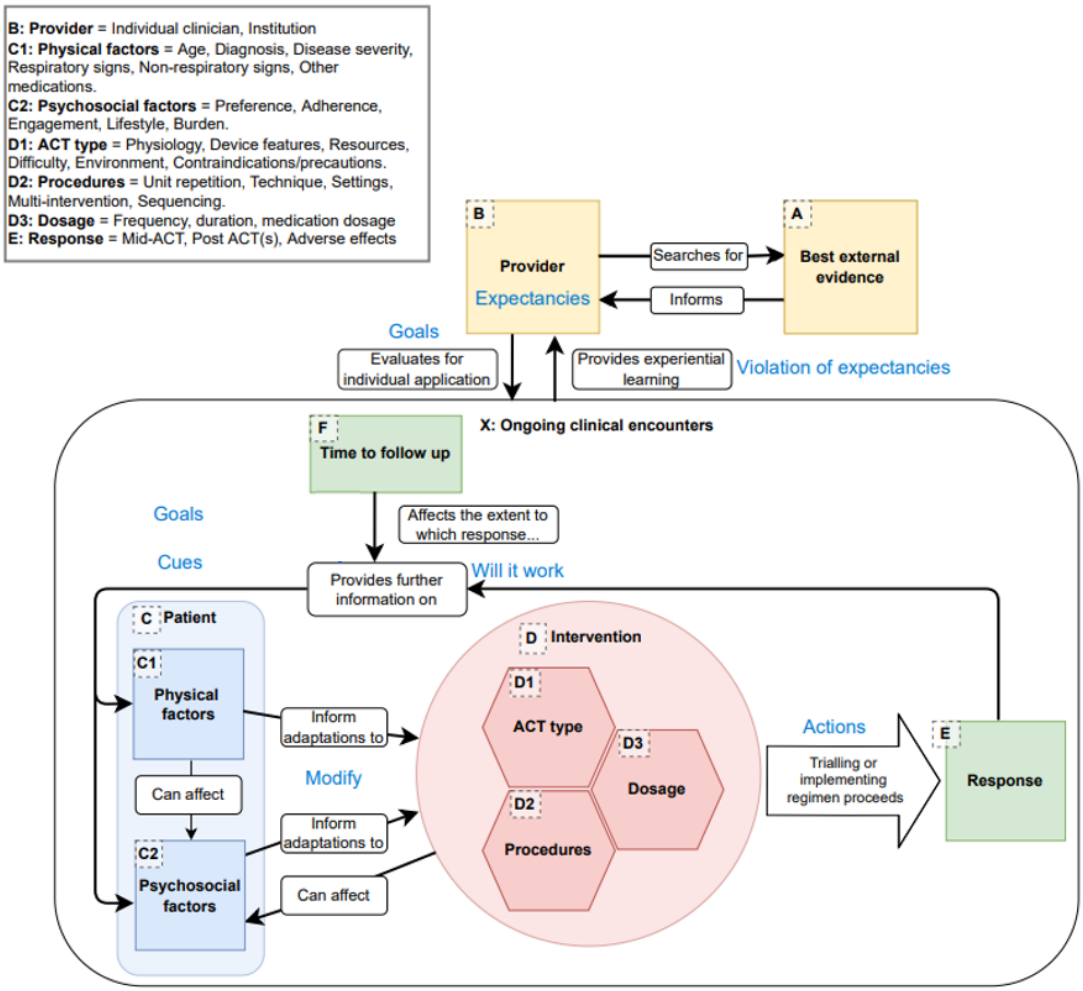


Figure 19: Working illustration of the mapping the RPDM to the ACT personalisation model. RPDM components were mapped onto relevant areas of the ACT personalisation model.

Informed by the mapping and content of the CTA interviews, the ACT personalisation model was revised to integrate the RPDM components and accurately reflect the iterative flow of ACT personalisation seen in the clinical decision-making of expert physiotherapists. The revised ACT personalisation model shown in Figure 20 was then taken forwards, informing subsequent work packages.

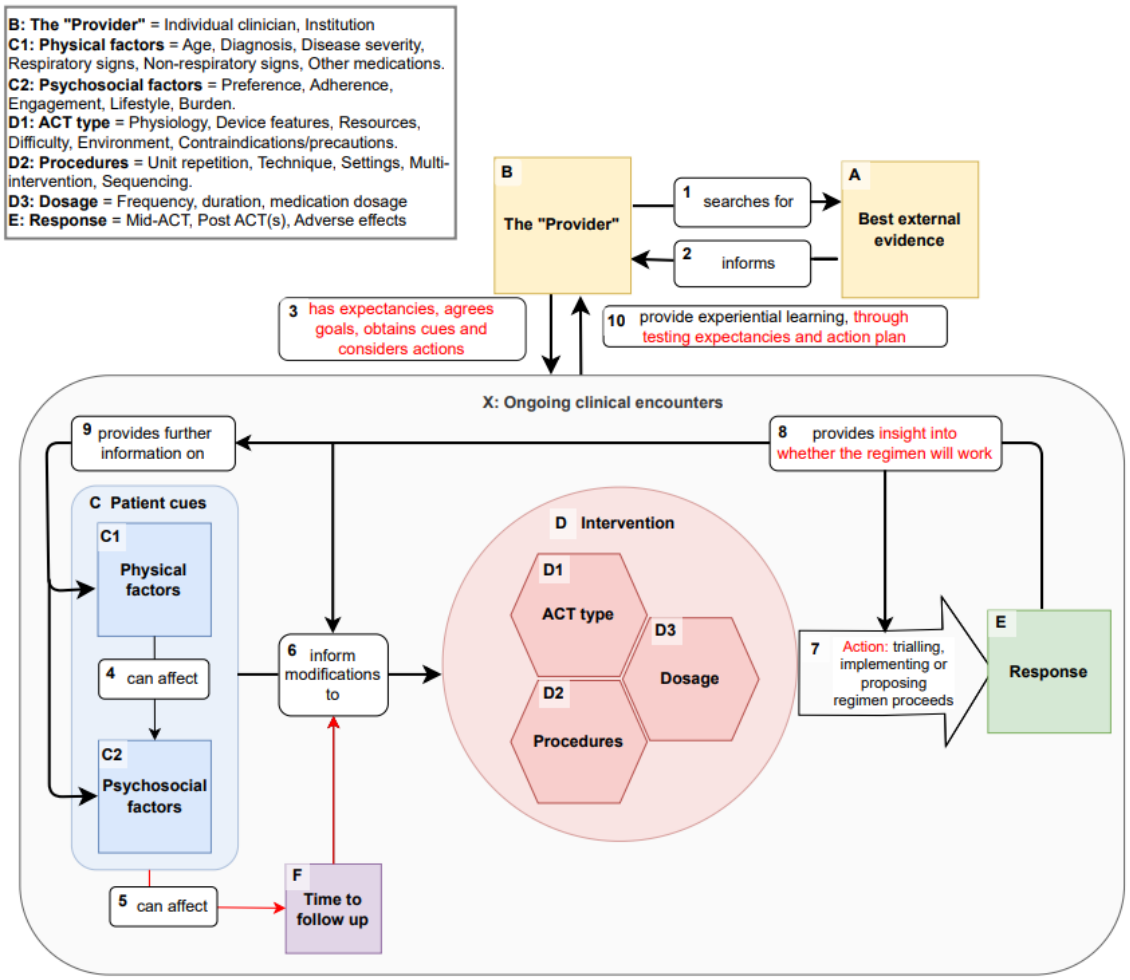


Figure 20: The updated ACT personalisation model (version 0.2). Changes from the previous version (0.1) are indicated by red text or arrows.

3.4 Discussion

This chapter provides information on how expert physiotherapists personalise ACT regimens. Employing the established critical decision method to explore a recent clinical ACT personalisation session in depth, permitted tacit decision-making to be made explicit. During ACT regimen reviews, expert physiotherapists commonly find the initial clinical situation as familiar even when they have not met the patient before, using patient cues to formulate goals for the session and plan a course of action. However, their initial expectancies are often violated, clinicians manage this seeking further information to revise their understanding of the case, and their goals or actions. Where possible the physiotherapists piloted the ACT regimen, or they mentally simulated the regimen to establish if it will work. Modifications were made to the ACT regimen prior to implementation.

Employing the ACT personalisation model developed in Chapter 2 permitted understanding of the modifications made to ACT regimens: a broad range of patient

characteristics are assessed to provide the clinicians with cues; all aspects of the intervention are considered to allow selection of the appropriate components for the individual and their circumstances; response, assessed either during or following the ACT regimen provides further information leading to an iterative cycle of modification; as the “provider” of ACT regimen recommendations, the physiotherapist is informed by their experience and may be influenced by their location.

These results confirm hypothesis H2, there are identifiable patterns in how expert physiotherapists personalise ACTs for children and young people with PCD in practice.

With two models providing different but to some extent overlapping perspectives on ACT personalisation, the ACT personalisation model was revised to integrate components of the RPDM. The updated model provides for the first time a more comprehensive picture of physiotherapy clinical decision-making in ACT regimen reviews.

3.4.1 Physiotherapists encounter and manage uncertainty to recommend personalised ACT regimens.

Expert physiotherapists were asked about how they personalise ACT regimens in difficult or non-routine cases, in order to elicit their tacit knowledge. This enquiry found that situations initially appear familiar to experts, but that uncertainty often subsequently arises. Uncertainty is common across healthcare settings, with treatment recommendations established as a specific opportunity for uncertainty (237). To implement a regimen, decision makers must manage uncertainty (148), common strategies for the management of uncertainty include reduction, suppression and acceptance (238). There were specific examples of the physiotherapists in this study employing such strategies: uncertainty was reduced through seeking more information (Cases 1.3, 2.4 and 5.3); uncertainty was suppressed by implementing an “interim” regimen when limited time was available (Case 2.5); uncertainty was accepted, weighing up the pros and cons of two approaches to implement a regimen (Case 4.4).

ACT regimens in PCD aim to effectively clear secretions and maintain long-term lung health, yet physiotherapists are required to assess if the regimen will work to make any necessary modification during a time-limited clinical encounter. Whilst mental simulation to establish if the regimen will work, a recognised feature of expert decision-making (218), may reduce uncertainty, the physiotherapists where possible piloted the ACT regimen which provided further reduction of uncertainty. The process of physically piloting the regimen provided physiotherapists with an opportunity to modify regimens, an opportunity which was used by most clinicians in this study. The anticipation of

potential problems has been identified as a strategy to reduce uncertainty by respiratory physiotherapists working in intensive care (239). Our physiotherapists drew upon their knowledge and expertise to anticipate potential problems: readily anticipating when psychosocial factors would result in a regimen not being completed (Case 2); and being guided by adverse effects to recognise when it would not be suitable to implement a regimen at home (Case 4). Both mental and physical simulation have requirements: time and equipment for physical piloting (Cases 1, 3, 4, 5, 6); expertise to provide experiences which can be drawn upon for mental simulation (240) and to identify relevant cues. As such, the assessment of will it work may be influenced by the individual clinician (241), and may prove more difficult for novices who may overlook important cues or lack the confidence to make a decision (Cases 1, 2, 3, 4, 6), (242).

Cues such as respiratory factors and disease severity are key components of ACT decision-making and at present, there is lack of sensitive tools to assess both lung health and the effects of ACT regimens (Section 1.5). The physiotherapists in this study recognised the limitations of current clinical tools such as lung function and auscultation. However, without a suitable alternative they manage uncertainty, utilising available information and bridging firm evidence of the effects of interventions with assumption-based reasoning (Table 8, “Will it work”). Without an accurate tool to assess the effects of ACTs, physiotherapists in this setting are managing the most common cause uncertainty in healthcare, a *“lack of information about the effects of treatments…long and short-term outcomes”* (243 p.306). Whilst evidence can provide a route to greater certainty (243), most physiotherapists struggled to identify potential tools or technologies which could aid decision-making, reflecting how familiar with uncertainty these experts have become. However, it may be possible to reduce such uncertainty through the provision of highly relevant information (238); two physiotherapists, both aware of the latter study methods, identified the potential of functional imaging to better understand the effects of ACTs.

3.4.2 A literature derived ACT model describes much of the personalisation of ACTs.

In Chapter 2, 29 factors were identified within current literature which may be considered by physiotherapists when tailoring ACT regimens to the needs and preferences of an individual (Chapter 2). Employing the ACT personalisation model which houses these factors for secondary analysis allowed a more context specific enquiry of the interview data and, an opportunity to stress-test the model.

The ACT personalisation model analysis found all physiotherapists drew upon a wide range of cues in their assessment, which was represented by the breadth of patient factors discussed in the context of their decision-making: the individual's age, diagnosis, disease severity, non-ACT medications, respiratory and non-respiratory signs, adherence, treatment burden, engagement, lifestyle, and preferences. Cues permitted them to consider many aspects of the intervention to select components tailored specifically for the individual: difficulty to complete the ACT, suitability for the environment it would be used in, underpinning physiology, device features, known contraindications and precautions, combining multiple components and sequencing of these, the patient's technique and number of repetitions, the frequency and duration of the ACT regimen. They mostly assessed the individuals' response, and all considered when they would next review them.

The content of the physiotherapy ACT personalisation reviews mapped closely to the findings of the scoping review, providing assurance that the scoping review reflects current clinical practice, and that ACT personalisation model provides a firm foundation for describing ACT personalisation. When coding to the ACT personalisation model it was possible to identify when the clinicians were drawing upon the best available evidence, without the RPDM it would have been difficult to establish transition points where clinicians stepped, sometimes briefly, out of the iterative tactic decision-making loop. Here, the RPDM provided greater structure for the identification of patterns of how the violation of expectancies disrupted the decision-making flow.

Seeking the perspectives of stakeholders is a key component of decision-making and the management of uncertainty (242), and in this study all physiotherapists involved the patient and/or their parent. This finding was not identified from the RPDM analysis, but from the analysis originating from the scoping review specifically through the psychosocial subfactor "preference". This illustrates the limitations of conceptual frameworks, whilst they provide clarity on relationships within the data, they are also limited and may highlight some aspects of the data whilst overlooking others (244). A process known as theoretical triangulation; using multiple frameworks, models or theories to consider the data (245) has added strength here, drawing together knowledge of naturalistic decision-making with ACT regimen personalisation literature. In this situation, clinicians are advising a carer-led, or self-management intervention in a long-term condition. Multiple experts or *stakeholders* are involved: the physiotherapist, patient, and carer. The clinician must integrate the viewpoints to implement a regimen that is acceptable to all. PPI members also reflected the importance of this, advising they would like to understand more about ACT options available and describing situations when relationships had not been optimal; when the

physiotherapist did not believe the adherence levels being reported; when a key component of the ACT regimen was unintendedly omitted for several years as the patient had believed it was no longer needed.

3.4.3 The revised ACT personalisation model represents the complexity of clinical decision-making in this clinical context.

CTA methodology is being increasingly used in healthcare settings, and CDM is a commonly used method of knowledge elicitation to understand how decisions are made under conditions of uncertainty (233). In this study whilst the CDM derived RPDM provided structure to analyse the decision-making of clinicians, the incidents did not all intuitively fit the model. Five out of six clinicians performed physical simulation of the ACT regimen when they had yet to commit to all components of the intervention. Whilst this process was aligned this with mental simulation phase of the RPDM to permit coding, the “modify” code was then required to capture rich data of iterative recognition informed modifications. Recognition of this limitation early in the analysis allowed scope for use of the ACT personalisation model to provide a complementary analysis. Approaching the analysis from two perspectives illuminated different aspects of the data (244), the strengths of each model supported the limitations of the other. Models should be progressed to incorporate new knowledge to better represent complexities in clinical decision-making (246). Integration of the RPDM into the ACT model has permitted the evolution of a more robust model which encompasses literature both two distinct fields, ACT personalisation and decision-making. Cardiorespiratory physiotherapy decision-making in acute care has been assessed using CDM by Thackray and Roberts (247) who developed a conceptual decision-making model. Comparing this model with the ACT personalisation model: both include assessment, evaluation of response and goals and reflect an iterative process; the model by Thackray and Roberts (247) place information processing, hypothesis testing and reflection in a balanced central role, whereas the ACT model provides more distinction between the task and the provider; the conceptual model of clinical decision-making in cardiorespiratory physiotherapy pertains to a broader clinical area, and the ACT personalisation model pertains to a more specific clinical context. As complementary models they align to promote the importance of understanding clinical decision-making in respiratory physiotherapy.

3.4.4 Strengths and limitations

The physiotherapists were asked to provide a recent clinical incident during which they had made an ACT personalisation decision. Using retrospective incidents may have caused inaccuracies or omissions in the case details, although the risk of this was

minimised by using non-routine cases (148). Information on the time period between the clinical encounter and interview was not captured and it is recognised that this data would have helped to rationalise the impact of recall. Case notes were not used to assess the accuracy of the case picture as the focus was on the decision-making process. As only one of six cases was new to the physiotherapist, most clinicians had knowledge of the case which pre-dated the decision-making incident. Decision-making in long-term condition management involves a series of decisions. Although time boundaries were set around the incident to maintain focus, the relevance of the ongoing clinician-patient relationship on decision-making, particularly expectancies and goals was difficult to qualify. This study sought to explore decision-making within a clinical encounter, exploration of longer-term decision-making in the cases was beyond the scope of this research question. Despite these limitations, using the RPDM provided a structure to explore how decisions are made in this complex area in which the patients are diverse and there are multiple paths to achieve the desired goal of effective airway clearance.

As the interviews were conducted by an expert physiotherapist, and a colleague of the physiotherapist participants, there is potential this may influenced both the data collection and analysis. Bracketing of prior beliefs and reflection were used to minimise the impact of this dynamic on analysis. Whilst participants were reminded of their anonymity would be maintained, it is possible that the physiotherapists may have filtered their responses to offer socially appropriate answers (248), especially in a niche clinical field. Data saturation was achieved from this small sample of six participants; fewer new concepts were identified as each case passed through analysis, and no new concepts were identified during analysis of the sixth case. As all participants worked as a part of the national PCD service, their practice shared commonalities. As practice is known to vary geographically and may be influenced by age and disease, future work could look to explore the personalisation of ACT regimens internationally, with adults and other CSLDs.

Whilst CTA can be used to understand decisions made by a team, this study only sought the views of physiotherapists, and as such the influence of patients and carers and the wider MDT within the decision-making process may have not been fully captured. Understanding the reasons for this was beyond the scope of this thesis, however, this finding is in keeping with previous studies, which reported that adolescents with long term conditions have varied preferences in how involved they wish to be in making decisions (249). This problem may mean that the CTA method, which was developed for rapid individual decisions in the face of environmental

challenges, may not be perfectly suited to protracted, iteratively revised shared decisions.

Triangulating between data sources is a criterion of trustworthiness in qualitative research (250). Here, the findings of the CTA interviews were triangulated with the findings of the scoping review and with PPI members, who described that although the cases differed to their own journeys, they were in keeping with clinical practice they have experienced. The agreements seen between the evidence base (scoping review), clinician perspectives (accounts of physiotherapists) and patient and parent perspectives (PPI group feedback) provides assurance in the findings. The scoping review considered how the specialty tells us ACTs *should* be personalised. This work package has built on this, using social science theory to illustrate how physiotherapists *do* make decisions about personalisation in naturalistic settings. It has identified that the personalisation of ACT regimens is not an event, but an iterative process that helps to manage the uncertainty that physiotherapists face.

The work in this chapter aligns the pragmatic view adopted for this thesis, described in Chapter 1. Using CTA to understand how physiotherapists make decisions in complex, real-world situations, it provides an important qualitative component to this mixed methods thesis. This reflects the pragmatist focus on understanding processes in context to inform practical action and resolve uncertainties. Exploring the limitations noted, such as the potential inaccuracies from retrospective recall and the difficulty fully capturing joint decision-making, show a pragmatic acknowledgement of the challenges of real-world research.

3.5 Conclusion

We know this is a *complex* situation: PCD is a heterogeneous condition in which mucus clearance is a problem (Section 1.2); ACTs are a core component of management, with multiple viable options to achieve the goal of effective clearance (1.3), therefore we *should* personalise ACT regimens. The scoping review amalgamated the current literature on what factors physiotherapists *should* consider when tailoring ACT regimens (Chapter 2, H1). This chapter has shown us how expert physiotherapists personalise ACTs (H2, Figure 8): using their experience to provide goals and expectancies, attending to key individual patient cues to select ACT regimen components; simulating the regimen to assess if it works; and refining the intervention to optimise it for the individual prior to implementation. Uncertainties are often encountered in ACT personalisation; expert physiotherapists manage by acquiring more information. However, clinicians are assessing lung function and the effects of ACT regimens with tools which are insensitive (1.4.1 and 1.4.3). Functional MRI may

provide information on lung health within the PCD population (H3) and accurate information on the effects of ACTs (H4), which *might* influence the personalisation of ACT regimens, if clinicians were to have access to this (H5). These uncertainties will be explored further in Chapter 4, 5 and 6.

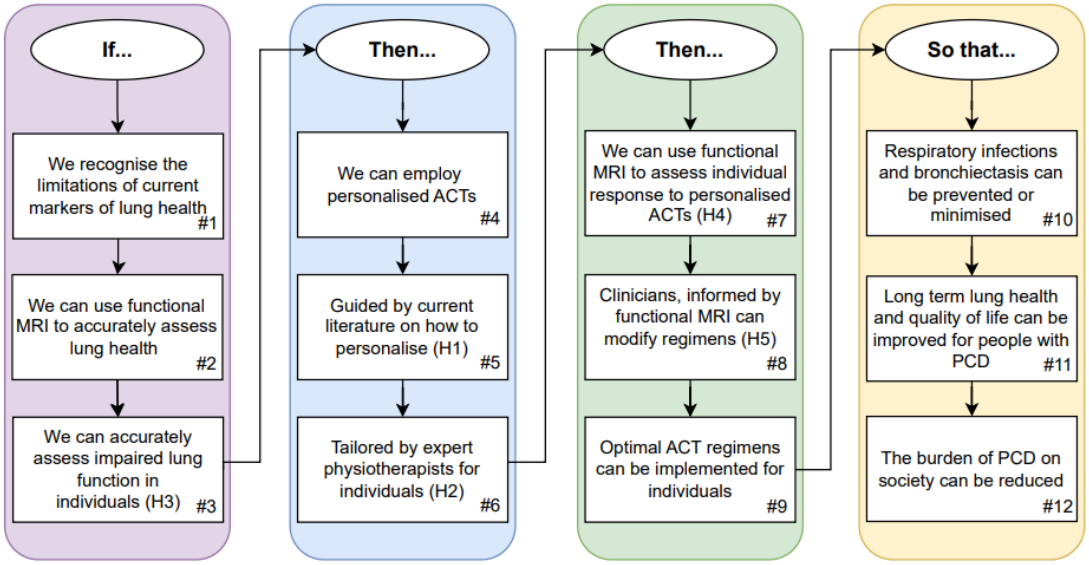


Figure 21: Programme theory for the thesis.

Chapter 4: Lung health in children with PCD is heterogeneous.

4.1 Introduction and objectives

In review of this thesis so far: Chapter 1 summarised that lung health in PCD is heterogeneous and whilst personalised ACTs are a key component of the management of PCD but the outcomes we have to assess the effects of ACTs are limited; Chapter 2 presented a synopsis of factors which should be considered when personalising ACT regimens, identified by a scoping review of current literature; Chapter 3 made explicit the tacit decision-making of physiotherapists when personalising ACT regimens, an iterative process in which uncertainties are encountered and managed. It remains unknown what the effects of personalised ACT regimens are.

This chapter aims to address a hypothesis generated in Chapter 1: *H3: Lung health in PCD will be found to be heterogeneous, as assessed by MRI-derived ventilation defect percentage (*Table 2).

To test this hypothesis, we assessed a cross-section of children and young people with PCD, with ^{129}Xe Ventilation MRI as an initial step to understanding the effects of personalised ACTs upon regional lung function. This chapter precedes a before and after study to assess the short-term effects of an individualised airway clearance regimen (Chapter 5).

Objectives

- To conduct a cross-sectional assessment of regional lung health in children and young people with PCD using ^{129}Xe and ^{1}H MRI.
- To assess the correlation between spirometry and ^{129}Xe and ^{1}H MRI.
- To assess the correlation and agreement between ^{129}Xe and ^{1}H MRI in children with PCD.

4.2 Methods

The data presented in this chapter and in Chapter 5 were collected as part of one single study. The data is being presented as two separate chapters: a cross-sectional analysis of baseline scans and a before and after (treatment response) study.

4.2.1 Sample

This was a prospective study of children with PCD recruited from four centres providing a respiratory service for children with PCD: Bradford Teaching Hospitals (BTHFT), Leeds Teaching Hospitals (LTHT), Royal Manchester Children's Hospital (RMCH) and Sheffield Children's Hospital (SCH). Sampling of the centres participating in the study was purposeful, taking into consideration proximity to the MRI unit in Sheffield. The sites included a PCD supra-regional centre (LTHT); two tertiary children's hospitals (RMCH and SCH); a large district general hospital with significant PCD experience (BTHFT). All eligible patients at these centres were invited to participate by a member of their direct clinical care team.

Inclusion criteria:

- Aged between five (the youngest age that a participant will be able to reliably lie still for the MRI) and 18 years.
- Confirmed PCD diagnosis as defined by the European respiratory society guidelines (15).
- Established on an ACT regimen for at least three months prior to recruitment.
- Under the clinical care of a PCD team at one of the participating centres (LTHT, BTH, RMCH or SCH)

Exclusion criteria:

- A contraindication to MRI scanning (ferromagnetic metallic implants, pacemakers, pregnant) as per the MRI screening questionnaire (Appendix 6).
- Resting oxygen saturation of <90% on air (using pulsed oximetry).
- Previous lung surgery.
- Those felt unable to follow the necessary steps required for ^{129}Xe scans, for example, to hold their breath for 10 seconds.
- Currently being treated with antibiotics for a PCD exacerbation.

Sample size

The sample size was calculated for the before and after treatment response component of the study (Chapter 5). For the purposes of sample size estimation, the primary outcome was the change in lung health, as measured by the ^{129}Xe image derived metric, VDP from pre-ACT to post-ACT, between the ACT group and the non-ACT group. As an exploratory study with no information on the variability of this outcome measure in PCD available at the start of the study, calculations for the ACT group were based on the longitudinal reproducibility of ^{129}Xe VDP in young people with CF with normal FEV_1 previously published by the POLARIS group (128). Smith *et al.*

(128) established a standardised difference or effect size of 1.6 to be of clinical and practical importance and applying their population standard deviation of 2.13 with 90% power to detect a standardised difference or effect size of 1.6 or more between the ACT and non-ACT groups as statistically significant at the 5%-two-sided level. Using this data with the calculation described Noordzij *et al.* (251) (below) a sample size of 37 subjects in the ACT group was indicated.

$$Sample\ size\ =\ 37 = \frac{2 \times (1.96 + 1 \cdot 28)^2 \times 2 \cdot 13^2}{1 \cdot 6^2}$$

Mindful of ethical concerns arising from withholding a clinically established intervention in a young population, a smaller size was used for the no-ACT group. The within-visit repeatability of ^{129}Xe VDP in people with CF reported by Smith *et al.* (128) was used to calculate the sample size for this group as shown below. Although Smith *et al.* (128) had a shorter time period of only 15 minutes between scans, this small sample would permit early exploratory work into the same day variability of VDP in children with PCD.

$$Sample\ size\ =\ 6 = \frac{2 \times (1.96 + 1 \cdot 28)^2 \times 0.82^2}{1 \cdot 6^2}$$

Recruitment

Potential patient participants were identified during routine clinical practice and invited to participate by a member of their direct clinical care team. Age-appropriate study information was provided for participants and their parents (if aged under 16). Copies of the participant information sheets are provided in Appendix 5. Following PPI recommendation, at least 24 hours was given to review the information prior to my contact, and ample time was given to the young person and their parent for questions. Consent, or assent as age appropriate was given prior to their inclusion in the study with language support as required. Targets for recruitment at the first initial three centres (LTHT. BTHFT and SCH) were based on the number of patients at the centre and proximity to the MRI unit. Active monitoring of recruitment identified potential participant engagement was lower than anticipated from initial PPI work and that the study was unlikely to achieve 43 participants from the three sites. As such, an additional site at RMCH which has a significant PCD caseload was opened in the second phase of recruitment. Details of recruitment targets and actual figures for screening, approach, and recruitment are provided in Table 10.

Table 10: Recruitment targets and actual recruitment numbers for each centre.

Site	Number of patient participants			
	Target recruitment	Screened	Approached	Actual recruitment (% approached)
LTHT	18	26	23	12 (52%)
BTHFT	17	29	21	13 (62%)
SCH	8	8	7	4 (57%)
RMCH	0	30	25	7 (28%)
Total	43	93	76	36 (47%)

A flow chart detailing reasons for exclusion and non-participation is shown in Figure 22. There were a broad spread reasons for not being eligible for the study, including not meeting the PCD diagnostic criteria. As ethical approval was not in place to include adults who did not have capacity to provide written informed consent, two individuals aged over sixteen were either not approached or were unable to take part following initial approach. Most individuals who declined participation did not provide a specific reason to the lead researcher for their decision. Five individuals in total declined due to the MRI proceedures, three due to perceived intolerance of being in the MRI scanner, and two due to their parents predicted their child would not be able to lie still during the scan.

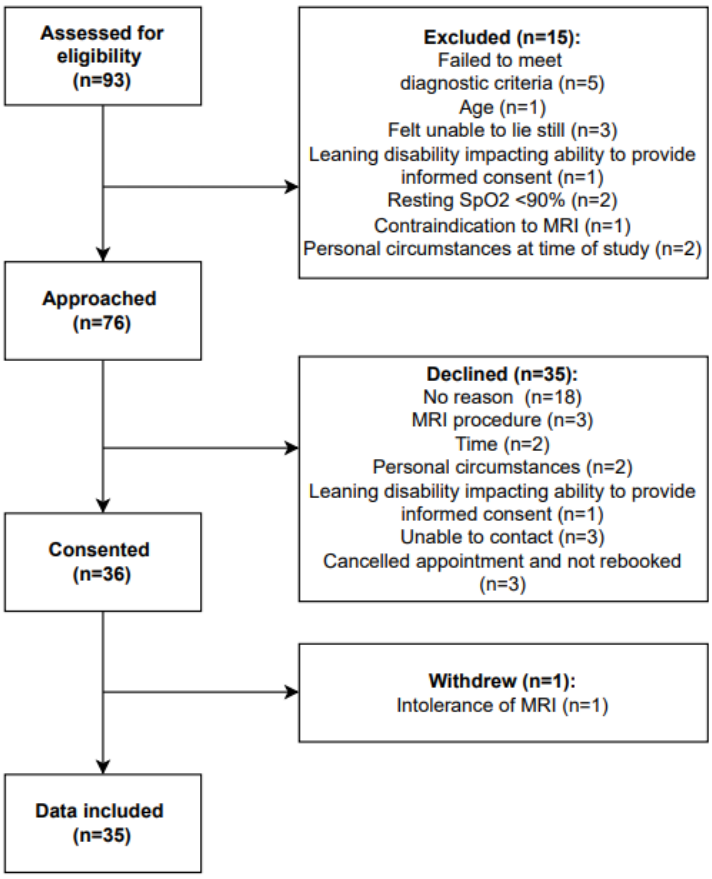


Figure 22: Flow diagram summarising the number of potential participants who were screened, approached and entered the study, and the reasons for non-participation.

4.2.2 Patient and public involvement

PPI members were involved throughout the study design and parents were particularly positive about the use of radiation-free imaging methods. The lead researcher sought their advice on patient and parent acceptability of the scan process and duration which was used to shape the participant information. Specific details were included such as: scan duration, parents being able to be present in the room, the Xenon gas has no taste, no needles involved in the process. Whilst most PPI feedback was accommodated, young members requested music during the scan but as participants are required to follow instructions for breath hold manoeuvres this was not possible. Based on young PPI member feedback, a video blog with additional information was created. The content was young PPI member led, the video was presented by a young PPI member and filmed by a parent.

Parent PPI members were involved in regular reviews of recruitment against the recruitment targets. Working within the boundaries of the process approved by NHS ethics, they guided adjustments to the process for example offering email and text contact following the initial approach and actions to take when potential participants did not respond to the lead researcher's contact.

4.2.3 Study schedule and acquisition of non-imaging data

Clinical details were obtained prior to the study visit for all patient participants from their medical notes and clinical team, including PCD diagnostic information, recent health, regular medications, and the ACT regimen which had been recommended by the physiotherapist who reviews the patient clinically. These details were confirmed during the study visit with the participant or parent for younger children. Any queries related to the clinical information arising during or following the study visit were confirmed with the clinical team. Participants attended the MRI unit at the University of Sheffield (UoS) for one study visit, Figure 23 provides a visual representation of the patient journey to the end of the first scan session.

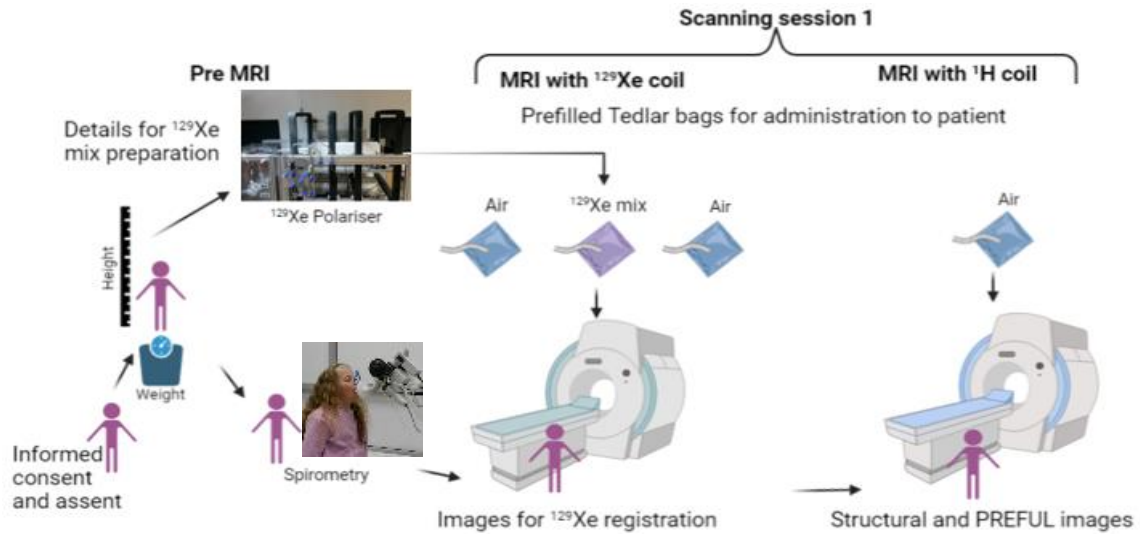


Figure 23: Patient journey from arrival and through the initial scanning session. Polariser picture from the POLARIS group image stock. Spirometry picture with written parental consent. Created in BioRender. Schofield, L. (2025) https://BioRender.com/ h08u101

Spirometry testing

Baseline spirometry was performed at the study visit to assist with defining the study population. As spirometry may cause inadvertent airway clearance it was performed before the first MRI. Spirometry was performed on a 'PFT Pro' (Vyaire, Basingstoke, UK), which was calibrated and verified prior to use as per standardised guidance with a 3-litre syringe and varied flow rates (110). Spirometry was performed with participants sitting upright, their feet flat on the floor. A bacterial filter mouthpiece was attached to the spirometer as the patient interface, and a nose clip used to ensure mouth-breathing during each attempt (Figure 24). Participants were coached through performance of correct spirometry technique: tidal breathing, full inspiration to total lung capacity; maximal exhalation to residual volume; rest prior to next attempt. The technical quality of each attempt was assessed, and feedback given to improve technique as indicated prior to the next effort. A minimum of three attempts were performed, with additional

further attempts as needed to achieve technically acceptable results as per published technical standards (110). If participants needed to clear secretions during spirometry testing this was permitted. Technically incorrect attempts were removed, and the following spirometry metrics calculated: forced expiratory volume in one second (FEV_1); forced vital capacity (FVC); the ratio of the highest FEV_1 to highest FVC (FEV_1/FVC). As the most commonly used metrics in paediatric CSLDs, they offer differentiation between restrictive and obstructive lung disease: simplistically, a reduced FEV_1/FVC and FEV_1 indicate an obstructive picture whereas a normal FEV_1/FVC and reduced FVC indicate a restrictive picture (252). The largest FEV_1 and FVC was recorded from technically correct attempts but not necessarily the same attempt. All spirometry metrics were assessed using a z-score, with -1.64 used as the lower limit of normal (253).

Figure 24: Depicts positioning for spirometry tests with the individual sitting upright, nose-clip in situ and lips firmly around the bacterial mouthpiece. Image produced with written parental consent and verbal young person assent.

Completion of the QOL-PCD questionnaire

Participants were also asked to complete health related quality of life questionnaire for PCD, the QOL-PCD to assist with defining the study population. The QOL-PCD has different versions for different ages: a child questionnaire and a parent proxy for those under 12 years and an adolescent questionnaire for those aged 13 to 17 years (229) (Appendix 7). The QOL-PCD comprises a number of domains: physical functioning; emotional functioning; treatment burden; social functioning; lower-respiratory symptoms (referring to lung symptoms); upper-respiratory symptoms (referring to nasal symptoms); ears and hearing symptoms; role (adolescents only); vitality (adolescents only); eating and weight (parent proxy only); health perception (parent proxy only). The QOL-PCD was performed after the second MRI scan session, using the online version of the tool with paper copies available if needed. Results were calculated automatically via the online tool; each domain is scored as a percentage, with higher scores indicating better quality of life.

4.2.4 Image acquisition

The MRI scanning took place on a 1.5T GE HDXt MRI scanner (GE, Milwaukee, WI, USA) using standard protocols. A ^{129}Xe transmit-receive radio frequency (RF) coil (Clinical MR Solutions, Brookfield, WI) was used during ^{129}Xe imaging, and the in-built transmit receive body coil was used for ^{1}H imaging in the same position as the ^{129}Xe MRI. High resolution ^{1}H images including PREFUL scans were then acquired with the patient repositioned with an 8-channel cardiothoracic array RF coil. Images illustrating the supine positioning of participants in the ^{129}Xe coil and MRI scanner are provided in Figure 25. The ^{129}Xe gas was polarised under regulatory licence (MS-18739), using an in-house POLARIS polariser (254).

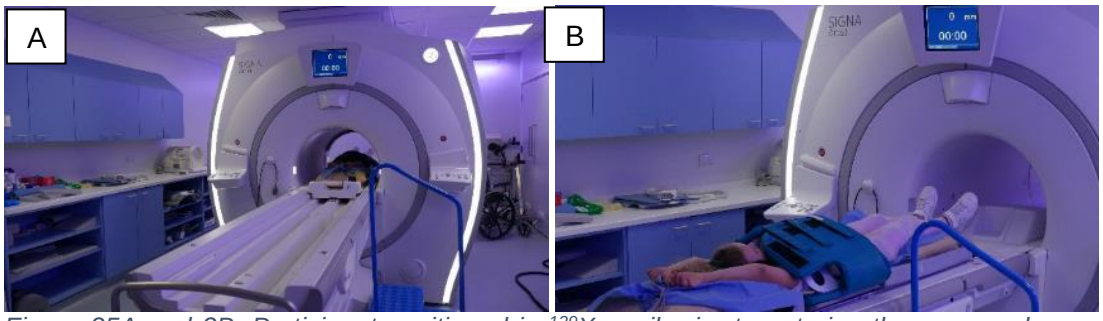


Figure 25A and 3B: Participant positioned in ^{129}Xe coil prior to entering the scanner bore, and then inside the scanner. Images produced with written parental consent and verbal young person assent.

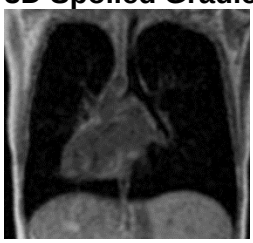
The following images were taken:

- ^{129}Xe Ventilation hyper-polarised gas breath-hold imaging of the lung performed at EITV and at TLC using 3D steady state free precession sequences with registered ^{1}H anatomical imaging (255).
- Structural proton ^{1}H MRI of the lung using a standard 3D gradient echo sequence acquired at three lung inflation levels: FRC, TLC and RV.
- Structural proton ^{1}H MRI of the lung using a radial 3D “ultra-short echo” pulse-sequence during free breathing (256).
- Free breathing ^{1}H MRI using 75 seconds of free-breathing analysed using the PREFUL technique (257) including registration, low-pass filtering, and calculation of fractional ventilation.

Further details of the scan sequences are provided in Table 11 and order of the sequences in Table 12. Each MRI session consisted of; 20-minute ^{129}Xe scan, 2-minute break, 30-minute ^{1}H scan. A parent/guardian was able to accompany the participant in the scanning room.

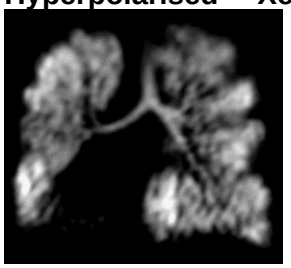
Table 11: Overview of imaging sequences performed.

3D Spoiled Gradient Echo (SPGR)



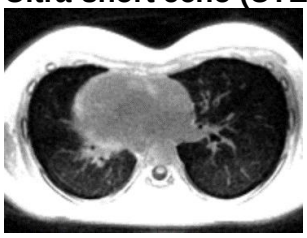
Description: T1 weighted images, taken at TLC and EITV (Figure 26).
Role: Images used for ^{129}Xe registration (255).
Scan details: Plane: Coronal. Slice thickness 5.0mm, 36 slices per acquisition. Field of view (FOV) 40.0. Scan duration: Typically, 6 second breath hold at TLC and EITV. Coil: body transmit-receive coil.

Hyperpolarised ^{129}Xe gas ventilation with steady state free precision



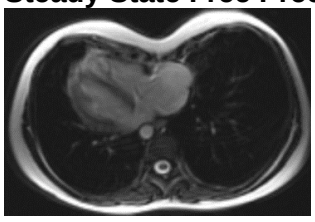
Description: Imaging of lung ventilation with ^{129}Xe as contrast. Taken at EITV and TLC (Figure 26).
Role: Functional MRI scan. Signal from ^{129}Xe offers visualisation of the distribution of ventilation. Used to calculate metrics and for visual analysis of ventilation in Chapter 6.
Metrics: ^{129}Xe VDP and VHI.
Scan details: Steady state free precession sequence. Plane: Coronal. Slice thickness: 10.0mm FOV 40.0. Scan duration: Typically, 6 second breath hold at different volumes (EITV and TLC). Coil: ^{129}Xe transmit receive flex quad coil

Ultra-short echo (UTE)



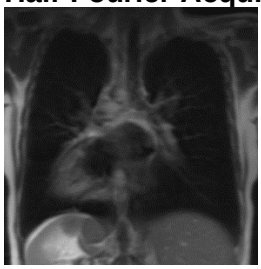
Description: Proton density weighted sequences which provide high-resolution isotropic 3D images.
Role: Structural MRI scan. Acquisition of the lung parenchyma with high-resolution images similar to CT. Images visually analysed by radiologist to assess for bronchiectasis and collapse. Images reviewed visually in Chapter 6 by clinicians.
Scan details: Plane: Any (isotropic). Slice thickness 2.0 FOV 35mm. Scan duration: 8 to 9 minutes, relaxed breathing, projections acquired during expiration at a lung volume near FRC. Coil: 8 channel array.

Steady State Free Precession (SSFP)



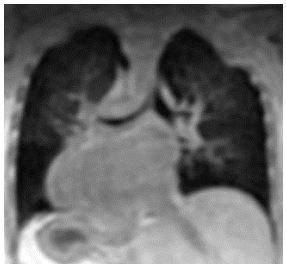
Description: Offers a combination of T1 and T2 weighted components with hyper intense signal from long T2 components
Role: Structural MRI scan. Allows visualisation of anatomy and can visualise mucus (122). Images visually analysed by radiologist to assess for bronchiectasis, collapse and mucus plugging.
Scan details: Plane: Axial, 25 slices Slice thickness: 10mm. FOV 40.0.Scan duration: Typically, 8 second expiratory breath hold. Coil: 8 channel array.

Half-Fourier-Acquired Single-shot Turbo Spin Echo (HASTE)



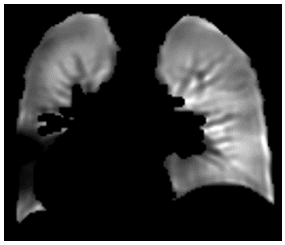
Description: A rapid T2 weighted sequence.
Role: Structural MRI scan. Allows visualisation of mucus. The acquisition speed reduces the impact of motion on the images. Images visually analysed by radiologist to assess for mucus plugging.
Scan details: Plane: Coronal. Slice thickness: 10mm, 18 slices. FOV 35.0. Scan duration: Typically, 8 second inspiratory breath-hold. Coil: 8 channel array

3D Spoiled Gradient Echo (SPGR)



Description: T1 weighted images, taken at TLC, EITV and approximately RV (Figure 26).
Role: At higher lung volumes mucus images may visualise mucus, and at lower volumes air trapping. Images visually analysed by radiologist to assess for mucus plugging and gas trapping (RV image).
Scan details: Plane: Any (isotropic) Slice thickness 5.0mm, 62 slices per acquisition. FOV 40.0. Scan duration: Typically, 6 second breath hold at TLC, EITV and RV. Coil: 8 channel array

Phase Resolved Functional Lung (PREFUL)



Description: Free-breathing SPGR image acquisition.
Role: Functional imaging method providing a contrast free surrogate of regional lung ventilation. Used to calculate metrics.
Metrics: ^{1}H VDP and VHI

Scan details: Plane: Coronal, 7 slices.
Slice thickness:15mm Slice gap: 5mm. FOV 48.0
Scan duration: 90 seconds per slice. Coil: 8 channel array

Table 12: MRI scan sequence order with details of coil used.

Order	Image sequence	Coil
1	Pre scan localiser	In-built transmit receive
2	SPGR at TLC	
3	SPGR at EITV	
4	^{129}Xe calibration	^{129}Xe
5	^{129}Xe at EITV	
6	^{129}Xe at TLC	
7	SPGR at TLC	In-built transmit receive
8	SPGR at EITV	
9	Pre scan localiser	^{1}H
10	HASTE	
11	SPGR at TLC	
12	SPGR at EITV	
13	SPGR at RV	
14	SSFP	
15	UTE	
16	PREFUL	

Hyperpolarised gas ^{129}Xe Ventilation MRI acquisition

Ventilation images were acquired by inhaling a titrated mixture of ^{129}Xe and medical grade nitrogen, which were administered via a Tedlar plastic bag. An MRI scanner sequence which only images the ^{129}Xe gas is used, to image the areas of the lung

which have been ventilated by the polarised gas. Images were acquired during a single breath-hold, with images taken at two lung volumes: an estimated end-inspiratory tidal volume (EITV) and total lung capacity (TLC). Volume-time graphs to illustrate the breathing manoeuvres performed by participants are shown in Figure 26. Participants were coached to perform at least two relaxed tidal breaths before then inhaling a fixed volume of the gases from a resting FRC lung volume. The total volume of inhaled gas was calculated based on the participant's height with the aim of achieving an approximate same lung volume across the group irrespective of the participant's size. This process of inhaling the volume of the bag from FRC provided an estimated volume of 60% of TLC, referred to as EITV. The volume of the gas, which ranged from 0.4 to 1.0 L comprised a scaled dose of ^{129}Xe balanced with medical grade Nitrogen as shown in Table 13, in line with previously published methods (128). For the acquisition of images at TLC, the process for an EITV gas inhalation manoeuvre were followed and then immediately and prior to exhaling, additional room air was inhaled to reach TLC (Figure 26B).

A separate ^{1}H MRI sequence was acquired immediately pre and post the ^{129}Xe image in order to estimate the lung volume at which the ^{129}Xe image was acquired as previously described (255).^{1}H images were acquired at EITV and TLC both immediately before and after ^{129}Xe image acquisitions using a ^{129}Xe coil to provide images for registration (255) and estimation of TCV. Acquisitions occurred during a separate breath-hold manoeuvre, using the same breathing manoeuvre as for the ^{129}Xe images, but with a matched volume of medical air replacing the ^{129}Xe gas mixture within the Tedlar bag.

Table 13: Inhaled gas volume and composition height-based calculations.

Patient height (standing)	**Total volume**	**Gas mixture composition**	
		EITV	**TLC**
Over 160cm	1.0 L	500 ml ^{129}Xe + 500 ml N_2	670 ml ^{129}Xe + 330 ml N_2
150-160cm	800 ml	450 ml ^{129}Xe + 350 ml N_2	600 ml ^{129}Xe + 200 ml N_2
140-150cm	650 ml	400 ml ^{129}Xe + 250 ml N_2	530 ml ^{129}Xe + 120 ml N_2
130-140cm	500 ml	350 ml ^{129}Xe + 150 ml N_2	470 ml ^{129}Xe + 30 ml N_2
Less than 130cm	400 ml	300 ml ^{129}Xe + 100 ml N_2	400 ml ^{129}Xe

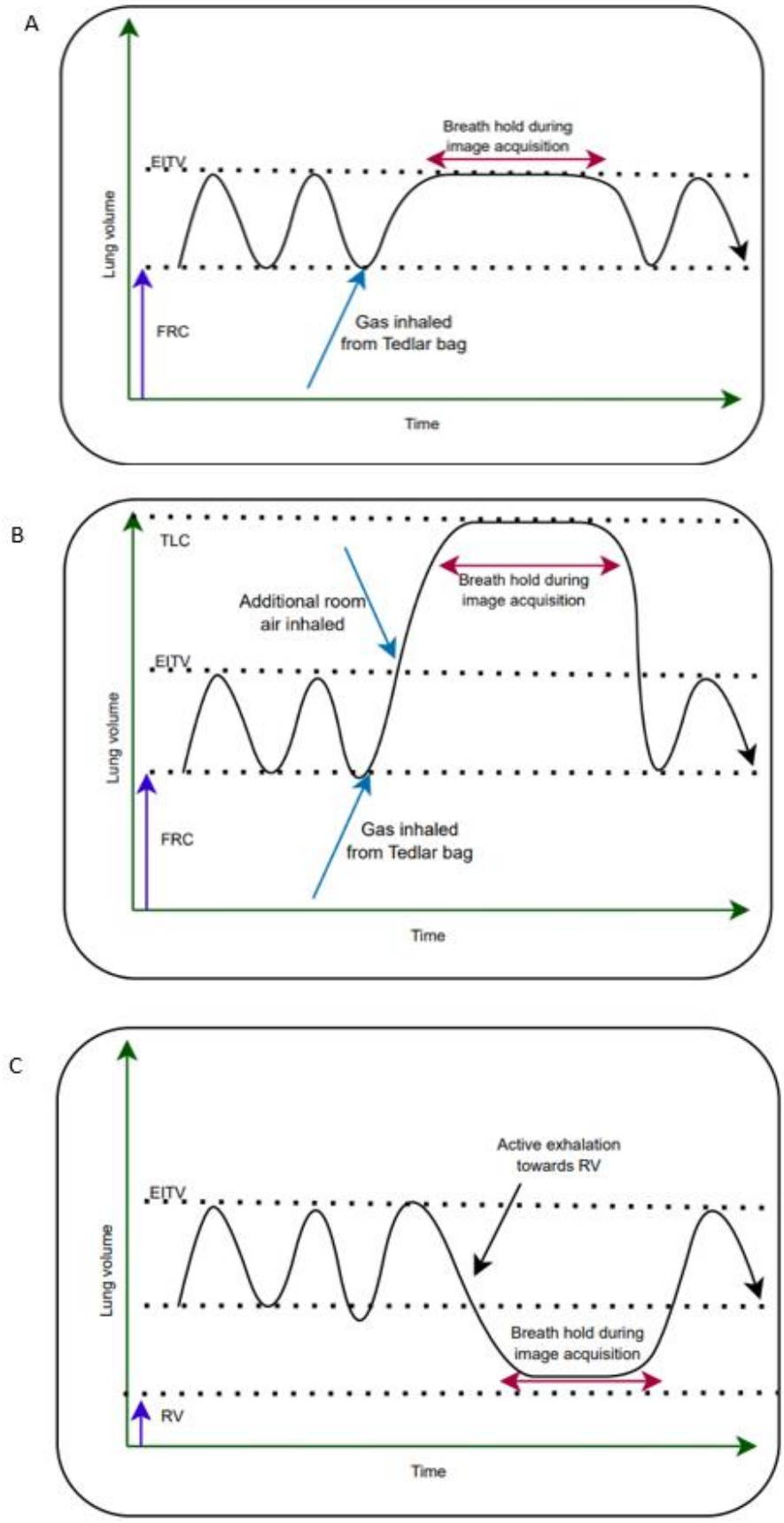


Figure 26: Breathing manoeuvres during image acquisition at end-inspiratory tidal volume (EITV) (A), total lung capacity (TLC) (B) and residual volume (RV) (C).

^{1}H anatomical image acquisition

^{1}H imaging sequences were performed at each time point to provide high resolution anatomical images to assess for features which can be typical in people with PCD including mucus, bronchiectasis, atelectasis, and collapse. A brief description of the sequences performed are provided in Table 11. As a detailed description of ^{1}H imaging methods is beyond the scope of this thesis, readers are directed to the literature for further information (256, 258-261).

4.2.5 Image analysis

Qualitative analysis of structural images

All images were reviewed for any significant clinical concerns by consultant radiologist and POLARIS MRI specialist Dr Andy Swift (UoS). Images were subsequently reviewed for clinical reporting with consultant paediatric radiologist Dr David Hughes (SCH) who has experience in both structural and ventilation MRI interpretation. Dr Hughes also assessed the ^{1}H structural images (UTE, SSFP and RV) for readability and the presence of four radiological findings in PCD which were deemed clinically informative by three consultant paediatricians who work with children with PCD: bronchiectasis, bronchial wall thickening, mucus plugging and air trapping. Dr Hughes reviewed the pre-ACT images for each case. If any of the images for a case were not readable, he then reviewed relevant images acquired at 4-hours post-ACT and, only if needed, the images acquired post-ACT.

Quantitative image analysis

Although a large number of HASTE, SPGR and SSFP images were acquired from the study participants, a full detailed analysis of these was beyond the scope of this project.

Image processing

Image post-processing permits quantitative analysis of the Ventilation images to calculate; the ventilation defect percentage (VDP); the ventilation heterogeneity index (VHI); the percentage of abnormally low ventilation (%). Further details are provided below.

Image registration

For estimation of the volume of the lung cavity, image registration was completed in ITK-snap software (version 3.6.0, www.itksnap.org). This process is to identify the ^{1}H image which aligns most closely with the acquired ^{129}Xe image. As shown in Figure 27,

using the ^{129}Xe image as an overlay, the ^{1}H images were assessed for alignment with the major airways, hemidiaphragms and lung edge at the peripheries including anterior and posterior of the thorax. The ^{1}H image selected was then used for estimation of the thoracic cavity volume during segmentation.

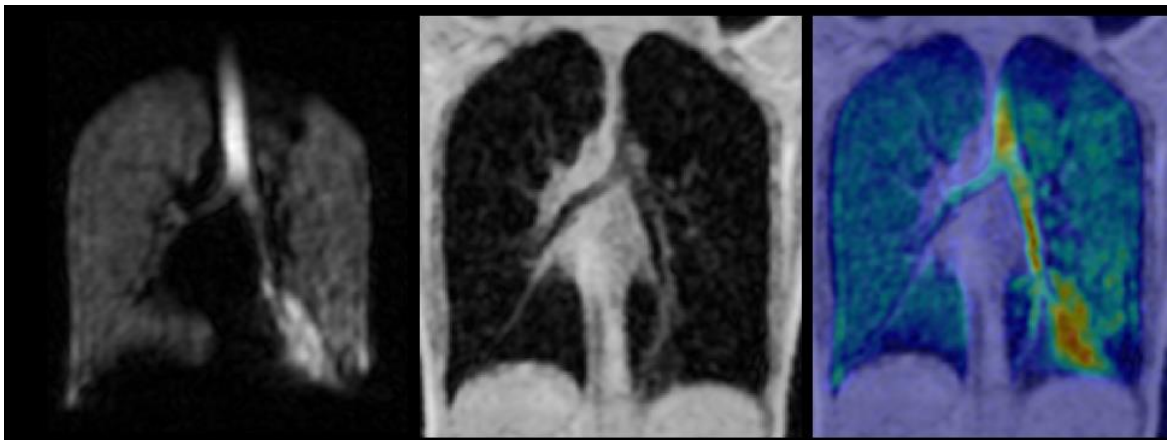


Figure 27: Example of an image registration using ITK snap. For each individual, their raw ^{129}Xe image (A) is compared to their ^{1}H images (B). The ^{129}Xe image is changed to jet colours to aid visualisation and displayed as an overlay to allow assessment of the major airways and lung edges across all slices.

Image segmentation

All ^{129}Xe images were analysed using locally developed protocols, with validated 3D image quantification methods (262). Segmentation is a process to produce an individualised template or "map" of the thoracic cavity, excluding structures in the thoracic cavity where ventilation signal would not be expected. Segmentation was completed using in house software via MATLAB (MathWorks, Natick, MA) with a semi-automated process as illustrated in Figure 28. Initially, an automated map of the estimated lung cavity was generated using deep-learning (263) or, if the deep-learning method produced a result that was improved by fuzzy-c means clustering, then a combined approach employing deep-learning and fuzzy-c means clustering was used (264-266). Segmentation included estimating areas of ventilated lung, unventilated lung, and major airways. Manual editing was performed on each slice of the mask using both the ^{1}H image and the ^{129}Xe image to ensure: the mask segmentation did not include structures where ventilation would not be expected such as major blood vessels; major airways were marked so they would be removed from the mask; the mask included all areas of lung including areas of lung with low or no ventilation; the mask edge aligned with the outline of thoracic cavity edge.

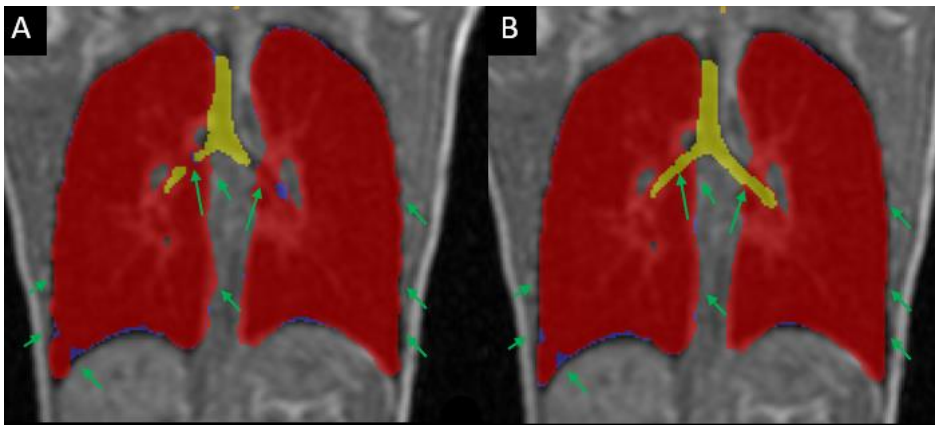


Figure 28: Example of semi-automated segmentation process in MATLAB which identifies the lung edges, major airways, and major blood vessel: the initial automated estimation (A), and manual revision (B). The segmentation masks show areas of ventilated lung (red), non-ventilated lung (blue) and major airways (yellow). The green arrows indicate where the automated mask needed revising (A) and changes post revision (B).

For individuals with situs inversus as demonstrated in Figure 29 images were flipped on a vertical axis prior for segmentation to optimise performance of the automated deep-learning segmentation. Images were flipped back to situs inversus orientation after the segmentation was completed.

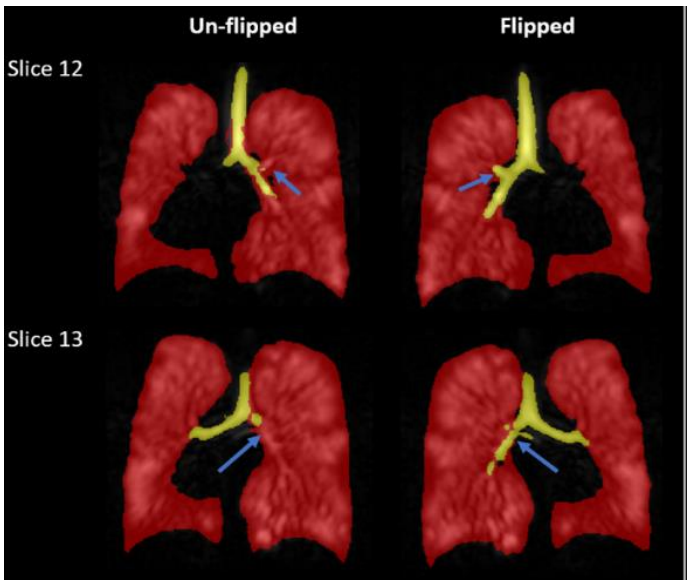


Figure 29: Example of automated segmentation performance on two central slices for an individual with situs inversus on un-flipped and flipped images. Arrows indicate airways which had improved identification when flipped.

Assessment of ventilation

Segmentation allowed the computation of metrics of ventilation calculated by the strength of the ^{129}Xe signal within the lung. As depicted in Figure 30, in healthy lungs ^{129}Xe signal is present throughout the lung fields, there are very minimal areas of lung where ventilation is expected but not seen, and the ventilation signal is very

homogenous (133). In lung disease, areas with either no ^{129}Xe signal or low signal are present. These are caused by obstructed lung units which have not been ventilated by the polarised gas or are poorly ventilated. Greater heterogeneity of the ^{129}Xe signal is also seen in lung disease, where unequal ventilation of the gas is seen in lungs representing areas of ventilation inhomogeneity(115).

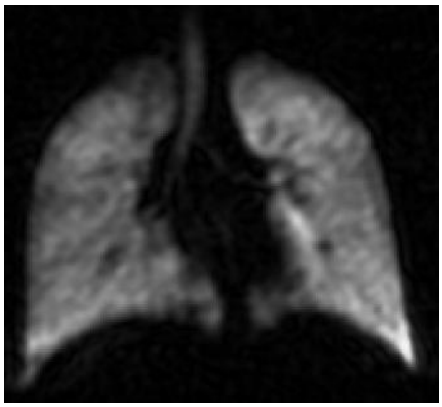


Figure 30: ^{129}Xe image of the lungs of a healthy child. from unpublished data held by the POLARIS team. This image was acquired as part of a separate research study (267), this image did not feature in the publication. ^{129}Xe signal is present throughout the lung fields and the signal is homogenous.

As shown in Figure 31, the ^{129}Xe ventilation signal within each image was categorised into a series of bins using an automated linear "binning" process as described by Collier *et al.* (268). For each image, the automated process sorted the voxels from low to high, to form a linear distribution and the signal was scaled based on the mean ventilation signal within the thoracic cavity. This ventilation distribution was then divided into six categories known as "bins" centred around the mean and the width of each bin equal to one standard deviation. The two central bins were combined into a single normal ventilation bin, the two highest bins combined into a single high ventilation bin. Each voxel was therefore assigned into one of four bins: high ventilation, normal ventilation, low ventilation, or ventilation defect.

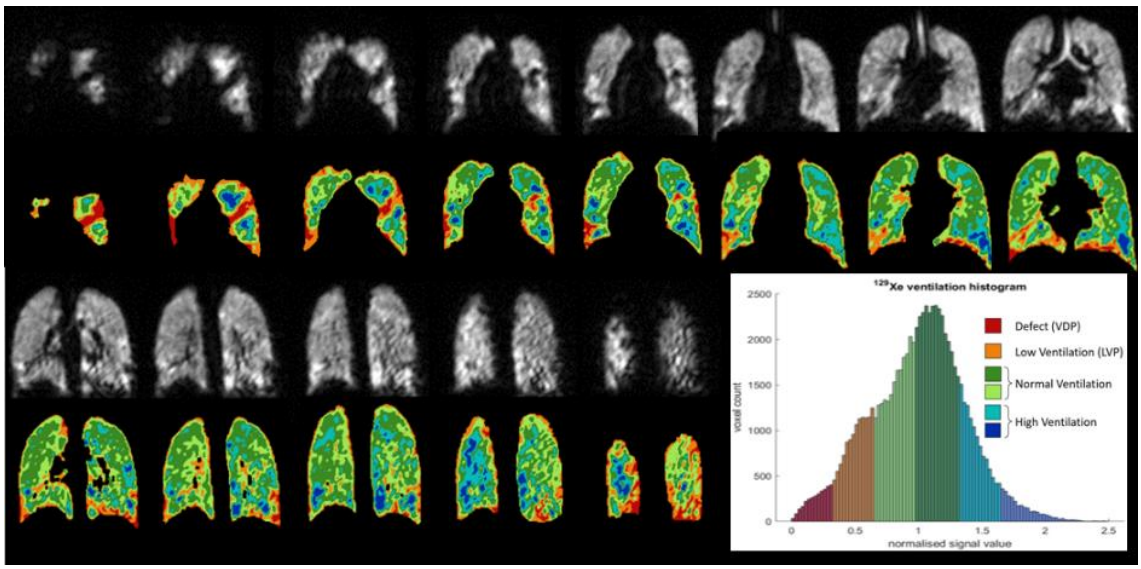


Figure 31: Example of a raw ^{129}Xe ventilation image and corresponding binning map. A single slice has been magnified to provide easy comparison of the variation in ventilation signal on the raw image and how this translates onto the binning map as areas of defect (red), low ventilation (orange), normal ventilation (green) and high ventilation (blue). The histogram shows the linear distribution of ventilation signal across the whole image and how it is divided into bins.

As the image voxel volume was known, multiplication of the voxel volume by the number of voxels provided a volume for the following metrics:

- Thoracic cavity volume (TCV) = number of voxels x voxel volume. This metric is in litres.
- Ventilated volume (VV%), the proportion of the lung with ventilation. These areas are visualised as white or grey within the ^{129}Xe images. VV%= (number of ventilated voxels x voxel volume)/ TCV * 100
- Ventilation defect percentage (VDP%), the proportion of the lung with no ventilation. These areas are visualised as black within the ^{129}Xe images. VDP%= 100- VV% (Figure 32).
- Low ventilation percentage (LVP%), the proportion of the lung with ventilation, but in which the ventilation signal is lower than that seen in health controls. LVP%= (number of low ventilated voxels x voxel volume)/ TCV * 100

VDP is used as the primary outcome measure as very low levels of VDP are seen in healthy individuals (VDP<1.2% in children (267)), and as detailed in Section 1.4.2, VDP in sensitive to abnormalities, change in disease and change with interventions.

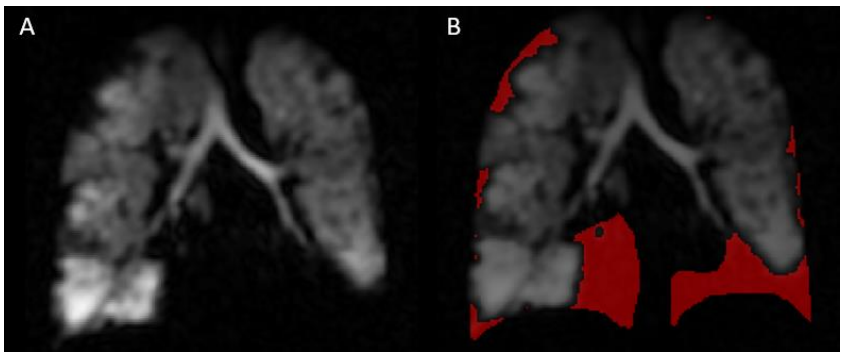


Figure 32: ^{129}Xe raw image (A) with ventilation signal visualised as white and areas with no ventilation signal as black. Defect mask displayed as red-black overlay on ^{129}Xe raw image to illustrate areas of no signal within the lung cavity known as ventilation defect which contribute to VDP% across the whole lung.

The ventilation heterogeneity index, an established measure of the heterogeneity of the ventilation signal within the lungs was calculated for all ^{129}Xe images. This measure looks solely at the ventilated areas of the lung cavity, therefore excluding areas with no ventilation. It is computed with an in-house automated process which assesses each ventilated voxel with the eight in-plane adjacent voxels. As illustrated in Figure 33, this 3x3 assessment window moves across all ventilated areas on each slice of the image. The number of pixels in the assessment window will affect the heterogeneity being assessed, however the process used is an established method (115, 262). From this local measure of ventilation heterogeneity, an automated calculation of standard deviation/mean and map of the co-efficient of ventilation is produced. Lower levels of VHI are seen in healthy individuals (VDP<9.5% in children (267)).

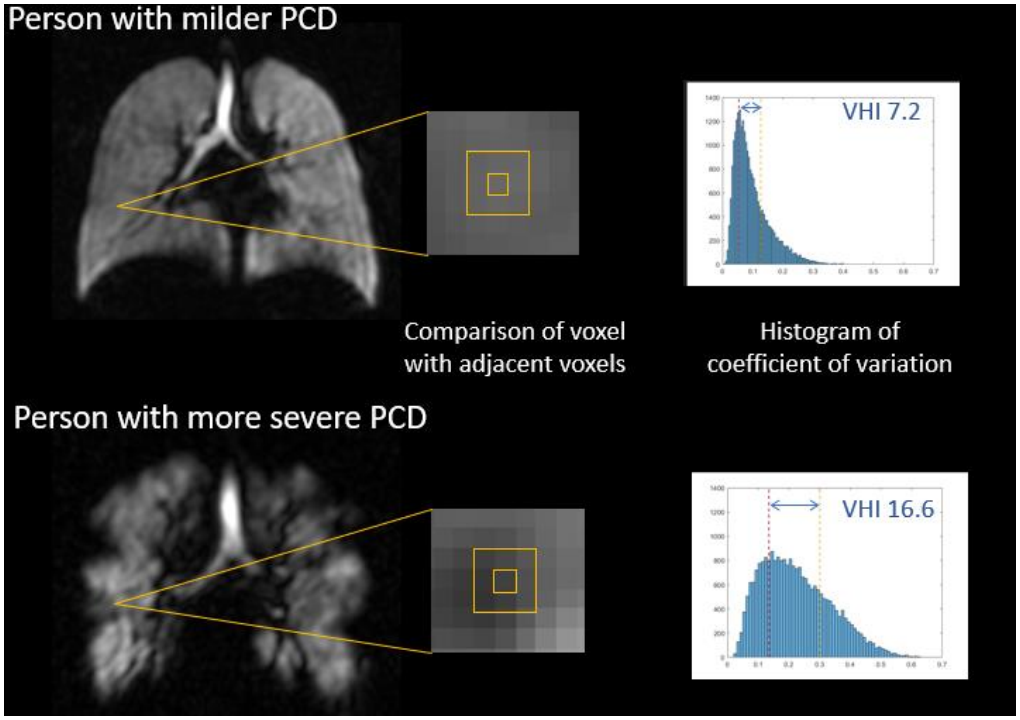


Figure 33: Representation of ventilation heterogeneity in two cases, one with milder PCD and a normal VHI and one with more severe disease and an abnormal VHI. 3x3 window illustrates how an assessment window compares the ventilation signal for each voxel and its eight adjacent voxels. A histogram of the coefficient of ventilation and VHI% is also shown for each case.

Whilst the ULNs have been described in relation to each of the metrics above, a summary of these is provided in Table 14.

Table 14: A summary of published upper limits of normal for ^{129}Xe and ^{1}H metrics.

Metric	Upper limit of normal
^{129}Xe VDP	1.2%
^{129}Xe VHI	9.5%
^{129}Xe VDP	Not yet established
^{129}Xe VDP	2.7%

Free-breathing image analysis

Phase resolved functional imaging (PREFUL) analysis was performed on free-breathing images using the methods described by Voskrebenzev *et al.* (257): registration, low pass filtering and calculation of fractional ventilation. The computation used MATLAB to run code developed by Andreas Voskrebenzev and Jens Vogel-Claussen at Hannover Medical School. The following manual input was required at stages of the automated computation for each image slice: 1) drawing of a region of

interest over the hemidiaphragm 2) marking a region of interest around the thoracic cavity with adequate margins to ensure the region of interest can accommodate expansion of the thorax during the free-breathing scan 3) identifying a central blood vessel, 4) selection of an inspiratory image without visible artefact for identification of the thoracic cavity during segmentation.

Once the PREFUL images were processed, they were then segmented following previously published methods (130), using the same processes previously described for the ^{129}Xe images:

- Semi-automated creation of surrogate maps of ventilation using spatial fuzzy-c means clustering to generate an automated mask which was manually edited.
- Automated segmentation to analyse and categorise the image voxels based on signal thresholds into high, normal, low and ventilation defect bins.
- Automated calculation VV%, VDP%, LVP% and VHI.

An example of a ^{1}H free-breathing (PREFUL) image and binning map is provided in Figure 34. An upper limit of normal ^{1}H VDP for can only be estimated from a small adult data set (^{1}H VDP ULN =2.7%) (130).

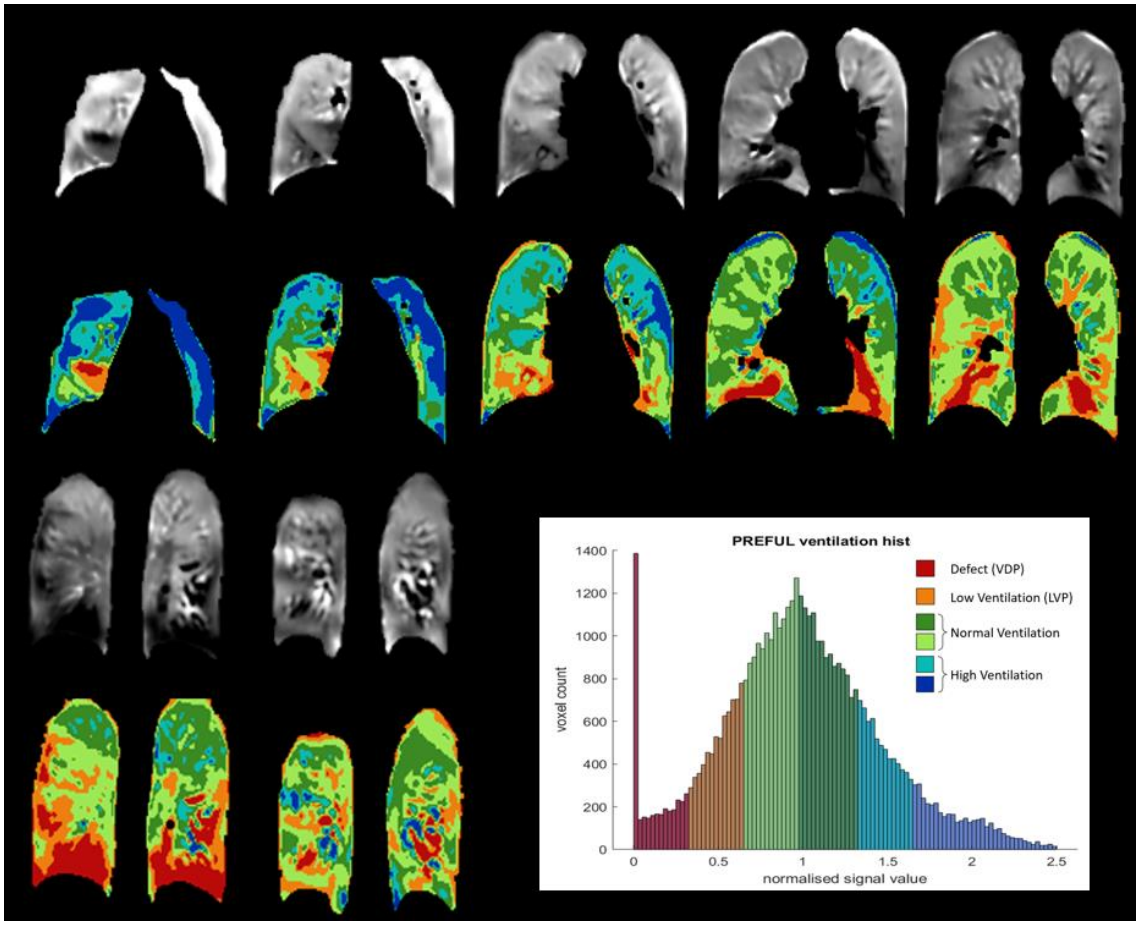


Figure 34: Example of a raw ^{1}H free-breathing PREFUL image and corresponding binning map. A single slice has been magnified to provide easy comparison of the variation in the surrogate of ventilation signal on the raw image and how this translates onto the binning map as areas of defect (red), low ventilation (orange), normal ventilation (green) and high ventilation (blue). The histogram shows the linear distribution of PREFUL ventilation signal across the whole image and how it is divided into bins.

4.2.6 Statistical analysis

All statistical analysis was performed using GraphPad Prism (version 9.5.1, San Diego, US). For both ^{129}Xe MRI and free breathing PREFUL ^{1}H MRI the following metrics were calculated; lung ventilation defect percentage (^{129}Xe VDP and ^{1}H VDP); the co-efficient of variance of ventilated image signal intensity (^{129}Xe VHI and ^{1}H VHI).

Prior to analysis, data fields for the whole cohort were assessed for normality with the Shapiro-Wilks test and depending on the outcome, data are presented as either mean ± SD, or median (range). Group comparisons were completed using statistical tests appropriate for the data set: the un-paired t-test for normally distributed data or Mann-Whitney U test where at least one data set was not normally distributed. When the data was paired, for example the comparison of ventilation at two different lung volumes, the Wilcoxon test, a type of t-test for paired data was used. To compare multiple groups, as

the data was not normally distributed, the Kruskal-Wallis analysis of variance test was used. Correlation and agreement between the measures of ventilation defect and heterogeneity (^{129}Xe VDP and ^{1}H VDP) were assessed using Spearman's rank-based correlation, and Bland-Altman plots of the difference in outcome versus the average respectively.

As airway clearance techniques often involve temporary increases in lung volumes to mobilise secretions it was important to assess the potential reversibility of ventilation defects with an increase in lung volume. As such, Ventilated volume VV(%) and TCV (l) metrics from ^{129}Xe images acquired at EITV and TLC were used to calculate a measure of ventilation abnormality reversibility, the reversible volume index (115):

$$Reversible\ volume\ index = \frac{VV\ (TLC) - VV\ (EITV)}{TCV\ (TLC) - TCV\ (EITV)}$$

The inspiratory and expiratory ^{1}H anatomical images were assessed for collapse, consolidation, mucus, and air trapping by a paediatric radiologist as a surrogate for structural CT.

4.2.7 Chapter acknowledgements

The contributions for this chapter from the lead researcher, Lynne Schofield, are as detailed below:

- Study design,
- Development of participant information sheets,
- Securing NHS/HRA ethical approvals and local approvals at UoS, LTHT, RMCH, SCH and BTHFT,
- Participant scheduling,
- Performing height, weight and spirometry for most participants,
- Providing access to the QOL-PCD questionnaire, transcribing the automated results.
- Administration of inhaled gases for most participants,
- Selecting the `^{1}H image for each ventilation image registration,
- Inputting standardised commands into MATLAB to run in-house automated segmentation programmes,
- Manual editing of all automated image segmentations,
- All statistical analyses.

Acknowledgments for specific contributions are also given to:

- Professor Jim Wild for: study design conceptualisation and implementation; as the head of the department overseeing all aspects of MRI planning and delivery

including underwriting polarisation; guidance throughout planning, data collection and analysis; governance.

- The direct care teams at LTHT, BTHFT, RMCH and SCH: screening potential participants against the inclusion and exclusion criteria; initial approach of potential participants; providing clinical details.
- Leanne Armstrong, research administrator, for scheduling the MRI slots, supporting administration of all patient study visits,
- Dr Laurie Smith and Demi Jakymelen, for providing spirometry support and guidance. These individuals also supported administration of the inhaled gases during study visits with sibling pairs.
- University of Sheffield radiographers David Capener, Jody Bray, Anna Zalewska, Shahgufta Fazal. These individuals were responsible for performing the MRIs for all individuals in the study. This involved screening safety checklists, testing and operating the MRI scanner, ensuring patient and parent safety and comfort throughout.
- Ryan Munro, Olly Rodgers, Dr Graham Norquay, Dr Guilhiem, Dr Neil Stewart who all helped in the preparation of the polarised ^{129}Xe gas mixture for inhalation.
- Dr Laurie Smith for guidance and support during study visits; advising on interpretation and analysis.
- Martin Brook, for transfer of MR images onto XNAT.
- Dr Alberto Biancardi for: setting up the ventilation and PREFUL analysis workflow, overseeing registration of the ventilation images and image segmentation; flipping images for analysis in cases with situs inversus; production of technical reports.
- Dr Helen Marshall: for advising on PREFUL methods; advising on data interpretation, analysis and on segmentation in cases with more complex images.
- PPI members for: reviewing participant information; providing feedback on study design; reviewing and advising on recruitment against targets.
- Consultant radiologists Professor Andy Swift and Dr David Hughes, for review of all study images, and Dr Hughes for writing MRI reports for every participant.

4.3 Results

4.3.1 Demographics

35 young people with a confirmed diagnosis of PCD were recruited and assessed (19 male (54%), aged 6.4-17.7 years). One additional child was recruited but withdrew due to intolerance of the scanner sounds from the outset of the initial scan sequence. 18 participants completed the full protocol, omissions occurred under the following circumstances: 1. due to the length of the protocol, 2. the PREFUL scan sequence was omitted for 15 participants either due to an unexpected delay starting the first scan (n=10) or signs indicating the participant would not tolerate the full protocol (n=5); 3. the participant was unable to co-ordinate TLC breath hold manoeuvre (n=1). The cause of unexpected delays starting was participants arriving after their scheduled appointment time (n=9) and a query arising from the MRI safety questionnaire (n=1). Two images acquired were excluded from the analysis: one TLC image due to a technical scanner issue, and one PREFUL image due to a computational analysis issue. A summary of the number of scans acquired and analysed is provided in Figure 35.

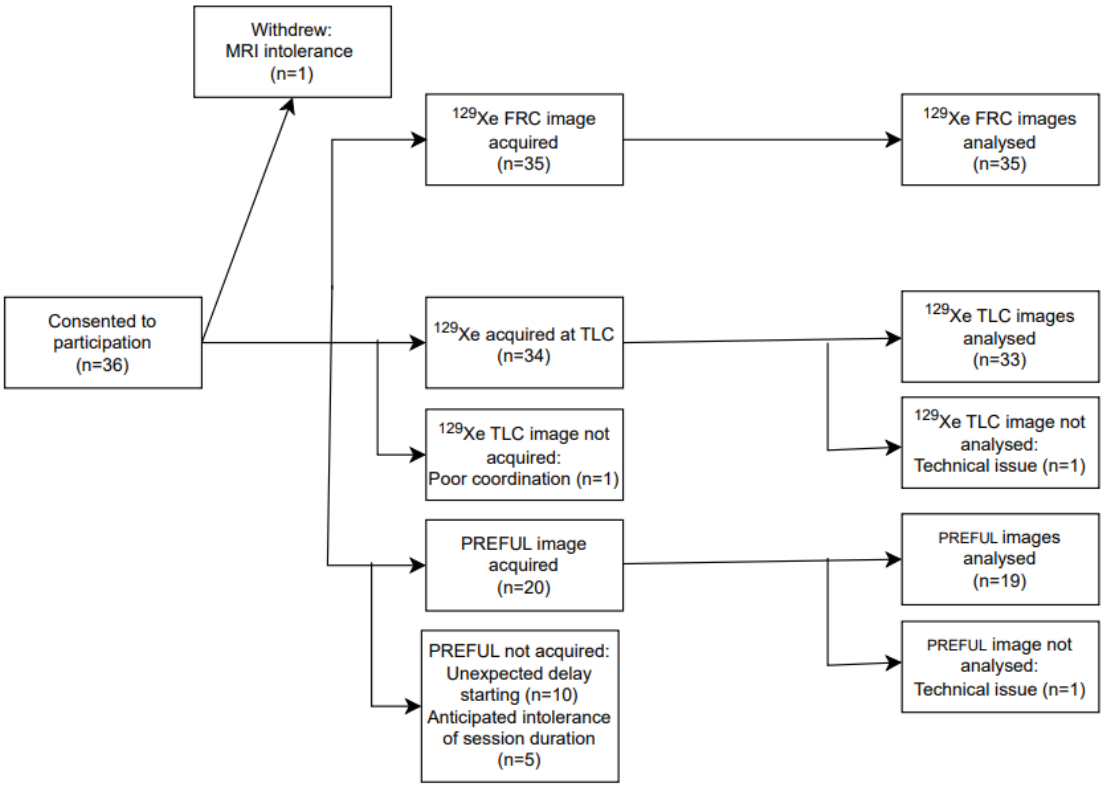


Figure 35: Flow diagram summarising the number of MRI scans acquired an analysed for ^{129}Xe FRC and TLC images, and ^{1}H PREFUL images.

In the study population, the average age of diagnosis was three years of age. 29 participants (82.9%) had ultrastructural cilial abnormalities, all those without ultrastructural abnormalities had PCD diagnosis confirmed by genetic testing. Five individuals (14%) had a positive pseudomonas aeruginosa culture within 12 months prior to the study visit. Most participants (n=30, 85.7%) had at least one course of antibiotics to treat a lower respiratory tract infection in the previous 12 months, the number of courses was varied: median 2.5 courses, range 0-9. Spirometry was performed in all participants, data for one participant was excluded as despite multiple attempts their technique did not meet recognised standards (269). There was no evidence of obstruction on spirometry (FEV_1/FVC z-score >-1.64) in 19 out of 34 participants (55.8%). In those with abnormal spirometry (n=15, 44.3%) (FEV1/FVC z-score <-1.64), the severity of obstruction varied: three had mild obstruction (FEV1 z-score >-2); two moderate obstruction (FEV_1 z-score -2 to -2.5); three moderate-severe obstruction (FEV_1 z-score -2.5 to -3); five had severe obstruction (FEV_1 z-score -3 to -4); two had very severe obstruction (FEV_1 z-score <-4). A summary of participant demographics, lung function and ^{129}Xe and ^{1}H metrics are shown in Table 15.

Table 15: Participant demographics including ultrastructural defects, QOL-PCD scores and lung function metrics. Data is presented as mean ± SD or median (IQR) depending on if data normally distributed. IDA=inner dynein arm defect, ODA= outer dynein arm defect, MTD= microtubular disarrangement. PsA=Pseudomonas aeruginosa.

	Data reported as mean ±SD or median (IQR)		
N. (unless stated)	35		
Sex	19 male (54%)		
Age (years)	12.3 ± 3.3		
Height (cms)	149.3 ± 17.2		
Weight (kgs)	44.1 ± 16.5		
Age at diagnosis (years)	3 (0-6)		
Ultrastructural defect			
IDA or MTD only	8 (22.9%)		
ODA only	8 (22.9%)		
IDA and ODA	13 (37.1%)		
No defect	4 (11.4%)		
No result	2 (5.7%)		
Number of antibiotic courses in last 12 months (oral/IV, planned/ unplanned)	2.5 (3)		
PsA (cultured in last 12 months)	5 (14%)		
ACT frequency (sessions/day)			
Prescribed	2.0 (2.0-2.0)		
Self-reported	1.0 (0.5-2.0)		
QOL-PCD domain	Child (n=17)	Adolescent (n=16)	Parent proxy for child (n=16)
Physical functioning	69.4 ± 21.0%	80.6 ± 26.5%	71.3 ± 26.8%
Emotional functioning	69.6 ± 16.7%	80.2 ± 16.9%	67.4 ± 18.8%
Treatment burden	62.3 ± 27.1%	72.2 ± 23.3%	63.0 ± 19.2%
Role	N/A	78.4 ± 20.8%	N/A
Social functioning	71.0 ± 30.2%	70.8 ± 19.3 %	75.7 ± 17.3%
Vitality	N/A	59.7 ± 27.8%	N/A
Upper respiratory symptoms	63.1 ± 26.7%	74.2 ± 15.6%	47.9 ± 18.4%
Lower respiratory symptoms	58.0 ± 22.9%	75.6 ± 15.8%	55.4 ± 19.7%
Hearing	69.6 ± 26.2%	93.2 ± 9.2%	77.8 ± 21.8%
Eating and weight	N/A	N/A	76.2 ± 27.8%
Health perception	N/A	N/A	67.0 ± 16.9%
Spirometry	(*n=34)*		
FEV_1 z-score	-1.5 ± 1.7		
% predicted	81.3 ± 20.6		
FVC z-score	-0.7 ± 1.5		
% predicted	90.1 ± 21.6		
FEV_1/FVC (z-score)	-1.5 ± 1.3		
% predicted	87.2 ± 11.7		

Comparing clinical demographics with FEV_1: no correlation was seen between FEV_1 and age (r=0.15, p=0.41) or age of diagnosis (r=0.37, p=0.03). Whilst those normal cilial ultrastructure had the highest FEV_1 z-score and those with ODA and IDA defects the lowest, no significant difference in FEV_1 z-score was seen between any of the ultrastructural defect groups: outer dynein arm defect (ODA) -1.0 ± 1.7, IDA or MTD -1.6 ± 1.5, ODA and IDA -2.3 ± 1.6, normal 0.7 ± 1.1. In the context of exacerbations and significant sputum cultures: no correlation was seen between FEV_1 and the number of courses of antibiotics in the previous 12 months (r=-0.05; p=0.8); no significant difference in FEV_1 was seen between those who had grown PsA in the last 12 months compared to those who had not (mean difference 0.33, p=0.7). Across the three versions of the QOL-PCD, moderate correlations (r>0.51) were found between FEV_1 z-score and social function (adolescent version only, r=0.75, p=0.001), emotional function QOL-PCD (chid version only r=0.69, p=0.004), eating and weight (parent proxy only r=0.57, p=0.03) and heath perception (parent proxy only, r=0.54, p=0.04). No correlations were seen with FEV_1 and physical functioning or lower respiratory symptom scores in any of the versions of QOL-PCD.

4.3.2 ^{129}Xe Ventilation MRI shows lung health in PCD is heterogeneous.

A summary of ^{129}Xe derived metrics are provided in Table 16 and an image from each of the participants in Figure 36. Most children had visible ventilation abnormalities, but the extent of ventilation abnormalities was heterogeneous across the group ranging from mild to more extensive (median ^{129}Xe VDP 6.3%, IQR 1.3-16.1%), as shown by two examples in Figure 37. 29 participants (82.8%) had a VDP above what is seen in healthy children; ^{129}Xe VDP was >1.2%, which is the upper limit of normal previously reported (267). Six children (17.1%) had very minimal ventilation abnormalities, with VDP ≤1.2%, comparable with that seen in healthy children. 25 participants (71.4%) had a higher than normal heterogeneity of ventilation (^{129}Xe VHI >9.5% (267)). Although VDP is not normally distributed, it is noted that the standard deviation of VDP in this population was 8.0, greater than the SD reported by Smith *et al.* (128).

Table 16: ^{129}Xe and ^{1}H MRI metrics. Data are presented as either mean or median (IQR).

MRI metric		Data reported as mean ±SD or median (IQR)
^{129} Xe Imaging		
At EITV	VDP (%)	6.3 (1.3-16.1)
	VHI (%)	11.3 ± 3.2
	LVP (%)	13.2 ±2.7
At TLC	VDP (%)	3.8 (1.4-11.9) *(n=33)*
	VHI (%)	10.3 ± 2.9 *(n=33)*
^{1}H imaging		
PREFUL	VDP (%)	6.0 ± 4.7 *(n=19)*
	VHI (%)	10.3 ± 1.8 *(n=19)*

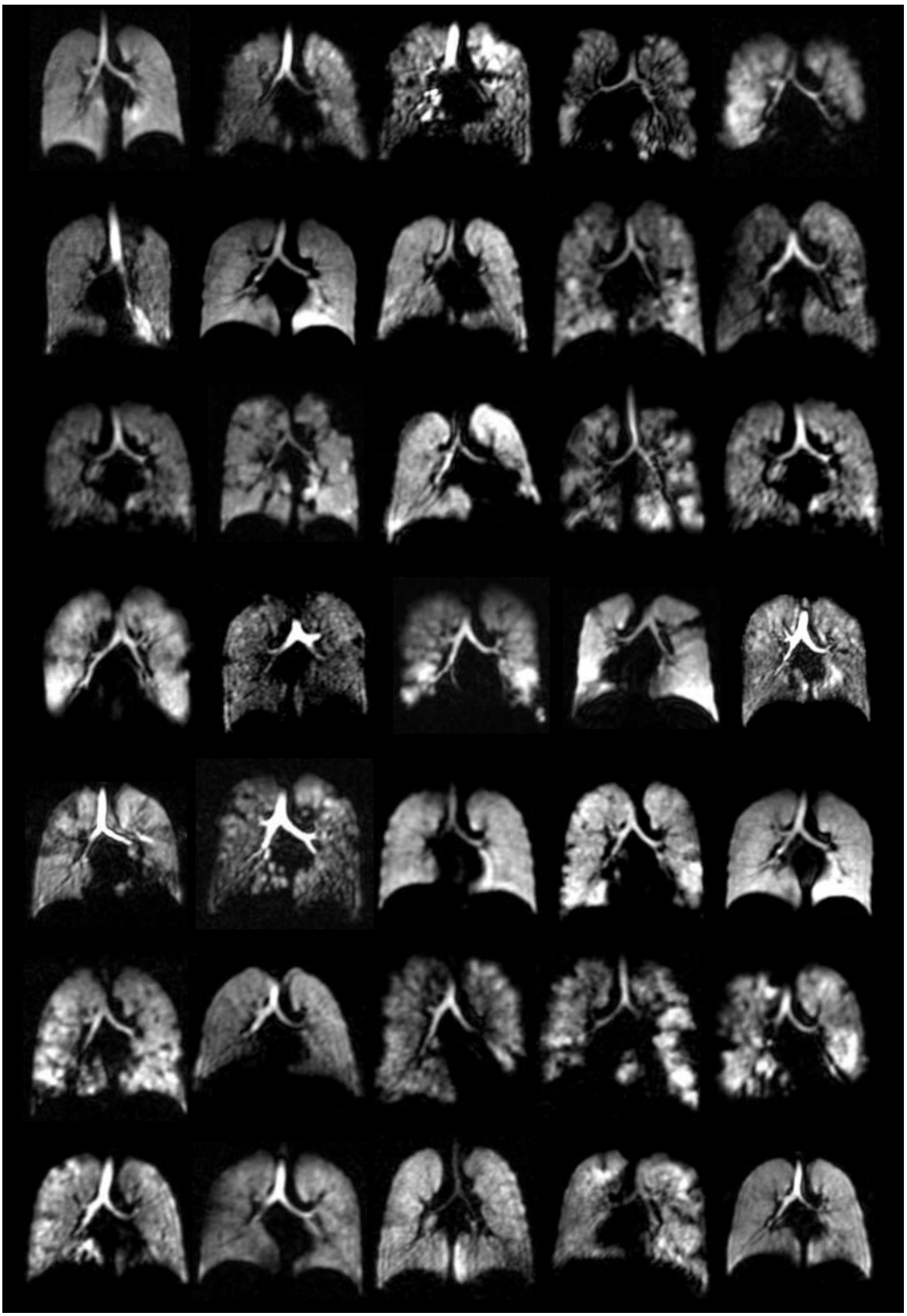


Figure 36: ^{129}Xe Ventilation MRI for all participants in the study. Each image depicts a different participant, showing a central slice from their ^{129}Xe Ventilation MRI. Images within this figure have been reduced in size to allow visual comparison between cases.

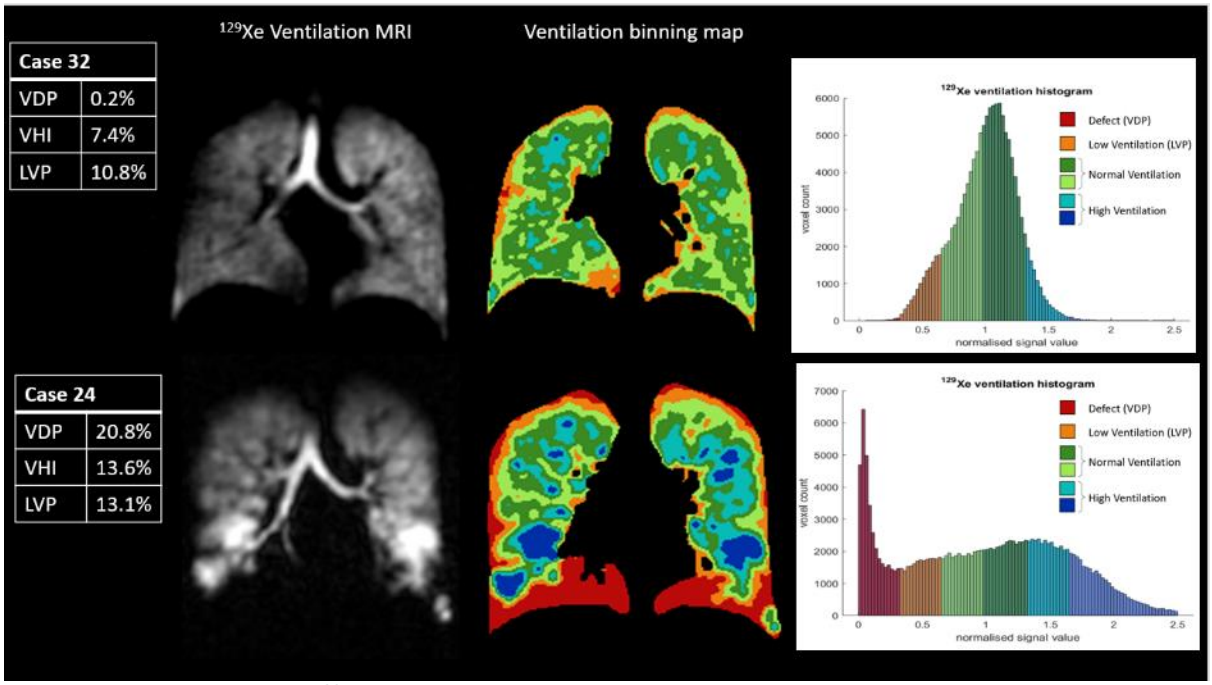


Figure 37: Examples of ^{129}Xe ventilation images with their corresponding binning map and ventilation histogram to demonstrate the range of abnormality seen in the participants; Case 32 with very mild disease and normal VDP and VHI, and Case 24 with more severe disease.

Whilst 3D analysis of ventilation abnormalities is beyond the scope of this thesis, screenshots of 3D images of one case is provided in Figure 38 to illustrate the 3D nature of defects seen.

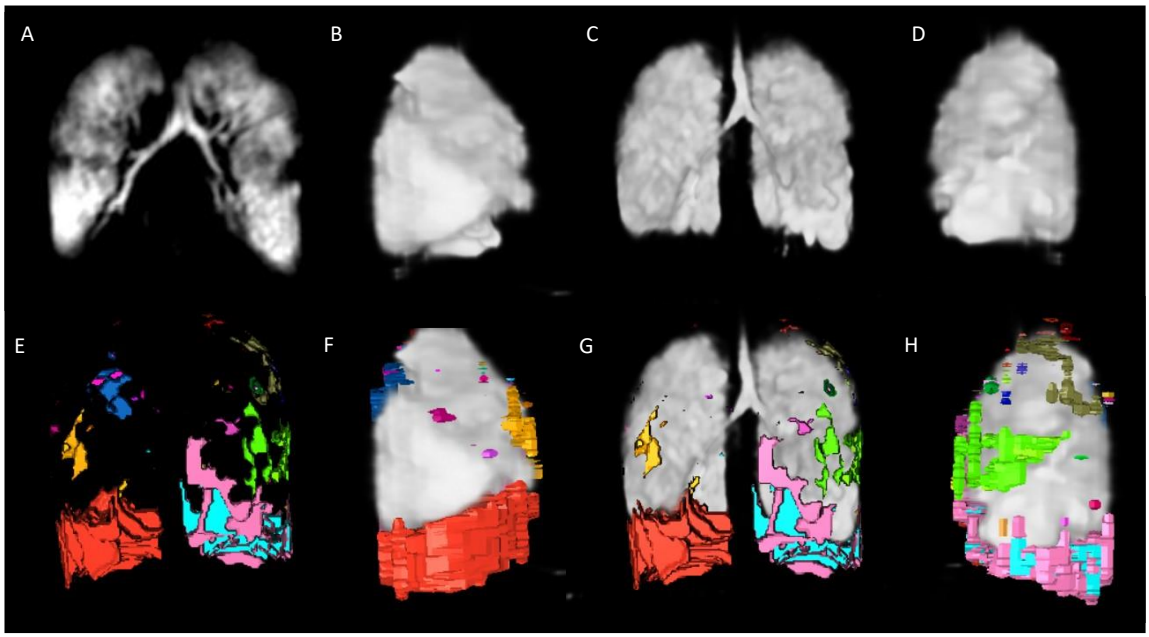


Figure 38: 3D visualisation of ^{129}Xe MRI images of Case 16 produced using Simpleware Scan IP (Synopsys, Inc, 2022) A depicts a 2D coronal central slice. B, C and D depict 3D anatomical views of ventilation, looking anteriorly (C), at the right lung (B), left lung (D). E shows the ventilation defect mask, with each colour showing a contiguous defect. F-H show the ventilation defect mask applied over the ventilation image looking anteriorly (F), at the right lung (G), left lung (H).

^{129}Xe VDP was similar between males and females, no correlation was seen with either age (r=0.07, p=0.68); or age of diagnosis (r=-0.31, p=0.07) (Figure 39A, E and F). 14 participants (40%) had situs inversus, no significant difference in ^{129}Xe VDP was seen between those with situs solitus and those with situs inversus (Figure 39C). Differences in ^{129}Xe VDP were seen when participants were grouped by ultrastructural defect; ^{129}Xe VDP was highest in those with either inner dynein arm (IDA) defects or microtubular disorganisation (MTD);(data presented as median (IQR): outer dynein arm defect (ODA) 5.8% (1.8-7.1%), IDA or MTD 11.0% (2.9-18.3%), ODA and IDA 8.9% (4.6-20.5%), normal (and a genetic diagnosis of PCD) 0.4% (0.3-2.9%). Whilst there was no statistically significant difference between the IDA or MTD defect and the normal cilial ultrastructure groups, a statistically significant group difference was seen between the IDA and ODA and normal cilial ultrastructure groups: IDA/MTD v ODA p>0.99; IDA/MTD v IDA and ODA p>0.99; IDA/MTD v normal p=0.15; ODA v IDA and ODA 0.91; ODA v normal p=0.91; IDA and ODA v normal p=0.047 (Figure 39**Error! R eference source not found.**B). ^{129}Xe VDP was higher in individuals (n=5) who had cultured Pseudomonas aeruginosa in the previous 12 months compared to those who had not (median group ^{129}Xe VDP 11.0% v 5.4%), but this difference was not statistically significant (p=0.15) (Figure 39D).

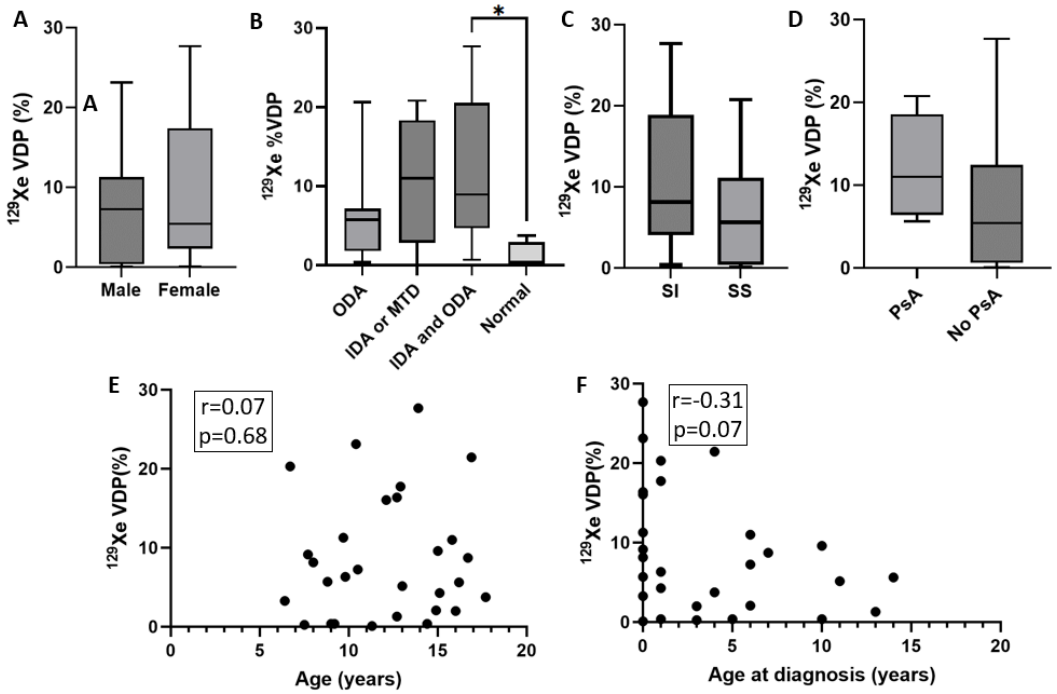


Figure 39: Relationship of ^{129}Xe VDP to sex (A), cilial ultrastructural defects (B), situs (C), positive pseudomonas growth in last 12 months (D), age (E) and age of diagnosis (F). SI: situs inversus, SS: situs solitus, ODA: outer dynein arm defect, IDA: inner dynein arm defect, MTD: microtubular disorganisation, normal: no ultrastructural defect identified.

These results confirm the hypothesis that lung health in PCD is heterogeneous, as assessed by MRI-derived ventilation defect percentage (H3).

4.3.3 MRI metrics correlate with lung function, but not with quality of life.

There was agreement between lung health assessed by ^{129}Xe ventilation MRI metrics and spirometry. A moderate correlation was seen between ^{129}Xe VDP and FEV_1, FVC and FEV1/FVC, the strongest and most statistically significant correlation being with FEV_1/FVC z-score: FEV_1 z-score (Spearman's rank r=-0.54, p=0.001); FVC z-score (r=-0.42, p=0.01); FEV_1/FVC z-score (r=-0.57, p<0.001) (Figure 40A-C). ^{129}Xe VDP was more sensitive to detect abnormalities than FEV_1; 16 participants (47%) had a normal FEV_1 (z-score > -1.6) yet 12 of these 16 individuals (75%) had raised VDP compared to healthy children (^{129}Xe VDP>1.2%). Conversely, three children had abnormal FEV_1 and normal ^{129}Xe VDP. Of the children with normal FEV1 and abnormal VDP, two had a restrictive pattern on spirometry (reduced FEV_1 and FVC yet normal FEV_1/FVC), as opposed to the more expected obstructive pattern in PCD. Examples of cases in which only one of the two lung health measures were abnormal (either FEV_1 or ^{129}Xe VDP) are shown in Figure 41.

^{129}Xe VHI correlated moderately with spirometry: FEV_1 z-score (r=-0.52, p=0.002); FVC z-score (r=-0.38, p=0.03), and FEV_1/FVC z-score (r=-0.58, p<0.001) (Figure 40D-F).

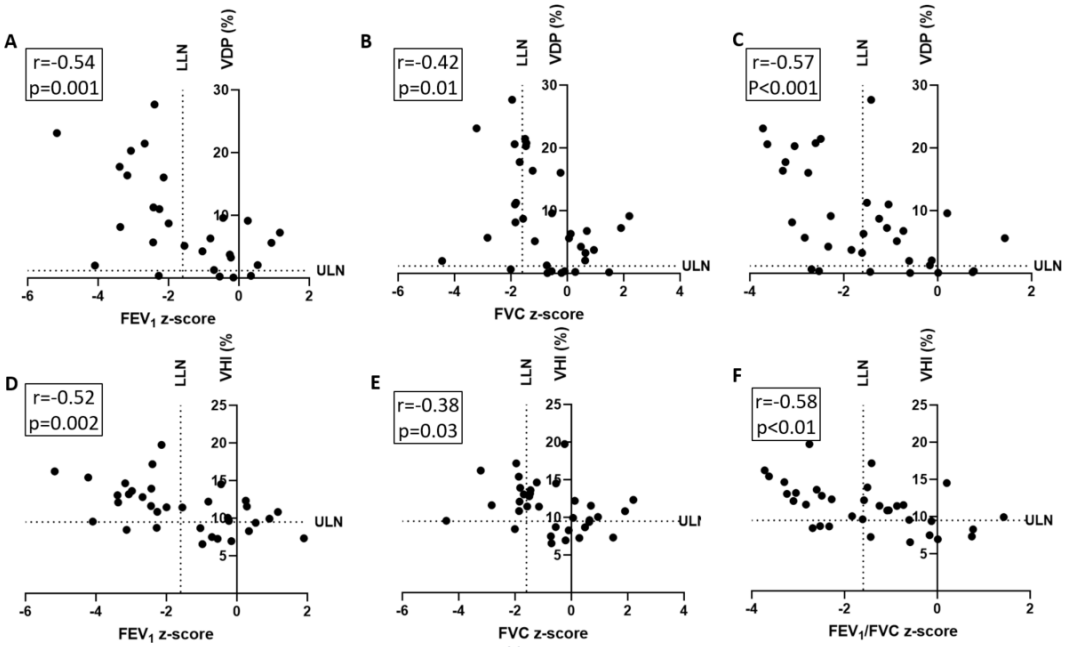


Figure 40: Spearman's rank correlations of ^{129}Xe VDP with spirometry metrics. Dotted lines indicate FEV_1, FVC and FEV_1/FVC lower limit of normal (LLN= -1.6), and VDP upper limit of normal (ULN= 1.2%).

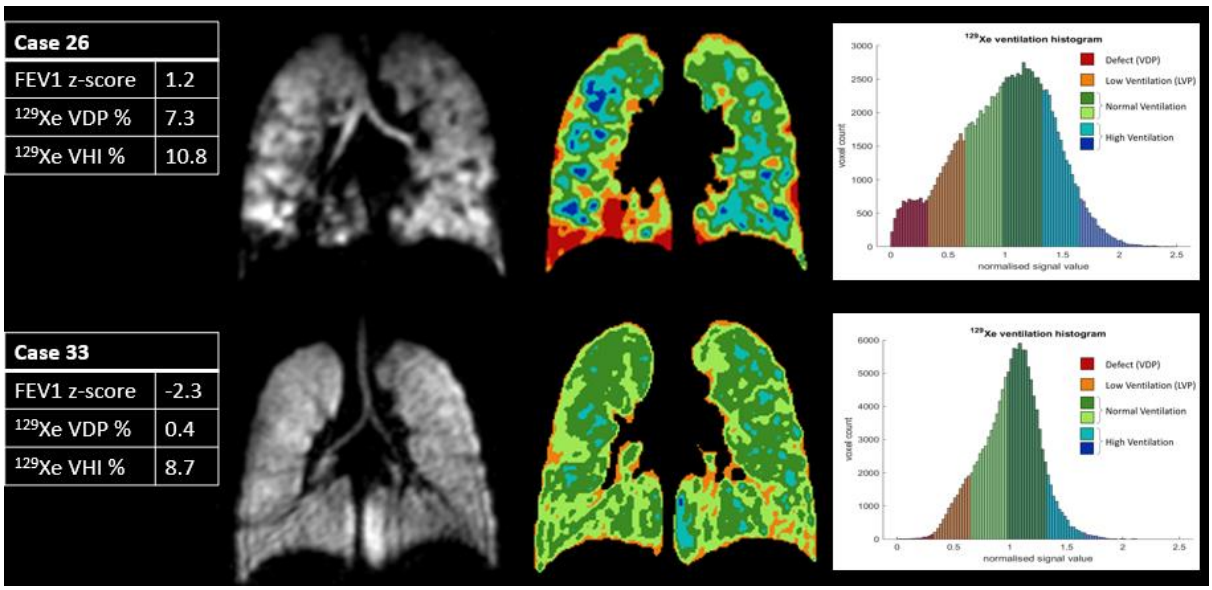


Figure 41: ^{129}Xe imaging data from an example cases with discordant spirometry and 129Xe VDP findings: Case 26 with normal FEV_1 but abnormal VDP; Case 33 with abnormal FEV_1 (moderate obstruction) but normal VDP.

When considering the proportion of the lungs with low ventilation, ^{129}Xe LVP appeared less informative than ^{129}Xe VDP. The correlation of LVP with FEV_1 z-score was weaker than VDP with FEV_1 (r=-0.41, p=0.02), but the addition of LVP to VDP marginally strengthened the correlation with FEV_1 (VDP+LVP r=0.57, p<0.001) (Figure 42).

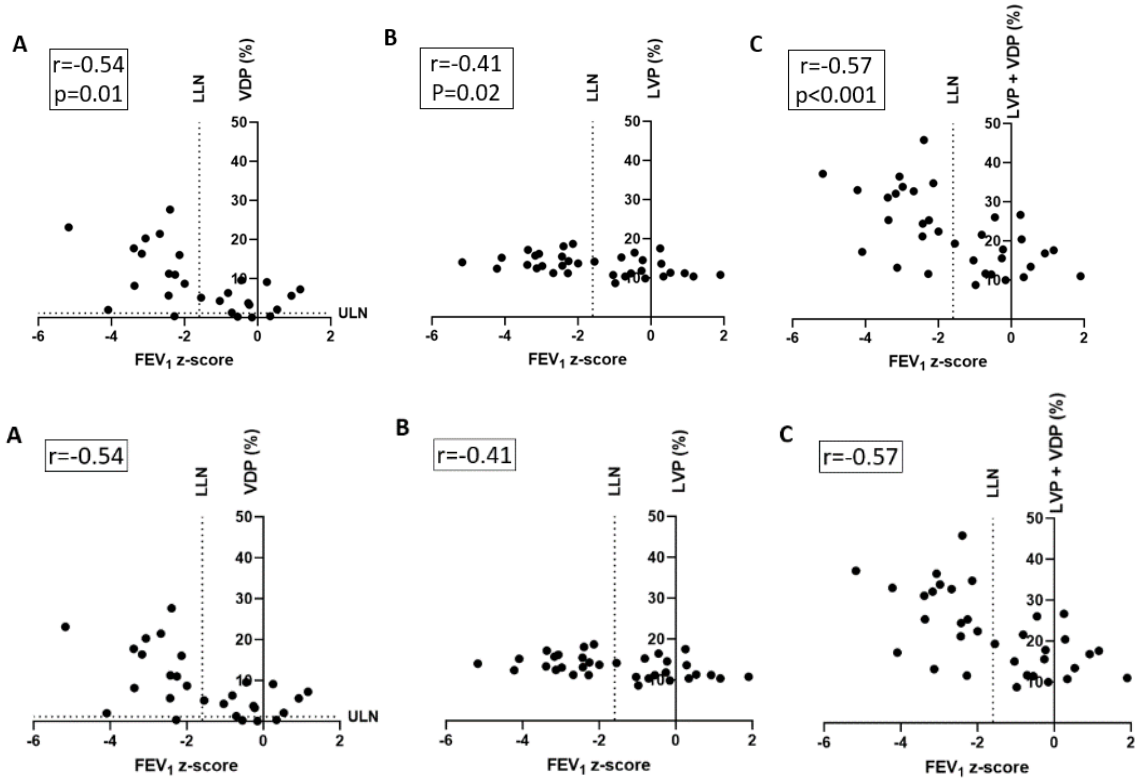


Figure 42: Spearman's rank correlations of FEV1 z-score with ^{129}Xe VDP (A), LVP (B) and VDP +LVP (C). Dotted lines indicate the upper limit of normal for ^{129}Xe VDP (A) and lower limit of normal for FEV_1 (A-C).

There was no correlation between ^{129}Xe VDP and the number of antibiotics administered in the last 12 months. Across the three versions of the QOL-PCD, only one domain showed a moderate correlation with ^{129}Xe VDP (social functioning of adolescent version, r=-0.57, p=0.02).

4.3.4 Ventilation commonly improves at higher lung inflation volumes.

31 out of 35 participants were successfully assessed at both EITV and TLC with ^{129}Xe Ventilation MRI; two individuals were unable to co-ordinate the TLC breathing manoeuvre; two TLC images were excluded due to acquisition errors.

As illustrated by Figure 43, for most individuals ventilation was improved at TLC compared to EITV; there was a reduction in ventilation defects at TLC and areas of ventilation were more homogenous. There was visual improvement of some ventilation defects, but other defects persisted (Figure 44).

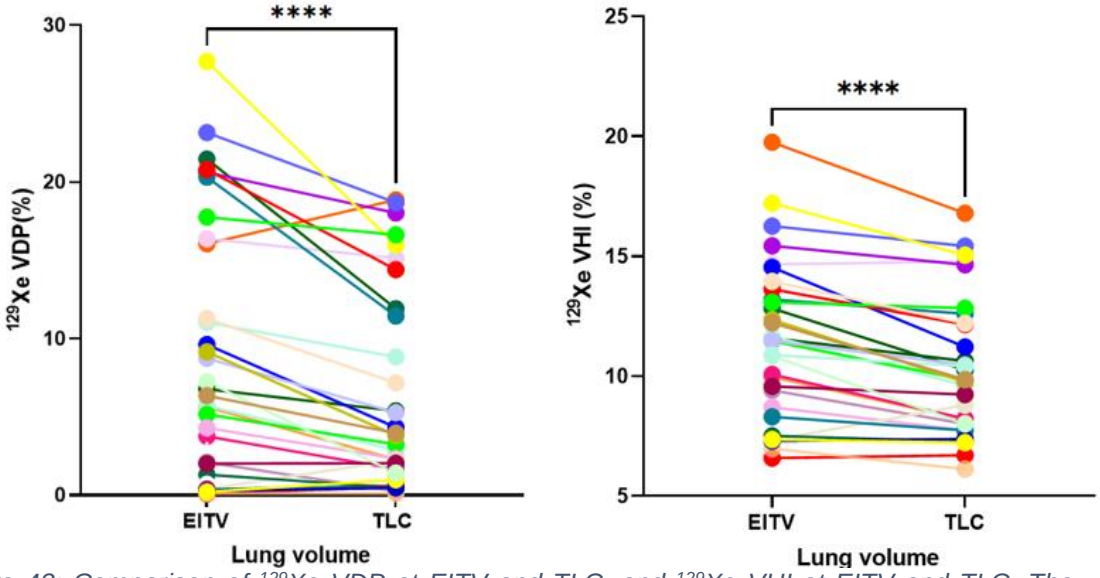
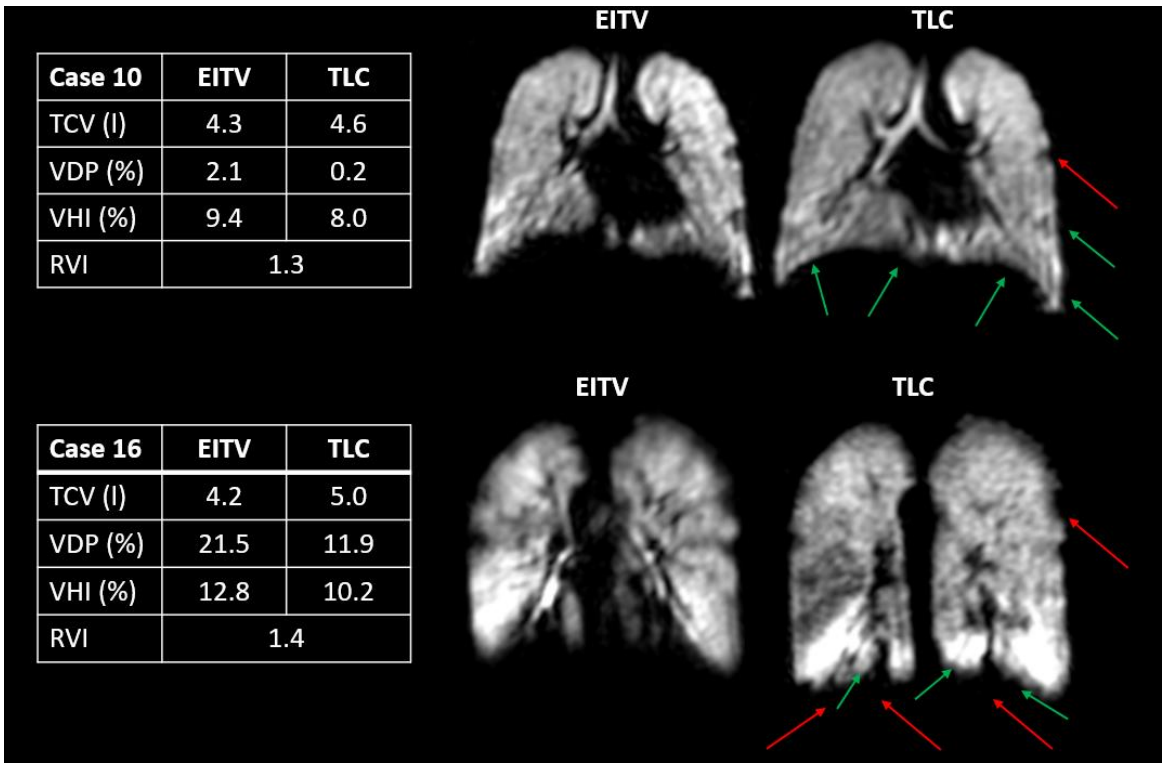


*Figure 43: Comparison of ^{129}Xe VDP at EITV and TLC, and ^{129}Xe VHI at EITV and TLC. The graphs depict before-after plots of ^{129}Xe VDP at EITV and TLC, and ^{129}Xe VHI at EITV for individual cases. Each colour represents data for one participant **** indicated a statistically significant difference (p<0.0001).*



Case 10	EITV	TLC
TCV (l)	4.3	4.6
VDP (%)	2.1	0.2
VHI (%)	9.4	8.0
RVI	1.3	

Case 16	EITV	TLC
TCV (l)	4.2	5.0
VDP (%)	21.5	11.9
VHI (%)	12.8	10.2
RVI	1.4	

Figure 44: Two case example where ventilation, assessed by ^{129}Xe images and metrics improved at TLC compared to EITV. Arrows indicate defects which have improved (green) and those which have persisted (red). Although both cases had a similar RVI, Case 10 with a lower VDP at EITV had almost a full resolution of defects at TLC, whereas for Case 16, despite resolution of some defects at TLC, some persisted and visible large defects remained.

When comparing images acquired at TLC and EITV, there was a significant improvement ($p<0.0001$) in ventilation metrics at TLC (data expressed as median difference (97.06% CI)): VDP -2.1(-3.5 to 1.1)%; VHI -1.0 (-1.8 to -0.6) .

Considering the change in VDP in relation to the change in lung volume; 25/33 69.7% of children had a reversible volume index (RVI) >1 indicating resolution of some defects at a higher lung volume (Median (IQR) improvement in VDP 2.0 (0-4.5%)). There was a moderate correlation between RVI and VDP at EITV ($r=0.61$, $p<0.001$) indicating those with more defects at EITV had more resolution of defects at TLC than those with mild disease (Figure 45). Figure 44 depicts two individuals with a similar RVIs, one case with mild disease and one with severe disease; this illustrates how in mild disease reversibility of defects can result in a very low VDP, in severe disease a similar level of reversibility is seen yet significant defects remain at TLC.

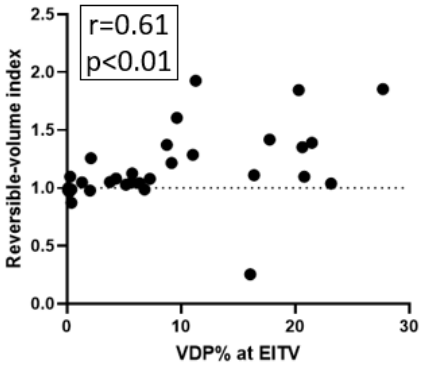


Figure 45: Scatterplot and Spearman's rank correlation of ^{129}Xe VDP at EITV and the reversible-volume index (RVI) (the dotted line showing RVI=1 represents equal change in TCV and VV).

4.3.5 Ventilation MRI is more sensitive to detecting abnormalities than structural lung MRI.

^{1}H SSFP images were acquired and were deemed readable for all participants at baseline. Of the 34 participants who performed the breathing manoeuvre to obtain an image close to residual volume (RV): 31 (91.7%) of the pre-ACT scans were readable; three were unreadable pre-ACT but images acquired 4-hours post-ACT were readable. UTE scans were performed for all participants (n=35). The pre-ACT scans were deemed readable for 24/35 (68.6%) participants, a further five participants (14.3%) had poor quality pre-ACT scans but scans from later timepoints were readable (n=3 at 4-hours post-ACT timepoint, n=2 at post-ACT timepoint). In the remaining six cases: one individual only tolerated the pre-ACT scan but the images unreadable due to motion; image acquisition issues limited interpretation to collapse but not bronchiectasis (n=3) or collapse and bronchiectasis but not mucus plugging or consolidation (n=2).

From the structural images it was possible to ascertain that: 19/34 (55.9%) participants with a readable UTE scans participants had a region of collapse; 18/31 (58.1%) participants with an adequately readable UTE had bronchiectasis; 17 of 34 (50.0%) participants with a readable RV image had evidence of air trapping. Whilst full regional assessment of structural abnormalities was not completed, it was notable that all participants with collapse identified on their UTE had a region of collapse identified in their middle lobe, located on the right in those with situs solitus and left in those with situs inversus. Ventilation defects corresponding to the areas of collapse were visible on ^{129}Xe imaging (examples of UTE, SPGR and ^{129}Xe ventilation images of two individuals with middle lobe collapse are shown in Figure 46).

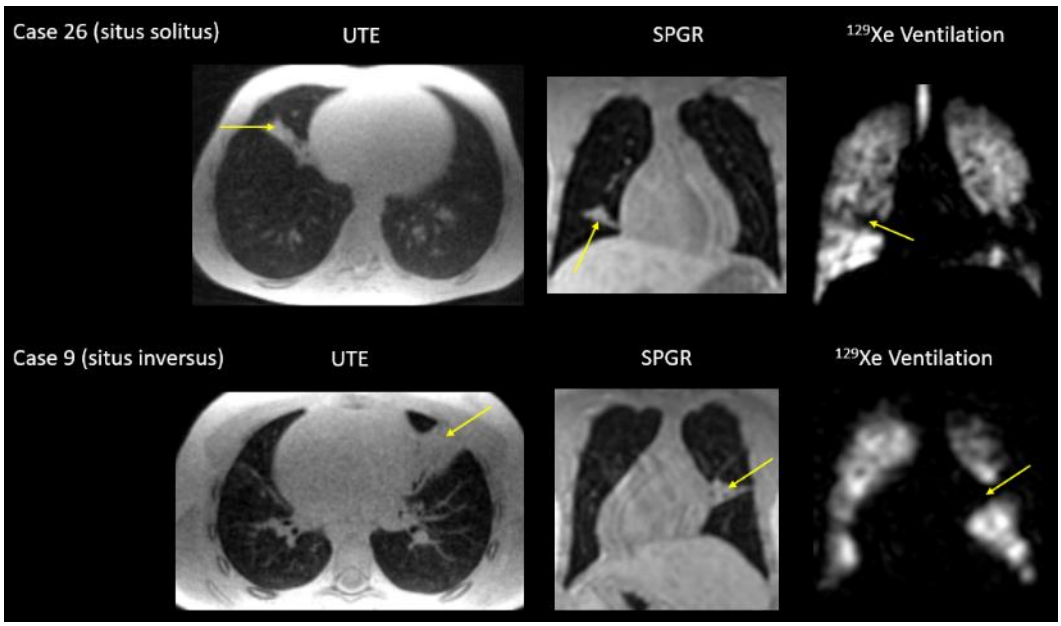


Figure 46: Examples of two cases with collapse in the middle lobe, located on the right in the case with situs solitus (Case 26) and on the left in the case with situs inversus (Case 9). A UTE, SPGR and 129Xe Ventilation image slice is provided for each case, arrows indicate area of collapse.

When visually comparing structural abnormalities identified by ^{1}H MRI with ventilation abnormalities identified by ^{129}Xe ventilation MRI there was evidence of where abnormalities were detected by both types of imaging, and areas where ^{129}Xe imaging was more sensitive to detect abnormalities, for example as shown in Case 28 (Figure 47).

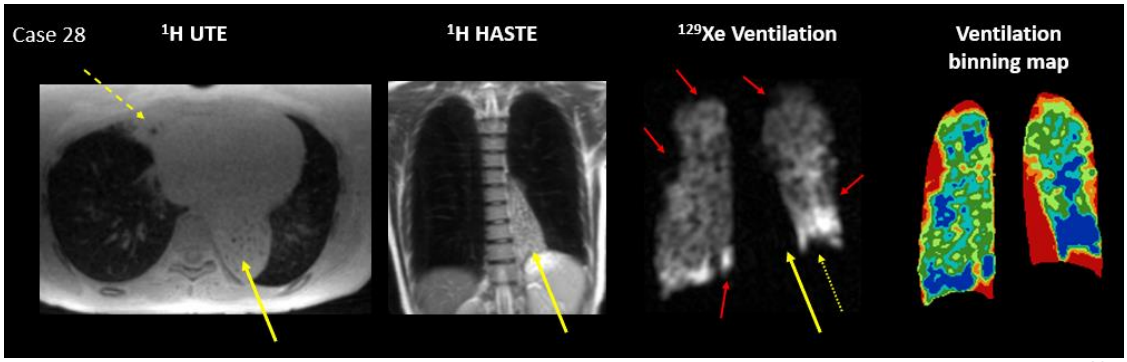


Figure 47: Case example to illustrate comparison of ^{1}H (UTE and HASTE images) and ^{129}Xe MRI (Ventilation image and binning map) findings. Arrows indicate areas where bronchiectasis corresponds to ^{129}Xe ventilation defect (yellow), and areas of ^{129}Xe defect with no evidence of abnormality on ^{1}H (red). Solid arrows indicate where comparison has been made on the slice depicted, dashed arrow where compassion was made with a more anterior ventilation image slice and dotted where comparison was made with a more inferior UTE slice.

When participants were grouped according to the presence of structural abnormalities, some differences in ^{129}Xe metrics were seen. More ventilation abnormalities were seen in individuals with bronchiectasis identified on UTE than those without (median difference (95.4% CI) ^{129}Xe VDP -5.4 (-9.5 to 0.9)%) although this did not reach

statistical significance (p=0.09). There was a statistically significant difference (p=0.0275) in VDP in those with an area of collapse compared to those without (based on UTE) (median difference (95.3% CI) ^{129}Xe VDP -5.0 (-9.5 to -0.5)%). There was a smaller difference seen when comparing individuals with air trapping identified on imaging acquired at RV with those without air trapping (median difference (95.1% CI) -0.9 (-3.0 to 9.8)%. No significant differences in ^{129}Xe VDP or VHI were seen when participants were grouped according to the presence of collapse, bronchiectasis, or air trapping.

Assessment of ventilation with ^{1}H PREFUL free-breathing MRI

19 participants were also assessed with ^{1}H PREFUL free-breathing MRI. As shown in Figure 48, there was a strong correlation between ^{129}Xe VDP and ^{1}H VDP (r=0.71, p<0.001). No correlation was seen between ^{129}Xe and ^{1}H measures of ventilation heterogeneity (r=0.34, p=0.15). Metrics of ventilation abnormalities were commonly higher when assessed with ^{129}Xe than ^{1}H: (data presented as bias (95% CI) VDP +4.0 (13.5 to -5.4)%; VHI +1.7 (7.5 to -4.1)%.

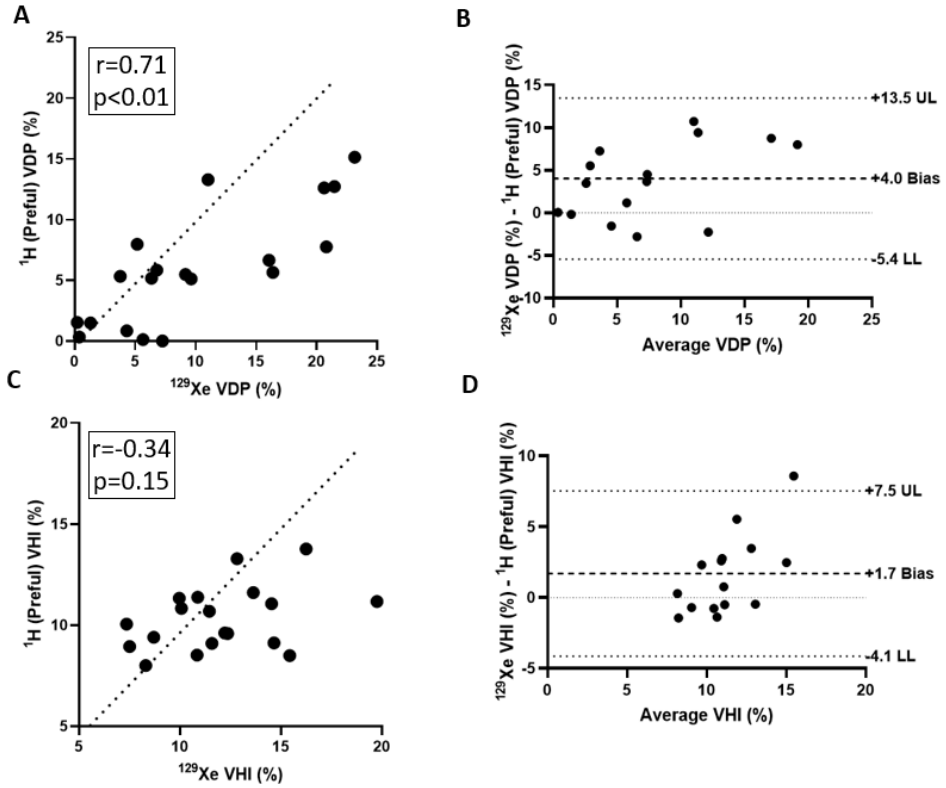
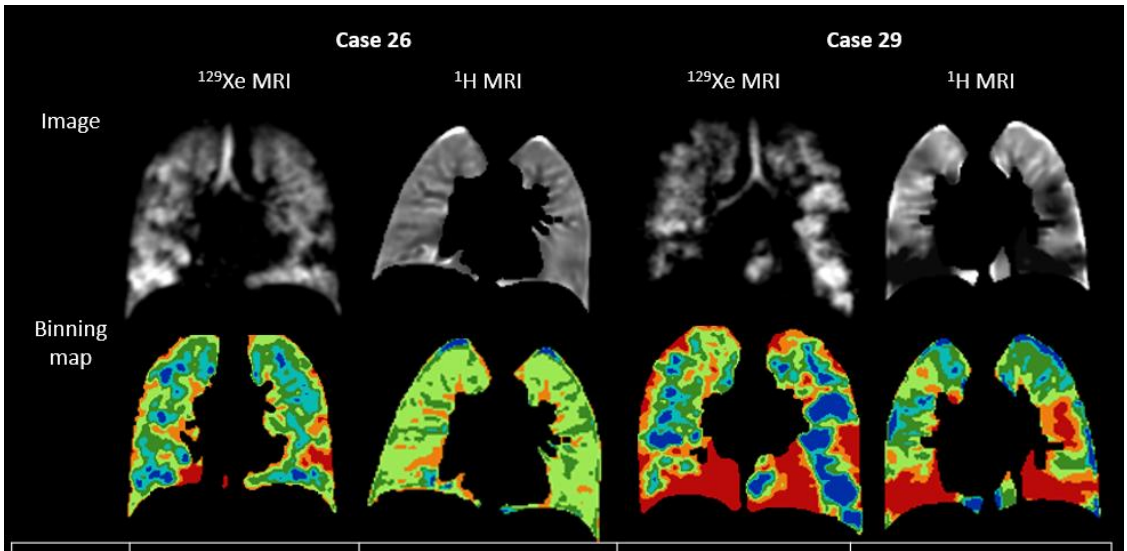


Figure 48: Comparison of ^{1}H free-breathing (Preful) and ^{129}Xe Ventilation MRI metrics. A and C depict scatterplots and Spearman's rank correlation of ^{1}H and ^{129}Xe VDP (A) and VHI (C), the dotted line illustrates r^2=1 (perfect correlation). B and D depict Bland Altman plots of average versus difference in VDP (B) and VHI (D). Bias is illustrated with a dashed line and 95% CI upper and lower limits of normal with dotted lines (UL and LL respectively).

^{129}Xe VDP was more sensitive to detecting abnormalities than ^{1}H VDP. Although an upper limit of normal (see Table 14) ^{1}H VDP for can only be estimated from a small adult data set (^{1}H VDP ULN =2.7%) (130), four of the six individuals with normal ventilation as assessed by ^{1}H VDP (^{1}H VDP<2.7%) had abnormal ventilation when assessed with ^{129}Xe MRI (^{129}Xe VDP>1.2). This divergence of assessment findings were more common in those with mild disease. Figure 49 provides two case examples to summarise the comparison of the two methods: the bias towards higher ^{129}Xe metrics than ^{1}H metrics; normal ^{129}Xe VDP with abnormal ^{1}H VDP (Case 26); visual image comparison showing some agreement in the location of ventilation defects assessed by ^{129}Xe and ^{1}H (Case 29).



VDP (%)	7.3	0.0	23.2	15.2
VHI (%)	10.8	8.5	19.9	13.8

Figure 49: Comparison of ^{129}Xe and ^{1}H images, binning maps, and metrics for two cases: Case 26 with abnormal ^{129}Xe VDP but normal ^{1}H VDP; Case 29 with abnormal ^{129}Xe VDP and ^{1}H (PREFUL) VDP.

4.4 Discussion

Assessing 35 children and young people with PCD, this study provides the largest cross-sectional ^{129}Xe MRI data set from individuals with PCD to date. Employing ^{129}Xe MRI VDP, an outcome measure which has greater sensitivity to detect abnormalities than FEV_1, it contributes further detailed information on the heterogeneous presentation of lung disease in children and young people with PCD. From these analyses we have found that lung health in children with PCD is heterogeneous, as assessed by both FEV_1 and ^{129}Xe Ventilation MRI. Employing FEV_1 to assess lung disease, 44.3% of the study population had obstructive airways disease, ranging from mild to very severe. However, ^{129}Xe Ventilation MRI showed that FEV_1 lacks sensitivity to detect abnormalities in this population: 82.8% of the study population had abnormal

ventilation assessed by VDP%; 75% (12 out of 16) of individuals with no evidence of obstructive airways disease using spirometry had evidence of ventilation abnormalities. Whilst ventilation abnormalities were common, the extent of abnormalities was varied, ranging from numerous widespread ventilation defects to minimal defects comparable with healthy controls. The clinical picture in PCD is complex; neither spirometry nor ^{129}Xe metrics (VDP and VHI) correlated with age, age of diagnosis, or number of antibiotic courses in the last 12 months, and very limited correlation was seen in with quality of life assessed by the QOL-PCD. ^{129}Xe VDP was significantly worse in those with both IDA or MTD and ODA defects compared to those with normal cilial ultrastructure. There was evidence of improvement of ventilation abnormalities at higher lung volumes and more reversibility was seen in those with milder lung disease. Whilst there was a correlation of lung health assessed by ^{129}Xe Ventilation MRI and ^{1}H VDP, ^{1}H was less sensitive to detect abnormalities in individuals with mild disease. These results confirm the hypothesis that lung health in PCD is heterogeneous, as assessed by MRI-derived ventilation defect percentage (H3).

4.4.1 A range of ventilation abnormalities are seen in PCD.

This study employed ^{129}Xe MRI to assess ventilation in children with PCD and found a range of lung health measured by ventilation defects and ventilation inhomogeneity. Hyperpolarised gas ventilation MRI (^{129}Xe and ^{3}He) has similarly identified ventilation abnormalities in previous research in children with PCD, and other similar obstructive lung diseases; CF, asthma, and prematurity-associated obstructive lung diseases (132, 133, 135, 143, 267, 270, 271). However, the variation in VDP across this study population, as assessed by the standard deviation, was greater than that previously reported in CF (128). As the pathophysiology of PCD and CF both involve impaired mucociliary clearance and retention of tenacious secretions (60) which results in peripheral airways disease, it is logical that ventilation defects and inhomogeneity are seen in both conditions. Whilst CF literature is often extrapolated to PCD, the differing appearance of PCD and CF CT scans (27) and the development of a PCD specific CT scoring tool (23) reflects the importance of understanding disease specific lung health in PCD. Ventilation defects are also seen in people with asthma (272) where airway inflammation causes variable and reversible small airways obstruction. This study identified ventilation defects in people with PCD and whilst impaired mucociliary clearance makes mucus plugging a likely cause, it is possible that ventilation abnormalities seen could also arise from airway inflammation.

The ventilation abnormalities seen in this study population show that for most individuals with PCD is impacting on their lung health, but that the severity of abnormality seen is variable. For the first time this study identified some individuals

with PCD without ventilation abnormalities. Normal ventilation was not seen in the small cohort of children with PCD assessed by Smith *et al.* (135) using ^{129}Xe MRI. The identification of individuals with PCD and normal ventilation in this study may be due to the larger sample. This study found those with IDA and ODA defects to have more significant disease than those with normal cilial ultrastructure, identified both by ^{129}Xe VDP and FEV_1. The impact of cilial ultrastructural defect on radiological disease severity has been previously explored in children with PCD. Assessing radiological abnormalities (bronchiectasis, bronchial wall thickening, atelectasis and mucus plugging) with a CT scoring system, Kinghorn *et al.* (28) found individuals with IDA or MTD abnormalities had higher disease scores. However, this finding was mainly a result of the high occurrence of mucus plugging in the IDA/MTD abnormality group and when assessed based on the other abnormalities, the combined IDA and ODA defect group had the highest disease score. As both inner and outer dynein arms provide motility to the cilia, it is logical to suspect defects in both dynein arms may have more significant impact on the efficacy of mucociliary clearance however, understanding of disease severity in PCD is in its infancy. This study provides some further evidence that cilial ultrastructural defects may influence disease severity and that ^{129}Xe Ventilation MRI provides a sensitive, radiation free of method of visually and quantitatively assessing lung health.

Previous research has suggested that an early PCD diagnosis is beneficial as it allows individuals to access specialist services, with regular surveillance and guidance for airway clearance, supported by correlations between early diagnosis and the stabilisation of lung function (121, 273, 274). However other studies have reported either no association (275) or a negative association (21) with age of diagnosis and lung function. This study found no statistically significant correlation between age or age of diagnosis and measures of lung health (^{129}Xe VDP or FEV_1). Although not statistically significant, this study found a negative correlation of VDP and age of diagnosis, indicating more ventilation abnormalities and more severe disease in those diagnosed younger, supporting the suggestion that children with more severe lung disease may be diagnosed at a younger age (21).

4.4.2 ^{129}Xe Ventilation MRI is more sensitive to detect abnormalities than current clinical outcomes or ^{1}H MRI.

Spirometry is the most commonly used outcome to monitor lung health in PCD yet previous research shows it has limitations: FEV_1 is insensitive to detect mild disease (107); FEV_1 can have poor correlation with structural changes seen on CT scans (106); FEV_1 can fluctuate during periods of stable disease (109). The findings of this study

provide further evidence to support this. We found ^{129}Xe to be more sensitive to detect abnormalities than spirometry, **75% of children and young people with PCD with normal spirometry values had significant ventilation defects**. This finding is in keeping with previous research in people with PCD (135, 276), CF (128, 131, 133, 271) and asthma (272) which also report greater sensitivity of hyperpolarised gas MRI than spirometry. As such, relying on spirometry alone for the clinical assessment of lung health may lead to instances of false assurance of normal lung heath in obstructive lung diseases. One study of children with prematurity-associated obstructive lung disease has shown discordance between spirometry and VDP, conversely with some children with abnormal spirometry having normal ventilation when assessed with ^{129}Xe MRI (267). This study also identified two individuals with evidence of obstruction (FEV_1/FVC and FEV_1 <-1.6) and normal VDP (VDP<1.2%), one of whom had no identified co-morbidity which would account for this. This demonstrates the different components of measuring lung health, FEV_1 assesses obstruction to expiratory airflow and ^{129}Xe assesses ventilation, both important and related but physiologically different.

The moderate correlation of ^{129}Xe VDP with FEV_1, FVC, and FEV_1/FVC in this study is in keeping with previous work in children with PCD; a similar correlation between ^{129}Xe VDP and FEV_1 identified by Wee *et al.* (276); a stronger correlation between ^{3}He MRI and FEV_1/FVC (135). Looking more broadly across paediatric CF and asthma, the correlation between VDP and FEV_1 has been variable, ranging from no correlation or a weak correlation (132, 270, 271) to a moderate correlation (143). Whilst the variability in correlation seen may arise from the differing study populations' disease type and severity, the variance illustrates the limitations of using spirometry alone. Spirometry is the most clinically used tool being both accessible and cost effective, but the limited and variable correlation seen in this study and previous research shows it cannot be used as a direct surrogate for Ventilation MRI.

Clinical assessment of people with PCD can be complex. The paucity of correlation between both ^{129}Xe VDP with spirometry and ^{129}Xe VDP or spirometry with quality of life, age, age of diagnosis, ultrastructural defects and number of antibiotic courses illustrates how children and young people with PCD may present with a mixed clinical picture. In keeping with previously published work which assessed for correlation between the QOL-PCD and spirometry and LCI (277), we found no correlation between QOL-PCD and spirometry and only very limited correlation of ^{129}Xe metrics with any version of the QOL-PCD, including no correlation with logically relevant domains such as lower respiratory symptoms and physical functioning. Although this study was not powered to assess for correlation, it does suggest that patient reported symptoms may not be a reliable indicator of lung health.

Using structural MRI, this study found 55.7% of children with PCD had areas of collapse and 58.1% had evidence of bronchiectasis. Whilst a detailed of comparison of MRI with CT both in terms of previous research and review of previous CT scans for the study participants is beyond the scope of this thesis, it is relevant to note pertinent research in the field. Previous research has reported bronchiectasis, bronchial wall thickening, mucus plugging, and atelectasis are common CT findings in people with PCD and may be more common in PCD than CF (24, 27). Further differences in PCD and CF have been highlighted in infancy; upper lobe collapse is seen in infants with PCD, but not in infants with CF. This study found the middle lobe, located either on the right in situs solitus or the left in situs inversus to be a common area of collapse in our PCD population. This aligns with previous research which also found the right middle lobe (25) or lingula (117) are most often affected.

With access to ^{129}Xe ventilation MRI limited to centres providing this specialist assessment, we wanted to explore the possibility to use free-breathing MRI as a surrogate to assess ventilation in children and young people with PCD. Whilst our results show a strong correlation between ^{129}Xe VDP and ^{1}H VDP, ^{129}Xe was more sensitive to assess mild disease, identifying an abnormal ^{129}Xe VDP in two-thirds of individuals with normal ^{1}H VDP. Weak correlations between ^{1}H VDP methods and both ^{129}Xe ventilation MRI and FEV_1 in children with CF have been previously reported (143). Whilst comparison of the findings with this study is limited due to differences in imaging acquisition and analysis methods, the weak correlations illustrate that whilst all markers of lung health, ^{1}H VDP, FEV_1 and ^{129}Xe MRI assess different physiological components: ^{1}H VDP signal change during free breathing; FEV_1 the volume of air in the first second of a forced exhalation manoeuvre; ^{129}Xe MRI ventilation signal within the lung fields. PREFUL imaging methods can also provide data on perfusion. Analysis of perfusion data was beyond the scope of this thesis however, ventilation and perfusion abnormalities have been found previously in people with PCD, including those with normal FEV_1 using matrix-pencil free breathing MRI methods (106). Rather than viewing ^{1}H as a surrogate to assess ventilation and an alternative to ^{129}Xe MRI, it is logical to recognise it as a separate marker which correlates with ^{129}Xe MRI and FEV_1 but provides alternative information. Free-breathing imaging techniques have not yet translated into clinical assessments and practice and as such the potential clinical role of this information is unknown.

Improvements in the distribution of ventilation at higher lung volumes was seen in most study participants, including the resolution of some ventilation defects, and a reduction in ventilation heterogeneity evidenced by reductions in VDP and VHI respectively. Deeper inspiration and breath holds facilitate opening of obstructed lung units through

collateral ventilation and interdependence, it is not surprising that similar improvements at higher lung volumes have been seen previously in people with CF (115) who also experience airway obstruction and secretion retention. The reversible-volume index (RVI), which assesses the change in ventilation in relation to the change in lung volume, was lower in this study population than in a cohort of individuals with CF (115). The lower RVI may be attributable to the lower VDP in our population, as individuals with a higher VDP have a greater potential to improve. As a key component of ACTs is ventilation to mobilise secretions, this further evidence of improved ventilation at higher lung volumes affirms elements of the underlying physiological ACT principles discussed in section 1.3.2. It is not yet known whether reversibility at higher lung volumes may influence clinical decision-making and personalisation of ACT regimens.

4.4.3 Strengths and limitations

This study used ^{129}Xe MRI, a highly sensitive outcome measure which permitted assessment of individuals with different disease severities: identifying individuals with normal spirometry and ventilation defects; individuals with abnormal spirometry and normal ventilation. ^{129}Xe MRI has provided information on the range of abnormalities seen in PCD quantitatively and qualitatively.

Conducting research with people with PCD, a community who are much less familiar with research participation than other populations such as people with CF was challenging. As PCD is a rare condition working to achieve the recruitment target was challenging. Working flexibly to open a fourth participant identification site allowed recruitment from the area to be optimised within the parameters possible of this PhD work package. The most common reasons for potential participants or their parents to decline were time off school or work, travel to the MRI unit, dislike of medical appointments or anticipation of the MRI scan process. A number of appointments were also cancelled at short notice due to participant ill health. Plans for disseminating the study findings to the patient community are in place, including the production of a short video for young people with PCD. It is hoped this will benefit patient engagement in future studies, especially those involving MRI.

As MRI is radiation-free, it is well placed for assessing children and young people, especially longitudinally. Both ^{129}Xe MRI and ^{1}H scans were well tolerated by most individuals, including those as young as 6 years old. However not all scans were able to be completed with all individuals: two children struggled with the noise of the MRI scanner, for one this prohibited any participation, the other restricted their UTE scan; two children were unable to perform the breathing manoeuvre for the TLC images;

some of the structural images were not readable due to patient motion. Whilst staff with paediatric training were present during the scan sessions for all younger participants, tolerance may have been improved with the addition of a play-based MRI familiarisation session.

Technical MRI issues affected a small number of image acquisitions. One participant was invited to return to repeat their assessment as technical issues resulted in poor images on their first visit. A susceptibility artefact was seen in the images for one participant, causing signal drop out close to the diaphragm, areas with this artefact were excluded from image analysis. Some of the participants were small and if this resulted in the coil not being optimally positioned around the chest this could affect the image quality. As such, a proforma was built by the MRI team which when positioned between the patient and the coil provided a reliable coil shape to optimise image quality.

This is the first study to assess people with PCD using free-breathing PREFUL methods. The PREFUL methods are less well established and as yet, there is no data available of the sensitivity, repeatability of the measure in this population. As the acquisition and analysis of free-breathing MRI methods varies between centres, comparison of the data set with previous literature is limited. This variance in methods also limits confidence in the upper limit of normal that was used for the ^{1}H VDP as the only healthy data set which used the same methods was a small (n=6) adult data set available from our centre. With only 7 slices acquired during PREFUL imaging, the coverage of the lung is more limited than with ^{129}Xe MRI which comprised 12 to 17 slices in the thoracic cavity depending on the patient size. Due to the different coils used for ^{129}Xe and ^{1}H image acquisition participants were removed from the scanner and repositioned in a new coil for the PREFUL image acquisition. This movement could have potentially caused inadvertent secretion clearance between the scans and is a potential source of natural variability.

Comparison of Ventilation MRI with other clinical outcomes was limited to spirometry and QOL-PCD. As a paediatric study, it was important to balance the impact for participants. High resolution CT (HRCT) scans are sometimes included as a comparator to MRI as the higher spatial resolution images can provide better discrimination of bronchiectasis and bronchial wall thickening. With PPI preference for a radiation-free imaging protocol and a primary aim of assessing ventilation abnormalities, CT was not included and comparison with historical CT scans not performed. Whilst the identification of bronchiectasis and bronchial wall thickening in PCD has been shown to be comparable between high-field (3T) MRI and CT (278), this study used a 1.5T scanner and qualitatively, some of the images acquired were not of

high enough quality to permit the assessment of bronchiectasis, bronchial wall thickening and consolidation.

As a global measure of lung function, the lung clearance index (LCI), a multiple breath washout metric is often used to assess lung health and as a comparator to spirometry and ^{129}Xe imaging. Inclusion of LCI in the study protocol was considered initially, but it was removed following advice from the funding panel to reduce the outcomes being assessed. Whilst inclusion of LCI would have provided further assessment of the study population and comparison between measures, a global measure, which is less sensitive than ^{129}Xe MRI and less commonly used than FEV_1 it would not have provided the regional information required for latter stages of the study.

The clinical data collected for the study was based on physiotherapist interviews in Chapter 3. A recent study by Chan *et al.* (267) which identified ventilation defects in some children with prematurity-associated obstructive lung disease raises the importance of birth history in the assessment of lung health. Whilst past medical history or co-morbidities were included, specific details on gestation and birth history were not collected, and so it was not possible to assess the impact of birth history on ventilation in the study population.

4.5 Conclusion

This chapter provides evidence relating to the programme theory shown in Figure 50: recognising the limitations of current markers of lung health (#1), using functional MRI to accurately assess lung health (#2) and assess impaired lung function (#3). ^{129}Xe Ventilation MRI, as a sensitive tool to detect ventilation abnormalities in PCD (#2) has provided further evidence that the clinical picture of PCD is complex: ventilation defects are seen in most children with PCD (#3); the extent of ventilation abnormalities are heterogenous; whilst ^{129}Xe MRI VDP correlates with FEV_1, ventilation defects are seen in most of those with normal lung function (#1); as the QOL-PCD domains have a very weak correlation with ventilation abnormalities, patient and parent reported symptoms may not be a reliable indicator of lung health (#1). This confirms the hypothesis that lung health in PCD is heterogeneous, as assessed by MRI-derived ventilation defect percentage (H3).

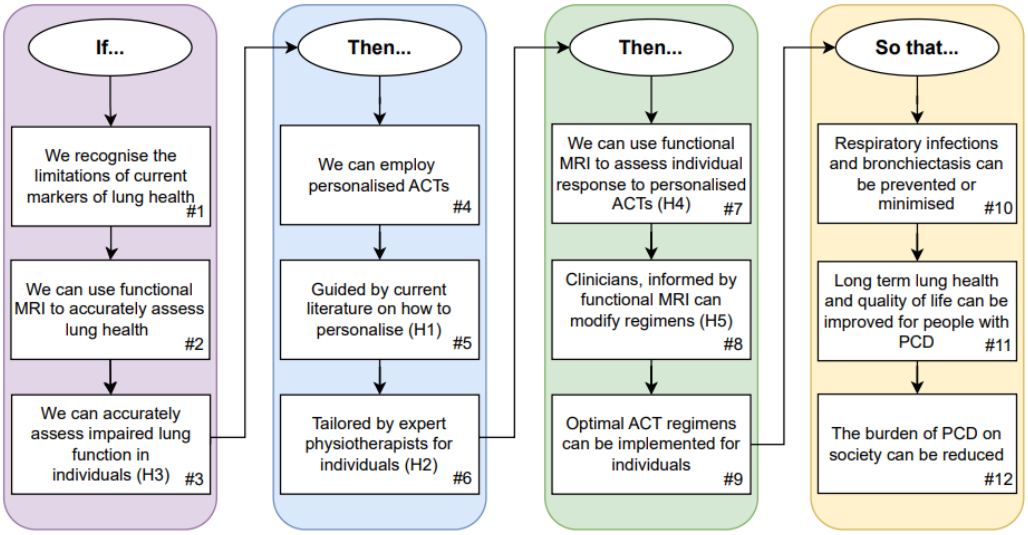


Figure 50: Programme theory for the thesis.

Reflecting back in the context of the ACT personalisation model (Section 3.3.3), this information aligns with cues about individual lung health (Figure 51, Box C1). It remains unknown if we can use functional MRI to assess individual response to ACTs (H4) or if clinicians informed by MRI modify regimens (H5). The pathophysiology of PCD makes it logical to propose that the ventilation abnormalities seen in PCD using ^{129}Xe Ventilation MRI are most likely to be a result of mucus obstructing the airways. As the primary method of managing impaired mucus clearance in PCD are the completion of an ACT which has been personalised for the individual, it is important to establish if completion of an ACT regimen does affect ventilation abnormalities.

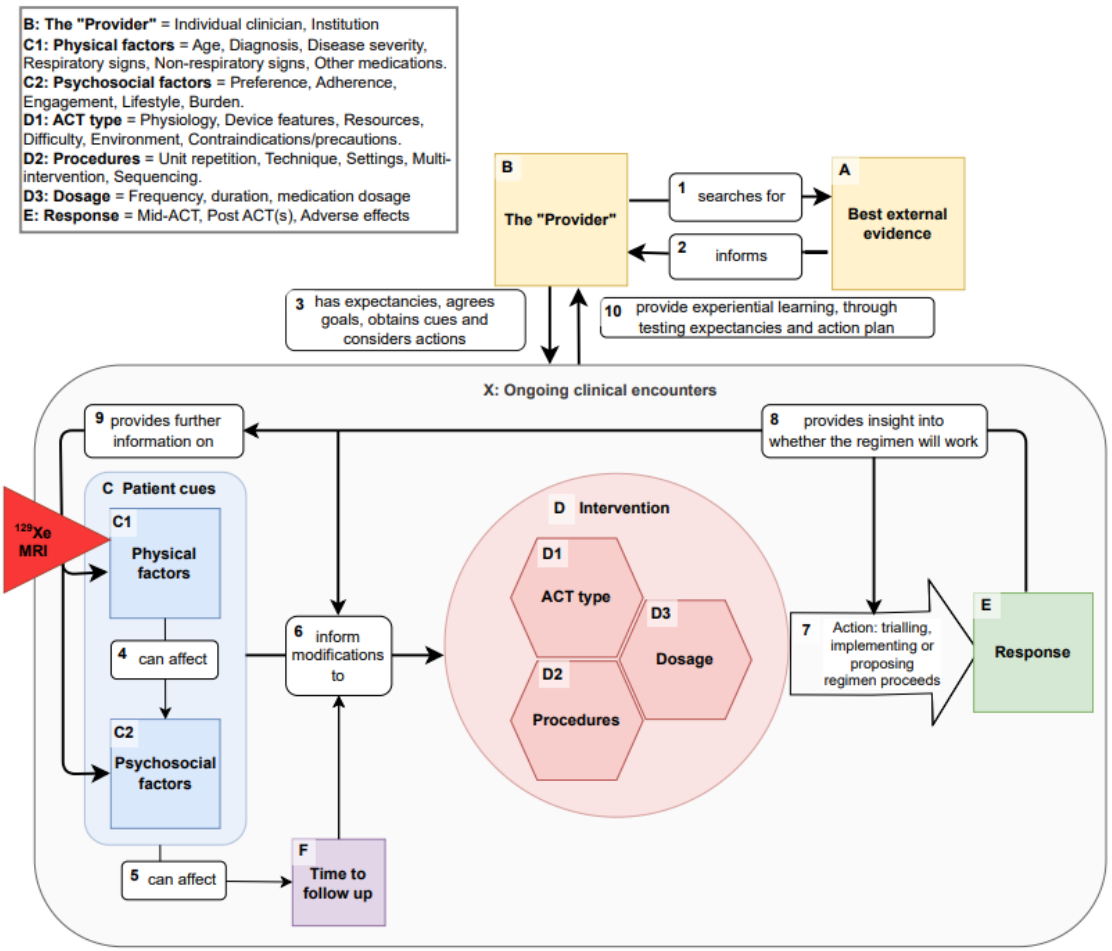


Figure 51: The ACT personalisation model (version 2) with the introduction of ^{129}Xe MRI as a physical factor providing a patient cue.

Chapter 5: Assessing the effects of personalised ACT regimens using functional imaging; a controlled before-and-after study.

5.1 Introduction and objectives

In review of this thesis so far: Chapter 1 summarised that personalised ACTs which aim to manipulate ventilation to facilitate clearance of secretions from the airways, are a key component of the management of PCD; Chapter 2 presented a synopsis of factors which should be considered when personalising ACT regimens, identified by a scoping review of current literature; Chapter 3 made explicit the tacit decision-making of physiotherapists when personalising ACT regimens, an iterative process in which uncertainties are encountered and managed; the effects of personalised ACT regimens remain unknown. Chapter 4 established that ventilation abnormalities are common in children with PCD prior to completion of an ACT session, and that the extent of ventilation abnormalities is variable. This chapter aims to address the fourth hypothesis generated in Chapter 1,

- *H4: There will be improvement in visual indicators of lung health, as measured, pre- and post-, by MRI-derived ventilation defect percentage, after personalised ACTs are completed* (see Table 2).

To test this hypothesis, we conducted a before and after study to quantify the short-term effects of personalised ACT regimens on lung health in children and young people with PCD.

Objectives

- To explore the natural variability in ventilation distribution in children with PCD using ^{129}Xe and ^{1} MRI.
- To conduct a controlled before and after study to assess the short-term effects of an individualised airway clearance regimen on regional lung function, versus no intervention, over 4-hours using ^{129}Xe and ^{1}H MRI in children and young people with PCD.
- To assess the correlation and agreement between ^{129}Xe and ^{1}H MRI pre, post, and 4-hours post-ACT.

5.2 Methods

The data within this chapter and Chapter 4 were collected as one single study data set, the data are presented as two separate chapters.

5.2.1 Sample

As all participants competing this study were included in the cross-sectional study, the sampling methods are all as per Section 4.2.1.

5.2.2 Recruitment

All participants were recruited as previously described in Section 4.2.2; no additional recruitment was required.

5.2.3 Allocation to group

Potential participants for the no-ACT group were identified in advance of them attending the appointment, with the aim of an equal percentage of confounding factors within the two groups. The confounding factors were agreed following discussion with three medical consultants who have experience of working with children with PCD: age, sex, disease severity (indicated by number of exacerbations requiring antibiotics in the last 12 months) and FEV_1. No consideration was given to the ACT regimen being used when allocating to the groups. Regular review of the age, sex and FEV_1 of both groups was undertaken during recruitment. Potential participants of the no-ACT group or parents of younger participants were invited to take part in the study as a no-ACT participant either prior to scheduling the appointment or prior to consent. If any participants or parents did not wish to complete the study as a no-ACT group member they would have taken part in the ACT group, however all potential no-ACT participants and parents accepted the invitation. The recruitment figures for each group at each centre are provided in Table 17.

Table 17: Recruitment numbers per centre at Leeds teaching hospitals (LTHT) Bradford teaching hospitals foundation trust (BTHFT), Sheffield Children's hospital (SCH) and Royal Manchester Children's hospital (RMCH).

Site	Number of patient participants	
	ACT	No-ACT
LTHT	10	2
BTHFT	10	2
SCH	3	1
RMCH	6	1
Total	29	6

5.2.4 Study schedule

Participants attended the MRI unit at the UoS for one study visit. All participants were asked to withhold completion of their ACT regimen, or activities which aimed to facilitate secretion clearance on the morning of the study visit. The schedule was devised to allow sufficient time for an ACT review and ACT completion between the

first and second MRI scanning sessions. Assessment by MRI was performed: pre-ACT, post-ACT, and 4-hours post-ACT, based on the clinically recommended minimal 4-hour interval between ACT regimens. The time between scans was standardised according to the time each scan session was commenced: pre-ACT (0 hours), post-ACT (+2 hours) and 4-hours post-ACT (+ 6 hours). A period of approximately five to ten minutes was common between completion of the ACT regimen and commencing the post-ACT scan during which participants had a brief comfort break and were repositioned in the MRI scanner. The study day schedule is shown in Table 18. The no-ACT group participants had the MRIs at the same time points but did not complete an ACT, instead they were free to move around and had access to either their phone or a tablet to watch online content. All participants were free to leave the MRI unit to have lunch and a break between scan-sessions two and three. As a pragmatic study design, the participants were able to choose how to spend this time and asked to wear a basic pedometer to provide a simple assessment of their activity level during this time.

Details of spirometry testing are as described in Section 4.2.3. As spirometry may have an effect on airway clearance due to the nature of the manoeuvre it was performed before the first MRI.

Table 18: Study visit schedule.

Order and content of study visit	ACT group (n=29):	Control group (n=6)
1 Height and weight	✓	✓
2 Spirometry	✓	✓
3 Oxygen saturations (finger probe)	✓	✓
4 Pre-ACT MRI (0 hours)	✓	✓
5 ACT review and ACT completion	✓	✗
6 Post-ACT MRI (+2 hours from baseline)	✓	✓
7 QOL-PCD	✓	✓
8 4-hours post-ACT MRI (+6 hours from baseline)	✓	✓

5.2.5 Airway clearance review and completion of the ACT regimen

As the subsequent work package involved exploring how clinicians make decisions about ACT personalisation with the introduction of MR images (Chapter 6), data which would provide clinicians with cues to establish a clinical picture of the case on the study day were collected. Both the ACT review and completion of the ACT regimen were video recorded to provide information to clinician participants in Chapter 6 which would mirror the cues available in a clinical review as closely as possible. As this data was qualitative, it was solely collected for the latter work package and was not included in the analysis of the data in this chapter.

ACT “clinical” review

An airway clearance review which aimed to mirror a typical clinical ACT review was completed with all participants in the ACT group. The content of the review was based on the factors considered when personalising ACT regimens identified through the scoping review and interviews with experienced PCD physiotherapists (Chapters 2 and 3). A template of the data collection form is provided in Appendix 8.

Clinical history including diagnosis, past medical history, medications, social history, airway clearance history, current recommended regimen was collected prior to the study visit (as per Section 4.2.3). This was verified with the participant and as age appropriate their parent, during the ACT review. Further information collected through consultation included: current regimen being completed including frequency, independence, physical activity, nasal symptoms, and management. An objective assessment was completed by the lead researcher which included pre-ACT with auscultation of the chest and palpation of the chest wall, to assess for thoracic expansion and tactile fremitus.

Completion of the ACT regimen

Participants in the ACT group completed their usual ACT regimen immediately after the first MRI scan. The ACT regimen followed the plan recommended by the participants’ physiotherapist at their local centre. If participants had a variety of ACT regimens they completed at home, for example if a different device was used in the morning than in the afternoon, the local physiotherapist confirmed which regimen they felt was optimal and this was performed on the day. Participants were supervised during their ACT, encouraged to complete their regimen to the best of their ability to reduce the impact of performing their technique poorly (97). The lead researcher assessed ACT response during the ACT regimen and provided a verbal summary of any cues seen which may not be apparent on the video. Cues included: huff and cough; pressures displayed on a manometer during use of a PEP or OPEP device; chest wall movement during the ACT. If any sputum was expectorated during the ACT regimen, it was shown to the camera at least once per participant, and the appearance of the sputum was qualitatively noted (colour, consistency). An objective assessment of ACT response was completed by the lead researcher post-ACT with auscultation of the chest and palpation of the chest wall.

Those in the no-ACT group were asked to not intentionally undertake any ACTs between the first and the last MRI. They were offered space to complete their ACT regimen following their final MRI, but no participants accepted use of the facilities for this.

5.2.6 Image acquisition

All images were acquired as per methods described in Sections 4.2.5-4.2.7. All scan sequences including ^{129}Xe imaging and ^{1}H imaging were performed at each of the three time points in the same order.

5.2.7 Image analysis

Image processing

Initial processing of the imaging data from each time point including registration, segmentation, assessment of ventilation, ventilation binning and free-breathing analysis followed the methods described in Sections 4.3.1. The lead researcher performed segmentation of all images, and no blinding was involved.

Same day variability

To provide a measure of same-day variability in ^{129}Xe MRI VDP without completion of an ACT, the coefficient of variation was calculated from the non-ACT data who had data from each of the three timepoints:

$$Single\ case\ {}^{129}Xe\ VDP\ CoV = \frac{VDP\ Standard\ deviation}{VDP\ Mean} \times 100$$

$$Group\ mean\ {}^{129}Xe\ VDP\ CoV = \frac{SUM\ (Single\ case\ VDP)}{n} \times 100$$

The group mean ^{129}Xe VDP, used as an estimate of natural same-day variability without interventions was used to calculate upper and lower limits of variation for each case in the ACT group:

$$Upper\ limit\ of\ {}^{129}Xe\ VDP = Pre\ ACT\ VDP + (Pre\ ACT\ VDP \times group\ CoV)$$

$$Lower\ limit\ of\ {}^{129}Xe\ VDP = Pre\ ACT\ VDP - (Pre\ ACT\ VDP \times group\ CoV)$$

Treatment response

To assess regional change in ventilation, a process known as treatment response mapping (279) was used to compare images acquired pre-ACT with post-ACT, and pre-ACT with 4-hours post-ACT.

An additional registration was performed on each pair of pre and post images (pre and post, pre and 4-hour post) with a supervised automated process using in-house software (280). All registrations were visually checked for quality of alignment, if poor alignment indicated the registration had failed, the treatment response data was excluded from the subsequent analysis. Two methods of analysing treatment response

were used, an established Signal treatment response map (TRM) method, and a new Volume TRM method.

Treatment response mapping, Signal TRM (STRM) method

Established in-house methods described by Collier *et al.* (279) were initially used to assess change in ventilation signal intensity in each voxel between the ventilation images for a participant acquired at different time-points. Voxels with abnormal ventilation in the low ventilation or ventilation defect binning categories (i.e., those with signal intensity < 0.66) in either the pre or post image were included in the analysis. To focus on pertinent changes, voxels which remained within normal ventilation categories (signal intensity >0.66, ventilation binning category normal or high ventilation in both pre and post image) were not included. The signal intensity change for each voxel within the analysis were displayed in a treatment response map to show those voxels with increased (improved) ventilation (green); and those voxels with reduced (worsened) ventilation (red). As shown in the Signal TRM in Figure 52, the magnitude of signal change was represented by the intensity of colour, with larger changes shown in darker colour.

Treatment response mapping, Volume TRM (VTRM) method

During initial data reviews with physiotherapists (Chapter 6), it was highlighted that areas which persisted over time without ventilation present were not visible on the TRM and discrete visualisation of this effect could also be clinically useful. To provide a TRM depicting persistent defects, a binary approach was required to classify voxels according to whether they had persisted in an abnormal ventilation category or changed ventilation bin category between the two images. In the Volume TRM, voxels were labelled as: persistent defect (ventilation defect bin in both images), persistent low ventilation (low ventilation bin in both images), ventilation improved (moved from ventilation defect or low ventilation up a ventilation binning category), ventilation worsened (moved down a ventilation binning category into ventilation defect or low ventilation). Voxels which were binned as normal or high ventilation in both images were discarded from the analysis. Figure 52 provides a visual comparison of the two TRM methods for one case: areas of persistent defect in the left lower lobe are more clearly displayed on the Volume TRM (bronze colour) than the Signal TRM; improvement in ventilation in the left apex is shown as a binary block (green) in the Volume TRM, more detail of the magnitude of improvement is shown by scaling of colour in the Signal TRM.

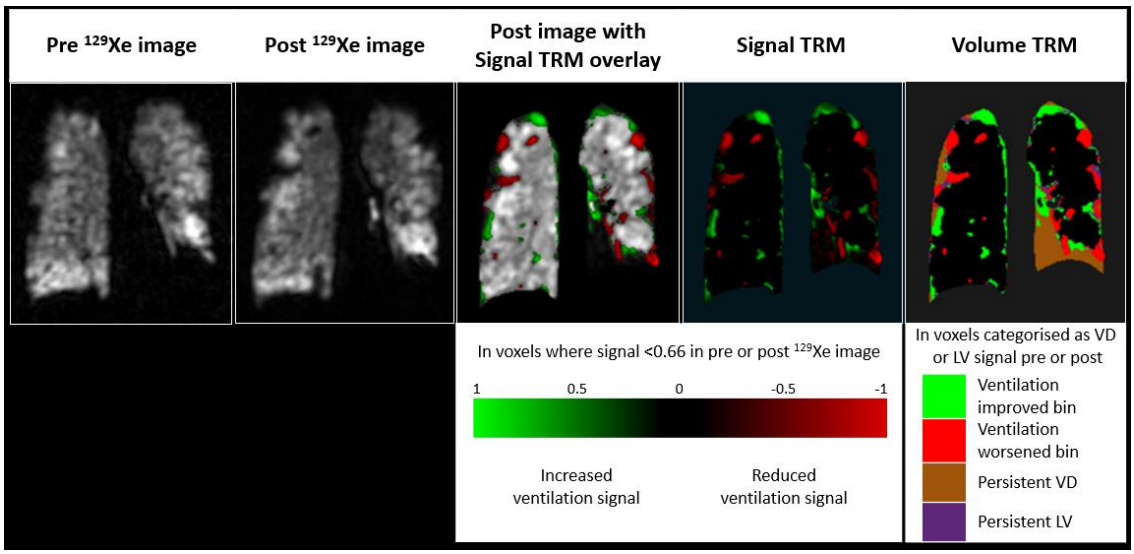


Figure 52: An example case showing pre- and post-ACT ^{129}Xe ventilation images, post-ACT ventilation image with the Signal treatment response map (TRM) displayed as an overlay, the Signal TRM and the Volume TRM. The legend below the signal TRM images indicate the change in signal strength colour coding used in the Signal TRM method. The legend below the Volume TRM image indicates the colours allocated to the TRM categories in the Volume TRM method.

As the voxel volume for each participant was known, the following metrics were produced by multiplying the voxel volume by the number of voxels in the category:

- Persistent ventilation defect as a percentage % of TCV (P-VD)
- Persistent low ventilation as a percentage of TCV (P-LV)
- Total ventilation change as a percentage of TCV.
  (% Change VTRM) = VTRM %Improved + VTRM %Worse

As the extent of defects seen in the study population ranged from minimal to significant defects (VDP range 0.1-27.7%), to facilitate comparison of persistent defects the metric for persistent defects is presented as a percentage of baseline VDP:

$$\%\ Persistent\ VDP = \frac{Persistent\ VDP}{Pre\ ACT\ VDP} \times 100$$

The results for the VTRM method are reported throughout Section 5.3.

5.2.8 Statistical analysis

All statistical analyses were performed using GraphPad Prism (version 9.5.1, San Diego, US). Prior to analysis, metrics for the whole cohort were assessed for normality with the Shapiro-Wilks test and depending on the outcome, data are presented as either mean ± SD, or median (interquartile range (IQR)). An assessment of variance over time was completed using the Friedman test, suitable for repeated measures of non-parametric data. Either the Mann-Whitney U test (non-parametric data) or unpaired

t-test (parametric data) was used for comparison of data sets. Correlation and agreement between the measures of ventilation were assessed using Spearman's rank-based correlation, and Bland-Altman plots of the difference in outcome versus the average.

5.2.9 Patient and public involvement

Patients and parents were involved in the initial study design, especially around the omission of the ACT session for the control group. Advice was sought from medical consultants regarding the risk to individuals in this group who felt the risk was low. Parent members felt it would be more acceptable for those in the control group to delay their ACT session rather than omit it. As such, provision was made for participants of this group to be able to complete their ACT regimen following the final MRI scan, allowing them time for a second daily session later in the day. They were consulted on the use of a pedometer to capture participant activity which was included as they felt this was acceptable.

A review of recruitment to date was undertaken at each quarterly PPI meeting during data collection. PPI members were involved in the development of an information pack for participants who were not local to Sheffield, to familiarise them with local facilities for the break between the second and third scan. PPI members were also consulted on potential causes for difficulty in performing breath hold manoeuvres seen in some of the early participants. Based on their feedback: prior to entering the scanner, participants were prompted to blow their nose to prevent irritation from postnasal drip; participants were reminder they could cough if needed between scans; in the follow up scans, participants were reminded to follow the instructions rather than pre-empting the steps.

5.2.10 Chapter acknowledgements

The acknowledgments for this chapter mirror those for Chapter 4. As such, all details provided in Section 4.2.7 are applicable to this chapter. Additionally, the contributions for this chapter from the lead researcher, Lynne Schofield, are as detailed below:

- Performing ACT regimen reviews,
- Supervising and guiding participants to perform their recommended ACT regimen,
- Video recording of the ACT regimen reviews and ACT sessions.
- Management and editing of the video recordings,
- Transcribing clinical review data

In addition to those acknowledgments detailed in Section 4.2.7, acknowledgments for specific contributions are also given to:

- Dr Alberto Biancardi for: development of volume treatment response methods and writing and the code for the signal TRM. Dr Biancardi also produced all TRMs.
- Dr Guilheim Collier for guidance on interpretation of the signal TRMs and support to produce scan IP image.

5.3 Results

5.3.1 Group demographics

35 young people (19 (54%) male, aged 6.4-17.7 years) with a confirmed diagnosis of PCD were recruited and assessed; 6 in the control (no-ACT) group, 29 in the ACT group. All individuals, and parents of those under 16, who were invited to take part without completing an ACT were willing to do so. 34 participants (6 control, 28 ACT) were assessed at all three time points, one participant unexpectedly needed to leave prior to the final scan. 18 participants completed the full protocol, omissions occurred under the following circumstances: 1. due to the length of the protocol, the free breathing ^{1}H (PREFUL) MRI scan sequence was omitted due to an unexpected delay starting the first scan (n=10) or signs indicating the participant would not tolerate the full protocol (n=5); 2. the participant was unable to co-ordinate TLC breath hold manoeuvre (n=1). Two images acquired were excluded from the analysis due to technical scanner issues (one pre-ACT at TLC which therefore excluded this data set; one post-ACT at EITV) and one PREFUL image was due to a post-processing issue. Following analysis, it was evident further individuals had struggled with the breathing manoeuvre at TLC. As such, TLC imaging data was discarded if: an increase in TCV from EITV to TLC was not seen; variance in TCV at TLC > 10% , (when variance = difference in TCV/ largest TCV *100); the corresponding pre-ACT TLC image did not meet the acceptability criteria above. This quality control process removed the following full data sets (n=3), post-ACT data point (n=2), 4-hours post-ACT data point (n=1), leaving five full data sets for the control group, and 24 pre-ACT, 22 post-ACT and 22 4-hours post-ACT images for the ACT-group.

An overview of the ^{129}Xe MRI and ^{1}H PREFUL scan data acquired and analysed is provided in Figure 53.

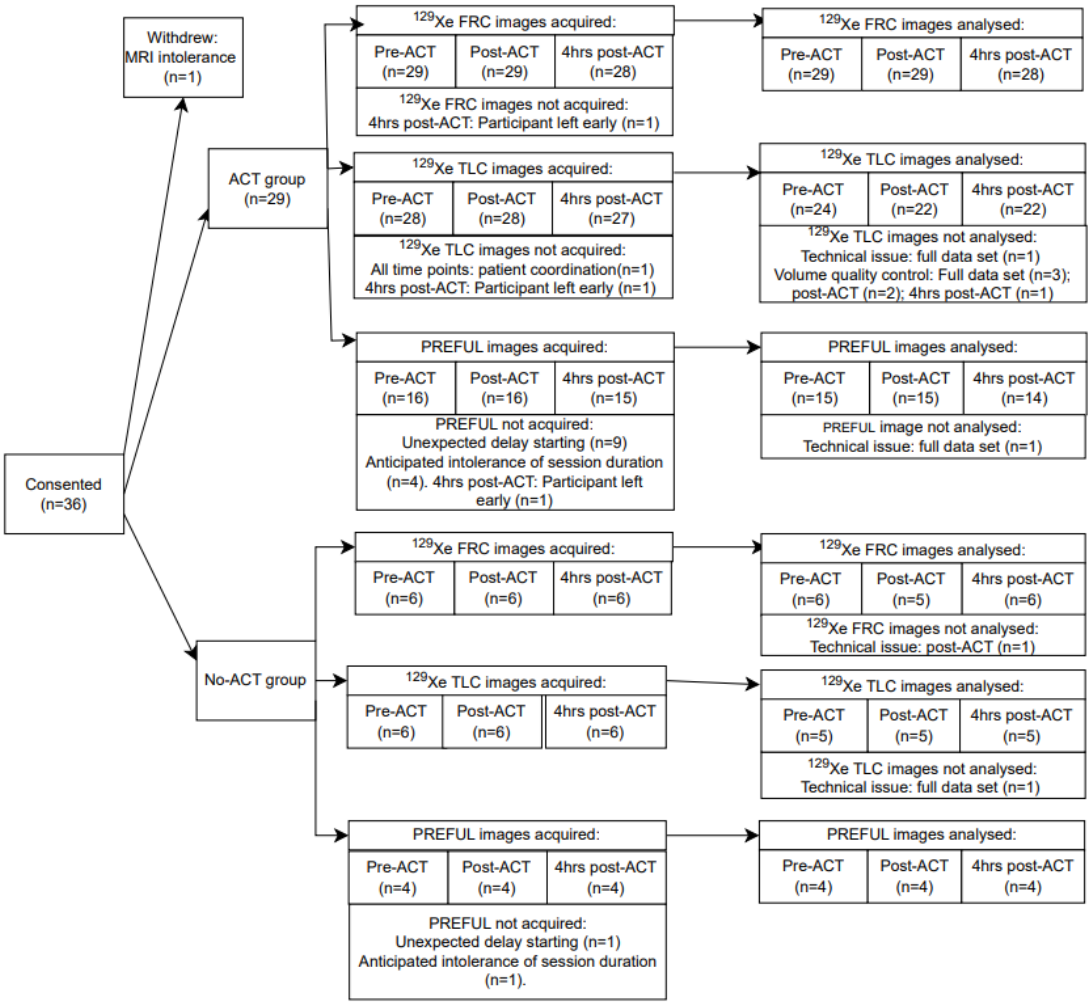


Figure 53: Flow diagram summarising the ^{129}Xe and ^{1}H PREFUL MRI scan data acquired and analysed for all participants at all time points.

As summarised in Table 19, the ACT and control groups were similar in sex, age, number of courses of antibiotics in the last 12 months and FEV_1. Whilst the ACT regimens participants were advised to complete were analogous between the groups, the self-reported frequency of ACT completion over the last 7 days was significantly lower in the control group; control group = mean 0.3 sessions/day, ACT-group = mean 1.0 sessions/day p=0.02. As participants were allocated to a group prior to their first scan (Section 5.2.3), baseline ^{129}Xe metrics were not available at the time of group allocation. The control group had a greater range abnormalities (higher IQR) and on average a lower VDP than those in the ACT group, but no statistically significant difference in ventilation abnormalities was seen between the two groups at baseline: (data presented as median (IQR)) ^{129}Xe VDP in the control group = 3.7 (0.2-20.7)% versus 6.3 (2.0-14.9)% in the ACT group (p=0.56); ^{129}Xe VHI in the control = 10.0 (7.2-

14.1), versus 11.5 (8.9-13.2)% in the ACT group (p=0.56). A summary of participant demographics for each group are provided in Table 19.

Table 19: Participant demographics and lung function for the control and ACT groups. Metrics are shown as mean ± SD or median (IQR) depending on if data normally distributed. IDA= inner dynein arm, ODA= outer dynein arm, MTD= microtubular disarrangement

		Control	**ACT**	**p-value**
N. (unless stated)		6	29	
Sex		50% (3) male	55% (16) male	
Age (years)		13.1 ± 3.0	12.1 ± 3.4	0.58
Height (cms)		154.8 ± 17.8	148.1 ± 17.1	0.39
Weight (kgs)		50.2 ± 15.6	42.8 ± 16.7	0.33
Age at diagnosis (years)		4.4 ± 4.2	3.6 ± 4.8	0.2
Cilial ultrastructural defect				
	IDA or MTD only	2 (33%)	6 (21%)	
	ODA only	2 (33%)	6 (21%)	
	IDA and ODA	1 (17%)	12 (41%)	
	No defect	1 (17%)	3 (10%)	
	No result	0	2 (7%)	
Number of antibiotic courses in last 12 months (oral and IV, planned and unplanned)		2.8 (2.3-4.0)	2.3 (1.0-4.0)	0.37
PsA (cultured in last 12 months)		1	4	
ACT frequency (sessions/day)				
Prescribed		2.0 (1.5-2.0)	2.0 (2.0-2.0)	1.0
Self-reported		0.3 (0.0-1.0) *(n=5)*	1.0 (0.8-2.0)	0.02*
Spirometry				
FEV_1	z-score	-1.5 ± 2.3	-1.6 ± 1.6 *(n=28)*	0.97
	% predicted	81.9 ± 27.5	81.2 ± 19.4	0.94
FVC	z-score	-0.6 ± 1.4	-0.8 ± 1.5 *(n=28)*	0.85
	% predicted	92.4 ± 16.3	89.6 ± 22.8	0.77
FEV_1/FVC	(z-score)	-1.6 ± 1.6	-1.6 ± 1.3 *(n=28)*	0.97
	% predicted	86.2 ± 14.8	87.4 ± 11.2	0.82
^{129}Xe baseline metrics				
VDP (%)		3.7 (0.2-20.7)	6.3 (2.0-14.9)	0.56
VHI (%)		10.0 (7.2-14.1)	11.5 (8.9-13.2)	0.56
Pedometer counted steps (scan 2 – 3).		4202 ± 2106 *(n=5)*	5377 ± 2701	0.54

5.3.2 Variation in ventilation distribution is seen without completion of an ACT.

Six individuals were assessed with ^{129}Xe MRI three times on the same day without completing an ACT between the scans. The time between scans is in accordance with the timing of the ACT group, as such the MRI sessions were timed: pre-no-ACT (baseline as 0 hours), post-no-ACT (+2hours), 4-hours post-no-ACT (+ 6 hours), throughout this section, the data from the MRIs are labelled according to these timings (baseline, +2 hours, +6 hours). It was not possible to segment the ^{129}Xe images for one individual at +2hrs due to an acquisition error. Four individuals in this group were also assessed with ^{1}H free-breathing PREFUL MRI methods at the three-time points. A summary of the ventilation metrics are provided in Table 20. Due to the size of this group, comparison of the data at each time point did not include assessment for statistical significance.

Table 20: ^{129}Xe and ^{1}H data for the no-ACT group. Data are presented as median (IQR) or mean ±SD depending on if the data was normally distributed.

Whole lung metrics	**Median (IQR) or mean ±SD**		
	Baseline	+2 hours	+6 hours
^{129}Xe VDP			
VDP (%)	3.7 (0.2-20.7)	5.2 (0.4-23.8) *(n=5)*	3.6 (0.4-20.6)
∆VDP		0.4 (-0.7-3.1) *(n=5)*	0.2 (-2.1-3.0)
% change in %VDP		23.7 (-8.7-210.9) *(n=5)*	47.4 (-15.7-197.7)
^{129}Xe VHI			
VHI (%)	10.0 (7.2-14.1)	11.4 (6.7-14.7) *(n=5)*	10.4 (6.8-14.8)
∆VHI (%)		0.0 (-0.2-0.3)	-0.2 (-0.8-1.4)
% change in VHI		-0.5 (-1.5-1.8) *(n=5)*	-1.1 (-7.8-12.0)
^{1}H VDP			
VDP (%)	6.9± 4.6 *(n=4)*	6.8 ± 3.2 *(n=4)*	4.1± 1.7 *(n=4)*

Assessment of same-day variability with ^{129}Xe Ventilation MRI

As shown by the individual time-by-time plots in Figure 54, the extent of ventilation abnormalities at baseline was broad in this group of six individuals: (Data presented as median (IQR) ^{129}Xe VDP baseline (0 hours) = 3.7 (0.2-20.7)%; ^{129}Xe VHI = 10.0 (7.2-14.1)%. Variability in the degree of ventilation defects was seen across the three assessment time points: VDP increased from the first to the second scan; 0 hours = 3.7% (0.2-20.7%), +2 hours = 5.2 (0.4-23.8)%. By the third scan, on average VDP had reduced and was more comparable to the first scan, ^{129}Xe VDP +6 hours = 3.6 (0.4-

20.6)%. Visual changes in the size and location of defects were seen, and as shown in Figure 55, the appearance of defects and change in defects were not always reflected by the change in VDP.

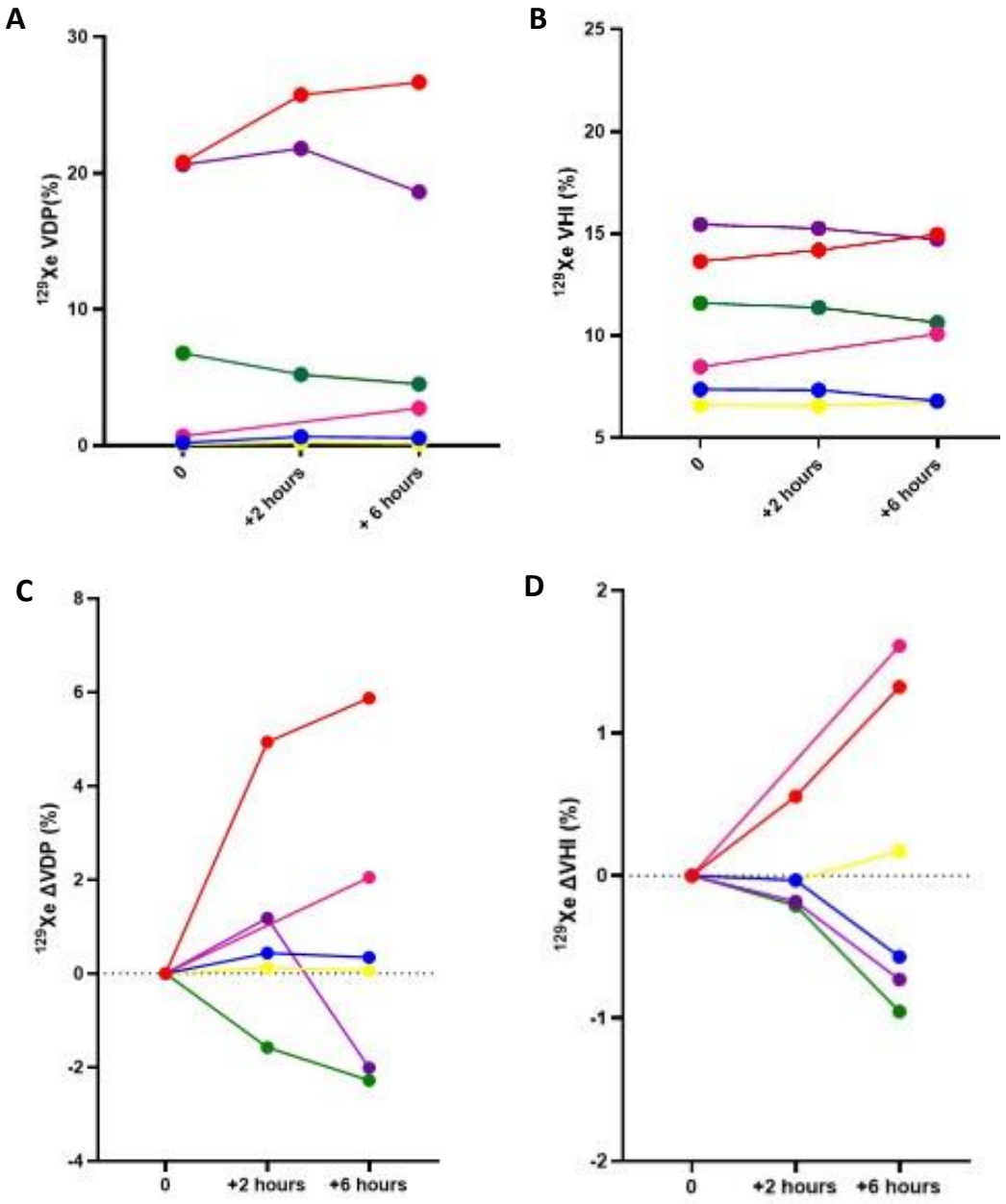


Figure 54: Same day values for ^{129}Xe VDP and VHI depicted as: time-by-time plots (A and B); ΔVDP (C) and ΔVHI (D); Each colour in graphs A-D showing change from baseline represents a single participant in the no-ACT group.

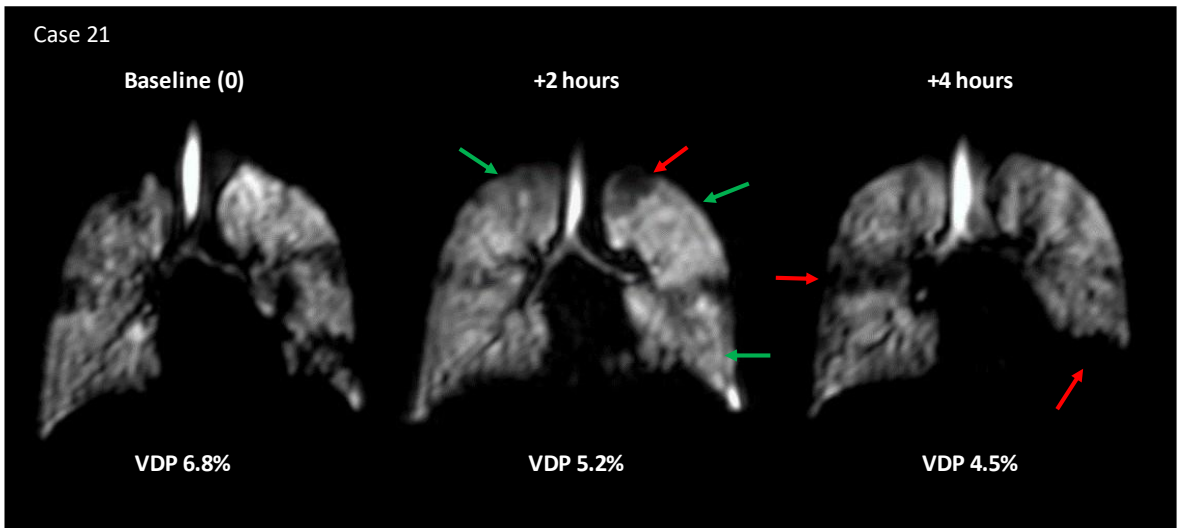


Figure 55: ^{129}Xe images from Case 21 (no-ACT group) at the three timepoints; baseline, +2 hours, and +6 hours-post. Whilst VDP improves and there is a resolution of some defects at +2 hours, other defects have emerged. Arrows indicate improvement (green) and worsening (red) in the appearance of ventilation defects.

The average change in ^{129}Xe VDP from baseline was small, but variance was seen across the group, with greater change from baseline seen at +6 hours when compared to at + 2hours; ∆129Xe VDP at +2 hours = 0.4 (-0.7-3.1)%, at +6 hours = 0.2 (-2.1-3.0)%. The time-by-time plots of 129Xe VDP from baseline in Figure 54C show individual change and the highest variance can be seen in one individual with a baseline 129Xe VDP = 20.8% (data set depicted in red). From baseline to +2 hours, 4/6 (80%) had an increase in VDP and one (20%) had a reduction. By +6 hours, 4/6 (67%) had a higher VDP% and 2/6 (33%) had a lower VDP% than at baseline. The average change in 129Xe VHI from baseline was very small, with some variance was seen across the group: 129Xe ∆VHI at +2 hours =0.0 (-0.2-0.3)%, at +6 hours = -0.2 (-0.8-1.4)%. Figure 54D shows the group was split with an increase in 129Xe VHI seen over time in three individuals and a reduction in the three others. Correlations of change in 129Xe metrics with baseline measures are not reported due to the small size of this group.

Assessment of repeatability of ^{129}Xe metrics.

Repeatability of ^{129}Xe metrics in this group was assessed using Bland-Altman to determine 95% levels of agreement (LOA) for repeatability in ^{129}Xe VDP and VHI between the baseline and follow-up scans (follow up – baseline).^{129}Xe VDP was on average lower at baseline than later in the day, with limits of agreement wider at +6 hours than at +2 hours from baseline: baseline to +2 hours, bias 1.0% LOA 5.7 to -3.7; baseline to +6 hours bias 0.7%, LOA 6.6 to -5.2 (Figure 56A and B). ^{129}Xe VHI was

very repeatable but greater variance from baseline was also seen later in the day; again, the limits of agreement were wider at +6 hours than at +2 hours from baseline: baseline to +2 hours bias 0.0% LOA 0.6 to -0.6; baseline to +6 hours bias -0.1, LOA 2.3 to -2.0 (Figure 56C and D).

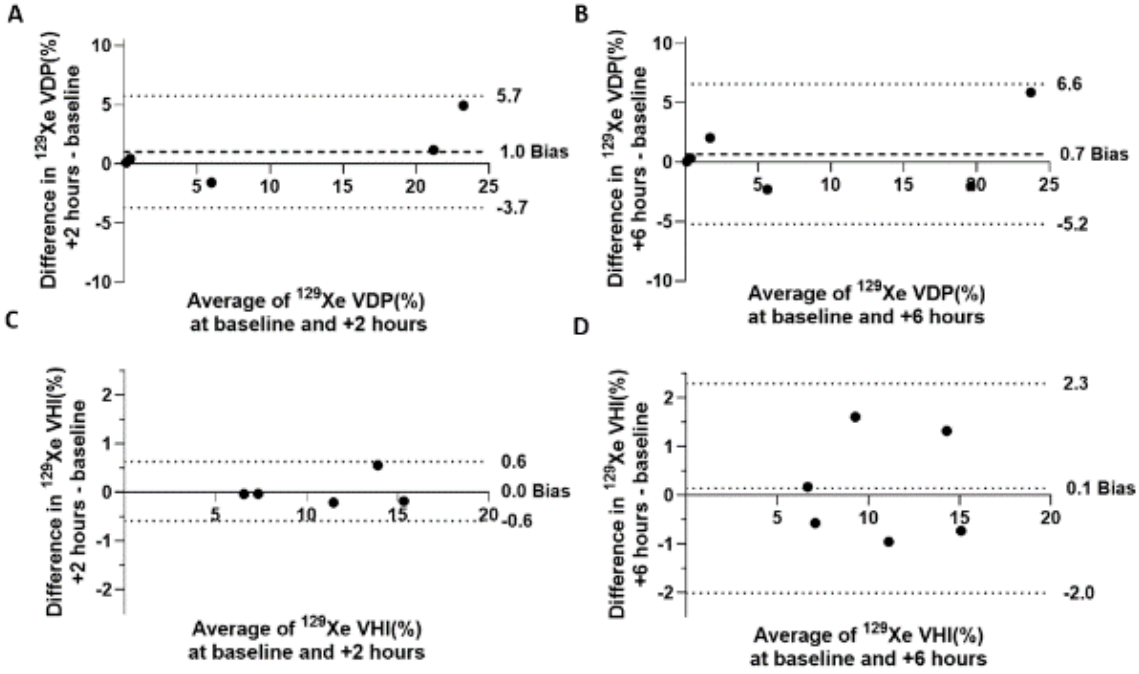


Figure 56: Bland Altman plots of difference versus average for: ^{129}Xe VDP at baseline and +2 hours (A) and at baseline and +6 hours (B); ^{129}Xe VHI at baseline and +2 hours (C) and at baseline and +6 hours (D).

From these data, there is one patient with more advanced VDP who appears to be an outlier in having significant variability in VDP when compared to the others. In this small data set, the inclusion of this individual is likely to have a large influence on the repeatability thresholds determined. To explore this, repeatability was also calculated excluding the outlying data set (Figure 57). The repeatability of ^{129}Xe VDP improved with the removal of this case, with smaller bias and tighter limits of agreement: baseline to +2 hours bias -0.0% LOA 2.3 to -2.3; baseline to +6 hours bias 0.4, LOA 3.9 to -3.1. The removal of this data set had less impact on the repeatability of ^{129}Xe VHI, especially at +6 hours: baseline to +2 hours bias 0.1% LOA 0.3 to -0.1; baseline to +6 hours bias 0.1, LOA 2.1 to -1.9.

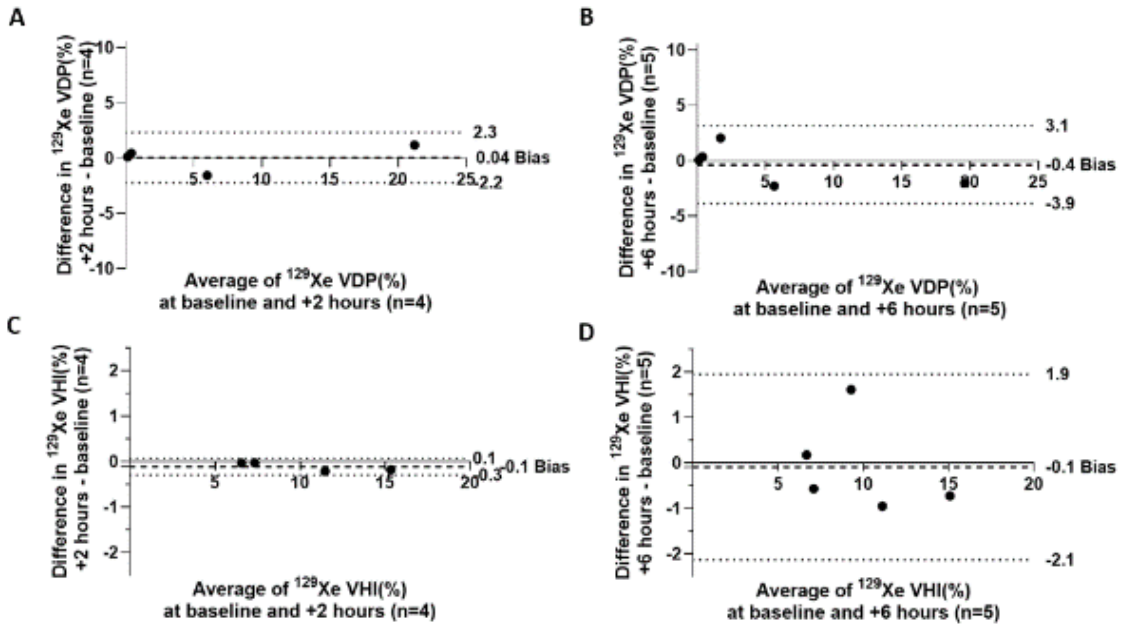


Figure 57: Bland Altman plots of difference versus average for: ^{129}Xe VDP when Case 18, with a larger variation in ^{129}Xe VDP was removed: at baseline and +2 hours (A) and at baseline and +6 hours (B); ^{129}Xe VHI at baseline and +2 hours (C) and at baseline and +6 hours (D).

To provide a group assessment of variability across the day, a coefficient of variance (CoV) for ^{129}Xe VDP and VHI was calculated from the five participants with data from all three time points. Individual variability across the three time points ranged from 7.9 - 49.2%, and the mean coefficient of variance across the group was found to be large: CoV ^{129}Xe VDP = 28.0%. Variability in ^{129}Xe VHI was smaller ranging from 1.7 – 4.7%, indicating less variability in this metric over the three timepoints: CoV ^{129}Xe VHI = 3.6%.

Assessment of change from baseline with ^{129}Xe treatment response maps

As illustrated by the case in Figure 58, whilst some defects changed over time with ventilation improving, worsening, or transiently changing between images, other defects persisted across the images at the three timepoints.

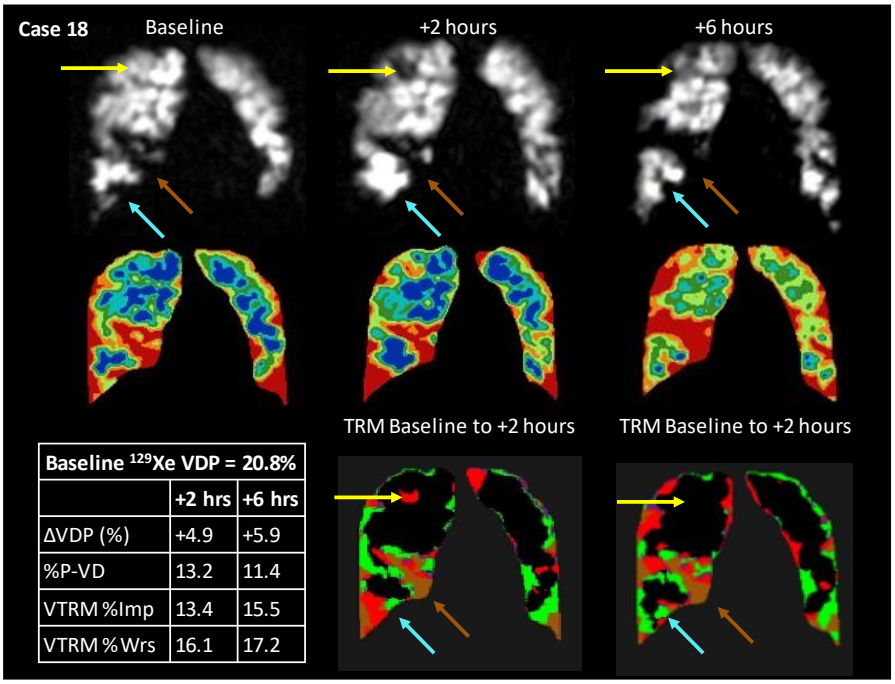


Figure 58: Example of change over time without an ACT in Case 18 (identified as a potential outlier with high variability in VDP over time). ^{129}Xe images from baseline, +2 hours and +6 hours depicted with corresponding binning maps below each image. Volume treatment response maps (TRM) which compare the binning of voxels baseline to +2 hours and then baseline to +6 hours are also shown. Arrows illustrate an area where: ventilation improved at +2 hours and then worsened (blue); ventilation worsened at +2 hours and then improved (yellow), where ventilation defect persisted across all three timepoints (bronze). Figures for baseline ^{129}Xe VDP, ΔVDP from baseline, and Volume TRM metrics for the percentage of persistent defects (%P-VD), percentage of the thoracic cavity improving (VTRM %Imp) and worsening (VTRM %Wrs).

The volume treatment response maps (VTRM) were used to quantitatively assess these changes, a summary of the metrics are presented in Table 21. The VTRM showed some of the ventilation abnormalities seen had persisted from baseline, and the range (IQR) showed the extent of persistent defects varied widely between individuals. At +2 hours, on average 18.4 (10.4-69.6)% of areas of VDP present at baseline persisted, this represented 1.3 (0.0-14.4)% of VDP. For areas of low ventilation (LVP, the average persistence was higher; on average 41.6±15.0% of areas of LVP persistent at +2 hours, representing 4.7±1.0% LVP. A similar pattern was seen at +6 hours: on average 19.4 (11.1-58.3)% of defects present at baseline persisted, equating to 0.7 (0.0-12.1)% VDP; 37.0± 13.2% of areas of low ventilation persisted, 4.2±0.9% LVP.

Table 21: Summary of the regional change metrics: ^{129}Xe ventilation change over time analysed using the volume TRM.

Regional response metrics		**Median (IQR) or mean ±SD**	
		+2 hours (n=5)	**+6 hours (n=6)**
Volume TRM			
Persistent ventilation defects	%TCV	1.3 (0.0-14.4)	0.7 (0.0-12.1)
	% baseline VDP	18.4 (10.4-69.6)	19.4 (11.1-58.3)
Persistent low ventilation	%TCV	4.7 ± 1.0	4.2 ± 0.9
	% baseline LVP	41.6 ± 15.0	37.0 ± 13.2
Change in ventilation category			
Improve (%)		9.3 ± 4.9	10.1 ± 5.3
Worsened (%)		9.2 (2.9-13.2)	7.0 (3.7-8.5)
Total change (%)		19.2 (7.2-27.1)	18.9 (8.6-25.5)

Using the VTRM at +2 hours, the average percentage of improvement and percentage of worsening was similar: (data presented as mean ±SD or median (IQR) VTRM improved = 9.3 ± 4.9%, worsened = 9.2 (2.9-13.2)%. Considering this as the proportion of the lung which had moved to or from abnormal ventilation signal, overall, on average a relatively large total change was seen at +2 hours, which varied between individuals: VTRM total change= 19.2 (7.2-27.1)%. At +6 hours, the average worsening was higher than at +2 hours, but there was still more improvement than worsening: VTRM improved = 10.1 ± 5.3%, worsened = 7.4 (4.8-11.8)%. These changes equated to 18.9 (8.6-25.5)% of the TCV which had moved to or from abnormal ventilation signal (defect or low ventilation).

The proportion of VDP which persisted over time was greater in those with more severe disease, as assessed by baseline VDP. Contrastingly the proportion of LVP which persisted over time was greater in those with milder disease). Two example cases, one with mild disease (Case 32) and one with more severe disease (Case 30) are provided in Figure 59 to illustrate the greater persistence of regions of LVP and greater persistence of regions of VDP in mild and severe cases respectively.

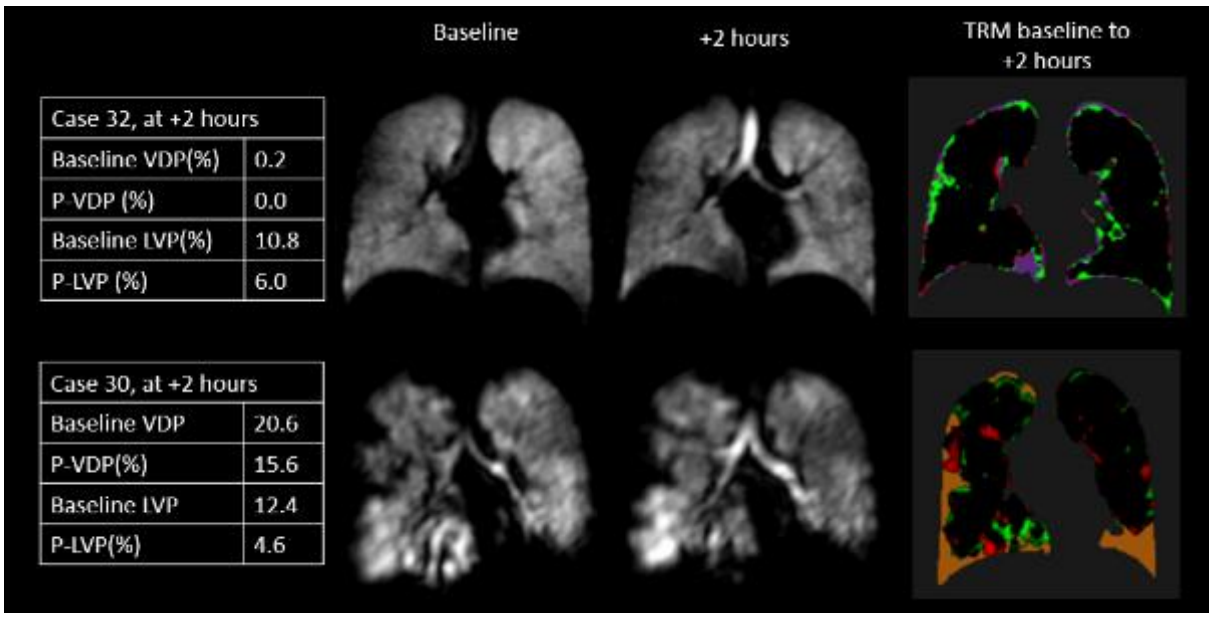


Figure 59: ^{129}Xe images and treatment response maps (TRMs) for two Cases, one with mild disease (Case 32) and one with more severe disease (Case 32). Colours on the TRM indicate areas of improvement (green), worsening (red), persistent low ventilation (purple) and persistent defects (gold).

Assessment of same-day variability with free-breathing ^{1}H (PREFUL) MRI

When assessed with ^{1}H PREFUL MRI, the group ^{1}H VDP reduced over time, and was lower at +6 hours than at baseline for three of the four individuals: (data presented as median (IQR)) ^{1}H VDP at baseline = 6.8% (2.6-11.4%); +2 hours = 6.9% (3.7-9.7%); +6 hours = 4.3% (2.5-5.7%) (Figure 60). As shown by the Bland Altman plots in Figure 61, the repeatability of ^{1}H VDP was higher over the shorter time interval: baseline to +2 hours bias 0.2% LOA 3.0 to -2.7; baseline to +6 hours bias +2.7, LOA 9.9 to -4.3.

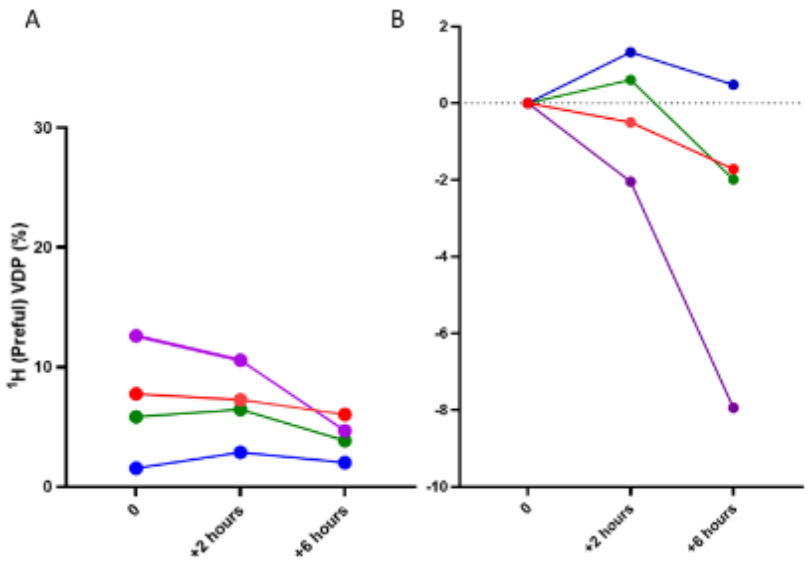


Figure 60: A and B depict same day variability in ^{1}H (PREFUL) VDP as a time-by-time plot (A), and Delta VDP showing change from baseline (B). Each colour represents a single participant in the control group.

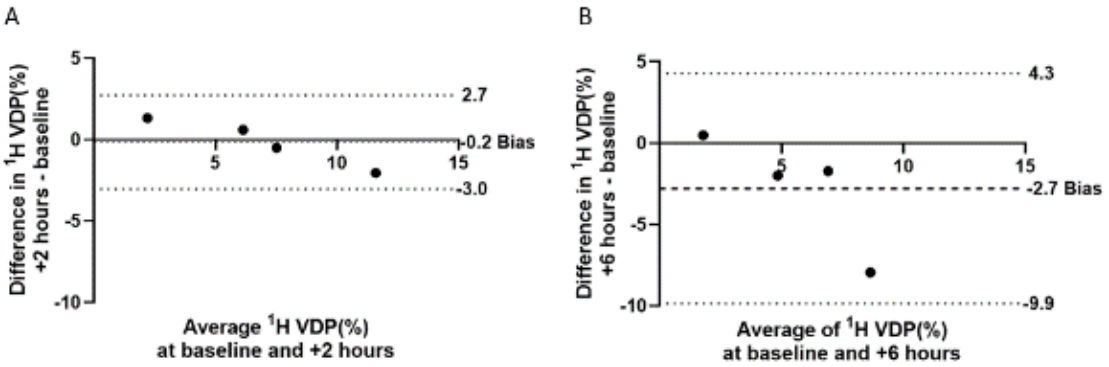


Figure 61: Bland Altman plots comparing baseline to +2 hours (C) and +6 hours (D) time points respectively for ^{1}H (PREFUL) VDP.

The mean group coefficient of variance (CoV) for ^{1}H VDP across the three time points was comparable to CoV in ^{129}Xe VDP: CoV ^{1}H VDP = 28.4%, CoV ^{129}Xe VDP 28.0%.

5.3.3 Personalised ACT regimens are used in children with PCD.

All 29 participants in the ACT group completed a personalised ACT regimen that had been recommended by their local physiotherapist. The regimens were highly personalised and whilst a large amount of qualitative data was captured on the videos, a summary of components which were meaningfully quantifiable are provided in Table 22 and Figure 62. Inhaled salbutamol was used at the start of the regimen by 18/29 (62.1%) participants, all of whom subsequently nebulised hypertonic saline. Hypertonic saline was commonly used (26/29, 89.7%): predominantly this was 7% solution concentration (23/29, 79.3%); where taken, this was delivered both sequentially prior to the use of a device (18/26, 69.2%), or combined with an ACT device such as an Aerobika® (8/26, 30.8%). Oscillatory PEP devices were the most used ACT type (23/29, 79.3%) with the remaining participants using PEP devices to perform PEP either to achieve expiratory pressures of 15-20cmH_2O (6/29, 20.6%), or to perform a Hi-PEP regimen with pressures of 40-100 cmH_2O (2/29, 6.9%). Whilst all participants used breathing techniques such as forced expiratory technique (FET) during their regimen, no participants used a breathing technique such as active cycle of breathing technique as their main ACT type. Further detail which varied highly between participants included: number of breaths per cycle, number and timing of FETs, number of cycles, order of positions and cycle details per position, device settings, pressures achieved during expiration through a device, device interface, use of overpressures. Some participants required guidance and encouragement to complete regimens as

recommended, this was done to reduce the chance that responses seen would be attributable to poor engagement or incorrect technique.

Table 22: Summary of the personalised ACT regimens completed during the study visit.

ACT regimen component	(n=29)
Inhaled medication	
Pre-medication with salbutamol	18 (62.1%)
Nebulised hypertonic saline (all)	26 (89.7%)
3% NaCl	1 (3.4%)
6% NaCl	2 (6.9%)
7% NaCl	23 (79.3%)
Nebuliser timing (in n=26 using neb)	
Sequentially (pre device)	18 (69.2%)
Combined (with device)	8 (30.8%)
Device	
OPEP (all)	23 (79.3%)
Aerobika®	21 (72%)
Acapella®	1 (3.4%)
RC Cornet®	1 (3.4%)
PEP (all)	6 (20.6%)
PEP mask	1 (3.4%)
Pari PEP	5 (17.2%) (3 standard, 2 Hi-PEP)

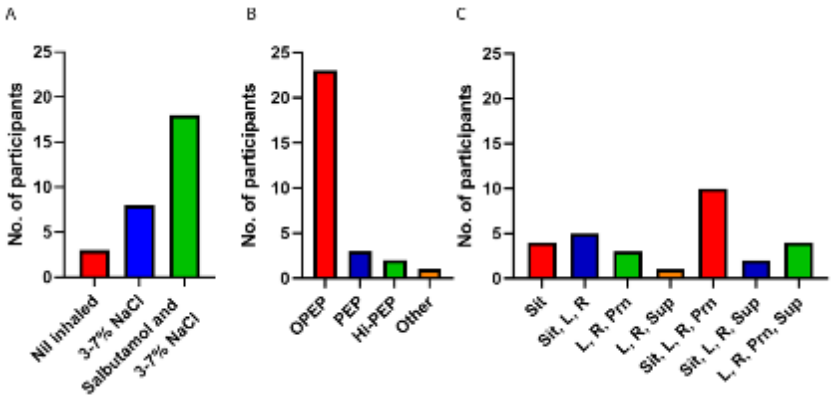


Figure 62: Histograms of ACT regimen components used: inhaled medications (A), main ACT type (B) and positions used during ACT regimen (C). NaCl= nebulised saline, OPEP= oscillatory positive expiratory pressure, PEP = positive expiratory pressure, Hi-PEP = high positive expiratory pressure, Sit=sitting up, L= left side, R= right side, Prn= prone, Sup= supine.

5.3.4 ^{129}Xe MRI shows that the individual ventilation distribution response to a single personalised ACT session is heterogeneous.

This section provides exploratory analysis of variability in ^{129}Xe metrics following a single ACT session. The change over time for all ^{129}Xe whole lung metrics are provided in Table 23.

Table 23: Summary of the ACT group whole lung metrics across the three time intervals. Metrics are provided as median (IQR).

^{129}Xe whole lung metrics (n=29)	Median (IQR) or mean ±SD		
	Baseline	Post-ACT	4-hours post-ACT (n=28)
VDP (%)	6.3 (2.1-13.7)	5.4 (1.4-13.3)	5.8 (2.2-15.3)
∆VDP		-0.3 (-2.8-1.4)	-0.8 (-2.5-0.6)
% change in VDP from baseline		-5.0 (-39.8-34.7)	-14.0 (-33.2-9.7)
VHI (%)	11.5 (9.1-13.1)	10.4 (8.3-13.0)	11.2 (8.4-13.4)
∆VHI (%)		-0.3 (-1.2-0.6)	-0.3 (-1.5-0.3)
% change in VHI from baseline		-2.6 (-11.6-6.8)	-2.6 (-10.4-2.8)

Assessment of ^{129}Xe VDP immediately post-ACT (+2hours)

Immediately post-ACT, the average ^{129}Xe VDP was lower than it was pre-ACT (baseline): (data presented as median (IQR)) pre = 6.3 (2.1-13.7)% versus post = 5.4 (1.4-13.3)%; this difference was not statistically significant (p=0.4). The average change in VDP from baseline was a small reduction (improvement): ∆VDP = -0.3 (-2.8-1.4)%. Assessing change as a percentage of baseline VDP, again on average this showed a small improvement, but the interquartile range showed this metric was varied across the group: % change in VDP = -5.0 (-39.8-34.7)%. As shown by the individual case spaghetti plots in Figure 63A and C, ACT response varied: VDP reduced post-ACT in 68.1% (n=18) and increased in 37.9% (n=11). Figure 64 shows images from three example cases illustrating that response was varied and included: some cases with resolution of defects (Case 12); cases with worsening visualised as distinct defects, some of which were wedge shaped (Case 34); cases with worsening where changes were more diffuse (Case 14). Change in ^{129}Xe VDP did not correlate with the level of defects at baseline: Spearman's rank correlation of baseline ^{129}Xe VDP with ^{129}Xe ∆VDP post-ACT r=-0.2, p=0.34) (Figure 63E).

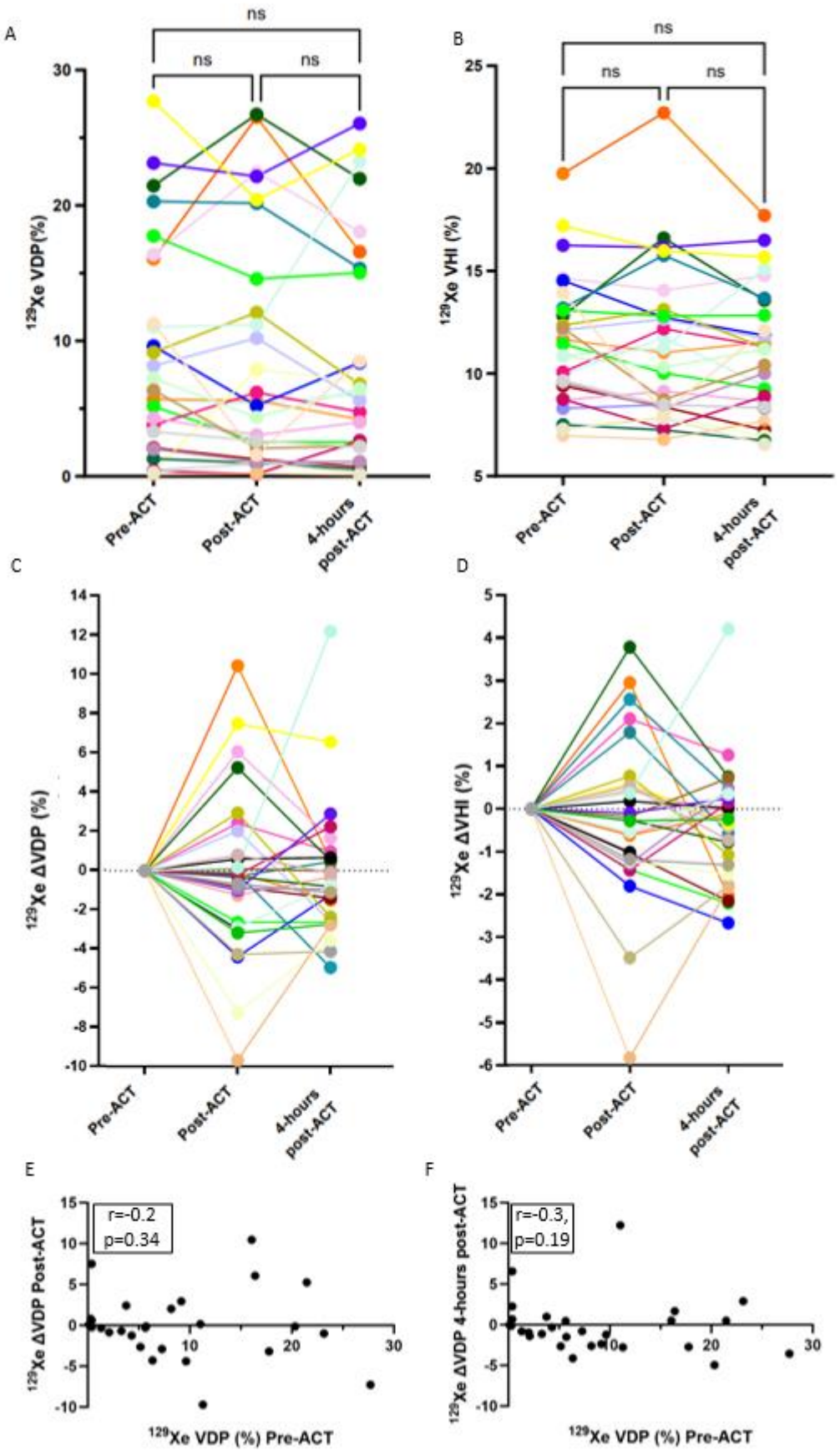

A
ns
ns
ns
^{129}Xe VDP(%)
Pre-ACT
Post-ACT
4-hours post-ACT
B
ns
ns
ns
^{129}Xe VHI (%)
Pre-ACT
Post-ACT
4-hours post-ACT
C
^{129}Xe ΔVDP (%)
Pre-ACT
Post-ACT
4-hours post-ACT
D
^{129}Xe ΔVHI (%)
Pre-ACT
Post-ACT
4-hours post-ACT
E
r=-0.2
p=0.34
^{129}Xe ΔVDP Post-ACT
^{129}Xe VDP (%) Pre-ACT
F
r=-0.3,
p=0.19
^{129}Xe ΔVDP 4-hours post-ACT
^{129}Xe VDP (%) Pre-ACT

Figure 63: Spaghetti plots showing time-by-time analysis of ^{129}Xe metrics VDP (A) and VHI (B) C and D depict ΔVDP and ΔVHI respectively, which as the change from baseline, takes the pre-ACT value for each individual case as 0. Each colour represents an individual case in the ACT group. The correlation of ΔVDP with baseline (pre-ACT) VDP is shown immediately post-ACT (E) and 4-hours post-ACT (F).

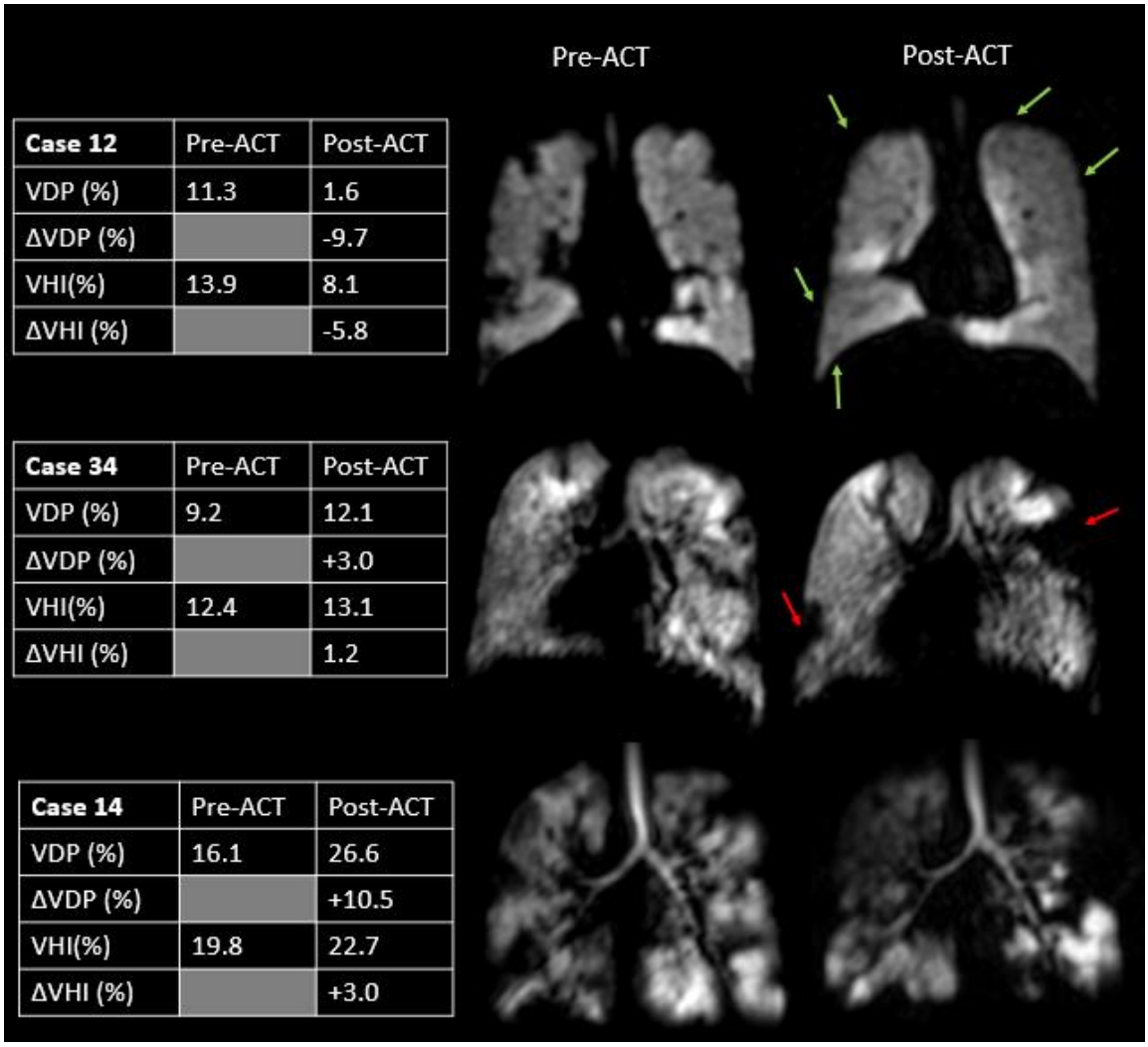


Figure 64: Individual response post-ACT in three individuals to illustrate the heterogeneity of response: Case 12, shows resolution of most visible defects and improvement in ^{129}Xe VDP and VHI; Case 34 shows large new defects, some of which are wedge shaped, with a corresponding increase in VDP and VHI; Case 14 shows diffuse worsening in ventilation with corresponding increases in VDP and VHI. Arrows indicated examples of defect resolution (green) and emergence (red).

Using the threshold of repeatability of ^{129}Xe VDP at +2hours calculated from the control group of >5.7 or <-3.7 (Section 5.3.2) to assess for significance of change in VDP, only 7/29 (24.1%) had a significant change in VDP following their ACT: three individuals had a significant increase (worsening) in VDP (ΔVDP >5.7%); 4/29 (13.8%) had a significant reduction (improvement) in VDP (ΔVDP <-3.7%). Those with a significant change in ventilation had more severe disease, as assessed by average VDP at baseline, compared to those who had no-significant change: (data presented as

median (IQR)) baseline VDP no-significant change group = 5.2 (1.7-8.9)%; significant change group = 16.1 (6.4-17.8)% (includes group who improved = 13.7 (7.2-25.2)%, group who worsened = 16.1 (0.4-16.4)%); 8/29 (27.6%) had a pre-ACT VDP <3.7%, so would not have been able to improve their VDP to cross the threshold of a significant change (∆VDP <-3.7%). When considering the lower threshold of significant change from the control data, excluding the outlier (∆VDP >2.2 or <-2.3), 6/29 (20.1%) had a significant increase in VDP = 6 (20.1%) and 8/29 (27.6%) had significant worsening in VDP.

An exploratory analysis employing the mean co-efficient of variance (CoV) in VDP (± 28% baseline VDP, calculated from VDP in the control group over the three timepoints) was used to calculate individual limits of expected variance over time without an intervention (Figure 66). Using this method to determine significant change, most individuals had a significant change in VDP post-ACT (∆VDP >± 28% of baseline ^{129}Xe VDP pre-ACT): 22/29 (37.9%) had a significant reduction (improvement) in VDP; 7/29 (24.1%) had a significant increase (worsening) in VDP.

Those who had improvement (reduction) in VDP immediately post-ACT were compared with those who had worsening (increase) in VDP using ∆VDP>0 to classify as improving and ∆VDP<0 as worsening. No difference between the groups was seen in age, age at diagnosis, presence of situs inversus, antibiotics in the last 12 months. No difference between the groups was seen in disease severity as assessed by FEV_1 (z-score) or baseline ^{129}Xe VDP. The proportion of females was higher in the group that improved: improved = 10/18 (55%) female, worsened = 3/11 (27%) female. More individuals who improved had taken inhaled salbutamol at the start of their ACT regimen: improved and took salbutamol = (14/18) 77.8%, worsened and took salbutamol = 4/11 (36.4%). Of the three individuals who did not nebulise hypertonic saline, one improved and two worsened. Comparing the ACT devices used between the two groups: of those who used an oscillatory positive expiratory pressure (OPEP) device 15/23 (66.1%) improved and 8/23 (34.7%) worsened; those who used a positive expiratory pressure (PEP) device with standard PEP pressures were split 50:50 between improved and worsening; both individuals who used a PEP device with a high-pressure PEP technique improved.

Assessment of ^{129}Xe VHI immediately post-ACT

On average, ^{129}Xe VHI was lower immediately post-ACT than at baseline: (data presented as median (IQR)) VHI at baseline = 11.5 (9.1-13.1)%, post = 10.4 (8.3-13.0)%. This aligned with on average a small reduction (improvement) in VHI immediately post-ACT: ∆VHI= -0.3 (-1.2-0.6)%. As shown by the individual case

spaghetti plots in Figure 63B and D, ACT response varied: VHI reduced post-ACT in 17/29 (58.6%) and increased in 12/29 (41.4%) .

Using the threshold for repeatability in ^{129}Xe VHI calculated from the control group to assess significant change (>0.6 or <-0.6), significant change in VHI was seen in 18/29 (62.1%); 7/29 (24.1%) with an increase (worsening) in VHI (>0.6%), and 11/29 (37.9%) with a reduction (improvement) in VHI (<-0.6%). Using the CoV in VHI seen over the three time points in the control group (>±3.6%) to assess significant change (Figure 66), most participants had significant change. 13/29 (44.8%) had a significant reduction (improvement) in VHI; 10/29 (34.5%) had a significant increase (worsening) in VHI.

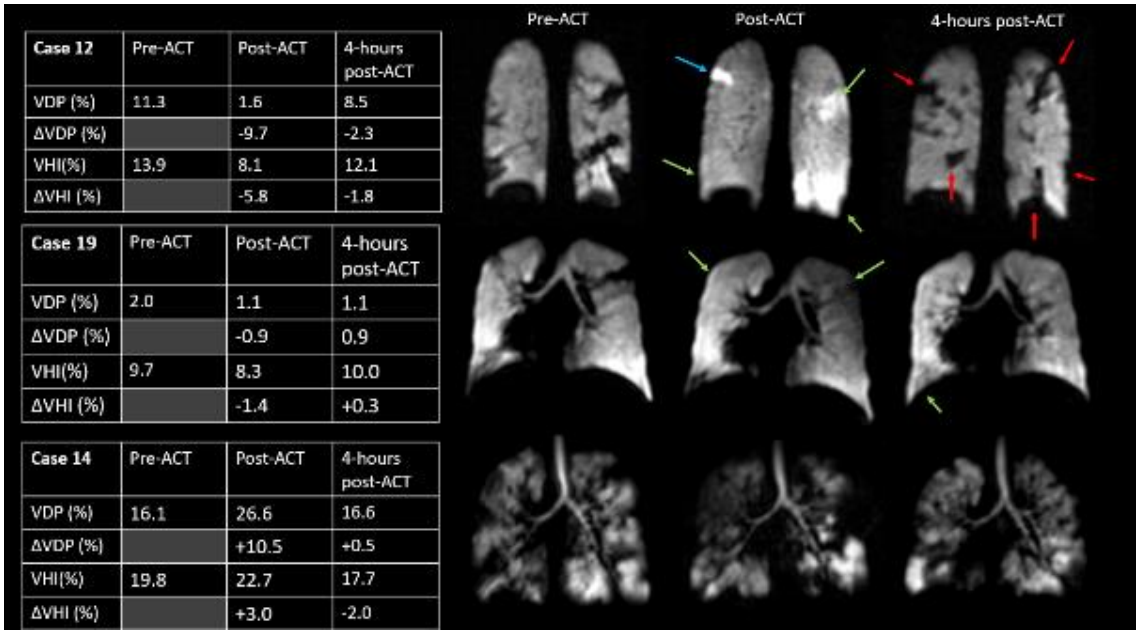
Assessment at 4-hours post-ACT (+6 hours)

Assessment of ^{129}Xe VDP

4-hours post-ACT, the average ^{129}Xe VDP was similar to immediately post-ACT: (data presented as median (IQR)) VDP +2 hours = 5.4 (1.4-13.3)% versus +6 hours = 5.8 (2.2-15.3)%. This reflected, on average, a reduction in VDP (improvement) from baseline: (median (IQR)) ΔVDP = -0.8 (-2.5-0.6)%. As depicted in Figure 63A, whilst individual variation in VDP over time was seen, no statistically significant group difference was seen (Friedman test p=0.24). In comparison to baseline VDP, 4-hours post-ACT 18/28 (64.3%) of individuals had a lower VDP (improved), 10/28 (35.7%) had a higher VDP (worsened). There was no correlation between ΔVDP at the final scan and baseline VDP: Spearman's rank correlation (r=-0.3, p=0.19, Figure 63F).

As shown in Figure 65, individual response at 4 hours varied. VDP remained stable across the two follow-up scans in three participants. In nine participants, for example Case 14 (Figure 65), the worsening in VDP seen immediately post-ACT was temporary; visual improvements in ventilation were seen on the final scan and their VDP had improved by 4-hours post-ACT, either returned towards, or improving beyond their baseline (n=3 and n=6 respectively). In 10/28 (35.7%), for example Case 12 (Figure 65), the improvement in VDP seen post-ACT was temporary as 4-hours post-ACT visually new defects had emerged and VDP had increased either towards baseline VDP (6/28, 21.4%) or some cases (4/28, 14.3%) was higher (worse) than baseline. 5/28 (17.9%) who had improvement in VDP post-ACT had further improvement by the final scan, for example in Case 19 (Figure 65). One individual (1/28, 3.6%) who had an increase in VDP post-ACT saw further significant worsening by the final scan (light blue data set in Figure 63C). This individual had rushed back to

the MRI unit and although they were given time for their breathing to settle after exertion, potentially they may have mobilised secretions without clearing them.



Case 12	Pre-ACT	Post-ACT	4-hours post-ACT
VDP (%)	11.3	1.6	8.5
ΔVDP (%)		-9.7	-2.3
VHI(%)	13.9	8.1	12.1
ΔVHI (%)		-5.8	-1.8

Case 19	Pre-ACT	Post-ACT	4-hours post-ACT
VDP (%)	2.0	1.1	1.1
ΔVDP (%)		-0.9	0.9
VHI(%)	9.7	8.3	10.0
ΔVHI (%)		-1.4	+0.3

Case 14	Pre-ACT	Post-ACT	4-hours post-ACT
VDP (%)	16.1	26.6	16.6
ΔVDP (%)		+10.5	+0.5
VHI(%)	19.8	22.7	17.7
ΔVHI (%)		+3.0	-2.0

Figure 65: Change post-ACT and 4-hours post-ACT in two individuals to illustrate the heterogeneity of response: Case 12, shows resolution of most visible defects post-ACT and improvement in VDP and VHI, at 4-hours post-ACT new defects have emerged, VDP and VHI have increased towards baseline. Case 34 shows resolution of most defects post-ACT and further improvement at 4-hours post-ACT, with improving VDP and VHI across the three time points. Case 14 shows a diffuse worsening in ventilation signal post-ACT which has improved on the final scan, VDP has improved towards baseline and VHI has improved beyond baseline. Arrows indicate areas where defects have resolved (green) and emerged (red). The blue arrow indicated and area of hyperintense signal post-ACT, potentially indicating abnormal regional ventilation which subsequently became an area of poor ventilation.

Using the threshold of repeatability of ^{129}Xe VDP at +6 hours calculated from the control group (Section 5.3.2), only 1/28 (3.6%) (baseline VDP 11.0%) had a significant increase (worsening) in their VDP from baseline (ΔVDP >6.6%). A significant reduction (improvement) in VDP from baseline (ΔVDP <-5.2%) was not seen in any participant. 12/28 (42.8%) had a pre-ACT VDP <5.2% so would not have been able to cross the +6 hours threshold for significant change (ΔVDP <-5.2%). When considering the lower threshold of significant change from the control data, excluding the outlier (ΔVDP >3.8 or <-3.1), 2/28 (7.1%) had a significant increase in VDP, and 3/28 (10.7%) had a significant reduction.

Using the CoV in ^{29}Xe VDP (± 28%) from the control group as a threshold to assess significant change in VDP (Figure 66 and Appendix 9.1), a significant change in VDP was seen in some participants at 4-hours post-ACT, but this was fewer than immediately post-ACT: 8/28 (28.6%) had a significant reduction (>-28%) in defects; 4/28 (14.3%) had a significant increase (>+28%).

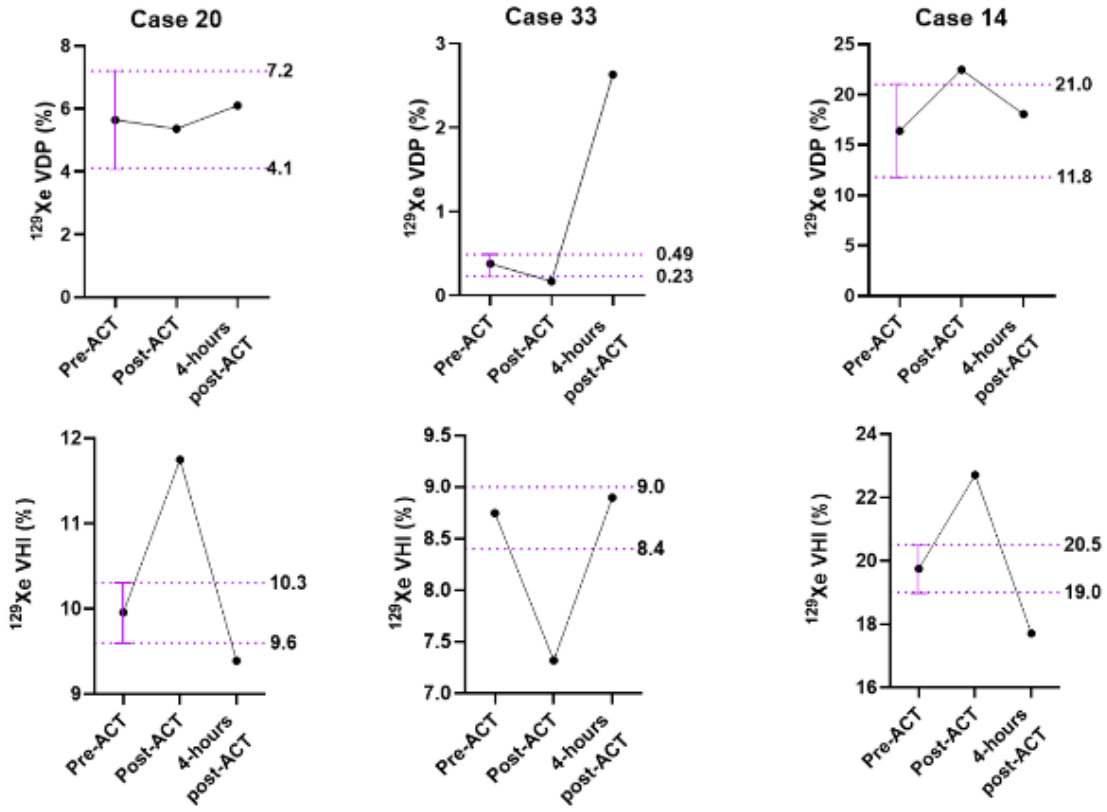
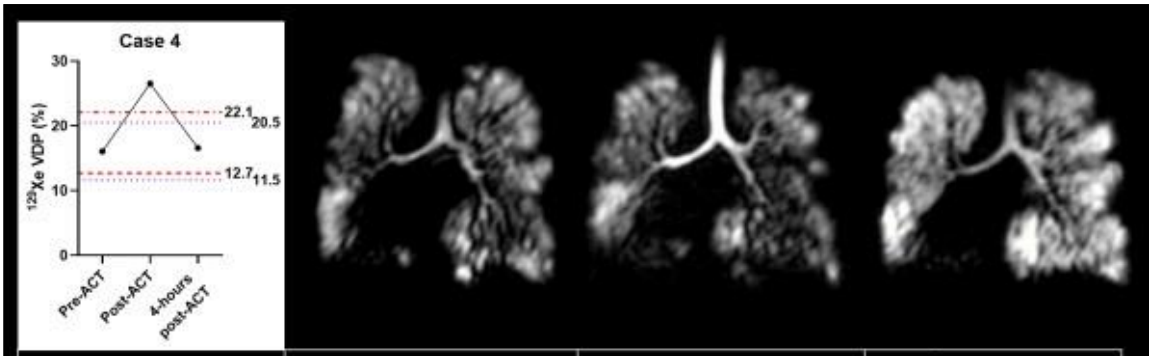
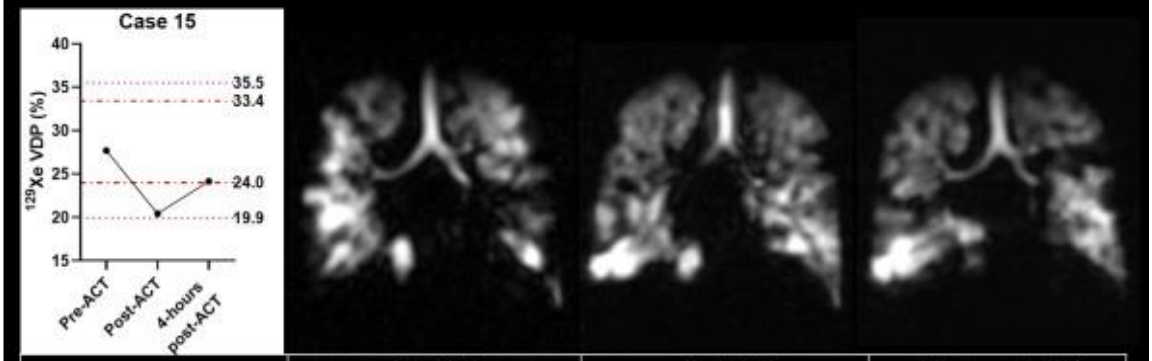


Figure 66: Three case examples depicting the assessment change in ^{129}Xe VDP and VHI over time in the context of individual coefficient of variance (CoV) parameters calculated from the control group. The purple bars depict the range of variability over time anticipated for each individual case, calculated from the same day variability in the no-ACT group. The purple dotted lines depict the upper and lower CoV values for each case at ±28% of pre-ACT VDP and ±3.6 of pre-ACT VHI.

Looking across the whole-time interval, 8/28 (27.6%) of participants had no significant change in VDP as determined by the CoV at either post-ACT or 4-hours post-ACT. In these eight cases: agreement of no significant change was seen in seven cases when using the CoV and repeatability thresholds (Case 4, Figure 67); the remaining case had a clinically significant reduction in VDP post-ACT, but due to a high pre-ACT VDP their threshold for significant change was large (Case 15, Figure 67).



	Pre-ACT	Post-ACT	4-hours post-ACT
VDP	16.4%	22.4%	18.1%
ΔVDP from pre-ACT		+6.0%	+1.7%
ΔVDP >5.7 or > -3.7		Yes	No
ΔVDP >±28% pre-ACT VDP		Yes	No



	Pre-ACT	Post-ACT	4-hours post-ACT
VDP	27.7%	20.4%	24.1%
ΔVDP from pre-ACT		-7.2%	-3.6%
ΔVDP >5.7 or > -3.7		Yes	No
ΔVDP >±28% pre-ACT VDP		No	No

Figure 67: Two example cases to illustrate the use of repeatability threshold and CoV threshold to assess for significant change in ^{129}Xe VDP. Agreement of a significant increase in VDP post-ACT is seen in Case 4 (change greater than both the repeatability threshold of 5.7% and the CoV threshold +28% of baseline VDP), and no significant change 4-hours-post-ACT. Disagreement is seen in Case 15: post-ACT, ΔVDP exceeds the upper limit of repeatability (>5.7%) but not the CoV threshold (>28% of baseline VDP); at 4-hours post-ACT, there is agreement between the methods which both show no significant change. For each case a spaghetti plot depicts the change in VDP over time with the repeatability threshold for significant change(>5.7% and <3.7) indicated shown by red dotted lines and CoV threshold for significant change (>±28%) by purple dotted lines.

Assessment of ^{129}Xe VHI

When compared to immediately post-ACT, at 4-hours post-ACT the average ^{129}Xe VHI had returned towards the level seen at baseline: (data presented as median (IQR)) VHI baseline = 11.5 (9.1-13.1)%, post = 10.4 (8.3-13.0)%, 4-hours post = 11.2 (8.4-13.4)%. The difference in VHI from baseline showed on average a very small reduction (improvement): ΔVHI = -0.3(-1.5-0.3)%. As depicted in Figure 63B, no statistically significant difference in VHI was seen between the three time-points (Friedman test

p=0.33; Dunn's multiple comparison test pre vs post p>0.9; pre vs 4-hours post p=0.42; post vs 4-hours post p>0.9).

The individual case spaghetti plots are shown in Figure 63B and D. While in most the change in VHI was small, the direction of change was varied: ^{129}Xe VHI was lower (better) 4-hours post-ACT than at baseline in 17/28 (60.7%) and higher (worse) in 11/28 (39.3%). Determining significant change using the repeatability of ^{129}Xe VHI (>2.3% or <-2.0%) calculated from the control group at +6 hours: 5/28 participants (17.9%) had a significant change in ventilation heterogeneity; 4/28 (14.3%) with a reduction (improvement) in VHI, and 1/28 (3.4%) with an increase (worsening). Employing the CoV of VHI seen in the control group (>±3.6% of baseline VHI) to determine significant change (Figure 66 and Appendix 9.2), significant change was seen in most participants: 14/28 (50%) had a significant reduction (improvement) in VHI; 6/28 (21.4%) had a significant increase (worsening) in VHI.

Looking across the timepoints only 3/28 (10.3%) had no significant change in VHI from baseline on either of follow up scans as assessed by the CoV in VHI. All these cases also showed no significant change as assessed by the repeatability of VHI in the control group. Two of these three cases had no change significant change in either VHI or VDP (as assessed by threshold of repeatability in VDP in the control group, or as assessed by the CoV in VDP in the control group).

Assessment of regional response following an ACT

A summary of the regional response metrics in the ACT group are provided in Table 24.

Table 24: Summary of the regional change metrics for the ACT group: ^{129}Xe ventilation change over time analysed using the volume treatment response map (VTRM) TCV= thoracic cavity volume.

Regional response metrics (n=25)		**Median (IQR) or mean ±SD**		
		Baseline	**Post-ACT**	**4-hours post-ACT**
^{129}Xe VDP (%)		6.0 (1.8-12.5)	5.3 (1.2-12.7)	5.8 (1.9-15.4)
Volume TRM				
Persistent ventilation defects	%TCV		1.1 (0.2-9.1)	1.3 (0.1-8.5)
	% baseline VDP		23.9 (11.8-48.0)	19.3 (12.0-47.9)
Persistent low ventilation	%TCV		4.7 ± 1.2	4.5 ± 1.2
	% baseline LVP		36.6 ± 12.8	35.9 ± 11.5
Change in ventilation category				
Improve (%)			12.0 ± 5.5	11.9 ± 5.5
Worsened (%)			7.1 (4.1-11.8)	8.6 (5.1-11.4)
Total change (%)			20.9 (11.6-26.6)	20.7 (13.0-26.3)

Immediately post-ACT, assessment with the Volume TRM (VTRM) showed on average more improvement than worsening: (data presented as mean ±SD or median (IQR)) VTRM improved = 12.1 ± 5.5, worsened = 7.1 (4.2-12.5). These changes equated to 21.3 (11.6-27.1)% of the TCV which had moved to or from abnormal ventilation signal (defect or low ventilation).

4-hours post- ACT a similar trend was seen. On average there was more improvement in ventilation than worsening VTRM improved = 12.2 ± 5.6, worsened = 8.3 (5.2-11.3). These changes equated to 20.8 (13.2-26.2)% of the TCV which had moved to or from abnormal ventilation signal (defect or low ventilation).

In some cases, change in ^{129}Xe VDP did not obviously reflect the changes in ventilation distribution visualised. Figure 68 depicts two example cases in which change in VDP does not obviously reflect the changes in ventilation distributions which are visualised: Case 6 had an overall reduction in VDP post-ACT caused by the resolution of some ventilation defects, however a large new ventilation defect had appeared by the right heart border; Case 7 has an overall worsening in VDP post-ACT, however the ventilation defects seen in the right lung at baseline have visually resolved post-ACT.

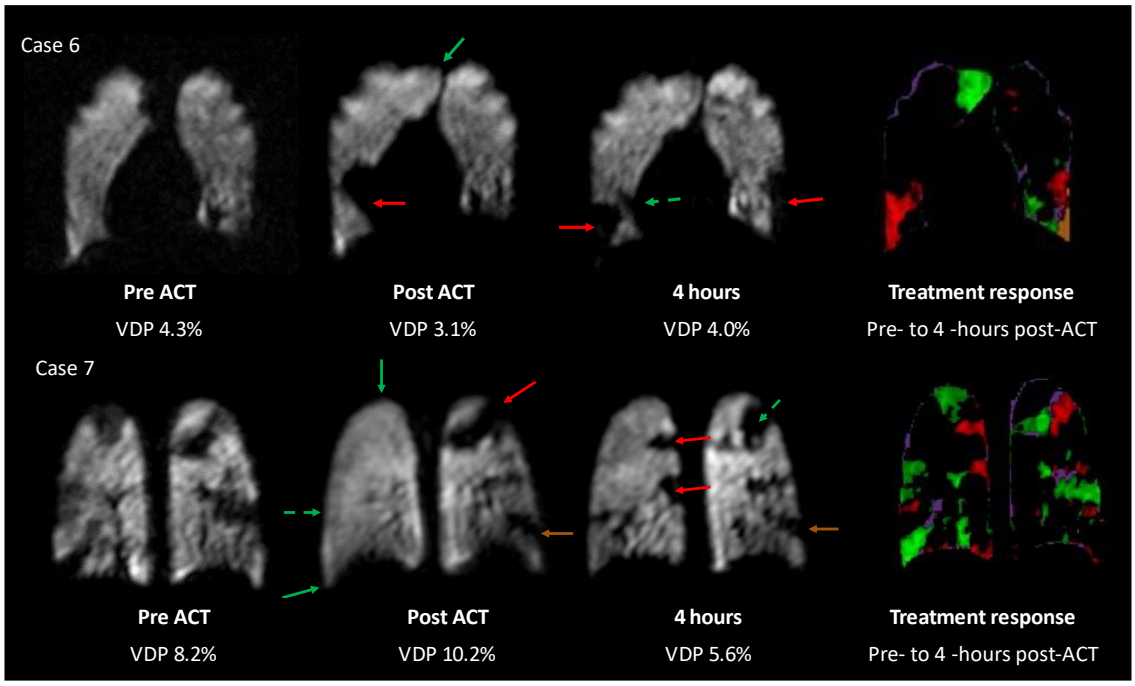


Figure 68: Depicts two cases in which changes in VDP does not reflect the changes in ventilation distributions which are visualised. Case 6 has a reduction in VDP post-ACT, but a large new defect has emerged by the right heart border. Case 7 has an improvement in VDP post-ACT but the defects in the right lung have visually resolved. Arrows indicate areas of improvement (solid green), partial improvement (dotted green), new or worsening defects (red) persistent defects (gold). The treatment response map show areas of improvement (green), worsening (red) persistent defects (gold) and persistent low ventilation (purple).

The volume TRM method showed that some of the ventilation abnormalities seen had persisted from baseline, and the range (IQR) showed the extent of persistent defects varied widely between individuals. Immediately post-ACT, on average 23.9 (11.8-48.0)% of VDP present at baseline persisted, which represented 1.1 (0.2-9.1)% of VDP. The proportion of areas of low ventilation which persisted was higher, on average 36.6 ±12.8%, equating to 4.7± 1.2% LVP. A similar pattern was seen at +6 hours: on average 19.3 (12.0-47.9)% of defects present at baseline persisted, equating to 1.3 (0.1-8.5)% VDP, and 35.9 ± 11.5% of areas of low ventilation persisted, equating to 4.5 ± 1.2% LVP.

Individuals with more severe disease had a higher proportion of their defects persist than those with milder disease. At both immediately post-ACT, and 4-hours post-ACT a strong significant correlation was seen between baseline VDP and %P-VD (0.96 both r= 0.8, p<0.0001) (Figure 69A and B). Conversely, the proportion of LVP which persisted in the follow up scans was higher in those with milder disease. The correlation of baseline VDP with %P-LV was strong and significant both immediately post-ACT and 4-hours post-ACT: r=-0.8, p<0.0001 and r=-0.7, p<0.0001 respectively (Figure 69C and D). These correlations mirror the equivalent correlations in the control group. As shown in Figure 70, the location of areas of persistent low ventilation included areas near the lung edge where signal may be diminished due to partial volume.

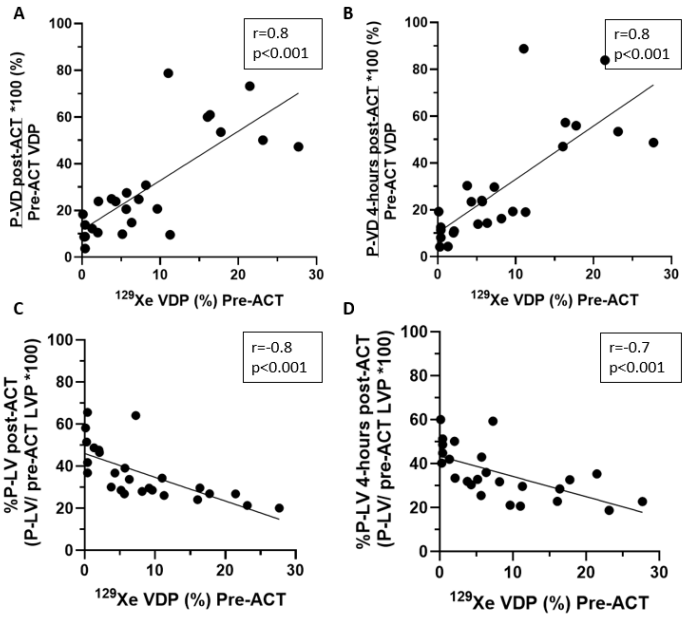


Figure 69: A and B depict the Spearman's correlation of persistent defects with pre-ACT VDP for the ACT group post-ACT (A) and 4-hours post-ACT (B). C and D depict the Spearman's correlation of persistent low ventilation with pre-ACT VDP for the ACT group post-ACT) and 4-hours post-ACT respectively.

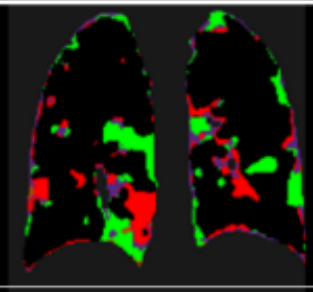
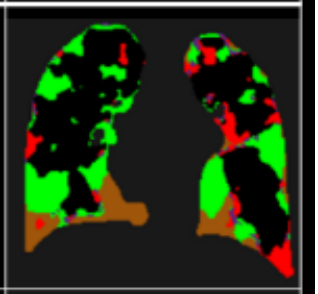
Case number	26	29
Pre-post-ACT volume treatment response map		
Pre-ACT VDP	7.3%	14.0%
P-VDP (post-ACT)	18.4%	11.6%
Pre-ACT LVP	10.4%	14.0%
P-LVP (post-ACT)	1.8%	5.8%

Figure 70: Two example cases, one with milder disease (Case 26) and one more severe disease (Case 29) with pre-post treatment response maps showing improvement (green), worsening (red), persistent defects (gold) and persistent low ventilation (purple). P-VD = persistent ventilation defect (%TCV),P-LV = persistent low ventilation (%TCV)

The overall volume of lung changing either to or from VDP or LVP was greater in those with more severe disease. As shown in

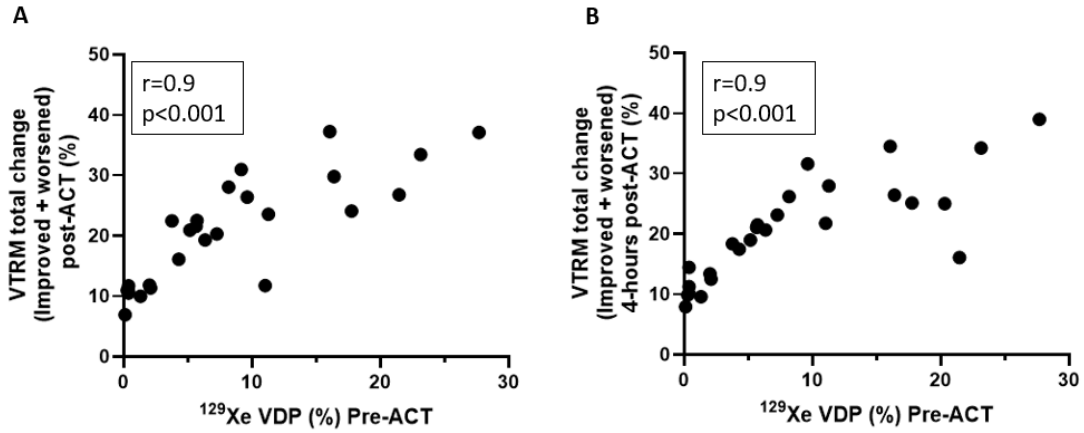


Figure 71, a strong and significant correlation was seen between baseline ^{129}Xe VDP and VTRM total change: at both post-ACT and 4-hours post-ACT r=0.9, p<0.0001.

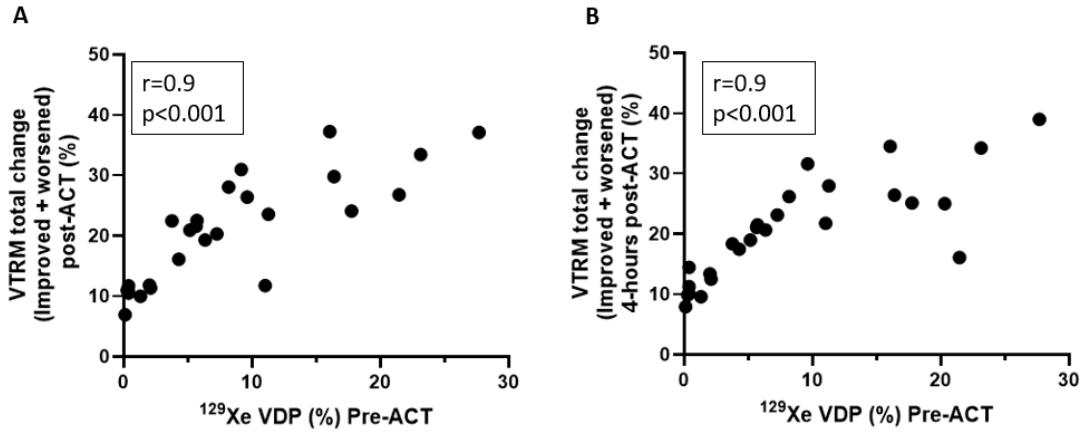


Figure 71: Scatterplots and Spearman's rank correlations of total change in ventilation category (improved + worsened) against pre-ACT ^{129}Xe VDP, at the post-ACT (A) and 4-hours post-ACT timepoints.

5.3.5 No significant change is seen when comparing the ACT group with the control group of n=6.

An overall comparison of the two groups is provided in Section 5.3.1. A summary of the ^{129}Xe whole lung metrics for the ACT and no-ACT (control) groups is provided in Table 25.

Table 25: Summary of whole lung ^{129}Xe metrics across three timepoints, Baseline (pre-ACT), +2 hours (post-ACT) and +6 hours (4-hours post-ACT). Metrics are provided as median (range).

Whole lung metrics	**Control group (n=6)**			**ACT group (n=29)**		
^{129}Xe VDP	Baseline	+2 hours (n=5)	+6 hours	Baseline	+2 hours	+6 hours (n=28)
VDP (%)	3.7 (0.2-20.7)	5.2 (0.4-23.8) *(n=5)*	3.6 (0.4-20.6)	6.3 (2.1-13.7)	5.4 (1.4-13.3)	5.8 (2.2-15.3)
ΔVDP (%)		0.4 (-0.7-3.1)	0.2 (-2.1-3.0)		-0.3 (-2.8-1.44)	-0.8 (-2.5-0.6)
% change in VDP		23.8 (-8.7-210.9)	47.4 (-15.7-197.7)		-5.0 (-39.8-34.7)	-14.0 (-33.2-9.7)
^{129}Xe VHI						
VHI (%)	10.0 (7.2-14.1)	11.4 (6.7-14.7)	10.4 (6.8-14.7)	11.5 (9.1-13.1)	10.4 (8.3-13.0)	11.2 (8.4-13.4)
ΔVHI (%)		0.0 (-0.2-0.3)	-0.2 (-0.8-1.4)		-0.3 (-1.2-0.6)	-0.3 (-1.5-0.3)
% change in VHI		-0.5 (-1.5-1.8)	-1.1 (-7.8-12.0)		-2.6 (-11.6-6.8)	-2.6 (-10.4-2.8)

Comparison of ^{129}Xe VDP between the two groups

At baseline, the average ^{129}Xe VDP in the control group was lower than in the ACT group, but there was no significant difference between the groups (p=0.56). At +2

hours, the average VDP was more similar between the two groups: (data presented as median (IQR)) control = 5.2 (0.4-23.8)%; ACT = 5.4 (1.4-13.3); p = 0.89. Although ΔVDP from baseline showed an improvement in those who had completed an ACT, and worsening in those who did not, the difference was small and not statistically significant: ^{129}Xe ΔVDP ACT = -0.3 (-2.8-1.44)%; control = 0.4 (-0.7-3.1)%; p=0.32. Comparison of percentage change in VDP between the two groups showed a non-significant difference: on average the control group had a 23.8 (-8.7-210.9)% increase (worsening) in their baseline VDP whereas those who completed an ACT were more stable, with on average a small reduction (improvement) in VDP (p=0.10). (Figure 72A).

Similar comparisons between the groups were seen at +6 hours (Figure 72B). The average ^{129}Xe VDP in the control group was lower than in the ACT group: control = 3.6 (0.4-20.6)%; ACT = 5.8 (2.2-15.3); p=0.81. On average those who had completed an ACT had a reduction (improvement) in VDP from baseline, whereas those who had not had increase (worsening), this was not statistically significant: ΔVDP ACT group = -0.8 (-2.5-0.6)%, control group =0.2 (-2.1-3.0)%, p=0.44. Again, comparison of the percentage change in VDP from baseline showed on average the control group had a worsening (increase) in VDP, whereas the ACT group had an improvement (reduction) in VDP, this difference was not statistically significant: % change VDP ACT =-14.0 (33.2-9.7)%, control =47.4 (-15.7-197.7)%, p=0.06.

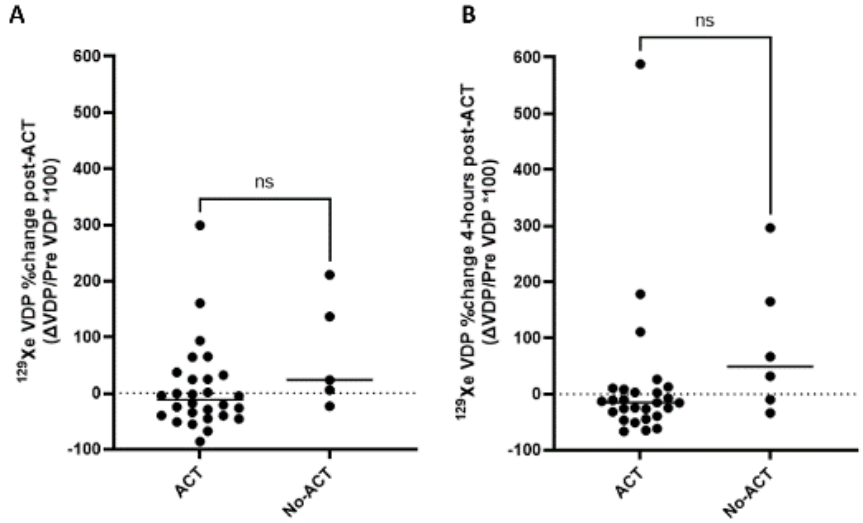


Figure 72: Scatter plots and Mann-Whitney tests comparing % change in VDP between the ACT and control (no-ACT) groups at +2 hours (A) and +6 hours (B) timepoints. Lines indicate the group median.

Comparison of ^{129}Xe VHI between the two groups

Data for comparison of ^{129}Xe VHI in the two groups is summarised in Table 25. At baseline, the average ^{129}Xe VHI was lower in the control group than the ACT group:

(data presented as median (IQR)) control = 10.0 (7.2-14.1)%, ACT = 11.5 (9.1-13.1)%. This difference was reversed at +2 hours, as VHI was higher in the control group than the ACT group, but this difference was not significant: control = 11.4 (6.7-14.7)%, ACT 10.4 (8.3-13.0)%, p= 0.71. Exploring this as change from baseline (∆VHI), the average change in both groups was small: ∆VHI ACT group= -0.3 (-1.2-0.6)% control group = 0.0 (-0.2-0.3)%, p=0.26. Assessing change as a percentage of baseline VHI, on average a very small improvement (reduction) was seen similarly in both groups: control = -0.5 (-1.5-1.8)%, ACT = -2.6 (-10.4-2.8)%, p = 0.67.

At + 6 hours, on average ^{129}Xe VHI was lower in the control group than the ACT group, but this difference was not significant: control = 10.4 (6.8-14.8)%, ACT 11.2 (8.4-13.4)%, p= 0.81. Change in VHI from baseline showed a small improvement, similarly in both groups: ∆VHI control = -0.2 (-0.8-1.4)%, ACT group = -0.3 (-1.5-0.3)%, p=0.23. Again, VHI assessed as a percentage of baseline VHI showed a very small improvement which was comparable across the groups: control = -1.1 (-7.8-12.0)%, ACT = -2.6 (-10.4-2.8)%, p=0.18.

Comparison of the groups using treatment response maps

Regional change in ventilation was seen in both the ACT and control groups using both TRM methods, a summary of these metrics are provided in Table 26 Table 26 The Volume TRM (VTRM) showed on average more change in the ACT group than the control group in terms of improvement, worsening, and total change, but these findings did not reach statistical significance: (data presented as mean ± SD or median (IQR)) VTRM improved: ACT= 12.0 ± 5.5%, control = 9.3 ± 4.9%, p = 0.32; VTRM worsened: ACT = 7.1 (4.1-11.8)%, control = 9.2 (2.9-13.2)%, p=0.83; VTRM total change ACT = 20.9 (11.6-27.1)%, control = 19.2 (7.2-27.1)%, p=0.52.

At +2 hours no significant difference was seen in the levels of persistent ventilation defects (P-VD) between the groups, although the average was higher in those who completed an ACT:P-VD (% baseline VDP) ACT= 23.9 (11.8-48.0)%, control = 18.4 (10.4-69.6)% (p=0.91). The average persistence of low ventilation (P-LV) was lower in the ACT group than the control group, but this was not significant: P-LV (% baseline LVP) ACT = 36.6 ± 12.8%, control = 41.6 ± 15.0%, p= 0.52.

Table 26: Comparison of regional response metrics in the ACT and control(no-ACT) groups. TCV = thoracic cavity volume, P-VD = persistent ventilation defects, P-LV= persistent low ventilation.

Regional response metrics	**Median (IQR) or mean ±SD**			
	Control		**ACT** (n=25)	
Baseline VDP	6.4 (20.6)		6.0 (1.8-0.2)	
	+2 hours (n=5)	**+6 hours** (n=6)	**+2 hours**	**+6 hours**
Volume TRM				
P-VD %TCV	1.3 (0.0-14.4)	0.7 (0.0-12.1)	1.1 (0.2-9.1)	1.3 (0.1-8.5)
% baseline VDP	18.4 (10.4-69.6)	19.4 (11.1-58.3)	23.9 (11.8-48.0)	19.3 (12.0-47.9)
P-LV %TCV	4.7 ± 1.0	4.2 ± 0.9	4.7 ± 1.2	4.5 ± 1.2
% baseline LVP	41.6 ± 15.0	37.0 ± 13.2	36.6 ± 12.8	35.9 ± 11.5
Change in ventilation category				
Improve (%)	9.3 ±4.9	10.1 ± 5.3	12.0 ± 5.5	11.9 ± 5.5
Worsened (%)	9.2 (2.9-13.2)	7.0 (3.7-8.5)	7.1 (4.1-11.8)	8.6 (5.1-11.4)
Total change (%)	19.2 (7.2-27.1)	18.9 (8.6-25.5)	20.9 (11.6-26.6)	20.7 (13.0-26.3)

Similar patterns were seen at +6 hours (4-hours post-ACT). The VTRM again showed on average more change in the ACT group than the control group, including more improvement, more worsening and more total change in the ACT group than the control group, but these findings were not statistically significant: VTRM improved ACT= 11.9 ± 5.5%, control = 10.1 ± 5.3%, p = 0.47; VTRM worsened: ACT = 8.6 (5.1-11.4)%, control = 7.0 (3.7-8.5)%, p=0.25; VTRM total change ACT = 20.7 (13.0-26.2)%, control = 18.9 (8.6-25.5)%, p=0.48.

At +6 hours both the average persistent VDP and persistent LVP were similar between the two groups: P-VD (%baseline VDP) control = 19.4 (11.1-58.3)%, ACT = 19.3 (12.0-47.9), p=0.94; P-LV (%baseline LVP) control = 37.0 ± 13.2%, ACT = 35.9 ± 11.5% p=0.8.

5.3.6 Individuals who pre-medicated with salbutamol showed greater change in ventilation distribution following their ACT regimen.

Within the ACT group it was possible to assess two subgroups, those who were prescribed inhaled salbutamol as a pre-medication to nebulised hypertonic saline (n=8) and those who were prescribed nebulised hypertonic saline without a pre-medication of

salbutamol (n=18). Those who were not prescribed hypertonic saline (n=3) were not included in this subgroup analysis.

Comparison of the groups at baseline.

A summary of the main demographics for the two subgroups are provided in Table 27. The two groups were comparable at baseline in terms of sex and age. 11/18 (61.1%) of individuals who were not prescribed salbutamol had confirmed ultrastructural cilial defects compared to 8/8 (100%) of those who were prescribed salbutamol. This was notable as in Chapter 4 this study found individuals with no cilial defects identified were found to have a lower baseline ^{129}Xe VDP. Despite both groups being prescribed a twice daily ACT regimen frequency, individuals who were not prescribed salbutamol reported a significantly lower completion of ACT sessions in the seven days prior to their study visit than those who were prescribed salbutamol: 0.7 (0.0-1.0) sessions v 2.0 (1.0-2.0) sessions, p=0.004. Mean FEV_1 (z-score) was normal in those not prescribed salbutamol (1.1 ± 1.5) and abnormal in those who were prescribed salbutamol but difference between the groups was not statistically significant (p=0.26). Baseline ^{129}Xe VDP and VHI on average was higher in the salbutamol group but no statistically significant difference was seen between the groups: (data presented as median (IQR)) baseline VDP salbutamol = 8.4 (4.9-16.1)%, no salbutamol =2.9 (0.4-16.7)% p=0.13; baseline VHI salbutamol =11.8 (9.9-14.6)% no salbutamol =9.7 (7.6-12.5)%, p=0.44.

Table 27: Demographics for individuals in the ACT group who were prescribed nebulised hypertonic saline as part of their ACT regimens. The individuals are split into two subgroups: those whose personalised ACT regimen does not include a pre-medication of inhaled salbutamol; those whose personalised ACT regimen does include a pre-medication of inhaled salbutamol. Data presented as mean ± SD or median (IQR).

		No salbutamol	**Salbutamol**	**p-value**
N. (unless stated)		**8**	**18**	
Sex		50% (4) male	50% (8) male	1.0
Age (years)		12.0 ± 4.4	12.5 ± 2.6	0.6
Ultrastructural defect				
	IDA or MTD only	1 (13%)	4 (22%)	
	ODA only	0 (0%)	5 (28%)	
	IDA and ODA	3 (38%)	8 (44%)	
	No defect	3 (38%)	1 (6%)	
	No result	1 (13%)	0 (0%)	
Number of antibiotic courses in last 12 months (oral and IV, planned and unplanned)		2.3 (1.0-3.8)	2.3 (0.8-4.0)	0.83
PsA (cultured in last 12 months)		0 (0%)	4 (22.2%)	
ACT frequency (sessions/day)				
	Prescribed	2.0 (2.0-2.0)	2.0 (1.2-2.0)	0.64
	Self-reported	0.7 (0.0-1.0)	2.0 (1.0-2.0)	0.004**
Spirometry				
FEV_1	z-score	-1.1 ± 1.5	-2.0 ± 1.7 *(n=17)*	0.26
	% predicted	85.7 ± 19.1	75.5 ± 19.6 *(n=17)*	0.25
FVC	z-score	-0.6 ± 1.4	-1.2 ± 1.5 *(n=17)*	0.17
	% predicted	96.9 ± 11.5	82.3 ± 25.3 *(n=17)*	0.39
FEV_1/FVC	(z-score)	-1.6 ± 1.6	-1.6 ± 1.3 *(n=17)*	0.86
	% predicted	87.3 ± 11.6	86.4 ± 11.8 *(n=17)*	0.86
^{129}Xe metrics at baseline				
VDP (%)		2.9 (0.4-16.7)	8.5 (4.9-16.1)	0.13
VHI (%)		9.7 (7.6-12.5)	11.8 (9.9-14.6)	0.44
Pedometer counted steps (scan 2 – 3).		4516 ± 2070	5922 ± 2933	0.24

Comparison of ACT regimen response between the groups using ^{129}Xe MRI whole lung metrics

A summary of the metrics assessing change are provided in Table 28. Post-ACT, ^{129}Xe VDP was similar in the two groups: (data presented as median (IQR)) no-salbutamol = 2.9 (0.4-16.7)%, salbutamol = 8.5 (4.9-16.1)% p=0.12. However as shown in Figure 73, on average the salbutamol group had a reduction (improvement) in VDP from baseline,

whereas an increase (worsening) in VDP was seen in those without salbutamol, this difference was statistically significant: ΔVDP no-salbutamol = 0.7 (-0.1-4.6)%, salbutamol = -1.1 (-3.4 - -0.1)%, p=0.009. A statistically significant difference was also seen in the percentage change in VDP (ΔVDP/pre-ACT VDP *100), with on average improvement in VDP in the salbutamol group and worsening in VDP in the no salbutamol group: %change VDP no-salbutamol = 44.5 (-1.6-264.3), salbutamol = -25.3. (-45.6-0.1), p=0.001.

At 4-hours post-ACT, no significant differences were seen between the whole lung metrics for the two groups. Average VDP was higher in the salbutamol group than the no salbutamol group: ^{129}Xe VDP no-salbutamol = 4.5 (0.8-13.6)%, salbutamol = 6.5 (2.6-17.3)% p=0.24). Change from baseline (ΔVDP) continued to show improvement in those who had taken salbutamol compared to those who had not, but there was a wide range of change seen in those who had taken salbutamol: ΔVDP salbutamol = -0.9(-2.7-1.1)%, no-salbutamol = 0.2 (-1.4-0.9)%, p=0.63 (Figure 73). The percentage change in VDP showed a small improvement from baseline in both groups: no-salbutamol = -11.0 (-36.1-140.1)%, salbutamol = -12.7 (-32.7-140.1)%, p=0.80.

*Table 28: A summary of the ^{129}Xe VDP and TRM metrics for the two subgroups. Data is presented as median (IQR) or mean ±SD. ** denotes a statistically significant difference between the salbutamol and no salbutamol groups, p<0.01.*

Whole lung metrics	**No salbutamol** (n=8)		**Salbutamol** (n=18)	
^{129}Xe VDP	**+2 hours**	**+6 hours (n=7)**	**+2 hours**	**+6 hours** (n=17)
VDP (%)	5.9 (1.2-17.1)	4.5 (0.8-13.6)	5.3 (2.4-16.1)	6.5 (2.6-17.3)
ΔVDP (%)	0.7 (-0.1-4.6)**	0.2 (-1.4-0.9)	-1.1 (-3.4 - -0.1)**	-0.9 (-2.7-1.1)
% change in VDP	44.5 (-1.6-264.3)**	-11.0 (-36.1-140.1)	-27.6 (-47.0 - -2.8)**	-12.7 (-32.7-9.2)
^{129}Xe VHI				
VHI (%)	9.8 (8.0-14.9)	9.8 (7.0-13.1)	10.8 (8.7-13.1)	11.7 (9.3-14.9)
ΔVHI (%)	0.6 (-0.4-2.5)	0.0 (-0.6-0.7)	-0.8 (-1.4-3.0)	-0.4 (-1.8-0.2)
% change in VHI	7.7 (-3.4-20.6)	-0.3 (-8.7-5.3)	-6.0 (-12.7-3.6)	-4.5 (-13.9-1.6)

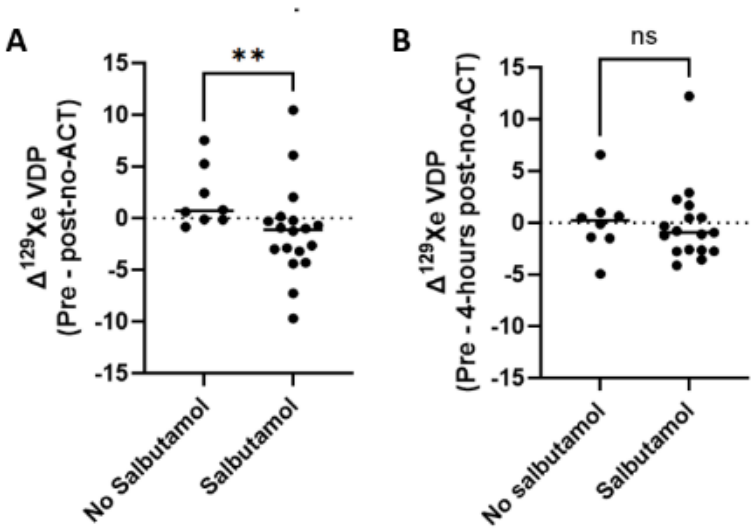


Figure 73: Scatter plot showing comparison of Δ[129]XeVDP post-ACT (A) and 4-hours post-ACT (B) in those who took salbutamol and those who did not. A dotted line a 0 indicates no change from baseline. Brackets show the significance of comparison of the group difference with the Mann-Whitney test.

Examples of two cases who completed similar regimens but with or without salbutamol in Figure 74.

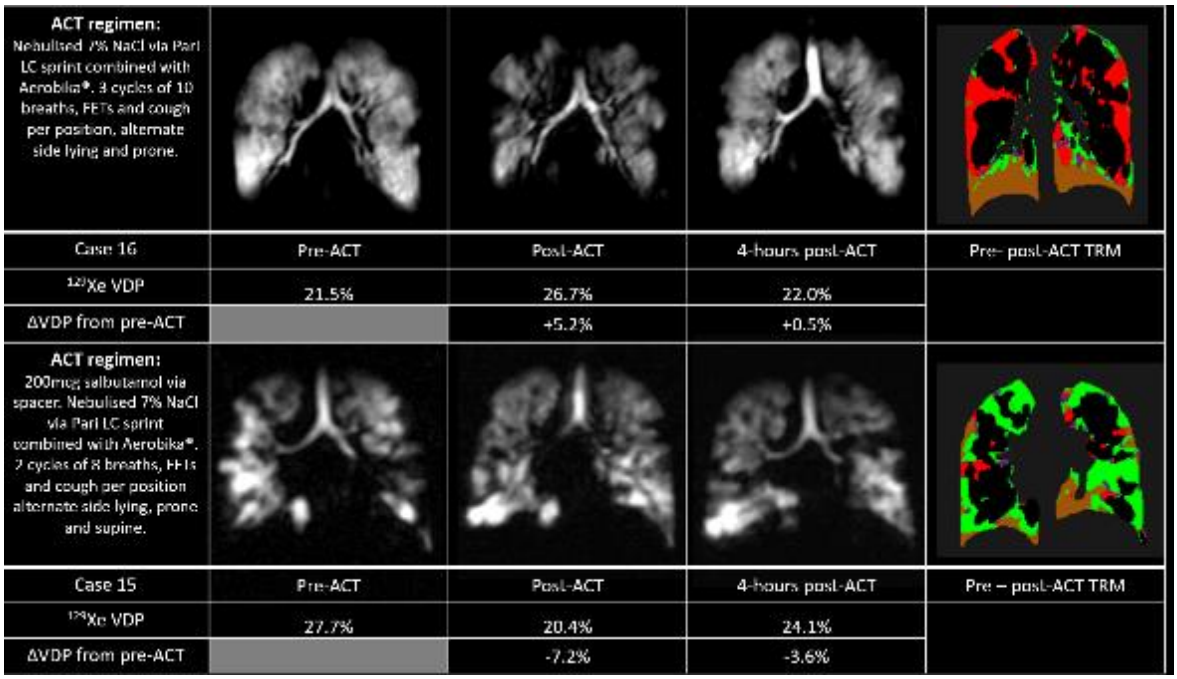


Figure 74: Examples of one case who did not take salbutamol (Case 16) and one can who did (Case 15). For each case [129]Xe images pre, post and 4-hours post-ACT with corresponding [129]Xe VDP are presented, with ΔVDP and the corresponding pre-post ACT treatment response map (TRM).

Comparison of ACT regimen response between the groups using ^{129}Xe MRI regional response metrics.

A summary of the regional response metrics using the Volume TRM (VTRM) are provided in Table 29.

*Table 29: A summary of the ^{129}Xe TRM metrics for the two subgroups. Data is presented as median (IQR) or mean ±SD. Statistically significant group differences are denoted as * when p<0.05 and ** when p<0.01.*

Regional response metrics	**No salbutamol** (n=7)		**Salbutamol** (n=16)	
	+2 hours	**+6 hours**	**+2 hours**	**+6 hours**
Volume TRM				
P-VD %TCV	0.5 (0.0-1.3)	0.2 (0.0-1.3)	1.9 (1.0-9.6)	2.0 (0.9-9.7)
% baseline VDP	23.5 (8.8-25.0)	12.5 (8.2-30.3)	24.3 (11.6-52.7)	23.7 (14.8-52.2)
Change in ventilation category				
Improve (%)	8.4 ± 2.9*	8.6 ± 2.6*	14.4 ± 5.2*	15.4 ± 8.2*
Worsened (%)	5.8 (4.9-12.5)	5.0 (3.3-8.0)**	7.5 (4.6-12.2)	10.3 (8.0-13.8)**
Total change (%)	11.7 (11.0-22.6)	12.5 (10.1-18.4)**	22.6 (16.9-29.4)	24.1 (19.4-30.7)**

Immediately post-ACT a statistically significant difference between the groups was seen in regional ventilation signal improvement, with greater improvement seen in those who used salbutamol: (data presented as mean ±SD or median (IQR)) VTRM improvement salbutamol = 14.4 ± 5.2%, no salbutamol = 8.4 ± 2.9%, p<0.01. Whilst the average change in the salbutamol group at 22.6 (16.9-29.4)% was greater than the no salbutamol group (11.7 (11.0-22.6)%), this difference did not reach statistical significance (p=0.09).

4-hours post-ACT the salbutamol group had significantly more improvement in ventilation than the no salbutamol group: VTRM improvement no-salbutamol = 8.6 ± 2.6%, salbutamol = 15.4 ± 8.2% p<0.05. However, the salbutamol group also had more worsening in ventilation signal: VTRM worsening no salbutamol = 5.0 (3.3-8.0)%; salbutamol = 10.3 (8.0-13.8)%; p=0.002. With both more improvement and more worsening seen in the salbutamol group, there was a greater total change: VTRM total change salbutamol = 24.1 (19.4-30.7)%, no salbutamol = 12.5 (10.1-18.4)%, p<0.002.

5.3.7 Changes in ventilation distribution are seen at higher lung volumes.

A summary of ^{129}Xe VDP data at two volumes end inspiratory tidal volume (EITV) and total lung capacity (TLC) are provided in Table 30. In Section 4.3.4, it was established that in most cases, ventilation defects improved at higher lung volumes at baseline.

Assessing the control group at +2 hours the average VDP was lower at TLC than at EITV: (data presented as mean (IQR)) ^{129}Xe VDP at EITV = 5.2 (0.4-23.8)%, at TLV = 3.6 (1.0-15.1)%. On average ΔVDP (VDP at TLC- VDP at EITV) showed a reduction in VDP: ΔVDP = -1.6 (-8.7-0.5)%. Whilst most cases showed an improvement in VDP at higher lung volumes, two individuals (40%) had an increase in VDP at TLC.

The changes seen when moving from EITV to TLC were smaller at +6 hours: average VDP was slightly lower at TLC than at EITV: VDP at EITV = 4.5 (0.4-22.6), at TLC = 4.1 (0.7-16.0); ΔVDP showed a small reduction (improvement) in VDP: ΔVDP = -0.4 (-6.7-0.4)%. Again, whilst most cases showed an improvement in VDP at higher lung volumes, two individuals (40%) had an increase in VDP at TLC.

Table 30: ^{129}Xe metrics illustrating changes in VDP from end inspiratory tidal volume (EITV) to total lung capacity (TLC).

^{129}Xe metrics	**Control group (n=5)**			**ACT group (n=24)**		
	Baseline	+2 hours	+6 hours	Baseline	+2 hours (n=22)	+6 hours (n=22)
VDP at EITV (%)	6.8 (0.1-20.7)	5.2 (0.4-23.8)	4.5 (0.4-22.6)	8.0 (2.6-16.3)	5.5 (1.7-18.8)	6.5 (2.2-16.6)
VDP at TLC (%)	5.4 (0.8-16.2)	3.6 (1.0-15.1)	4.1 (0.7-16.0)	3.9 (1.8-11.8)	4.1 (1.5-14.3)	3.4 (1.1-13.8)
ΔVDP (TLC-EITV)	-1.4 (-4.5-0.6)	-1.6 (-8.7-0.5)	-0.4 (-6.7-0.4)	-2.3 (-5.1 - -1.2)	-0.9 (-4.2-0.0)	-0.9 (-4.3-0.1)
Reversible volume index	1.0 (1.0-1.2)	1.0 (1.0-1.6)	1.0 (1.0-3.4)	1.1 (1.0-1.4)	1.0 (1.0-1.2)	1.0 (1.0-1.2)

In the ACT group, immediately post-ACT VDP was on average lower at TLC than EITV: VDP EITV = 5.5 (1.7-18.8)%, TLC = 4.1 (1.5-14.3)%. Change between EITV and TLC showed on average an improvement in VDP: ΔVDP = -0.9 (-4.2-0.0)%. Whilst most cases showed an improvement in VDP at higher lung volumes, 5/22 (22.7%) had an increase in VDP at TLC.

At 4-hours post-ACT a similar pattern was seen: VDP was on average lower at TLC than EITV VDP EITV = 6.5 (2.2-16.6)%, TLC = 3.4 (1.1-13.8)%; ΔVDP showed on average an improvement in VDP: ΔVDP = -0.9 (-4.3-0.1)%. Whilst most cases showed an improvement in VDP at higher lung volumes, 5/22 (22.7%) had an increase in VDP at TLC.

In individuals with improvement in VDP at TLC, visually this appeared as a resolution or partial resolution of defects as demonstrated by Case 26, Figure 75. In cases with an increase in VDP at TLC, visually defects appeared larger, or new defects were apparent at higher lung volumes, for example Case 6 in Figure 75. In the control group, an increase in VDP at TLC was only seen in cases with mild disease: baseline VDP<0.3% (at EITV). However, in the ACT-group these individuals had a range of

disease severity (pre-ACT VDP% at EITV range 0.3-16.1%). As no changes were seen on structural ^{1}H UTE images taken during the same scanning session, changes were felt to be most likely as a result of the movement of small obstructive secretions.

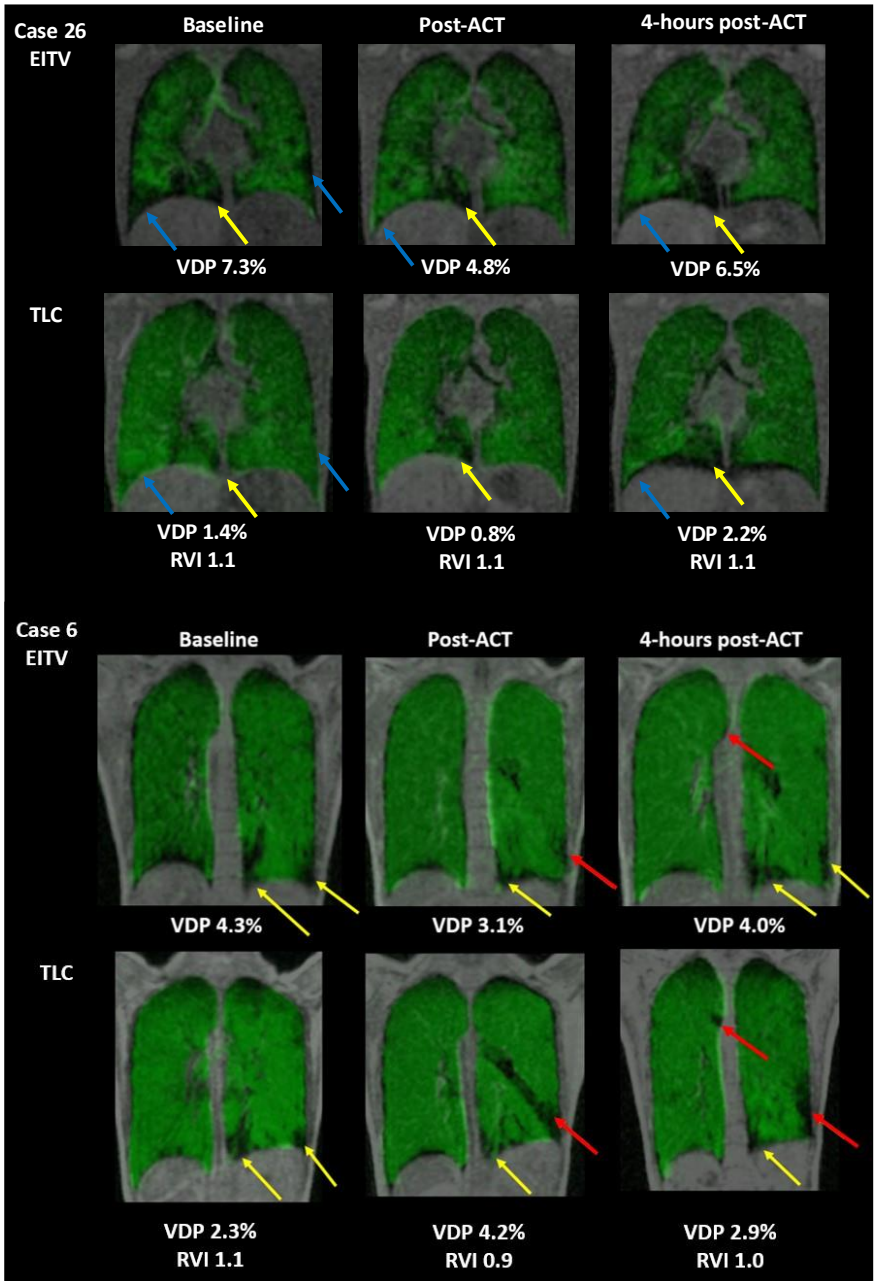


Figure 75: Examples of two cases at end inspiratory tidal volume (EITV) and total lung capacity (TLC). Case 26 shows improvement in VDP and visible resolution of some defects at TLC. Case 6 shows worsening of some defects at TLC. Images are displayed with the lung ventilation defect percentage (VDP) and reversible volume index from EITV and TLC. Arrows indicate visual resolution of defect at TLC (blue), worsening of defect at TLC (red) or persistence of defect at TLC (yellow).

5.3.8 Free breathing MRI methods may provide alternative information on individual ACT regimen response.

15 participants in the ACT group, were successfully assessed with both ^{129}Xe Ventilation MRI and free-breathing ^{1}H (PREFUL) MRI at all three time points (baseline, post-ACT, and 4-hours post-ACT (Table 31).

Table 31: Free breathing ^{1}H (PREFUL) MRI and ^{129}Xe MRI data for the 15 participants of the ACT group who were assessed with both methods.

	^{129}Xe	**^{1}H**
VDP (%)		
Pre-ACT	7.3 (4.3-16.1)	5.8 ± 4.9
Post-ACT	5.4 (2.5-22.2)	6.9 ± 6.3
4-hours post-ACT *(n=14)*	6.6 (2.5-19.0)	5.6 ± 5.3
∆VDP (%)		
Pre to post-ACT	-0.3 (-2.6-3.0)	0.5 (-1.0-4.1)
Pre to 4-hours post-ACT *(n=14)*	0.1 -1.5-1.2)	-1.2 (-4.2-0.9)
%change		
Pre to post-ACT	-4.3 (-39.7-37.1)	31.7 (-8.7-147.6)
Pre to 4-hours post-ACT *(n=14)*	-2.3 (-32.1-16.0)	-14.5 (-86.1-59.6)

Immediately post-ACT across the group there was no significant difference in ^{1}H VDP from baseline: (data presented as mean ± SD or median (IQR)) VDP baseline = 5.8 ± 4.9%; post-ACT = 6.9 ± 6.3%; p=0.29. Change over time was also assessed as change from baseline (^{1}H ∆VDP): on average there was a small increase (worsening) in VDP immediately following the ACT: ^{1}H ∆VDP = 0.5 (-1.0-4.1)%. A shown by the individual case spaghetti plots in (Figure 76), ACT response assessed by ^{1}H VDP varied: VDP reduced (improved) post-ACT in 7/15 46.7% and increased (worsened) in 8/15 (53.3%).

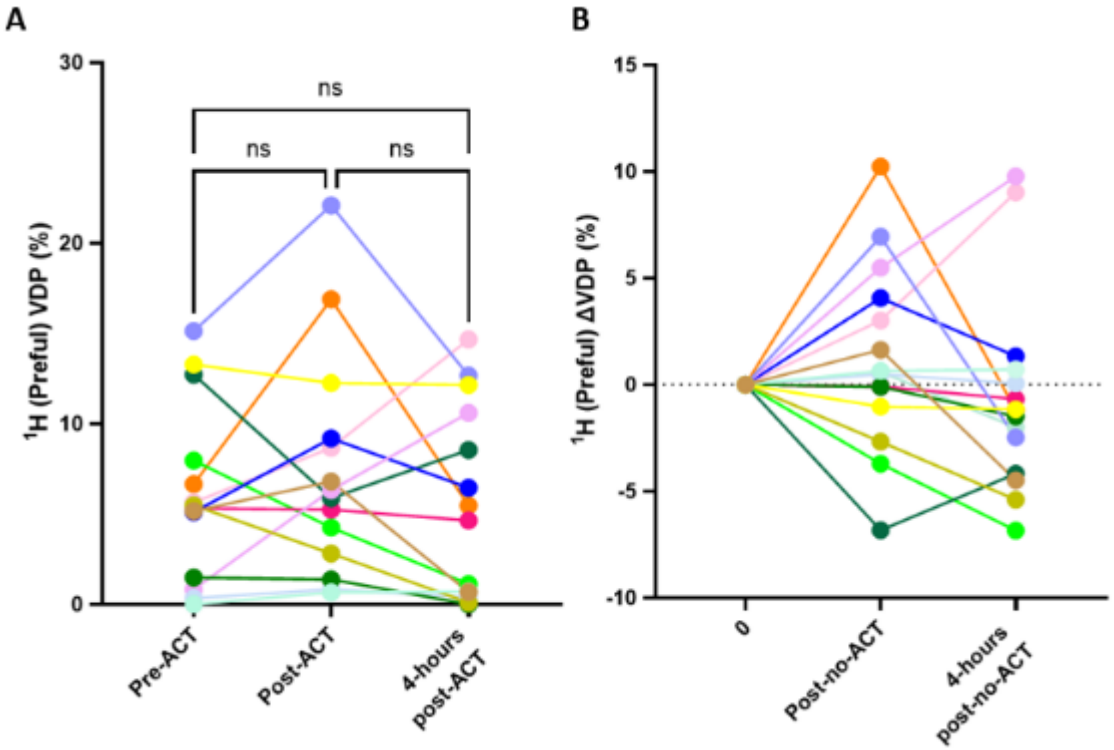


Figure 76: Spaghetti plots showing time by time analysis with free breathing ^{1}H (PREFUL) methods. (A) depicts ^{1}H VDP and B ^{1}H ΔVDP, pre, post and 4-hours post-ACT. Each colour represents the data for an individual participant in the ACT-group.

Using the threshold of repeatability of ^{1}H VDP at +2 hours calculated from the control group at +2 hours (>5.7 or <-3.7) (Section 5.3.2) to assess for significance of change in ^{1}H VDP post-ACT, 6 participants had a significant change in VDP: 3/15 (20.0%) had an increase (worsening) in VDP and 3/15 (20.0%) had a reduction (improvement) in VDP. Significant change was also assessed using the mean co-efficient of variance (CoV) of ^{1}H VDP observed in the control group (CoV> ± 28.4% baseline ^{1}H VDP) (Figure 77 and Appendix 9.3). A significant change was seen in most participants: 3/15 (20.0%)had a significant reduction (>-28%) in ^{1}H VDP; 8/15 (53.3%) had a significant increase (>28%) in ^{1}H VDP.

Reviewing the group again at 4-hours post-ACT, on average ^{1}H VDP was similar to baseline: VDP baseline = 5.8 ± 4.9%, 4-hours post-ACT = 5.6 ± 5.3% (p=0.27). On average there was a small improvement in ^{1}H from baseline: ΔVDP =-1.2 (-4.2-0.9)%. 64.3%) had a reduction in VDP from baseline, whereas 5/14 (35.7%) had an increase in VDP.

Using the threshold of repeatability of ^{1}H VDP at +6 hours calculated from the control group at +2 hours (>6.6 or <-5.2) (Section 5.3.2) to assess for significance of change in ^{1}H VDP at 4-hours post-ACT, only one individual had significant change. Significant change in ^{129}Xe VDP (>± 28%) was seen in fewer participants than immediately post-

ACT. 3/14 (21.4%) had a significant reduction (>-28%) in defects; 5/14 (35.7%) had a significant increase (>28%) in defects.

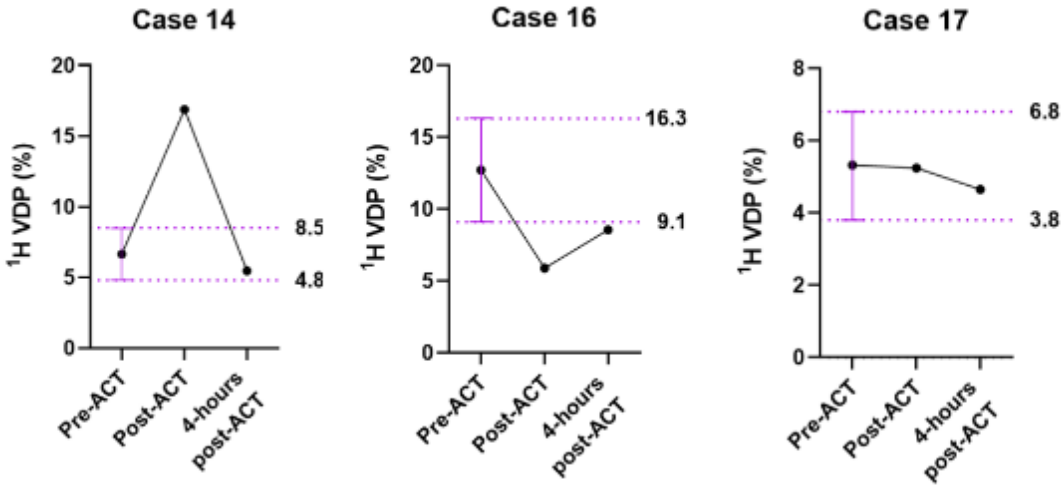


Figure 77: Three case examples depicting the assessment change in ^{1}H VDP over time in the context of individual coefficient of variance (CoV) parameters. The purple bars depict the range of variability over time anticipated for each individual case, calculated from the same day variability in the no-ACT group. The purple dotted lines depict the upper and lower CoV values for each case at ±28% of pre-ACT VDP.

Comparison of ^{129}Xe VDP and ^{1}H (PREFUL) VDP following an ACT

The correlation between ^{1}H %VDP and ^{129}Xe %VDP was variable across the three time points (Figure 79A-C). Compared to the significant moderate correlation seen between the two metrics at baseline (r=0.7, p=0.009), post-ACT the correlation between the two metrics weakened (r=0.5, p=0.06). By 4-hours post-ACT the significant moderate correlation of the metrics was present again (r=0.78, p=0.002). Table 32 provides a comparison of the individual assessment of significant change in ^{29}Xe VDP using the CoV for ^{129}Xe VDP, and significant change in ^{1}H VDP using the CoV for ^{1}H VDP. Of the 15 participants who were assessed by both methods post-ACT: agreement was seen in 8/15 (53.3%); in 2/15 (13.3%) a significant change was identified with ^{1}H VDP but not ^{129}Xe VDP; in 5/15 (33.3%) divergent changes were seen, with one metric flagging significant worsening and the other flagging significant improvement.

At 4-hours post-ACT the agreement of significant change was seen in 7/14 50% . In the remaining cases, 2/14 (14.3%) had significant change only identified with ^{129}Xe VDP and 5/14 (35.7%) had significant change only identified with ^{1}H VDP. Examples of cases with agreement and divergence are provided in Figure 78.

Table 32: Comparison of significant changes identified by ^{129}Xe VDP and ^{1}H VDP. Each number represents the number of cases. Squares marked in green indicate agreement and in peach indicate divergence.

			^{129}Xe VDP					
			Post-ACT			4-hours post-ACT		
			Sig. increase	Sig. decrease	No sig. change	Sig. increase	Sig. decrease	No sig. change
^{1}H VDP	Post-ACT	Sig. increase	3	4	1			
		Sig. decrease	1	1	1			
		No sig. change	0	0	4			
	4-hours post-ACT	Sig. increase				0	0	3
		Sig. decrease				0	3	2
		No sig. change				2	0	4

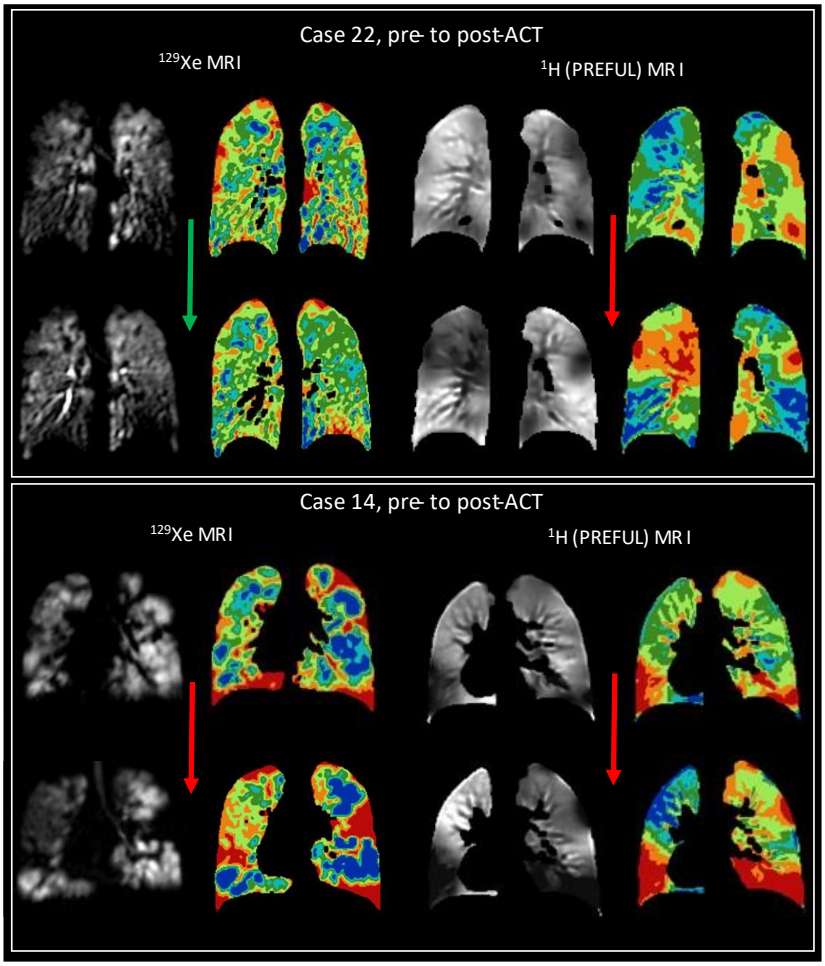


Figure 78: Comparison of ^{129}Xe and ^{1}H (PREFUL) for two cases, for each case raw ^{129}Xe MRI and ^{1}H (PREFUL) images are shown with their corresponding ventilation binning map. In Case 22 there was divergence; ^{129}Xe VDP significantly reduced but ^{1}H VDP significantly increased. In Case 14 there was agreement; both ^{129}Xe and H VDP significantly increase.

As shown in the Bland-Altman plots in Figure 79D-F, VDP as assessed by ^{129}Xe VDP was consistently higher than as assessed by ^{1}H VDP across all three time points. The 95% confidence interval (CI) of the limits of agreement of the two metrics were wider both post-ACT and 4-hours post-ACT than pre-ACT: data presented as bias (95%CI); pre-ACT 3.7 (1.5 to -1.5); post-ACT 3.2 (17.5 to -11.0); 4-hours post-ACT 4.6 (16.2 to -6.9). There was no correlation between ^{1}H ΔVDP and ^{129}Xe ΔVDP: pre to post ACT (r=0.4, p=0.2); pre to 4-hours post-ACT (r= 0.4, p=0.2).

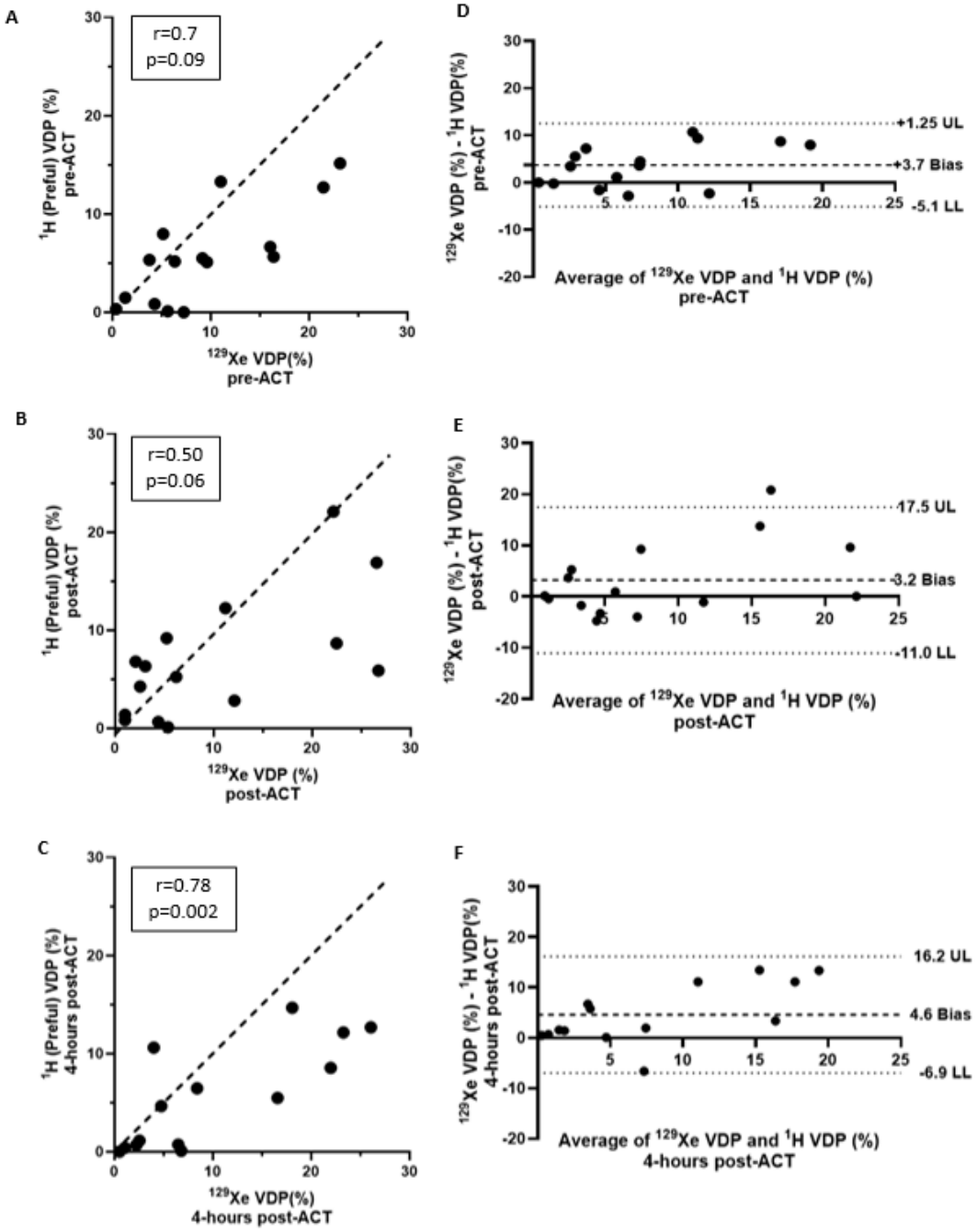


Figure 79: Comparison of free breathing ^{1}H (PREFUL) VDP and ^{129}Xe VDP. A, B and C depict scatterplots and Spearman's rank correlation of ^{1}H VDP and ^{129}Xe VDP, pre, post and 4-hours post-ACT respectively. The dotted line depicts r^2=1 (perfect correlation). D, E and F show Bland Altman plots of average versus difference of ^{129}Xe VDP and ^{1}H VDP pre, post and 4-hours post-ACT. (B) and VHI (D). Bias is illustrated with a dashed line and 95% CI upper and lower limits of normal with dotted lines (UL and LL respectively).

5.4 Discussion

This study assessed children with PCD who did not complete an ACT regimen three times in the same day with ^{129}Xe ventilation MRI and . When assessing these changes as a proportion of the lung, larger changes were seen in those with more severe

disease when compared to those with milder disease, however in mild disease the changes represented a much higher proportion of their baseline abnormality. We calculated a coefficient of same-day variation of the primary metrics of ventilation distribution (^{129}Xe VDP and VHI and ^{1}H VDP) for children with PCD.

The data confirmed that the recommended ACT regimens for individuals with PCD are highly personalised. Whilst no significant group change was seen in ventilation abnormalities following a personalised ACT regimen, response varied with some individuals improving and others worsening post-ACT. Using treatment response mapping (TRM) to assess regional change showed that individuals with more severe disease had a higher persistence of their defects following an ACT. The distribution of ventilation post-ACT may be better in those who use salbutamol prior to nebulised hypertonic saline during their ACT regimen. Whilst in most cases ventilation improved at higher lung volumes, in some individuals, defects appeared larger at higher volumes, this was more commonly seen post-ACT and 4 hours-post ACT. Free breathing ^{1}H MRI provided information on ventilation abnormalities but often there was poor agreement in the assessment of treatment response when using ^{129}Xe VDP and ^{1}H VDP. The results partially support the hypothesis (H4), *in some cases* there is improvement in visual indicators of lung health, as measured pre- and post-, by MRI-derived ventilation defect percentage, after personalised ACTs are completed.

5.4.1 Ventilation distribution varies over the day in those who do not complete an ACT.

This study for the first time assessed the same-day variability of ventilation distribution in children and young people with PCD who did not complete an ACT regimen. The findings show the distribution of ventilation changes over time, with the resolution of some defects, persistence of some defects and emergence of new defects.

Previously published studies have shown high same-day repeatability of ^{129}Xe metrics in people with CF (128, 281, 282). The technical repeatability of ^{129} Xe VDP in CF reported by Smith *et al.* (128), was used to calculate the sample size for the ACT-group in this study, employing the value of ^{129} Xe VDP ±1.6% as the threshold for significant change. However the control group in this study had greater variability in ^{129} Xe VDP (+5.7% and -3.7% post-no-ACT timepoint); and a higher co-efficient of variance than previously reported in young people with CF, who were of a similar age with a similar average FEV_1 (281): (data presented as this study population (mean ±SD) v comparison population (median (IQR) (281)) CoV 28% v 11.8%; age 13.1 ± 3.0 v 15 (3); FEV_1 (% predicted) 81.9 ± 27.5% v 84.0 (20)%. With ^{129}Xe repeatability data in PCD limited to a conference abstract of a current study (276) it is unclear if the higher

variance seen in this study compared to the published literature in CF is due to pathophysiological differences between the two conditions. Whilst PCD and CF have impaired mucus clearance in common, there are differences in mucus movement and mucus load that may influence variability in defects over the day (Chapter 4). Other potential causes for this difference in repeatability include different centre imaging acquisition processes (281) and time between the scans. In contrast to this study, which had a total of six hours between the first and last scans, Smith *et al.* (128) and Munidasa *et al.* (281) had a much shorter inter-scan interval and as their participants remained in the scanner, there would be less opportunity for secretion movement and clearance than in the current study. As this is the first study which has assessed same-day repeatability over a longer time interval, with greater variation in all whole lung metrics (^{129}Xe VDP and VHI and ^{1}H VDP) at +6 hours than at +2 hours, this indicates natural variability may been seen over a greater time period and therefore the time interval between scans may affect repeatability of all these metrics.

5.4.2 Whilst no overall change in ventilation defects are seen following an ACT, individual response is heterogeneous.

Whole lung metrics

In this study cohort, there was no statistically significant group difference following a single ACT, however significant changes in ventilation distribution were found in most individuals, with some individuals improving following an ACT and others worsening. Contrastingly a study by West *et al.* (283) has reported significant improvement in ventilation defects in 80% of children and adults with CF. The ACT regimens used in their study all involved high-frequency chest wall oscillation (HFCWO) with personalised device settings. However but it is unclear why some individuals were not given their usual prescribed medications which would be taken as part of their ACT regimens, including salbutamol (40%), saline (47%) and DNase (35%). The contrast in the findings of West *et al.* (283) with the current study could be attributable to a number of factors including population, intervention study protocol and methods. HFCWO although commonly used in North America, is not routinely recommended in the UK (62). This study did not use HFCWO, instead the Aerobika®, an oscillatory PEP device was most commonly used. Previous studies comparing OPEP with HFCWO (284) have shown no significant difference as assessed by FEV_1, although the limitations of this outcome measure are recognised. Mindful that performing spirometry may cause airway clearance, this study only involved spirometry prior to the baseline MRI, so completion of additional spirometry before the second MRI may have caused additional airway clearance in the HFCWO study. This study population also had a lower pre-ACT

VDP (median 6.3% v 15.2%), but a lower FEV_1 (median 78.3% v 92.2%) making it difficult to compare the populations as differences in ventilation metrics may arise from different MRI acquisition and processing methods rather than a true population difference.

Regional change

Whilst this study found no significant change in ^{129}Xe VDP following an ACT regimen, regional changes were seen, indicating whole lung metrics may not provide the full picture. Regional changes in ventilation have been demonstrated in previous studies assessing the effects of standardised ACTs with Ventilation MRI (138-140, 142). Whilst no overall change in $^{129}Xe/^{3}He$ VDP was seen in any of these studies, changes were seen in regional ventilation in the following circumstances: in eight out of 15 adults with bronchiectasis after 3 weeks of using an Aerobika® 10-20 breaths and huff-coughs in sitting, four times a day (139); in adults with COPD, more commonly in those with higher baseline VDP, following three to four weeks of using an Aerobika® for 10-20 breaths, huff-coughs in sitting, four times daily (140); in children with CF following a single standardised ACT comprising 20-30 minutes of percussion in postural drainage positions (138); in children with CF immediately following 20 minutes of “chest physical therapy” (142). Whilst changes in regional ventilation were seen in these studies, in contrast to the current study, the standardised ACT regimens they used do not reflect the personalised ACT regimens which are commonly used in the UK. As regional ^{129}Xe MRI metrics are a novel outcome, the clinimetric performance of these metrics are currently unknown. Further work is needed to establish the suitability of regional changes in ventilation distribution to establish if these are suitable outcomes to assess the effects of interventions.

ACT regimen components

This study found greater improvement in ventilation in children with PCD who pre-medicated with salbutamol before nebulised hypertonic saline in ACT regimens than those who did not. Current recommendations are to pre-medicate with inhaled salbutamol before nebulised hypertonic saline only in specific cases: when there is a history of benefit from bronchodilators or evidence of bronchospasm on trial of the hypertonic saline (62). Whilst these findings indicate there may be benefit to this practice, interpretations of these findings requires a degree of caution; those who were prescribed salbutamol had a higher VDP than those who were not and whilst not statistically significant, it is possible that the larger changes seen in the salbutamol group may be attributable to their disease severity. A small study which assessed children with CF using ^{3}He MRI found improvement in ventilation defects following

administration of a bronchodilator, and a subsequent worsening in ventilation defects following nebulised DNase and airway clearance (141). Whilst interpretation of these findings in a clinical context is limited, as their method of performing airway clearance immediately post DNase conflicts with UK clinical practice recommendations (172) and insufficient details of the ACT regimen are provided, this study also found evidence of improvement in ventilation following administration of salbutamol at the start of an ACT regimen. As a significant reduction in ^{129} Xe ventilation defects and ventilation heterogeneity was found following administration of a bronchodilator in children with severe asthma (285), further studies to assess the effects of salbutamol within ACT regimens using ^{129}Xe MRI is needed.

5.4.3 Free breathing ^{1}H (PREFUL) MRI methods provide complimentary information to ^{129}Xe MRI.

This study assessed whether free breathing ^{1}H (PREFUL) methods as surrogate for ^{129}Xe Ventilation MRI could be used to assess treatment response following an ACT. Free breathing ^{1}H (PREFUL) methods have been successfully used to assess intervention response, and demonstrated positive change in two previous situations: following antibiotics for an acute exacerbation (281) and 8-16 weeks of modulator therapy (286) in people with CF. This study found a moderate correlation in ^{1}H VDP and ^{129}Xe VDP pre-ACT, immediately post-ACT and 4-hours post-ACT. As the two methods showed agreement of response in some cases and divergence in others, this supports the theory that the methods provide complimentary information (Section 4.5.2). Munidasa *et al.* (281) who assessed response to antibiotics following an acute exacerbation in people with CF reported one case of divergent ^{1}H VDP and ^{129}Xe VDP findings and proposed this may be due to a reduction in inflammation causing improved parenchymal density without an improvement in ventilation. Assessing response over a shorter-term it is unlikely the differences seen in this study arise from changes in inflammation, as such it is reasonable to consider alternative physiological reasons. As ^{1}H MRI (PREFUL) methods assess the change in ventilation during respiration, they may provide information on regional compliance of the lungs. Divergence of response as assessed by ^{1}H VDP and ^{129}Xe VDP may arise where areas of lung which expand following effective ventilation of neighbouring areas via interdependence; normal ventilation signal would be seen on ^{1}H MRI, but a mucus obstructed airway could result in no or low ^{129}Xe ventilation signal. Conversely, normal ventilation signal could be present on ^{129}Xe MRI but not on ^{1}H MRI if the active inhalation and breath hold manoeuvre involved in ^{129}Xe MRI acquisition methods provides ventilation via channels of collateral ventilation in lung units which fail to open with the relaxed free breathing ^{1}H acquisition methods. ^{1}H MRI (PREFUL) provides information on lung ventilation which

complements rather than replaces ^{129}Xe MRI. As this study (Chapter 4) found ^{1}H VDP to be less sensitive to detect abnormalities than ^{129}Xe VDP, further work is needed to establish the clinimetric properties of PREFUL imaging to establish if this is a clinically suitable outcome measure.

5.4.4 Strengths and limitations

Inclusion of a small group who did not complete an ACT.

The inclusion of a group who did not complete an ACT provided for the first-time data on same day variability of ventilation distribution in PCD. As regular ACTs are widely recommended in PCD, yet many patients struggle with compliance, risks associated with delaying a routine ACT session to participate in the no-ACT group were felt to be small. However, without data to support this risk assessment, the group size was limited, and participants were invited to participate in this group, rather than being randomly allocated. The size of this group limited the statistical comparisons which could be drawn from the data, especially considering the range of ventilation abnormalities seen in the study population. However, the inclusion of this group has provided initial data, flagged the importance of understanding same day variability, and will be important in the planning of future studies.

Criteria for allocation to the control group were based on discussions with expert clinicians in the field. Aiming for similar lung health across the two groups, FEV_1 as the current gold standard for assessing lung health was used to guide group allocation, however a notable but non-significant difference in baseline ^{129}Xe VDP was seen between the two groups. The impact of this difference is unknown, but it further highlights that FEV_1 and ^{129}Xe VDP provide complimentary rather than surrogate information on lung health. Despite no difference in the recommended frequency of ACT completion between the groups, there was a statistically significant difference in the self-reported frequency of ACT completion in the seven days prior to the study visit between those in the ACT and control groups. It is possible that group allocation may have been influenced by unconscious bias arising from an assumption that those who are less compliant with home regimens may be more agreeable to participate in the control group.

Individuals in the control group did not complete an ACT regimen however, they did undertake study tasks which involved changes in their natural respiratory pattern; the performance of spirometry which involves maximal inhalation and forced exhalation; breathing manoeuvres which involved breath holds for image acquisitions. Whilst there was no quantification of cough frequency during the study visit, it was not uncommon

for participants of both groups to have a productive sounding or visibly productive cough during spirometry or the scan sessions. Secretion retention is a recognised pathophysiological feature of PCD (287), and as the cough mechanism remains unaffected by PCD, it is physiologically reasonable that movement of secretions will have occurred with any inadvertent coughing.

Study design

Previous studies assessing the effects of ACT regimens with Ventilation MRI have used standardised regimens (138-140), in contrast to this study that pragmatically assessed the effects of regimens tailored to the individual by their physiotherapist. Whilst this approach aligns more readily with the real-world context of clinical practice, it is possible that the variety in ACT regimen components used has influenced the results. Whilst it was possible to compare treatment response in those who took salbutamol and those who did not, comparison of other regimen components was not possible due to the number of participants. Comparison of ACT regimen components was not an aim of the study, and as a prospective development study it has highlighted this as potential avenue for future work. Whilst guidance was given to encourage patients to perform their ACT in an effective way, some individuals still struggled especially younger patients. Recent studies have shown that patient technique can often result in suboptimal pressures, breath repetitions and expiratory durations (81, 288). As quantitative monitoring of ACT regimen components was not available for this study, it is not possible to ascertain the variance or potential impact of technique quality or expiratory flow pattens on the results. This study recruited patients from four centres in the North of England. Whilst no notable difference in VDP at baseline or treatment response was identified in participants recruited from different centres, this may limit national and international generalisation of the findings.

Assessment of significant change

Any ventilation defects resulting from mucus obstruction have potential to change with secretion clearance, therefore it is logical that greater change in the distribution of ventilation may be seen in individuals with more secretions. The study population included individuals with a range of disease severity; some individuals had minimal ventilation defects and others had more marked abnormalities. The variation in VDP seen across the group is greater than previously reported in CF (128). As this CF data informed the sample size calculations, it is likely that a larger sample size would be needed to assess change in this more varied population, As this study also found greater change in ^{129}Xe VDP over time in children with PCD who did not complete an ACT compared to the CF population used for the initial sample size calculations, it was

important to ensure the methods of assessing change following ACT were suitable across the study population. When employing a single standardised threshold based on repeatability in the control group (^{129}Xe ΔVDP >5.7% or <-3.7% post-ACT) only a handful of participants had change deemed as significant; six participants immediately post-ACT, one participant 4-hours post-ACT. Whilst this may indicate that the ACT regimens are not having a significant effect on ventilation defects, it is possible employing this repeatability threshold had limitations. For example, individuals with a baseline VDP < 3.7% (n=8) would not have had scope to improve their VDP enough to cross the level of significance post-ACT, at 4-hours post-ACT this principle applies to eight individuals with baseline VDP < 5.2%. As the control group was small, one individual case with larger change in VDP had a notable impact on the repeatability of VDP. Analysis without this case identified a further seven cases with significant change post-ACT and three at 4-hours post-ACT. This indicates warrant for further assessment of same day variability without an ACT in PCD, so that more confidence in repeatability can be gained from a larger data set. However, with greater change in those with more severe disease and a higher baseline VDP in those identified with significant change, this method remains biased to those with greater disease. When using an individually scaled threshold of significant change (> ±18% pre-ACT ^{129}Xe VDP) derived from the co-efficient of variation (CoV) in VDP seen in the control group, significant change was seen in a greater proportion of individuals; 19 participants immediately post-ACT, and 12 at 4-hours post-ACT. This method identified significant change in an additional 13 cases post-ACT and 11 4-hours post-ACT compared to the 95% CI method. There was only one case post-ACT in which their post-ACT change was identified as significant with the 95% CI method and non-significant with the CoV method. This case had the highest pre-ACT VDP (27.7%) in the study and had a clinically significant improvement (^{129}Xe ΔVDP -7.2%). In more severe disease, 28% of baseline VDP is large and therefore clinically significant change may not pass this threshold. This method of assessing significant change is biased towards those with milder disease and the clinical significance of relatively small changes in VDP% in those with mild disease remains unknown. To overcome the limitations of both of these approaches there may be a role for using a combination of both methods in populations with heterogenous levels of ventilation abnormalities or with a larger data set, it may be possible to provide separate CoVs for those with mild, moderate, and severe disease. Relative change in FEV_1 has been used to assess response to interventions in CF, although the limitations of this are well described, and the importance of establishing what is a clinically important difference for an individual (289). LCI is another commonly used outcome to assess intervention response, but the minimal clinically important difference in LCI is also still to be established (290). Learning from research in people with CF has

highlighted the potential benefit of grouping or stratifying participants according to their disease severity (289), however researchers working in rare diseases such as PCD will also need to be mindful of achieving a sufficient sample.

Timing of the assessment of response

This study assessed the short-term effects of a single ACT regimen. Whilst further work is needed to understand the longer-term impact of ACTs and disease trajectory in PCD with ^{129}Xe VDP, this study has provided novel information on the short-term effects of a single ACT session, a valuable first step to develop future study designs. This study imaged patients post-ACT to capture any immediate effects and 4-hours post-ACT, to reassess ventilation at the anecdotally recommended minimum time interval between ACT regimens, however the optimal time to assess change following completion of an ACT is unknown. The distribution of ventilation in individuals appeared different post-ACT compared to 4-hours post-ACT, raising the question of what the optimal time is to assess the effects of ACTs. One previous study in people with CF assessed variance in lung function over time following a personalised ACT regimen (291). In children they reported a very small non-significant improvement in FEV_1 (ΔFEV_1 = 1.0%) immediately following the ACT, and a small but significant worsening in FEV_1 (ΔFEV1=-4 to -6%) 0.5-3 hours post ACT. The optimal time to reassess participants following ACTs remains unknown, but it is clear that outcomes may look different depending on the time of assessment.

Assessment of regional response

Responding to clinician feedback, this study explored a novel phenomenon of the persistence of regions of ventilation abnormalities, specifically the persistence of ventilation defects and low ventilation. As individuals with more severe disease have structural changes which are unlikely to respond to a single ACT session, it is logical that those with more severe disease will have a higher proportion of defects which persist over the day than those who have milder disease, whose defects are likely to be caused by reversible mucus plugging. The negative correlation of baseline VDP and proportion of persistent low ventilation potentially highlights the limitations of using low ventilation as a metric; the areas of low ventilation in those with mild disease arise around the lung edge where partial volume reduces signal; in more severe disease the low ventilation is seen more centrally due to true abnormal ventilation which will change and therefore not persist with change in ventilation distribution. This study was not powered to assess changes in regional metrics but does demonstrate the importance of further research in regional response metrics as whilst ventilation MRI is highly

sensitive, the whole lung metrics are not permitting us to capture the changes which are occurring following ACT.

MRI methods

Technical limitations of ^{129}Xe MRI can arise from image acquisition, registration, and segmentation. As consistent lung inflation levels are required for the accurate comparison of images, standardised acquisition processes were used with all participants trained on the breath-hold manoeuvres prior to entering the scanner. However, variability in lung inflation levels across the three timepoints for some participants were seen at end-inspiratory tidal volume and total lung capacity. This was discussed with PPI members who felt participants could be pre-empting instructions or cough supressing which could result in them not reaching FRC prior to inhaling the ^{129}Xe from the Tedlar bag. Whilst participants were guided to manage their cough and follow instructions to minimise these potential barriers, future studies with repeated scans may benefit from spirometry guided MRI to ensure consistency of volumes.

For image registration where possible, an image acquired either immediately before or after the ^{129}Xe sequences were selected, however on occasions where the proton image quality was low, images from other time points were selected, focussing on the best alignment of the thoracic cavity. The consistency of segmentation was optimised with all images segmented by one individual, images across the three timepoints segmented in succession and segmentation cross-checked to ensure decisions, for example re lung boundaries were consistent. When queries arose from more difficult cases, for example an individual with short-rib syndrome, advice on the correct identification of lung boundaries was sought from an experienced member of the POLARIS team and when needed, an experienced radiologist.

5.5 Conclusion

This chapter provides evidence relating to the programme theory in Figure 80: we can use functional MRI to assess the effects of ACT regimens (#7). Whilst the overall group change in those who completed an ACT showed no significant difference to those who did not, individual response was seen with some participants improving and others worsening. As baseline lung health is varied in PCD, individualised thresholds of assessing the significance of change may provide an appropriate method to assess response alongside more established methods using repeatability. Assessment with treatment response maps provided a novel method for assessing response, which did show significant change related to pre-medication of salbutamol before nebulised hypertonic saline. Reflecting on the ACT personalisation model (Figure 81), this study has used ^{129}Xe MRI to assess baseline lung health (Chapter 4) and response to an

ACT intervention (Chapter 5). These information sources theoretically offer cues about patient lung health and ACT response which may inform ACT personalisation knowledge. There is need to understand how clinicians use this data from MRI when reviewing personalised ACT regimens.

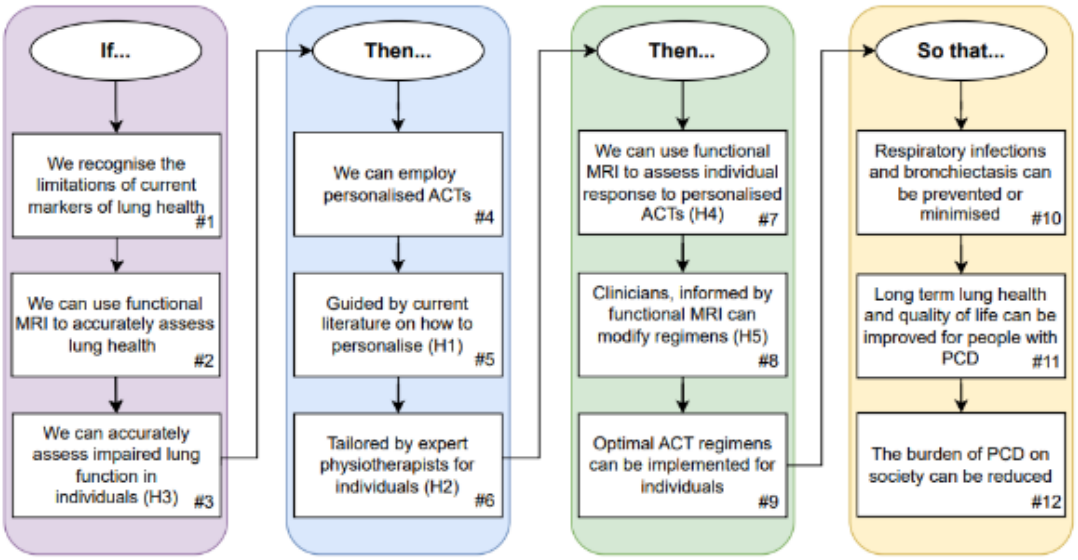


Figure 80: Thesis programme theory.

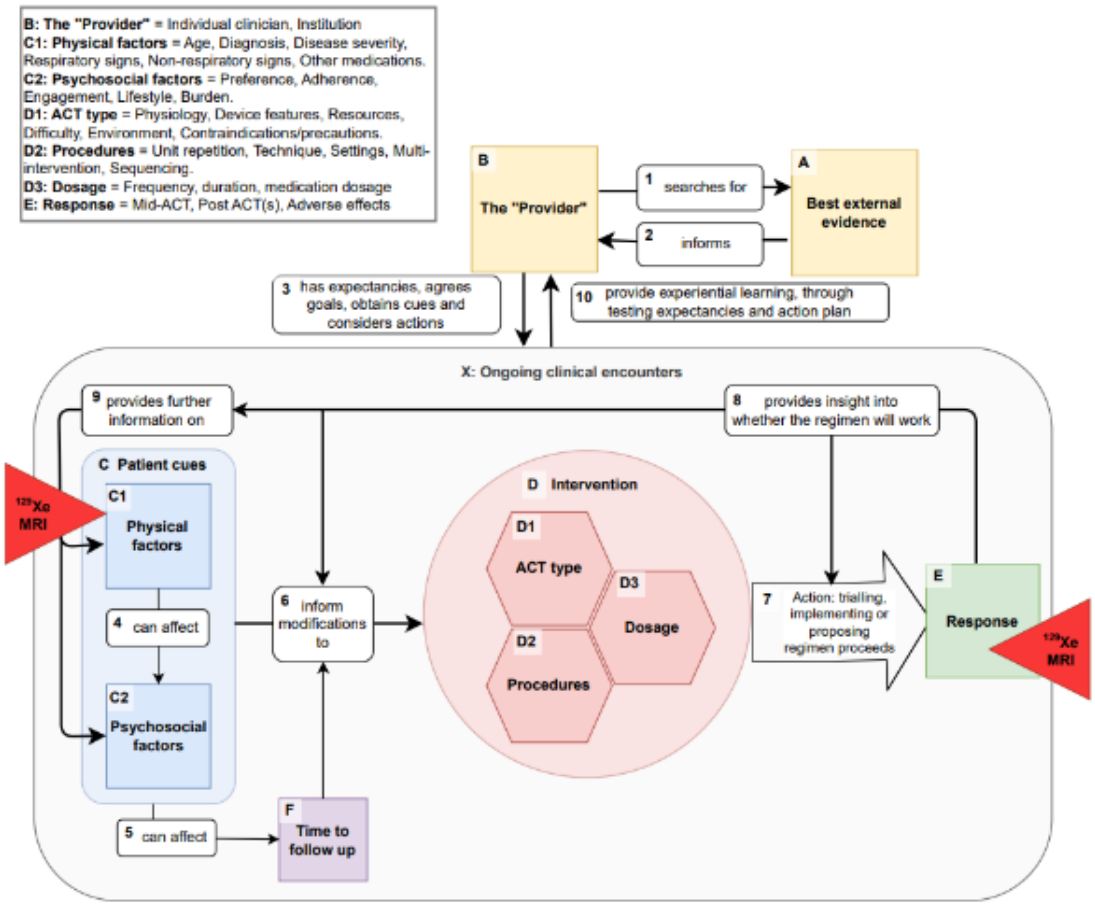


Figure 81: The ACT personalisation model. Red triangles indicate where ^{129}Xe MRI may theoretically be used in ACT personalisation.

Chapter 6: Functional imaging informs expert clinicians during the personalisation of ACT regimens.

6.1 Introduction and objectives

Personalised airway clearance techniques (ACTs) are recommended for people with ciliary dyskinesia (PCD) with clinicians assessing patient cues and selecting intervention components to iteratively tailor regimens for individuals. Physical patient characteristics are an important in ACT personalisation and lung health in PCD is varied, but FEV_1 which is the most widely used tool to assess lung health individuals with PCD is flawed, especially when assessing individuals with milder disease (Chapter 4). Ventilation MRI can assess response to ACT regimens, preliminary data shows response is diverse; an improvement in ventilation distribution is seen following an ACT in some individuals, and worsening is seen in others. It remains unknown if or how imaging information influences clinicians' ACT personalisation decision-making. This chapter aims to address two of the hypotheses generated in Chapter 1:

- *H3: Lung health in PCD will be found to be heterogeneous, as assessed by MRI-derived ventilation defect percentage.*
- *H5: Functional imaging will inform expert physiotherapists in the personalisation of ACTs for children with PCD (Table 1).*

We conducted a mixed methods study using cognitive task analysis and case study methods to explore how clinicians make decisions about ACT personalisation when presented with functional lung imaging data. As a mixed methods study, in this chapter the hypothesises clarify the purpose of the investigation rather than providing formal statement for statistical testing (292).

Objectives

1. To conduct a ‘think aloud’ study to show how clinicians make decisions about ACT personalisation in three stages:
    a. With clinically available data from recent history, watching a video-taped consultation of an ACT regimen review and ACT regimen completion.
    b. With the introduction of structural MR images.
    c. With the introduction of functional MR images.

2. To conduct a mixed methods multiple case study, integrating quantitative MRI data and qualitative interview data in order to delineate the clinical scenarios where imaging led to divergent changes in ACT recommendations.

6.2 Methods

6.2.1 Research design

A mixed methods approach was indicated to:

i. permit the exploration of novel imaging into the real-world context of ACT regimen personalisation,
ii. understand how it may influence clinical practice,
iii. offer a comprehensive exploration of a complex clinical area,
iv. deliver insights through data integration which would not be otherwise possible,
v. offer a patient-centred study design with analysis focussed at the level of the case.

The design draws upon two approaches:

1. Cognitive task analysis (CTA), which explores cognitive processing in real life settings (148) to show how clinicians make decisions about ACT personalisation.
2. Case study method (CSM), which triangulates multiple data sources to contextually understand decisions (293) was used to integrate the CTA and MRI data.

Mixed methods design

The mixed methods multiple case study design used is a convergent mixed methods design, chosen to obtain complementary data on how expert physiotherapists use functional lung MRI to guide ACT personalisation for children with PCD. By collecting and analysing qualitative and quantitative data separately and then integrating the findings during interpretation, the aim was to develop a more comprehensive understanding of the research problem than could be achieved by either approach alone. Equal emphasis was placed on the qualitative and quantitative components, as both were considered essential for addressing the research questions. The qualitative component, involving interviews with physiotherapists, provided insights into their clinical reasoning and decision-making processes when presented with MRI findings. The quantitative component, consisting of MRI-derived measures of lung health (e.g., ventilation defect percentage), provided objective data on the heterogeneity of lung disease and response to ACT in children with PCD.

The sequence of data collection and analysis was concurrent, with the qualitative and quantitative data collected and analysed separately before integration. Quantitative MRI data were analysed to assess lung health and response to ACT in those same cases. At the same time, quantitative MRI data were analysed to assess lung health and response to ACT in those same cases, physiotherapists were interviewed about their clinical reasoning and decision-making while reviewing MRI findings for specific cases. The findings from both components were then integrated using joint display tables and the identification of case types based on the alignment or misalignment of MRI findings with the clinical picture.

By using a convergent design with equal priority given to the qualitative and quantitative components and concurrent data collection and analysis, this study sought to obtain a balanced and holistic understanding of how functional lung MRI influences ACT personalisation in PCD. The integration of findings from both components allowed for the identification of areas of convergence, complementarity, and discordance, providing a more nuanced understanding of the research problem than could be achieved through a single method alone.

CTA design

A CTA design known as “experiment-like tasks”, which are used to probe the reasoning of experts in situation which resembles a familiar task (148) was used to explore how clinicians make decisions about ACT personalisation with the introduction of MRI data. To simulate the introduction of novel MRI findings into current clinical physiotherapy the task was designed to initially resemble a familiar situation, the clinical review of an ACT regimen for a known patient, with the subsequent unfamiliar introduction of novel MRI data. The content of the clinical review was informed by earlier work (Chapter 3), with the aim of anchoring the clinician in familiarity to reducing the risk of them being reticent during the task (148). To capture tacit real-time decision-making during the task, a CTA method known as think aloud problem solving (TAPS) was used. TAPS, a well-established of method which has been successfully used to capture experts drawing upon knowledge to make decisions, invites participants to speak aloud their thoughts without prior planning, (148). Similar research methods have been used successfully in previously published research: knowledge elicitation within clinical research tasks have employed simulation with video (294-296) and the TAPS method was used by Morra *et al.* (297) to capture clinicians’ interpretation of clinical imaging.

Clinicians were invited to “think aloud” while reviewing data of patient participants who were under their clinical care. Task stimuli included:

1. A video showing the case undergoing an ACT review and completing their personalised ACT regimen.
2. Information from the case's structural MRI.
3. Information from the case's functional MRI.

Further details of the task and stimuli are provided in Section 5.2.3 and Table 34.

Case study method design

To integrate the CTA findings with the MRI data, case study research which permits empirical enquiry of a phenomenon in a real-world situation and opportunity to draw upon multiple data sources providing depth to the investigation (293) was employed. A multiple-case design was chosen; this design permitted comparison of individuals in a heterogenous population (293). Cases were at the level of the patient, data pertaining to each case from quantitative and qualitative information sources were drawn together. As depicted in Figure 82, the embedded units of analysis for each case were: routinely available clinical data; structural MR images; ^{129}Xe MRI data acquired pre-ACT; ^{129}Xe MRI data acquired post-ACT and 4-hours-post ACT; free breathing ^{1}A theoretical replication design was adopted, using cases to "predict contrasting results with anticipated reasons" (293 p.57). using the initial theory that MRI data would either affirm or challenge current ACT personalisation decisions (See Section 5.3.2). The theory suggests that exposure to MRI data will influence clinicians' judgment of the clinical picture by stimulating cognitive integration of visual and numerical data, leveraging the functional and highly sensitive insights that MRI provides into lung health and treatment response. This change will occur because the comprehensive and detailed visual and quantitative information from MRI scans enable clinicians to perceive and interpret disease severity and the effects of ACT regimens more accurately, thus altering their decision-making process towards more personalised and effective ACT strategies.

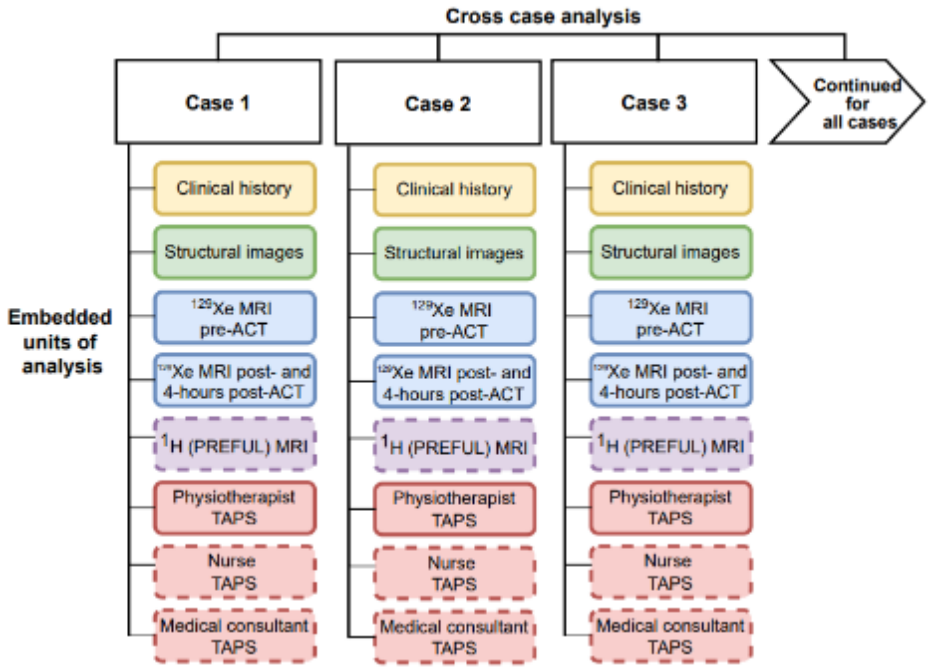


Figure 82: Schematic representation of the multiple case study design depicting the embedded units of analysis within each case and the overarching cross case analysis. Units of analysis were available either for all cases (solid line) or some cases (dotted line).

6.2.2 Sample

Clinician sample

Criterion sampling of clinicians was used (298), with specific criteria:

- MDT clinicians (physiotherapists, medical doctors, and nurses), working with young people with PCD.
- Based at one of the centres participating in the before/after study (LTHT, BTH, SCH or RMCH, Section 4.2.1).
- Clinicians with at least five years clinical experience, at least two years in caring for young people with CSLDs.

Physiotherapists who met these pre-determined criteria were purposively selected to review all cases under their care, as they would have the relevant knowledge and experience to provide insights on ACT personalisation using MRI.

Recruitment

Clinicians working in the PCD services at the research sites were known to the North of England branch of the National PCD management service and as such were identified through clinical practice. They were invited to volunteer by an email distributed by LTHT's Research Governance Manager. A copy of the participant information sheet for clinicians is provided in Appendix 5.7.

Sample size

As per Section 4.2.1, study sites were purposefully selected, based on proximity to the MRI facility in Sheffield and presence of a PCD service. From these centres, all physiotherapists overseeing the physiotherapy care for children with PCD were approached (n=7), all physiotherapists who were approached responded indicating their agreement to participate. Two of the seven physiotherapists who were initially approached did not participate due to: patient participants being predominantly under the care of a colleague (n=1); a period of absence (n=1).

As ACTs regimens are usually prescribed by physiotherapists, physiotherapists were invited to review the data for all cases under their care. Interviews were scheduled with a clinician when the MRI data from a patient participant under their care was ready for review. To ensure that the study was completed within the time available and following PPI guidance to minimise the time between patients attending their study visit and receiving their MRI results, data collection for the before-and-after MRI study overlapped with clinician review study. As such, following a patient study visit the MRI data was prepared for review by the clinicians. Interviews were arranged sequentially as the data was ready following the patient participant's MRI study visit. Every case was reviewed by physiotherapists until information power was felt sufficient to meet the research objectives (further details below). However stratified sampling was also used to ensure cases from all centres were included: as RMCH opened for patient recruitment significantly later than the other sites, data collection was paused at the two centres with more cases available for review (LTHT and BTHFT) to ensure that the perspectives of clinicians at all sites were included.

To provide an additional broader perspective and assess for agreement with other MDT members who may advise more generally about ACTs, nurses and medical consultants working in paediatric PCD services at participating centres were also approached with the aim to include at one nurse specialist and medical consultant per site who were invited to review two cases each. Six medical consultants were approached: two completed reviews of two cases; two only completed a review of one case, as they had a period of absence (n=1) or did not respond to request to review the second case (n=1); completed the initial training but did not participate due to a change in their role (n=1); declined (n=1). Three nurse specialists were approached at three of the four centres were approached: all who were approached participated in two reviews; at the remaining site physiotherapy and medical participants did not identify any nursing colleagues to approach. A summary of the reviews completed at each site by different clinicians is provided in Table 33. Two sampling approaches were used: firstly, convenience sampling, including those cases with MRI data available at the

point when clinicians were available; secondly maximum variation sampling, selecting cases that varied significantly to capture a wide range of perspectives. The criteria for variance in the cases was based on the clinical role of the clinician participating and informed by the physiotherapist's clinician impression of the case during their review: for medics, cases were selected to provide maximum variation in lung health; for nurses, cases were selected to provide maximum variation in adherence to treatments.

Table 33: Summary of cases reviewed by different clinicians at different sites. All reviews by a clinician type at one site completed by one individual unless otherwise stated.

Site	Physiotherapist reviews	Nurse reviews	Medical consultant reviews
LTHT	7 (6 participant A, 1 participant B)	2	2
BTHFT	6	2	1
SCH	3	2	2
RMCH	4	0	1
Total	20	6	6

Qualitative data collection continued until the information power was felt sufficient to meet the research objectives (299), this was reached after 20 cases. The concept of study data holding the information power to answer a research question involves consideration of the aim in the context of the specificity of the sample, interview dialogue quality, theory and analysis methods (299). Hennink and Kaiser (300) found theoretical saturation is commonly achieved in 9-17 interviews in studies with homogenous populations and narrow objectives. Although this study used in-depth interviews with a homogenous group of experienced respiratory clinicians, more cases were needed to capture the diversity of the heterogenous population (age, disease severity). As an exploratory study with a complex objective of understanding how MRI impacts the nature of decision-making in ACT personalisation additional cases were required. To assess this, data analysis was completed in parallel to data collection, cross-case analysis was used to identify when the thematic saturation was achieved (301), and data collection then ceased.

Sampling of cases (for multiple-case design)

The multiple-case design, cases were included if they met the following criteria: quantitative data MRI acquired pre, immediately post ACT and 4 hours post-ACT.

- Assessed with ^{129}Xe MRI at three time-points (pre-ACT, post-ACT, and 4-hours post-ACT).
- MRI data reviewed by a physiotherapist during an ACT personalisation TAPS interview.

Cases were excluded from the multiple-case design if they did were not assessed at all three timepoints with MRI (n=1) or had two physiotherapists reviewing their data in the TAPS interview (n=1).

For the multiple-case design, initial cases analysed were screened to select two cases with contrasting results on how the MRI informed ACT personalisation, : where MRI aligned with, or with a version of the clinical picture and in contrast, where the MRI challenged or conflicted with the clinical picture (see Section 5.2.4). Each subsequent case was compared to the two initial cases to assess for replication in how MRI informed clinicians (293). When contradictory results arose, the initial propositions were reviewed and retested with further cases (see Section 5.3.2). The addition of cases continued until at least three replications were identified for each rival circumstance to provide confidence in the findings (293), and care was taken to ensure that at least one case from each centre was included in the analysis.

6.2.3 Data collection

As most clinician participants were lung MRI-naïve, visual training was developed with the support of Dr David Hughes (Consultant Radiologist, SCH) and completed with all clinician participants to familiarise them with the techniques used prior to their first data review. An additional refresher session was provided for one clinician who had a longer period between their training and research interview.

The stimulus was structured with three stages of information introduction as shown in Table 34.

Table 34: Stimuli provided in the task.

Stage		Stimuli	Details
1		Information which would be available in routine clinical practice	History: diagnosis, medications, exacerbation frequency and cultures from previous 12 months, current recommended ACT regimen. Routine clinical markers: pre-ACT lung function, pre- and post-ACT auscultation. Video of ACT review: patient/parent perspectives of ACT regimen completion and effects, physical activity levels, recent symptoms. Video of ACT regimen completion.
2		Structural MR images	^{1}H MR images: RV, UTE. Structural images were routinely shown from pre-ACT timepoint. Images from post and 4hours post ACT were available and offered to clinicians where; change in mucus plugging or air trapping was identified by a consultant radiologist, or when the quality of pre-ACT images was poor, due to low SNR or patient motion.
3		Functional MR images	HPG Ventilation MR images and technical reports: ^{129}Xe images at EITV and TLC pre, post and 4hours post ACT. Free-breathing (Preful) images pre, post and 4hours post ACT.

The clinical history was provided on a typed template (Appendix 8) and spirometry report format similar to that available in clinical practice. Structural imaging data was all viewed via an imaging information software platform (XNAT OHIF Viewer, Washington University School of Medicine, Plugin version 3.0.1), images were loaded, and contrast adjusted to enable viewing of the lung fields. To moderate the volume of data reviewed by clinicians, as changes were not commonly identified between time points on the structural MR images, these were only routinely provided from the pre-ACT time point. The functional imaging for a sequence was first viewed by the clinicians on XNAT, then participants were provided with the technical reports which include MRI metrics (VDP, VHI as well as TCV) and binning maps. When reviewing the post-ACT images, they were displayed on split screen next to the pre-ACT image with synchronised scrolling enabled and the technical reports from pre- and post-ACT were available. Similarly for 4-hours, on XNAT the screen was split into three sections to display the sequence of pre- post and 4-hours post images for direct comparison, and technical reports available for comparison. Following review of the post-ACT and 4-hours post-ACT images, the corresponding treatment response map was shown. A visual summary example of ^{129}Xe MRI data reviewed by clinicians is provided in Figure 83. Clinicians were able to move through the data at their own pace, scrolling back through the slices

or returning to previous images as they felt they needed. In some reviews, clinicians wanted to review the clinical records for the case, for example to retrieve details of their last consultation or review a previous CT report. As a pragmatic study exploring the introduction of MRI into current clinical practice, clinicians were permitted to review previous notes as they felt needed.

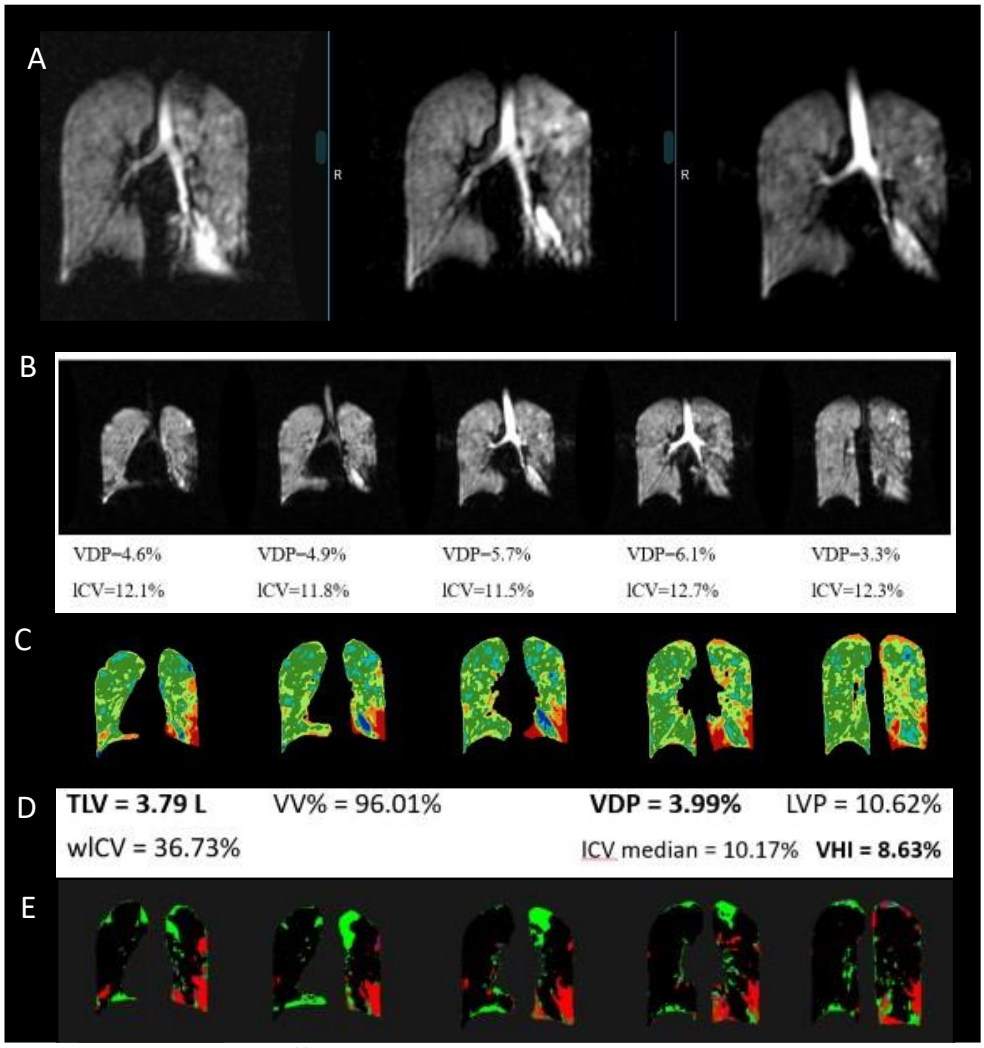


Figure 83: Example of ^{129}Xe MRI imaging data at the 4-hours post-ACT timepoint reviewed by clinicians. A depicts the side-by-side comparison of images on XNAT comparing pre-ACT (left), post-ACT (centre) and 4-hours post-ACT (right). B, C and D depict excerpts from the technical report showing the raw images (B), ventilation binning maps (C), whole lung metrics (D). E depicts an excerpt from the treatment response (pre to 4-hours post-ACT).

A Think-Aloud Problem Solving (TAPS) (148) approach was used to capture their tacit decisions whilst appraising the case information. If whilst reviewing the data, there was a period without speech the clinicians were prompted to “keep talking”. Clinicians were invited to pause the video or seek clarification at any point and the video was paused at any points where the clinicians were talking more in depth about their clinical interpretations. Standard prompts were used to facilitate think aloud during case appraisals (Appendix 10). As depicted in Figure 84, after each subset of information

had been reviewed, clinicians were prompted to think aloud their clinical decision with prompts to ascertain: if the information was as they expected for the case; to consider if the ACT regimen was working effectively; if they were to review the case in the near future what they would recommend.

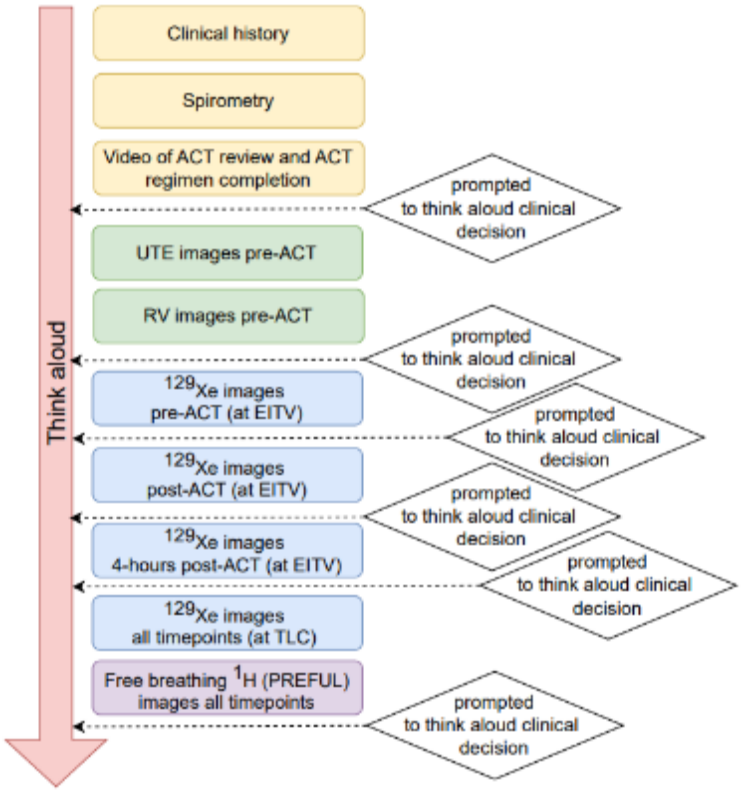


Figure 84: Schematic representation of the data review process in the experiment-like task. Data included existing clinical data (yellow), structural imaging (green), functional imaging (blue and purple). Clinical decisions were prompted at key points in the review.

With the exception of the first TAPS task in which two physiotherapists reviewed the data for one case together, the interviews were all conducted in-person and as a 1:1. Audio recordings were captured on an encrypted digital Dictaphone and relevant observational notes were taken at all TAPS tasks.

All data for the CSM multiple-case analysis was collected as part of the before-after study (Chapter 4) and TAPS study, no new data was collected. Multiple sources of evidence were used including clinical history, patient/parent reported information, lung function, MRI data, clinician perspectives. Key fields from these sources were identified during the pilot case; gender, age, PCD genetics, electron microscopy abnormality, number of antibiotics in previous 12 months, FEV_1, PCDQOL lower respiratory symptom score, frequency of ACT completion (patient/parent reported), ACT regimen, structural MR findings, ventilation MRI findings, ACT personalisation decisions, PCD clinical care centre.

6.2.4 Data analysis

Interviews were transcribed by the lead researcher or an administrative member of the research team. Transcripts were anonymised in respective of both clinicians and patients. In order to understand how clinicians make decisions about ACT personalisation with the introduction of structural and functional imaging data, Framework analysis described by Ritchie and Spencer (302), was selected for analysis of the TAPS interviews. Framework provided a systematic and comprehensive approach to reviewing the clinical decision-making during the data reviews using the ACT personalisation model. As an exploratory study in a novel area and working with a new model, whilst providing a clear structure, Framework permitted amendments to the codes as appropriate during analysis. The analysis involved:

1. Familiarisation, listening to interview recording and re-reading the transcripts to become immersed in the case, noting down initial ideas.
2. Identification of a thematic framework; the ACT personalisation model had previously been identified for the analysis. The arrows within the ACT personalisation model were used as the codes; the model was reviewed and revised following analysis.
3. Indexing of the transcript data to codes derived from the ACT personalisation model. Data was managed and indexed using NVivo (1.7.1, QSR international). Coding was checked for consistency across cases after each indexing for the first five cases and then after each block of five cases. Example excerpts and codes were checked with Prof Hind.
4. Charting data for each code across the cases was managed using NVivo with key excerpts extracted into a spreadsheet.
5. Mapping to identify patterns in ACT personalisation, aiming to provide explanations for tangible shifts in ACT regimen personalisation.

Data integration

The data was integrated at the following stages:

- The ACT personalisation factors identified in current literature through the scoping review (Chapter 2) formed the ACT personalisation model which was used for analysis of the cognitive task analysis (CTA) interviews with expert physiotherapists in Chapter 3.
- The cues identified by the physiotherapists in the CTA interviews (Chapter 3) were used to develop the content of the clinical data form used to collect data on the patient participants when they attended for the MRI study visit (Chapter 4).

- The existing clinical data collected in Chapter 4 was provided to clinicians as stimuli in TAPS task in Chapter 6.
- The MRI data acquired pre-ACT (Chapter 4) post-ACT and 4-hours post-ACT (Chapter 5) were provided to clinicians as stimuli in TAPS task in Chapter 6.
- The ACT personalisation model developed from the scoping review (Chapter 2), refined by PPI input, the CTA interviews and recognition primed decision model (Chapter 3) was used for analysis of the TAPS interviews (Chapter 6).
- The quantitative MRI data analysis, both cross-sectional data (Chapter 4) and treatment response data (Chapter 5) were integrated with the qualitative TAPS analysis findings (Chapter 6). Further details of this are below.

A schematic overview of the data integration is provided in Figure 84.

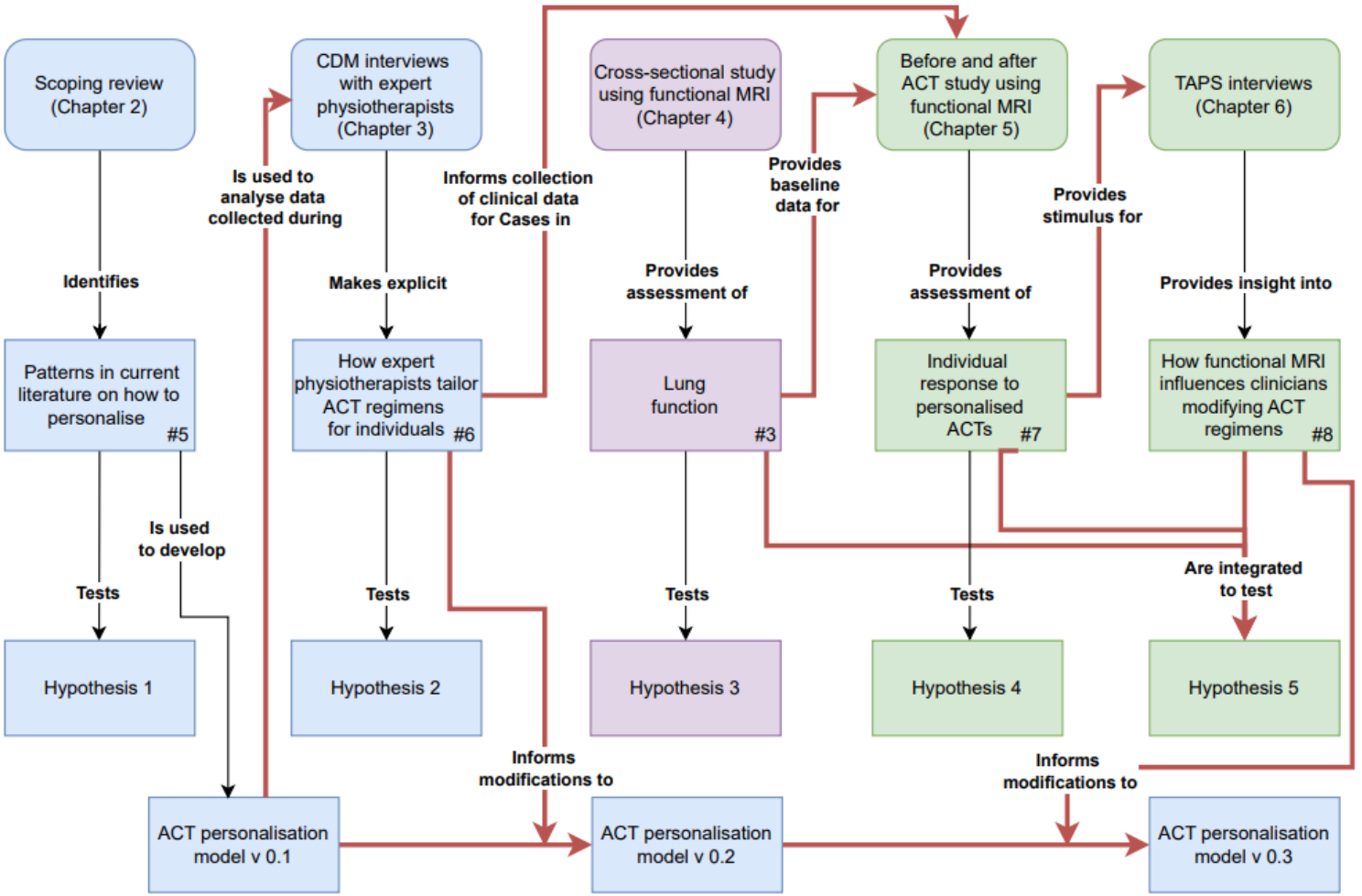


Figure 85: Schematic representation of the data integration points throughout the thesis.

All data integration was performed by the lead researcher with feedback from the project advisory group and PPI members as outlined in each of the specific chapters. Excerpts from the transcripts of every case were integrated with the clinical data and MRI data for using joint display tables (151, 303). An inductive approach was used, closely examining the data from the clinician interviews, along with the MRI findings and existing clinical data to understand where imaging led to divergent changes in ACT recommendations. To verify face validity, were triangulated with case clinical history and presented with excerpts of transcripts to PPI members for feedback. Meta-inferences were drawn, bringing together the separate inferences derived from previous chapters following the first three stages of meta-inference generation described by Younas *et al.* (304): identifying knowledge-based inferences (Chapters 4 and 5); experienced-based inferences (Chapter 6); and data-driven inferences (Chapter 6). As an exploratory study further data and analysis beyond the scope of this thesis would be required to provide further conclusions and as such the meta-inferences drawn are provisional.

The CTA and CSM data analysis was conducted in an overlapping sequential manner, with CTA from earlier cases screened to identify potential candidate cases for the initial CSM cases. Inductive orientation provided the criteria for two initial conflicting case types as described in 5.2.2. Triangulation between the data sources was used with pattern matching to ascertain when cases aligned with the initial case types or when they were challenged. The presentation of case types was with the aim of providing analytic generalisations (293) of *when* MRI may influence ACT personalisation for physiotherapists. As nurses and medical consultants would not typically recommend specific ACT modifications, analysis of their case classification is limited to interpretation of the case picture.

6.2.5 Patient and public involvement

The patient and public involvement group (PPI) were consulted on the study processes which were required prior to a clinician data review which included: a patient participant attending for their study visit; initial image reviews by radiologists; image processing; preparation of the technical reports, treatment response map and ACT review video. As the MRI reports were only released back to the clinical team following the clinician data reviews, PPI members highlighted the importance of minimising delays to this process. As data collection was paused briefly at some centres whilst data was collected at RMCH (as described in Section 6.2.2), based on PPI guidance, in cases where there was a delay with images being the sent to the clinical team parents of participants were

notified of this. PPI members reviewed the initial data analysis with case types and reflected these were clear and logical.

6.2.6 Chapter acknowledgements

The contributions for this chapter from the lead researcher, Lynne Schofield, are as detailed below:

- Study design conceptualisation,
- Development of participant information sheet,
- Securing NHS/HRA ethics approval and LTHT site approval,
- Collation of the patient participant data for the interviews
- All data collection,
- Some interview transcription,
- All coding and analysis,
- ACT model review.

Acknowledgments for specific contributions are also given to:

- Anne Gowing, Research governance manager at LTHT for the initial approach of participants.
- Professor Dan Hind for guidance on study design conceptualisation; development of the study interview; overseeing of coding and analysis. For guidance throughout planning, data collection and analysis.
- Leanne Armstrong (research administrator at UoS) and Lucy McGann (clerical officer at LTHT) for transcribing interview recordings,
- PPI members for data verification and providing feedback on results.

6.3 Results

12 clinicians from the four centres participated: five specialist physiotherapists, three specialist nurses and four specialist medical consultants. 21 cases were reviewed by physiotherapists, and six by nurses and six by medical consultants. A summary of the number of cases reviewed at each centre are provided in Table 35.

Table 35: Summary of data reviews completed by clinicians at each of the participating centres: Bradford teaching hospitals foundation trust (BTHFT), Leeds Teaching hospitals (LTHT); Royal Manchester Children's Hospital (RMCH); Sheffield Children's Hospital (SCH). All reviews were completed by one clinician unless specified.

Site/clinician type	Cases available	Specialist physiotherapist	Medical consultant	Nurse specialist
BTHFT	10	6	1	2
LTHT	10	8 (2 physios)	2	2
RMCH	6	3	1	0
SCH	3	3	2	2

Data from 19 case TAPS tasks met the inclusion criteria for the multiple case analysis, two cases were excluded; one case with MRI data at two timepoints, one case that was reviewed by two clinicians simultaneously. The clinicians involved in these TAPS tasks included four physiotherapists from four centres, three nurse specialists from three centres and four medical consultants from four centres.

CTA analysis

The results presented in this section summarise the cross-case/themes in the context of the current ACT personalisation model (Figure 86), providing example excerpts and overviews of convergence and divergence.

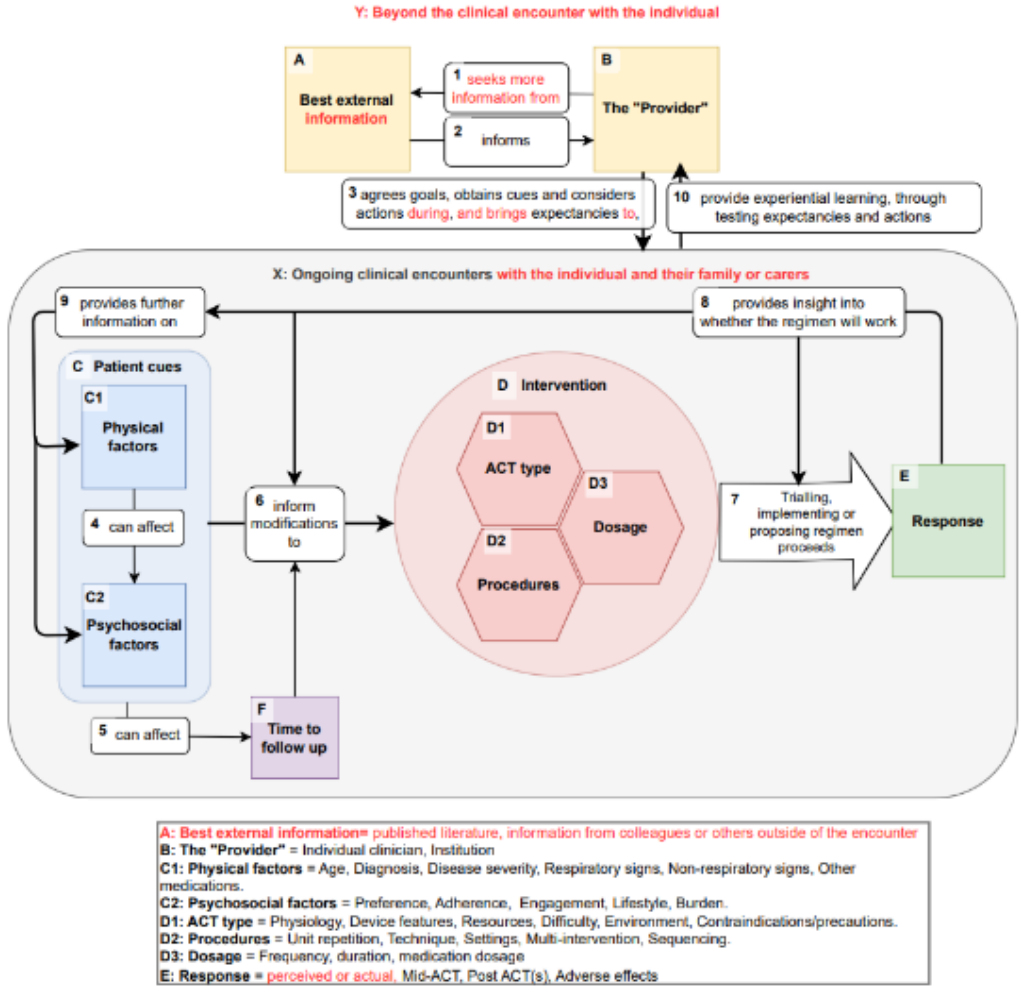


Figure 86: Revised ACT personalisation model version 0.3 (changes from previous version are marked in red)

Completion of the ACT regimen during each study visit is Action 7 within the clinical encounter of this experiment-like task.

Table 36: Model phases with example excerpts from the interviews.

Model phase (Arrow, Figure 86)	**Applicable stimulus** (available for all cases)	**Interview excerpt**
The "provider" seeks more information from best external information (1)	All	*I wonder how much supine would help compared to sitting up just from the you know anatomically, I don't know I probably just need to do a bit more research myself about that (Physiotherapist, Case 11)*
Best external evidence informs the "provider" (2)	All	*I feel like we're kind of more hard set in "you have to do your physio twice a day, 90 breaths" because that's what the evidence says or you know, case studies say (Physiotherapist, Case 2).*
The "provider" agrees goals, obtains cues, and considers actions during, and brings expectancies to ongoing clinical encounters with the individual, and their family or carers (3)	All	*She is generally very well so it's interesting that she was quite so crackly… I think she is…relatively good from an adherence point of view…I would have never told her to just do two lots of ten…I feel like it is a conversation I have a lot with her about doing it in multiple positions and not just doing it 20 blows. (Physiotherapist, Case 22)*
Physical factors can affect psychosocial factors (4)	Clinical data ACT review	*From a chest perspective I think he feels that his quality of life is reasonable (Medic, Case 20).*
Patient cues can affect time to follow up (5)	Clinical data ACT review	*If that was at clinic and we saw this…MRI…I wouldn't necessarily want to give her something and not see her again I would probably want quite a quick, follow up. (Physiotherapist Case 5).*
Patient cues and time to follow up inform modifications to intervention (6)	Clinical data ACT review Pre-ACT imaging	*We know about the right middle change and were trying to target that with physio, which he does his position every time, potentially could do his neb in that position (Physiotherapist Case C9)*
Response provides insight into whether the regimen will work (8)	ACT review Imaging Post-ACT and 4-hours post ACT	*On the right lung periphery…there a couple of patches that look slightly worse which probably says that we should still be doing it in both left and right side lying…even if you want to get improvement in that left hand side. They are mostly green though aren't they…It makes me think that physio does something (Physiotherapist Case 31).*
Response provides further information on patient cues (9)	ACT review Imaging Post-ACT and 4-hours post ACT	*I am thinking he looks very unsure, and that he doesn't look like he is used to doing this very regularly (Physiotherapist Case 10).*
Ongoing clinical	All	*From a physio point of view, it makes you*

encounters provide experiential learning to the "provider", through testing expectancies and actions (10)		*look at it differently that actually you don't, just because they've got PCD…do they really have to do the physio twice a day, every day? (Physiotherapist Case 2)*

6.3.1 Observation of the ACT regimen leads to ACT regimen modifications.

In most cases, clinicians proposed ACT modifications following observation of the ACT regimen (Arrow 8 to Arrow 6 or 9, Figure 86). In some cases, this was to ensure ACT regimen was being completed as prescribed, for example when reduced adherence or incorrect technique was identified (Cases 6, 7, 10, 14, 16, 22, 24, 26, 34). In other cases, more substantial regimen modifications were proposed, for example introduction of nebulised hypertonic saline (Cases 4, 5, 6, 8, 10, 11, 12, 17, 29, 31, 35). Clinicians reported limited opportunity to observe ACT regimens in clinical practice due to time pressures:

"They don't tend to bring their equipment … and we don't have time to go through the physio like, the full….when…you trust a family and you think that they're compliant you…step back a little bit… not that they're doing anything wrong we just obviously need to go through the routine again." (Physiotherapist watching ACT video for Case 20).

However, some clinicians described some limitations in assessing ACT regimens through video as opposed to in-person:

"*I'd normally always get my hands on and have a feel so it's difficult when you're not able to" (Physiotherapist).*

6.3.2 Imaging provides clinicians with cues about the patient's physical health which inform ACT modifications.

Clinicians said that the baseline structural and functional imaging provided cues about the individual's lung health (physical factor, Box C1, Figure 86), including details of areas of collapse, bronchiectasis, and poor ventilation. Excerpts illustrating examples from the TAPS tasks are provided in Table 37 and a map of ACT regimen modifications which were proposed, illustrating which cues prompted modifications of components of the intervention in Figure 4.

Table 37: Excerpts from examples of where MRI data provided clinicians with cues about the patient's physical health. Details are provided to illustrate the corresponding arrow in the ACT personalisation model (Figure 86).

Model phase (Arrow, Figure 86)	Excerpt from an example Case:
Physical factors from structural imaging:	
Aligns with expectancies.	"She's got some thickening…in her perihilar regions…particularly on that right hand side…I've probably seen that on her CT". *(Physiotherapist reviewing UTE images for Case 31).*
Challenges expectancies (10)	*"I would expect to see the secretions or areas of poor ventilation because she so productive…I wouldn't necessarily expect to see (collapse) on the right." (Physiotherapist reviewing UTE images for Case 5).*
Inform (proposed) modifications to…(6)	
Procedure	"I am thinking…to do some real focused stuff on that left side." *(Physiotherapist reviewing UTE images for Case 7).*
Dosage	*From MRI scan we can't see any areas from sputum plugging or secretions then why are we using hypertonic, so I would probably take that away." (Physiotherapist reviewing UTE scan for Case 2).*
ACT type	"To look at like autogenic drainage…especially if he is air trapping a little bit." *(Physiotherapist reviewing RV images for Case 10).*
Physical factors from pre-ACT ventilation imaging: Challenges expectancies…(10)	
Better than expected	*"They correlate with…the structural one, but I think I still anticipated she would have more peripheral defects… They're probably less abnormal again than I had anticipated." (Physiotherapist reviewing Pre-ACT ^{129}Xe images for Case 31).*
Worse than expected	*"I'm surprised at how many defects and how significant they are looking at those images." (Physiotherapist reviewing Pre-ACT ^{129}Xe images for Case 34).*
Inform proposed ACT modifications to…(6)	
Procedure (patient technique)	*"He does rush and doesn't always go to full capacity or definitely with his neb, he could do a much better technique with that…recruit his airways before his airway clearance before…his Aerobika." (Physiotherapist reviewing Pre-ACT ^{129}Xe images for Case 26).*
Procedure (patient positioning)	*"There's little pockets all over where he's got defects… doing different position for drainage is indicated…he doesn't do anything in sitting. (Physiotherapist reviewing Pre-ACT ^{129}Xe images for Case 12).*
ACT type	"Would he be better with a PEP or something similar.*"(Physiotherapist reviewing Pre-ACT ^{129}Xe images for Case 34).*

Following review of the structural images (^{1}H UTE and RV commonly pre-ACT), during some reviews (Cases 11, 16, 22, 26, 31, 34) clinicians reported that the imaging findings aligned with their expectancies. In other cases, clinicians reported the structural imaging challenged their expectancies (Arrow 10, Figure 86), appearing either better (Case 4) or worse (5, 7, 10) than the clinical picture they had of the case. In some cases, including those where the expectancies had been upheld, challenged or not explicitly stated, pre-ACT ^{1}H MR imaging provided information which informed modifications to the ACT regimen (Arrow 6, Figure 86): the positions used during the ACT regimen to target regional structural abnormalities (Cases 7, 12, 22, 24, 26, 29); dosage (Case 2, 5, 7); ACT type (Case 5, 10) (Figure 86).

Review of the baseline functional MRI data (pre-ACT ^{129}Xe MRI) challenged the clinicians' expectancies in some cases (Arrow 10); when ventilation images appeared better anticipated (Cases 10, 20, 31) or worse than anticipated (Cases 4, 5, 7, 14, 17, 22, 29, 34). In most cases, including those where baseline ventilation MRI findings aligned with expectancies for the case, pre-ACT ^{129}Xe imaging data provided information which informed modifications to the ACT regimen (Arrow 6, Figure 86): procedures, very commonly this was specifically positioning (Cases 4, 5, 6, 11, 12, 20, 22, 26, 27, 31, 34) or patient technique (Case 11, 16, 24, 26); ACT type (Case 7, 34) (Figure 86). In cases where regional abnormalities differed between the structural and ventilation images, clinicians revised their positioning recommendations upon viewing the pre-ACT ventilation images (Cases 4, 7, 12, 22).

A map of the ACT modifications proposed at each stage of the ACT data review (Figure 87) provides visual analysis of the data across the cases. Data which would be available clinically, which included observation of the ACT regimen stimulated clinicians to propose modifications across all components of the intervention, with the exception of positioning; the sole dotted arrow on the map in Figure 87 relates to Case 27 in which observation of the regimen affirmed the clinician's decision that their current use of positioning was appropriate. ^{1}H structural scans often prompted clinicians to propose modifications to positioning, and in some cases dosage or ACT type. ^{129}Xe MRIs from pre- and post-ACT very commonly prompted modifications to positioning. ^{129}Xe images from immediately post and 4-hours post-ACT commonly prompted modifications to be proposed to inhaled medications.

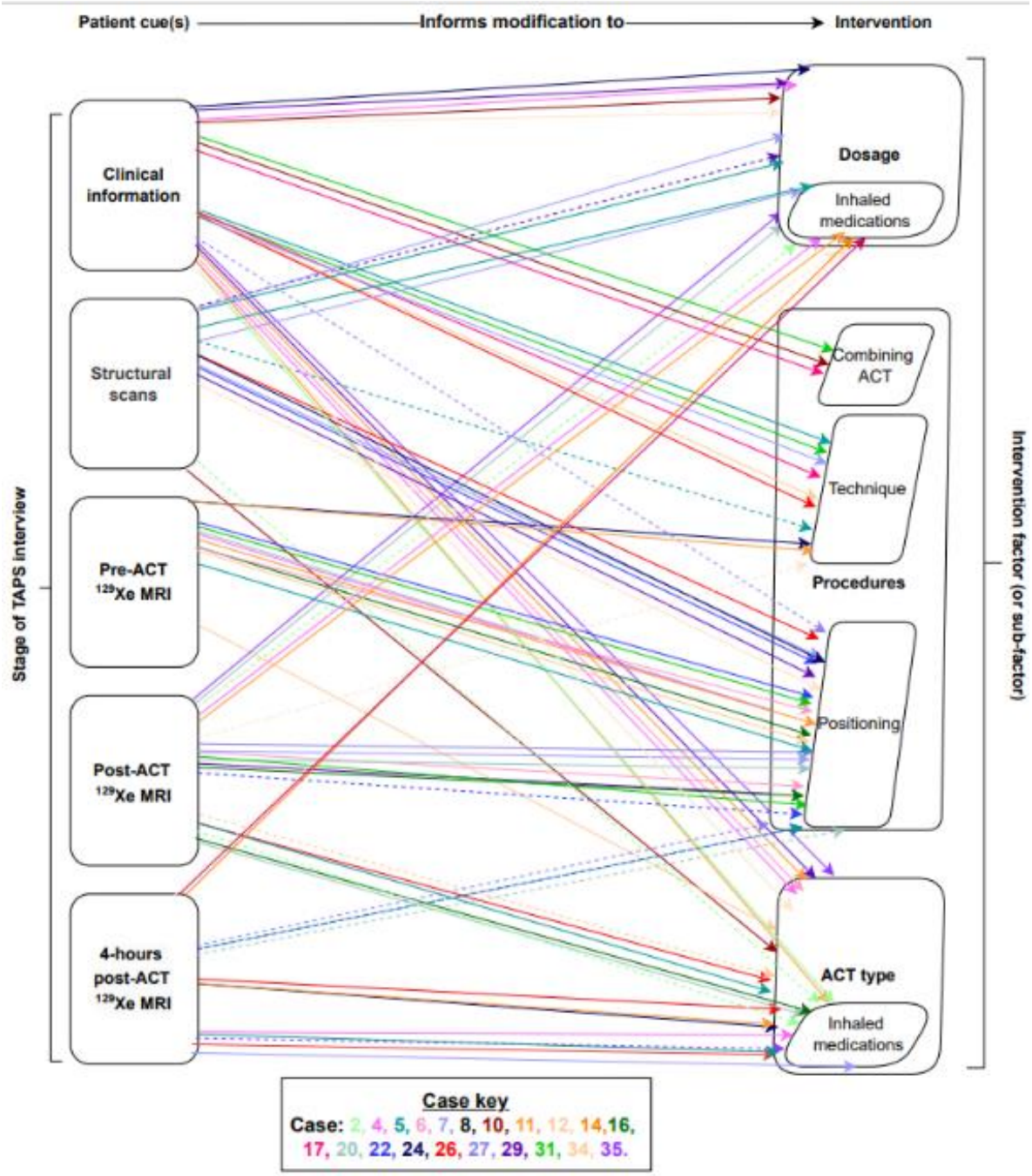


Figure 87: A map depicting analysis of the proposed ACT modifications proposed clustered by stage of the TAPS interview. Stages of the TAPS interview are shown on the left, with arrows linking proposed modifications to the intervention factor on the right. Within each of the main intervention factors, more subfactors are shown to illustrate those which were more present during the TAPS reviews. Each colour represents one case, each arrow indicates a proposed changed, or dashed arrow affirmed change.

These findings support the hypothesis from Chapter 1, which stated: lung health in PCD will be found to be heterogeneous, as assessed by MRI-derived ventilation defect percentage (H3); expert physiotherapists will see application of functional imaging to guide personalisation of ACTs for children with PCD (H5).

6.3.3 Imaging provides clinicians with insight into whether the ACT regimen will work.

Clinicians' expectancies about whether the ACT regimen would work were based on their knowledge of PCD, the case and cues acquired from the clinical information and observation of the ACT video (Arrow 3, Figure 86). Comparison of the pre-ACT and post-ACT Ventilation MR images provided clinicians with imaging information about treatment response (Box E, Figure 86), which provided insight into whether the regimen would work (Arrow 8, Figure 86) excerpts from example cases for this are provided in Table 38.

Table 38: Excerpts from examples of where MRI data provided clinicians with information on ACT regimen response to understand, "will it work?".

Model phase (Arrow, Figure 86)	Excerpt from an example case:
Response assessed by imaging:	
Aligns with expectancies	
Tests expectancies…(10)	
Better than expected	*"She's getting an improvement in her ventilation defects because of the physio…it probably is doing more than it looks like it's doing or certainly feels like it's doing" (Physiotherapist viewing post ACT 129Xe imaging for Case 31).*
Worse than expected	*"I didn't expect it, I mean she cleared more secretions as well…It's not made the ventilation any better from the images, it looks like they're all worse" (Physiotherapist viewing pre-post TRM for Case 17).*
Provides insight into whether the regimen will work, informs modifications to…(8 and 6)	
Procedure (patient positioning)	*"Maybe doing some breaths in supine…because actually the rest of his lung fields…look a bit more green, so it must be that anterior bit that has got worse." (Physiotherapist viewing post-ACT ventilation binning map for Case 27).*
ACT type	*"It'd be interesting just to see what he would be like with ACBT… with him not recruiting collateral ventilation in his bases." (Physiotherapist viewing post-ACT ventilation binning map for Case 26).*
Dosage (patient technique)	*He could feel…something fluttering in that left base…I would say to him that if you think that you've identified some secretions and you think you then move it, do another cycle (Physiotherapist viewing pre-4-hours post-ACT TRM for Case 35).*
Patient psychosocial factors inform modifications to…(6)	We need to do it more often and see if we can make it shorter so it's more manageable…if he's gone swimming, he does his neb when he gets back and some big huffs and coughs, if we can juggle it that way. *(Physiotherapist reviewing the 4-hours post-ACT ^{129}Xe MRI images for Case 12).*

Some clinicians reported the treatment response seen on imaging aligned with their expectancies (Cases 5, 11, 20, 26), others described that the response seen on imaging was better (Cases 27, 31) or worse than they expected (Cases 14, 17, 22, 24, 34) (Arrow 10, Figure 86).

In most cases, post-ACT ^{129}Xe imaging data provided information which informed modifications to the ACT regimen (Arrows 8 and 6 or 9, Figure 86): to procedures, specifically positioning (Cases 6, 7, 20, 27, 29, 31); ACT type (Case 5, 16, 20, 26), dosage (Case 4, 11, 20, 35). In some cases, ACT changes which were previously tentatively proposed were affirmed during the review of the post-ACT ^{129}Xe imaging data: changes to dosage (Case 2, 12); ACT type (Case 2, 34); procedures (Case 5) (Figure 86).

Reviewing the ^{129}Xe imaging data acquired 4-hour post-ACT prompted modifications to the ACT regimen in some cases (Arrow 8 and 6 or 9, Figure 86): procedures; ACT type (Cases 4, 5, 7, 11, 24, 26); dosage (Cases 14, 17). Of these changes, most were related to inhaled medications (Cases 4, 5, 7, 11, 14, 17, 26) (Figure 86). Previously proposed ACT regimen modifications were affirmed during the review of the 4-hours-post-ACT images in some cases, including dosage (Case 12), positioning (Cases 5, 20, 27) and ACT type (Case 35).

In two reviews the physiotherapist observing the ACT regimen felt it was not optimised, but post-ACT images showed improvement (Cases 8 and 10), the physiotherapists discarded the proposed modifications and decided to continue with the existing regimen. In a few cases (Cases 7, 11, 12, 26), whilst MRI informed modifications these were reconsidered in light of psychosocial factors (Arrow 6, Figure 86).

These findings support the hypothesis from Chapter 1, which stated: functional imaging will inform expert physiotherapists in the personalisation of ACTs for children with PCD (H5).

6.3.4 Imaging challenges expectancies and provides experiential learning.

During some TAPS tasks, imaging challenged the clinicians' expectancies, interrupting their tacit decision-making (Arrow 10, Figure 86). Clinicians reflected more broadly on the imaging, drawing upon: physiological reasoning to provide explanations for the findings; recollection of previous cases for comparison; drawing upon best available information (Arrow 1, Figure 86). Some clinicians described uncertainty which limited their expectancies, goals or actions arising from: absence of MRI metric reference data

for the PCD population; absence of guidance on how to act upon abnormal findings from functional MRI; inability to readily reassess the case with MRI following implementation of any modifications; increased complexity of data, for example when areas of worsening ventilation were highlighted on the treatment response map but there was an overall improvement in ^{129}Xe VDP.

Table 39: Excerpts from examples of where MRI data challenged the provider's expectancies or goals, prompted them to seek guidance or provided conflicting cues.

Model phase (Arrow, Figure 86)	**Excerpt**
Challenges expectancies (10)	*I think I expected them to be better immediately post physio, because...they're breathing at a higher volume than your tidal volume during the physio session I think I'd...anticipated...more improvement at that point rather than 4 hours later. (Physiotherapist reviewing 4-hour post-ACT ^{129}Xe images for Case 31).*
Seeks more information from…(1)	
Provider knowledge	
Physiological reasoning	*"Has the hypertonic taken…longer to impact the viscosity of the secretions...immediately you don't...clear a lot, but as the time goes on you start to mobilise more" (Physiotherapist reviewing the 4-hour post-ACT ^{129}Xe images for Case 4).*
Previous experiences	*"This is definitely not as bad as the last patient."* *(Physiotherapist reviewing Pre-ACT ^{129}Xe images of Case 26).*
Best external information	
Reference values	*"In what context 5% when you're a XX-year-old with PCD is that good or bad I don't really know" (Medic reviewing Pre-ACT ^{129}Xe images of Case 20).*
Limitations of MRI knowledge base	"I don't really know what difference we're looking for...you're always going to get mucus plugging and ventilation defects probably at different points of the day or time....it could just be that it is as good as that you're always going to see this I don't know" *(Medic following review of all data).*
Structured guidance	*"I have the framework which isn't super evidence based but is standard practice for what to do with worsening structural changes, but I don't know how much (the ^{129}Xe ventilation MRI) should be influencing my treatment in the face of structural things that don't look different…I don't know what to do with him now" (Medic reviewing pre-ACT ^{129}Xe images).*
Limited experience in reviewing MRI	*"It's difficult when I don't have a lot of experience with what's normal and what's not normal and especially in this population."* *(Medic following review of all data).*
Limitations of ACT knowledge base	*I don't know what I can do about those images specifically…* *I don't know how much evidence there is to say if you did physio in this position can you target that segment or zone and if you do how long do you actually have to lay there for. (Physiotherapist reviewing 4-hours post-ACT ^{129}Xe imaging).*

Challenges goals:	*"If you look at the pre physio one…it can't get any better so I would…expect they were going to be similar."* (Physiotherapist reviewing 4-hours post-ACT ^{129}Xe image for a case with mild disease).
Conflicting **cues**	*"It is a bit confusing because…parts of his scans definitely showed… more left sided problems, those pictures the black and white pictures don't sort of fit with that."* (Physiotherapist reviewing comparing post-ACT ^{129}Xe imaging with pre-ACT UTE).
Absence of **response**	*"The anterior section is…remarkably improved particularly in the bases… is that because of the positions that she does it in? I suppose that's difficult to tease out without doing it differently and doing it again isn't it."* (Physiotherapist reviewing the 4-hours post-ACT ^{129}Xe images).

There was evidence of provider factors influencing MRI preferences which may have influenced the extent to which imaging informed ACT regimen modifications (Arrow 3). These included: provider preference of imaging type or method of data presentation; provider capacity on the day; their training and familiarity; perceived clinical interpretation and utility. Ventilation imaging data was presented as raw images, metrics, ventilation binning maps, and treatment response maps, preferences for the presentation of MRI varied between clinicians and for some clinicians between cases. There was evidence of limitations of the TAPS process in some interviews, including clinicians' motives, reticence, and unease during the think aloud process.

Table 40: Excerpts from examples of where provider factors during the TAPS review may have influenced ACT personalisation (Arrow 3, figure 3).

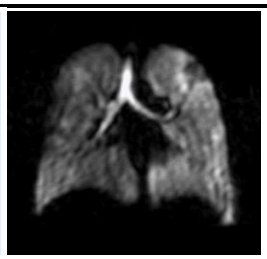
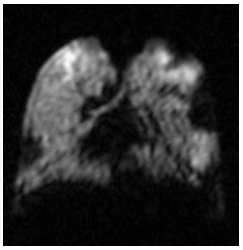
Factors influencing provider	**Excerpt**
Preference	
MRI type	*"I like these scans... these are my favourite like I can look at these and understand them more than some of the other scans" (Physiotherapist reviewing Pre-ACT ^{129}Xe images).*
MRI presentation method	*I like the (ventilation binning maps), I like the colour, it kind of tells me a little bit more without me working it out." (Physiotherapist reviewing Pre-ACT ^{129}Xe images).*
Capacity	*"This is the only time though I've felt like it's not helpful….Maybe it's just confusing me because I've had about three hours sleep."(Physiotherapist reviewing post-ACT ventilation binning maps).*
Training	*"It was good to…see the images, the different binning maps, and things… in the training because then it wasn't like a big shock when you look at them. I think it is quite hard to compare because there is a lot of images." (Physiotherapist at the end of a TAPS task)*
Familiarity	*"I think it gets easier when you do a few in a row like when I had done a couple at a time it was easier but once you get into the swing of it, it is not too bad." (Physiotherapist at the end of TAPS task)*
Clinical interpretation	*"I'm not sure what the PREFUL ones add clinically, I'm not sure what to do with the information they give." (Medic reviewing PREFUL images)*
Clinical utility	*"TLC shows you the best that they can be… I suppose that is useful to know…especially for someone that exercises…he does have the ability to ventilate it is not a permanent obstruction to ventilation." (Medic following review of ^{129}Xe images acquired at TLC)*
TAPS interview process	
Motivation	*"Unless you are tricking me, and you are showing me the images the other way round pre and post? ...I was trying to look at it with a positive eye, but I failed…I was desperately wanting to see an improvement." (Medic reviewing post-ACT ^{129}Xe images for Case 16).*
Screening thoughts	*"When I feel like I've got something to say, I will." (Medic when prompted to think aloud).*
Unease	*"I'm feeling like I'm going to give the wrong answer and that's quite hard" (Physiotherapist when reviewing UTE images for their second case)*

Multiple case analysis

The CTA findings showed across the cases there were instances where the MRI findings had fallen within what clinicians had expected and where they had differed

from what they expected. From this two initial cases (summarised in Table 41) were selected to explore contrasting results on how the MRI informed ACT personalisation: where MRI aligned with, or with a version of the clinical picture (Case 10 which was later classified as Case type X) and in contrast, where the MRI challenged or conflicted with the clinical picture (Case 34, later classified as Case type Y). Subsequent cases were used to test the case type, assessing for theoretical case replication.

Table 41: Initial case types with overview of the initial cases.

Case type X: MRI aligns with (a version of) case clinical picture 	**Case type Y: MRI challenges case clinical picture** 
Summary **Clinical picture:** Good lung health (FEV_1 107.9%), low to moderate adherence to ACT regimen (once daily 7% NaCl combined with Aerobika, in sitting, prone and alternate side lying). Cleared large volumes of yellow secretions. Auscultation improved but some evidence of retained secretions. **Clinical picture-informed decision:** Increase frequency to twice daily. **Imaging:** Low VDP (2.1%) which improved post (2.3%) and 4-hours post-ACT (0.7%). **Imaging-informed decision:** Accept once daily ACT plus exercise for ACT.	**Summary** **Clinical picture:** Good lung health (FEV_1 103.0%, no recent antibiotics) good adherence to ACT regimen (once daily Aerobika, in sitting). Cleared small volume of secretions. Auscultation clear pre, post reduced air entry with crackles. **Clinical picture-informed decision:** No change. **Imaging:** VDP higher than expected (9.2%) and increased post-ACT (12.1%) **Imaging-informed decision:** Numerous changes (ACT type and procedures).

The proposed ACT modifications varied, spanning minor to multi-component changes. In some Case Y interviews, clinicians expressed uncertainty regarding appropriate modifications. It was unclear if theoretical replication was being seen, so further cases were added to allow more detailed assessment. The initial case types were revised: Case type Y was split into two, Y1 where the clinician proposed changes and Y2 where the clinician was unsure what changes to propose; to reflect the variation in the magnitude of regimen changes proposed in Case types X and Y1, recognition of this variation was incorporated into the case type parameters (Figure 88). The revised case types were then tested with subsequent cases (293), with 19 cases in total included.

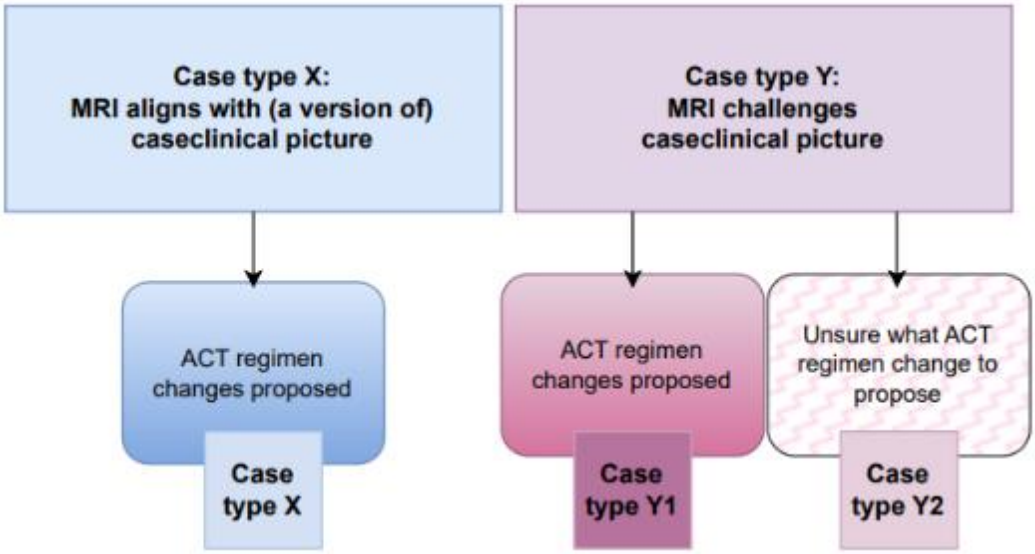


Figure 88: Diagrammatic representation of Case types, X, Y1 and Y2.

A summary of the clinical data and main quantitative metrics are provided in

Table 42. Lung disease as assessed by spirometry and ^{129}Xe VDP and VHI pre-ACT was milder in individuals classified as type X and worst in those classified as type Y2, although Case type X had on average more courses of antibiotics than other case types. Patient reported quality of life was on average higher across all domains for Case type X than Case types Y1 and Y2; Case type Y2 had the lowest scores across most domains of the PCD-QOL. Whilst all groups were prescribed on average twice daily ACT, those in Type X on average reported a slightly higher frequency of ACT completion in the last seven days than those classified as the other case types. ACT response as assessed by ^{129}Xe VDP showed on average Case types X and Y2 had an improvement in ventilation defects post-ACT, whereas those in Case type Y1 had a worsening, although all case classification groups included some individuals for whom ^{129}Xe VDP improved and some for whom it worsened.

*Table 42: Group demographic for the cases classified as type X, Y1 and Y2, including ultrastructural defects, QOL-PCD scores, lung function and ^{129}Xe VDP metrics. Data is presented as mean ± SD or median (range) depending on if data normally distributed. * Indicates metric not available at the time of the TAPS interview. IDA=inner dynein arm defect, ODA= outer dynein arm defect, MTD= microtubular disarrangement. PsA=Pseudomonas aeruginosa.*

	Data reported as mean ±SD or median (range)		
Case type	**X**	**Y1**	**Y2**
N. (unless stated)	7	7	5
Sex	7 male (100%)	4 male (57%)	3 male (60%)
Age (years)	13.6 ± 2.8	12.9 ± 3.6	9.8 ± 3.3
Age at diagnosis (years)	6 (7)	4 (11)	0 (1)
Ultrastructural defect			
IDA or MTD only	1 (14%)	3 (43%)	1 (20%)
ODA only	2 (29%)	1 (14%)	0 (0%)
IDA and ODA	3 (43%)	1 (14%)	4 (80%)
No defect	1 (14%)	2 (29%)	0 (0%)
No result	0 (0%)	0 (0%)	0 (0%)
Number of antibiotic courses in last 12 months (oral and IV, planned and unplanned)	2.5 (8.0)	1 (4.0)	1 (4.0)
PsA (cultured in last 12 months)	2 (29%)	1 (14%)	0 (0%)
ACT frequency (sessions/day)			
Prescribed	2.0 (1.0)	2.0 (1.0)	2.0 (0.0)
Self-reported	1.4 (1.6)	1.0 (2.0)	1.0 (1.3)
QOL-PCD domain			
Physical functioning	91.4 ± 14.8	74.3 ± 24.2	70.0 ± 27.5
Emotional functioning	90.5 ± 12.2	75.0 ± 13.6	66.7 ± 11.8
Treatment burden	80.3 ± 17.2	71.1 ± 10.3	76.3 ± 14.8
Role	82.4 ± 16.8 (n=5)	72.3 ± 11.1 (n=4)	66.7 (n=1)
Social functioning	82.3 ± 19.0	74.3 ± 20.1	60.4 ± 29.6
Vitality	73.4 ± 16.8 (n=5)	52.8 ± 30.6 (n=4)	55.6 (n=1)
Upper respiratory symptoms	86.7 ± 6.7	64.8 ± 17.9	56.7 ± 11.6
Lower respiratory symptoms	79.0 ± 10.9	73.0 ± 10.4	54.0 ± 21.7
Hearing	94.1 ± 9.3	86.9 ± 12.6	62.5 ± 33.4
Spirometry			
FEV_1 z-score	-0.4 ± 1.6	-1.1 ± 1.1 (n=6)	-3.0 ± 1.5
% predicted	95.1 ± 18.7	87.2 ± 12.5 (n=6)	63.4 ± 17.3
FVC z-score	3.3 ± 0.9	-0.1 ± 1.5 (n=6)	-1.8 ± 1.4
% predicted	95.1 ± 18.7	98.8 ± 1.5 (n=6)	84.2 ± 15.6
FEV_1/FVC (z-score)	-0.5 ± 1.3	-1.4 ± 1.1 (n=6)	-3.0 ± 0.5

% predicted	96.3 ± 9.9	88.6 ± 9.0 (n=6)	75.1 ± 7.3
^{129}Xe VDP (%)			
Pre-ACT	5.6 (21.1)	9.2 (15.7)	8.2 (18.9)
Post-ACT	1.5 (21.1)	7.9 (24.0)	10.2 (19.1)
4-hours post-ACT	6.1 (21.5)	7.0 (20.7)	5.6 (22.1)
ΔVDP pre- to post-ACT*	-0.3 (15.0)	2.4 (14.9)	-0.1 (3.3)
ΔVDP pre to 4-hours post-ACT*	-0.8 (3.4)	0.5 (14.9)	-1.5 (7.9)
% change post-ACT*	-5.0 (246.4)	32.3 (14.9)	-1.9 (53.94)
% change 4-hours post-ACT*	-10.8 (244.7)	3.3 (1768)	-24.4 (44.3)
^{129}Xe VHI (%)			
Pre-ACT	10.0 (6.4)	11.4 (12.4)	12.1 (7.5)
Post-ACT	8.5 (9.4)	12.2 (14.8)	12.7 (7.0)
4-hours post-ACT	9.4 (6.8)	11.3 (10.7)	11.7 (7.9)

6.3.5 When MRI aligns with the clinical picture clinicians, clinicians are confident about if and how to modify the ACT regimen.

The MRI findings for seven cases (Cases 10, 12, 16, 20, 26, 27, 35) were felt to align with the clinicians' expectancies of the individual. Five of the seven cases in this group had normal FEV_1 (z-score>-1.6%), four on whom had abnormal baseline ^{129}Xe VDP% (>1.2%), six had an improvement in ^{129}Xe VDP% post-ACT. In some cases, the existing clinical information was contradictory making the clinical picture unclear, for example, in someone with a high secretion load and above average lung function. In these cases, the clinicians held more than one possible version of what could be going on, or multiple versions of their expectancy. When ^{129}Xe MRI aligned with a version of the clinical picture, the clinicians were confident to proposed their actions: reassured by MRI, the clinician retracted their regimen observation informed suggestion to increase ACT frequency to revert to the original prescribed plan (Case 10); feeling assured the regimen was working well but making adjustments to optimise further through positioning or ACT type (Cases 16, 20, 26, 27); recommending changes they had already considered (Case 35).

6.3.6 When MRI challenges the clinical picture clinicians, clinicians are confident the ACT regimen needs to change but in some cases are uncertain about how to modify it.

The MRI findings for 12 cases challenged the clinicians' expectancies of the individual (Arrow 10). In seven of the 12 cases (Cases 2, 14, 17, 22, 24, 31, 34) the

physiotherapists re-evaluated the information, considered their actions rapidly (Arrow 3) and were confident to propose MRI informed modifications (Case type Y1). Three of the seven cases with repeatable lung function technique had normal FEV_1 (z-score>-1.6%), and abnormal baseline ^{129}Xe VDP% (>1.2%). Response post-ACT in this group was split between worsening (n=4) and improvement (n=3) in VDP. For these individuals, clinicians proposed a programme of ACT modifications based on MRI:

"Would he be better with a PEP or something similar where you've got a bit more control over inspiration and whether that would give you better resolution from a ventilation point of view if you're getting reversibility with a bigger lung volume instead of looking at the oscillatory effects from the Aerobika" (Physiotherapist reviewing Case 34).

However, in five cases of the twelve cases where clinicians' expectancies were challenged, (Cases 5, 6, 7, 11, 29) the clinicians felt uncertain how to proceed and wanted to reassess the patient prior to proposing modifications or became more unsure with the MRI findings (Case type Y2). The individuals in this group did not have mild disease; all had abnormal FEV_1 (z-score>-1.6%) baseline ^{129}Xe VDP. Response assessed post-ACT in this group was mixed, with four individuals showing improvement and two showing worsening in VDP. In two of these cases (Cases 5 and 29), despite parents reporting baseline symptoms the physiotherapists felt the participant was unwell, taking cues from increased secretion load and more extensive abnormalities on MRI than the clinician would expected. The clinicians felt a medical review, potential admission and inpatient physiotherapy input was required, and felt admission would permit iterative modifications through regular assessments:

"(The participant) might even need something like, I don't know… something like passive positive pressure like the bird…I would assess from morning to afternoon if she was in hospital and I would potentially change what I'd do morning to afternoon or do 3 smaller sessions if I could" (Physiotherapist reviewing Case 5).

In two of three remaining cases (Cases 6, 7), the MRI data was more complex to interpret: increasing ^{129}Xe VDP post-ACT with visual areas of improvement (Case 7); an unusual worsening was seen at TLC (increase in ^{129}Xe VDP with corresponding visible defect) (Case 6). In these remaining cases, the clinicians' level of uncertainty changed throughout the review: becoming less certain as the review progressed (Cases 6 and 11); proposing changes but planning a further review first (Case 7).

All cases classified according to the presented case types, but two individual cases did not align as readily into their classification. Firstly, Case 16 was classified as Type X: when the MRI findings aligned with the clinician's expectancy of poor lung function (FEV_1 = 67%; ^{129}Xe VDP pre-ACT= 21.5%); pre-medication of salbutamol was proposed when they reviewed the post-ACT images which showed a deterioration in

^{129}Xe VDP post-ACT (^{129}Xe VDP post-ACT= 26.7%); the physiotherapist felt the lack of positive response to the ACT regimen was attributable to the cases' marked disease and poor adherence to their home ACT regimen. Case 16 is an outlier from the others classified as Type X, with more marked disease than other cases in the group (Excluding Case 16, the group ^{129}Xe VDP pre-ACT range = 0.4-11.3%). Secondly, Case 6 was classified as Type Y2: when the post-ACT MRI findings post-TLC showed an increased defect which was worse at a higher lung volume, the clinician described feeling confused, proposed some changes but also felt the ACT regimen may already be optimised and concluded the interview with a plan to review them in clinic. Case 6 was the only one in the Y2 group who had a significant improvement in their ^{129}Xe VDP as assessed by a change greater than the coefficient in variation; this case had an atypical finding of increased ^{129}Xe VDP on images acquired at TLC when compared to EITV which correlated with visual findings of a large stripe shaped defect which was more apparent at TLC than EITV.

Assessment of case classification at the level of the clinician for physiotherapists identified that the cases reviewed by one physiotherapist were all classified as type Y1. This physiotherapist had prior experience of Ventilation MRI. For the other three physiotherapists who did not have prior experience of Ventilation MRI, the cases they reviewed were classified more variably, with two physiotherapists reviewing all case types and one reviewing cases classified as X and Y2. No other distinct difference was seen between physiotherapists or between initial and later cases reviewed by the same individual. Assessment of case classification at the level of the clinician for nurses and medical consultants was not undertaken due to the small numbers of cases reviewed by each individual clinician.

6.3.7 Agreement is seen in MDT members classification of cases as type X or Y, but some divergence is seen in how MDT members use MRI data.

Of the six cases reviewed by both a physiotherapist and a medical consultant, agreement on the case classification as type X or Y was seen in five of the six cases. Divergence was seen in Case 34; when reviewing their pre-ACT ^{129}Xe MR images the physiotherapist felt the clinical picture and MRI data aligned but the medical consultant did not:

"I'm surprised at how many defects and how significant they are looking at those images" (Physiotherapist); *"It is not outside of what I would expect"* (Medical consultant).

^{129}Xe ventilation images affirmed clinical concerns for both physiotherapists and medical consultants in the following circumstances: clinical information indicated poor compliance with home ACTs and bilateral ventilation defects were visualised (Cases 22 and 26); good compliance but high sputum volume and low FEV_1 caused concern, UTE showed no acute changes but extensive ventilation abnormalities which did not improve post-ACT were seen (Case 29).

Despite agreement on case classification, whilst physiotherapists proposed specific modifications to the ACT regimen in most cases, this occurred less frequently during the medical consultants' reviews. Medical consultants proposed specific changes in two cases: both classified as Case type X; Case 26 had a worsening in ^{129}Xe VDP post-ACT; Case 20 had visible areas of change post-ACT with a small improvement in ^{129}Xe VDP.

"I don't know whether it would be worth doing more… of his oscillating device… but certainly more on the right" (Medical consultant reviewing Case 20).

In three cases medical consultants did not propose specific changes but: planned to review the MRIs with the case's family and to jointly make any regimen changes (Cases 29 and 34); planned to seek advice from physiotherapy and PCD colleagues to plan an appropriate course of action (Case 29). Medical consultants more commonly described the limitations of MRI to inform ACT modifications than physiotherapists:

"You have to take into clinical context …when he's well he's very well I wouldn't change something based on just something I can see". (Case 27)

Of the six cases reviewed by both nurses and physiotherapists, agreement was seen in the case classification for five out of the six cases, divergence was seen in Case 34, the physiotherapist felt the MRI looked worse than expected, whereas the nurse felt this aligned with the obstruction identified by their spirometry (FEV_1:FVC) but caveated this with their ability to assess this:

"I'm surprised at how many defects and how significant they are" (Physiotherapist); "It is not outside of what I would expect but I am not sure I am experienced enough to say whether it is good or bad or exactly as I would expect It to be for him." (Nurse).

Whilst the nurses voiced that their physiotherapy colleagues would be make the ACT recommendations, two of the three nurses suggested specific ACT regimen changes which they felt may be considered following review of the MRI data.

Whilst the use of ventilation imaging for patient education was not a focus of the interviews, most clinicians (3/5 physiotherapists, 3/3 nurses and 3/4 medics) suggested the role of MRI in patient or parent education, and was notably present in every nurse TAPS interview:

"This would also be good to show to the patient…and… the parents…this is showing how well-ventilated the lungs are…we've got poor ventilation here…it's about using it as a visual incentive." (Nurse reviewing images for Case 5).

Physiotherapists described using MRI to help patients understand their ACT regimens and facilitate change which may otherwise not accepted:

"His Aerobika technique…I've tried to change it a few times but he's adamant he's happy with it that way… this image really shows that but when he's doing his physio he's blowing out, the forced expiratory and he might be distally collapsing his airways, I think he might be able to visualise that by looking at these...to understand what his techniques are causing to happen" (Physiotherapist reviewing Case 29).

6.3.8 Modifications to the ACT personalisation model

The ACT personalisation model was refined following the CTA and multiple-case design analysis, the changes are depicted by the red text in Figure 89. Arrow 1 previously reflected "the provider searching for best external evidence". The TAPS interviews refined the action of searching for, into the aim of the search; seeks guidance from. Previously, box A was labelled "best external evidence", reflecting the evidence-based practice which underpins clinical decision-making. However, in the absence of evidence in the TAPS interviews, clinicians sought the best available information, so this label was amended the represent a broader field of sources including published evidence, colleagues, and others outside the clinical encounter. Previously, the model described the provider has expectancies, agrees goals, obtains cues and considers actions. Whilst physiotherapists were reviewing the case information, they were actively considering their actions and there was evidence that rather than holding expectancies, they appropriately brought them to the clinical encounter (Arrow 3, Figure 6). Finally, the case classifications identified situations (Case type X) where clinicians decision-making remained predominantly within the ongoing clinical encounter (Box X) and cases where expectancies were challenged (Case type Y). As in Case type Y reflected encounters which were non-routine, this area of the model in which clinicians move outside of the routine ongoing encounters during a protracted or less confident decisional shift, was labelled as "Y: beyond the typical clinical encounter with the individual". Box X then become ongoing typical clinical encounters, with their individual and their families or carers to reflect the more routine decision-making and the involvement of the individual, families or carers described by the physiotherapists.

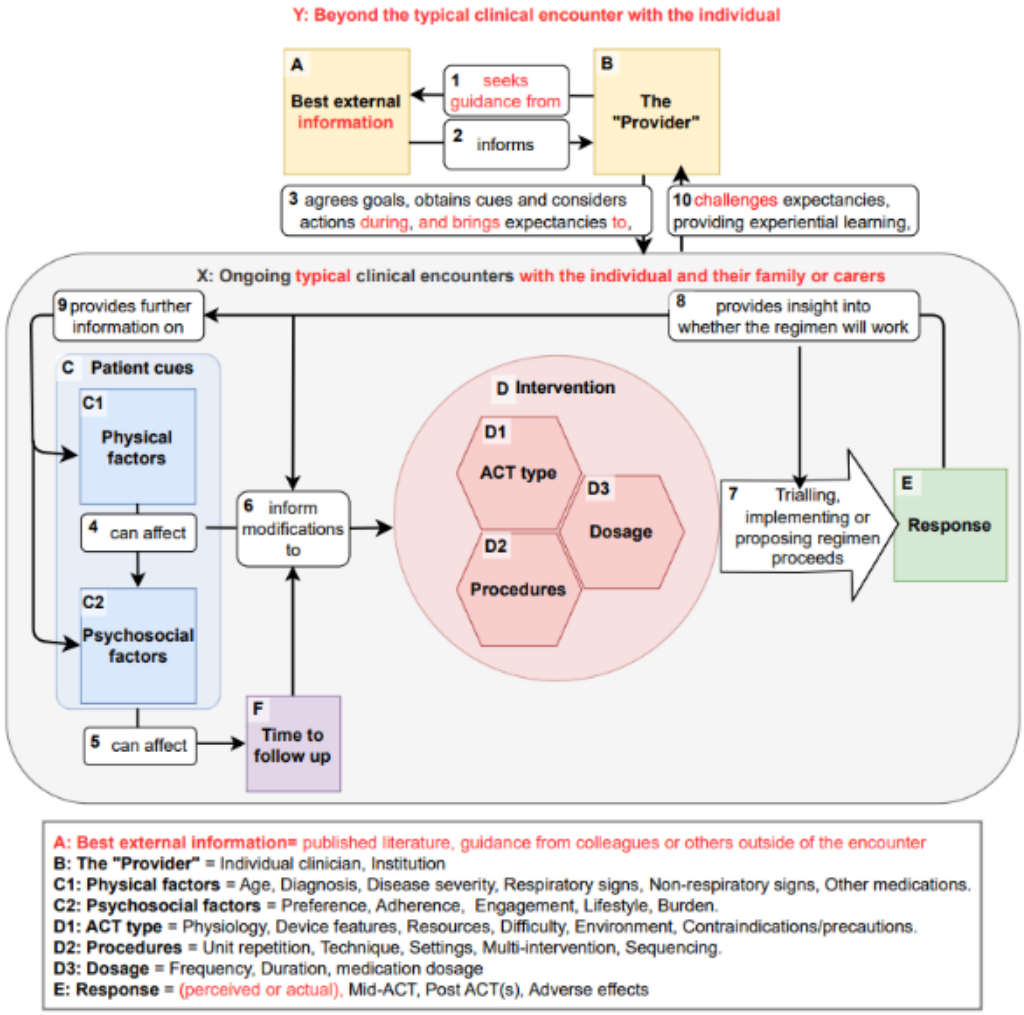


Figure 89: The updated ACT personalisation model (version 0.3). Changes from the previous version (0.2, Section 3.3.3) are indicated by red text.

6.4 Discussion

We captured the clinical decision-making of expert physiotherapists by asking them to think aloud whilst they reviewed data which would be available to them clinically, and data from structural and functional MRI which is not routinely available in clinical practice. Whilst observation of an ACT regimen was included as routine clinical data, this opportunity prompted clinicians to propose modifications to the regimens. Structural MRI scans in some cases provided cues about the patients' physical health which informed ACT modifications. However, more sensitive ventilation MRI provided new data which more commonly challenged clinicians' expectancies in most cases prompted ACT modifications. Assessing response to the ACT regimens with ^{129}Xe ventilation MRI data acquired post-ACT or 4-hours post-ACT provided clinicians with cues to if the regimen would work, sometimes this was different from what the clinicians had expected. In some cases, further modifications were made following review of response data, at 4-hours this was commonly in relation to inhaled

medications. Where MRI challenged expectancies, there was opportunity for experiential learning, clinicians reflected on their previous knowledge or sought best external information to manage uncertainty or discuss issues which were causing their uncertainty.

Through integration of the clinician interviews and data from the MRI scans this study evaluated if and when MRI precipitated shifts in ACT regimen personalisation. Three case types were identified: where the MRI aligned with the case clinical picture (type X); where the MRI did not align with clinical data and the physiotherapist proposed ACT regimen changes (Case type Y1) where the MRI did not align with clinical data and the physiotherapist did not propose ACT regimen changes (Case type Y2). Whilst a range of individuals were seen in all case classifications; Case type X generally had mildest lung disease of the three groups, with normal spirometry and a lower ^{129}Xe VDP, and a higher quality of life scores; Case type Y2 included those with more marked lung disease, with abnormal spirometry, higher ^{129}Xe VDP and lower quality of life scores.

These findings support the hypothesis from Chapter 1, which stated: lung health in PCD will be found to be heterogeneous, as assessed by MRI-derived ventilation defect percentage (H3); functional imaging will inform expert physiotherapists in the personalisation of ACTs for children with PCD (H5).

6.4.1 Imaging can inform ACT regimen modifications in the reviews of most children with PCD.

This study made explicit the tacit decision-making of expert physiotherapists and MDT clinicians by asking them to “think aloud” whilst reviewing a series of information sources pertaining to clinical cases under their care: information which would be available clinically; structural imaging data; and novel functional imaging data. When provided with additional cues from pre-and post-ACT imaging, clinicians revised their perspectives about the physical condition of individual cases under these circumstances: when pre-ACT imaging data appeared better than expected; when pre-ACT imaging data appeared worse than expected; when treatment response assessed by imaging diverged from expectancies built from observation of the ACT regimen and previous knowledge of the case. As more of the cases had ventilation abnormalities identified on functional imaging than structural imaging, it is logical that modifications to the ACT regimen were more commonly proposed following review of functional rather imaging data (^{129}Xe MRI) than structural imaging data (^{1}H MRI). Modification of the positioning used during the ACTs was commonly seen, driven by the identification of regional structural and more commonly ventilation abnormalities on imaging. Positioning to optimise regional ventilation during ACT regimens is a recognised

component of ACT regimens (63) and this study highlights the potential role of regional information from MRI in guiding ACT personalisation. In addition to modifying ACT procedures, the response in ventilation abnormalities assessed post-ACT or 4-hours post-ACT assessed from ventilation images, binning maps, treatment response maps and ^{129}Xe metrics VDP and VHI were used to modify dosage and ACT type. Often the changes proposed related to inhaled medicines that are used within ACT sessions (inhaled salbutamol and nebulised hypertonic saline). In contrast, changes to inhaled medicines arose from routine clinical data in only two cases, highlighting the limitations of existing clinical data to assess such medications.

Whilst previous studies have assessed the effects of ACTs using ^{129}Xe MRI as explored in Section 5.4.2 (138-140, 142, 283), these studies did not involve clinical review of the data or assess the impact of the data on clinical decision-making. The impact of introducing novel thoracic imaging techniques into physiotherapy practice has been explored previously in the context of lung ultrasound win physiotherapist clinical decision-making on intensive care (305). Neindre *et al.* (305 p.172) found "physiotherapy treatment was changed in 62% of cases (n=93) after physiotherapists were presented with TUS (thoracic ultrasound) findings, with significantly more changes when clinical and ultrasound diagnoses were discordant rather than concordant. Whilst a large range of cues are involved in the personalisation of ACT regimens, if considering a direct comparison of FEV_1 with VDP%, in all of the cases with normal spirometry and abnormal ventilation defects (FEV_1 z-score >-1.6% and ^{129}Xe VDP pre-ACT >1.2%) clinicians were confident to propose ACT regimen modifications, with cases classified as type X or type Y1. Both this study and the work of Neindre *et al.* (305 p.172) show imaging has potential to influence physiotherapy clinical decision-making, in situations where imaging provides novel information.

The personalisation of ACT regimens is complex; we found cases where clinicians considered imaging informed ACT modifications but refrained from implementing changes due to psychosocial factors: treatment burden, adherence, engagement, and preferences. For example, an increase in duration was proposed to improve ventilation abnormalities but as this would increase treatment burden, the clinician felt this would be unacceptable to the patient. Contrastingly clinicians also reported ACT modifications may be more acceptable to patients if employing MRI for patient education. In chapters 3,5 and 6 we have confirmed that young people with PCD are commonly advised to complete their personalised ACT regimens twice every day at home, but that patient engagement with this is variable, with regimens often reported to be completed less frequently than recommended. Adherence to daily treatments in long-term conditions is complex; but patient education is one component of the multifaceted approach needed

to support individuals with long-term conditions to undertake treatments (306). Our clinicians described a role for MRI in patient education, with images in the coronal plane and the colour coded binning maps described as being intuitive and accessible. The evidence base supporting visual aids for patient education is growing, with personalised 3D printed models (307), for example of patient tumours and virtual reality among recent developments. Adherence and patient education were beyond the scope of this thesis, but this may be an area for future research.

6.4.2 Clinicians' levels of certainty can vary when using imaging to inform ACT modifications.

Clinical decision-making involves employing established processes of recognition, expectancies, actions, and goals to select, modify and implement a course of action. MRI findings to ACT regimen personalisation provided clinicians with additional information on the patient's physical condition, their treatment response, and over the course of multiple cases, material for comparison. In case types where the MRI findings aligned with the expected clinical picture, or a version of suspected clinical picture, the physiotherapists were confident in their course of action (Case type X). In some cases where the MRI findings challenged the clinical picture, physiotherapists felt confident to propose changes (Case type Y1), but in other cases they did not and planned to seek more information through a clinical review (Case type Y2). Whilst variation of clinical presentation was seen within all case types, physiotherapists more commonly faced uncertainty in how to proceed with ACT modifications in those with more severe disease than those with mild disease. Smith *et al.* (308) reported physiotherapists experienced greater uncertainty in decision-making for more complex patients in intensive care, whilst different clinical environments and acuity this supports the theory that greater complexity may be seen in those with more severe disease, therefore making the management more challenging. These insights both an understanding of the clinicians' reasoning (qualitative) and the patient-specific MRI results (quantitative), so would not have been possible without data integration demonstrating the benefits of mixed methods research.

Uncertainty in clinical decision-making is seen across healthcare settings (309). The physiotherapists in this study described different sources of uncertainty which align with those described previously by Eachempati *et al.* (246): limited personal knowledge and expertise pertaining to MRI; clinical uncertainty, as assessment with MRI post-modifications was not available and currently there is no published evidence or guidance in this field; ethical uncertainty with multiple ACT modifications available without evidence of superiority, potential for patients to choose options which the

physiotherapist believes is sub-optimal and in younger patients, parent-proxy decisions. Lipshitz and Strauss (238) state the uncertainty can be managed, reduced, or suppressed, it is possible that different strategies were available to be employed in Case types Y1, compared to Y2. For example, in some Y1 cases, when pre-ACT modifications proposed less confidently were supported by post-ACT MRI data, uncertainty was reduced, contrastingly in two of the Y2 cases, subsequent data provided conflicting information, uncertainty was increased. In all Y type Cases expectancies were challenged, but the extent of protracted decisions was a key management strategy of Case type Y2 as physiotherapists planned to assess the patient further prior to modifying their ACT regimen or felt an admission would be beneficial, allowing frequent reviews to iteratively assess response to modifications. As in Case type Y1 imaging challenged the clinical picture but clinicians proposed modifications, strategies to supress their uncertainty may have been employed, acting with a false sense of certainty or employing physiological reasoning to manage and move forwards (238). Two cases aligned less readily with the case types indicating potential divergence from the preliminary case classifications proposed in this exploratory study. Case 6 had an atypical feature, with a worsening in the distribution of ventilation at a higher lung volume and an unusual visual defect. Exploring this case further with MRI experts affirmed this finding was unusual and provided a potential cause for the physiotherapist's difficulty in interpreting the MRI data. Case 16 was classified as Type X but had notably greater lung disease than the other Type X cases. The physiotherapist proposed introducing a pre-medication of salbutamol but felt the MRI data was within the expected presentation of the case. Clinical circumstances provided the clinical perspectives of another MDT who proposed a different course of action including a bronchoscopy, suggesting different clinicians may take different courses of action following review of MDT data. Review of case classification at the level of the clinician identified that one physiotherapist who was more familiar with ventilation MRI was involved only in cases which were classified as type Y1, in contrast to the physiotherapists who were more naïve and were involved in cases with varied classifications. Whilst this is a very limited data set from which to draw conclusions, it aligns with previous literature which recognise the role of the provider and their experience in decision-making (242). It is possible that prior experience permitted this individual to adjust their expectancies more rapidly and reengage with modifying the ACT regimen, or the difference between individuals' willingness to proceed in uncertain situations (246).

As physiotherapists are at the forefront of personalisation of ACTs in UK practice, their TAPS reviews were solely used for the majority of the analysis in this chapter.

However, as MDT working is common within clinical practice, nurse specialists and medical consultants were also reviewed the data for a limited number of cases to provide an additional broader perspective and assess for agreement between MDT members. Agreement across MDT members interviews were seen in case classification was seen in the majority of cases who were reviewed by more than one MDT members. This may have been influenced by the close working relationship of participating colleagues but provides strength in the case classification system developed.

The mixed methods approach has supported the evolution of inferences over the courses of the thesis. In Chapter 3, the CTS interviews identified physiotherapists rely patient cues from clinical assessment and patient or parent reported information to personalise ACT regimens, but they face uncertainty in optimising ACT regimens with absence of a sensitive outcome measure with only access to clinical tools with limited ability to assess lung health and treatment response. Chapters 4 and 5 permitted the identification of data-driven inferences: lung health in children with PCD, as assessed by MRI-derived ventilation defect percentage (^{129}Xe VDP) is heterogenous; changes including improvement and worsening in ^{129}Xe VDP were observed following completion of a personalised ACT regimen in some individuals. The CTA in Chapter 6 identified further experience-based inferences: physiotherapists proposed ACT regimen modifications when MRI findings provided new information about lung health or treatment response that challenged their previous clinical decision-making; in some cases when MRI findings did not align with the case clinical picture, physiotherapist wished to reassess the case in light of the MRI findings rather than proposing changes at the point of MRI review. Whilst these findings alone make a novel contribution to the knowledge in this field, the use of mixed methods research which integrates the data allowed for further meta-inferences to be drawn. Qualitative data confirmed the knowledge-based inference: expert physiotherapists saw value in functional lung MRI for guiding personalisation of ACT regimens in children with PCD; however, how MRI influenced decision-making varied based on the degree of alignment between imaging findings and the clinical picture. Data integration expanded understanding; MRI findings that provided new information about lung health or treatment response prompted physiotherapists to propose ACT regimen modifications, as the imaging challenged their clinical reasoning based on current assessment tools. Discordance between experience-based and some qual/quant data-driven inferences illuminated that in some cases, physiotherapists felt uncertain about how to interpret and apply MRI findings to ACT personalization, especially when imaging results did not align with their clinical

reasoning. This reveals a need for structured guidance on using novel imaging information to optimise ACT regimens.

6.4.3 Strengths and Limitations

TAPS study design.

An experiment-like task was designed to simulate the introduction of imaging into existing clinical practice. Inclusion of a video-recorded ACT regimen was used to familiarise clinicians with existing clinical data. However, for most cases, the physiotherapist reported they had not recently observed their ACT regimen and as such, they indicated modifications were needed at this stage of the review, to either correct to the prescribed regimen or modify to prescribed regimen. It is in unclear to what extent this may have influenced subsequent clinical decision-making when reviewing the MRI data. However, this highlights that ACT regimens may not be optimise without the opportunity to observe regimens, with physiotherapists identifying barriers such as time and patient or parent engagement with this process as limiting factors. MDT members often seek the views of one another in respiratory practice (239) the isolated decision-making within the TAPS task may differ from clinical practice where patients are often reviewed in multidisciplinary clinics.

Recognising that an abundance of information can cause uncertainty, and there is a limit to the volume of information which can be processed during decision-making (243), with structural and ventilation images available from three time points for most cases, we selected which images to present to the clinicians, choosing those which were felt to be most relevant to ACT decision-making based on each case's radiology review. Whilst this provided some inconsistency in the methods and introduced subjectivity, it was essential to ensure the interviews were accessible, as some clinicians reported the volume of data for review was significant. The clinicians were not asked what information would allow them to feel confident in the ^{129}Xe MRI findings, this line of inquiry may have provided information on specific knowledge gaps which could have informed future research.

Think aloud methods were used to capture real time clinical decision-making. Whilst clinicians appeared to verbalised their clinical reasoning, it is recognised that this method can disrupt internal cognitive decision-making (148) and as such, it is possible that modifications arising from more natural internal clinical reasoning may have differed. Whilst in most TAPS exercises the clinicians readily engaged with this approach, a two clinicians described feeling uncomfortable with the prompts, one of

whom became more comfortable in latter interviews, and one did not trust the information they were being given.

As this study did not follow patient participants beyond their attendance at the study visit, it is not known whether the proposed ACT modifications were implemented and what the response of any implemented modifications were. Clinicians highlighted this as a potential cause of their uncertainty and potentially this would be a useful component of future research.

Multiple-case method

Case study method is not designed to provide statistically generalisable results, more analytically generalisable theoretical propositions (293). This study has presented a theory of classifying cases based on physiotherapists uncertainty and ability to propose ACT modifications during reviews and has drawn comparisons between the patient cues of the individual cases in each of these case type groups. However, clinical variation was seen within these groups and with a limited number of patient data sets and clinicians who were recruited from a small number of centres, the generalisability of the findings are limited. The provider both in terms of the individual, and their location can influence ACT personalisation (Chapter 2) and clinician will have brought their experiences and expectancies to the ACT reviews (Chapter 3). As the recruitment centres all have close collaboration with the North of England PCD service, the ACT personalisation and decision-making seen in this study may not represent that of other regions in the UK and internationally. This study aimed to reach theoretical saturation, when the information power was felt sufficient to meet the research objectives (299); with five physiotherapy participants and 29 cases available for review, data collection was ceased at 21 cases when no new concepts were being identified. The perception of theoretical saturation can be influenced by the perspective of the research and with only one individual analysing the transcripts it is possible that further concepts may have been identified by a second researcher. However, triangulating the physiotherapist interviews with data from other clinicians and quantitative this provided opportunity to explore the data further and minimise the risk of missing key concepts were minimised. Additionally, this approach aligns with the study context as an explanatory rather than an explanatory study.

Overall mixed methods study design

The integration of data integration at numerous points within the study provides opportunities for specific limitations. As interpretation of the scoping review data influenced ACT personalisation model which was used for data analysis in Chapters 3 and 6, bias of the lead researcher in the initial scoping review analysis could have

influenced the subsequent analysis. However, revision of the model as new data was presented, and triangulation of the data has increased strength and rigour of the model. Basing the data collection on data from the CTA findings from Chapter 2 may have provided bias towards the clinical practice of the physiotherapists participating in that part of the study. Whilst the recruitment of clinicians from across England was appropriate for this exploratory study, it may be beneficial to consult an international field in future inquiries. As the physiotherapists participating in the study recommended the ACT regimens that the patient participants completed, it is likely the treatment response assessed by MRI was influenced by the practice of the physiotherapist. As the qualitative interviews with clinicians were based on reviewing the quantitative MRI data, the MRI findings likely influenced the direction and content of the qualitative interviews. Conversely, the quantitative MRI data was collected from patients under the care of the clinicians interviewed, so the clinicians' prior knowledge of these cases may have affected their interpretation of the MRI data. Whilst there are numerous instances of sections of the study influencing each other, this reflects the real-world context in which ACTs are personalised for individual where there is a complex relationship between decision-making of clinicians and patient outcomes. The inferences drawn from the multiple-case study would not have been possible if analysing the qualitative or quantitative data in isolation.

Novel information

The clinicians involved all had clinical experience of working with people with PCD, however, most were new to viewing and interpreting MR images. The level of exposure and training required for clinicians to be competent in interpreting this novel imaging modality is unknown, an uncertainty which has been echoed by the lung ultrasound (LUS) literature (310). Clinician training was provided and whilst clinicians reported this increased their knowledge of the MRI techniques used in the study, unlike lung ultrasound which has established accreditation processes (311), there was no formal assessment of competence of image interpretation. It is widely accepted that clinical guidelines improve are the quality of clinical decisions, especially in situations of uncertainty. As this study employed a ventilation MRI, a novel outcome, to guide ACT population, a novel application, it was not possible to provide the clinicians with guidelines from which to base their decisions. As subjectivity and conflict in information can provide uncertainty (243), the provision of additional quantitative interpretations of images may have provided out clinicians with greater confidence. Providing both raw images and interpreted images with visual categorisation of regional ventilation and regional response allowed the images to be accessible to clinicians with different preferences, a format which may be useful for future research and practice.

Bias

As the lead researcher is physiotherapist working with children with PCD, a firm understanding of the field, this allowed them to prompt relevant enquiries to deepen understanding during the tasks. As they had worked with all clinician participants prior to their participation in the study, there is a risk participants may have provided social desirable answers (248). To limit the influence of social desirability on participant responses and analysis a number of steps were taken: building trust (312), reassuring participants regarding confidentiality, anonymity and that their responses were not assessed for correctness; use of the TAPS method, to capture clinicians interpretations in real time and minimise cognitive screening of responses; triangulation of interview data with other sources. Recognising the risk of bias of the lead researcher's beliefs and perspectives, reflective journaling was undertaken throughout the study and meetings with PPI members and supervisors were used to discuss any specific studies queries to provide a broader perspective for management of the study.

The trustworthiness of the study, as described by Williams and Morrow (313), was strengthened through a number of means: transparent reporting of the research methods including data integration; for transparency of analysis quotes from clinician participants have been provided, imaging data and metrics along have been provided for each case involved in the multiple-case method (Appendix 11) ; example interview excerpts for key decisional shifts with checked with PPI members; triangulation of qualitative data with multiple other data sources; triangulation of the classification of different MDT members; reflexive journaling during data analysis.

6.5 Conclusion

Personalised airway clearance techniques (ACTs) are recommended for people with ciliary dyskinesia (PCD) to prevent infections and the development of bronchiectasis. Regimens are informed by patient characteristics including lung health, and as the most commonly used marker of lung health, FEV_1 has limited sensitivity to change, ventilation MRI offers a more sensitive tool to assess baseline lung health and regional lung response to ACTs. Individual response to personalised ACT regimens is varied and therefore may be optimal. This chapter has found: physiotherapists propose modifications to the ACT regimen commonly following observation of the ACT regimen; functional and in some cases structural imaging acquired at baseline informs clinicians about the individuals lung health and in most cases ACT modifications are proposed when clinicians have this information; response as assessed by ventilation MRI informs physiotherapists about the effects of the ACT regimen in some cases prompting modifications, often in relation to inhaled medications. This preliminary data partially

supports the hypothesis (H4) (Figure 90) that expert physiotherapists see application of functional imaging to guide the personalisation of ACTs. Functional imaging does guide expert physiotherapists in ACT modification decision-making when the imaging provides information which aligns with their expectancies, and in some cases where it challenges their expectancies. In some cases where the physiotherapist expectancies are challenged and the case had increased symptoms or more marked abnormalities, the physiotherapist wished to reassess the patient in light of the MRI findings.

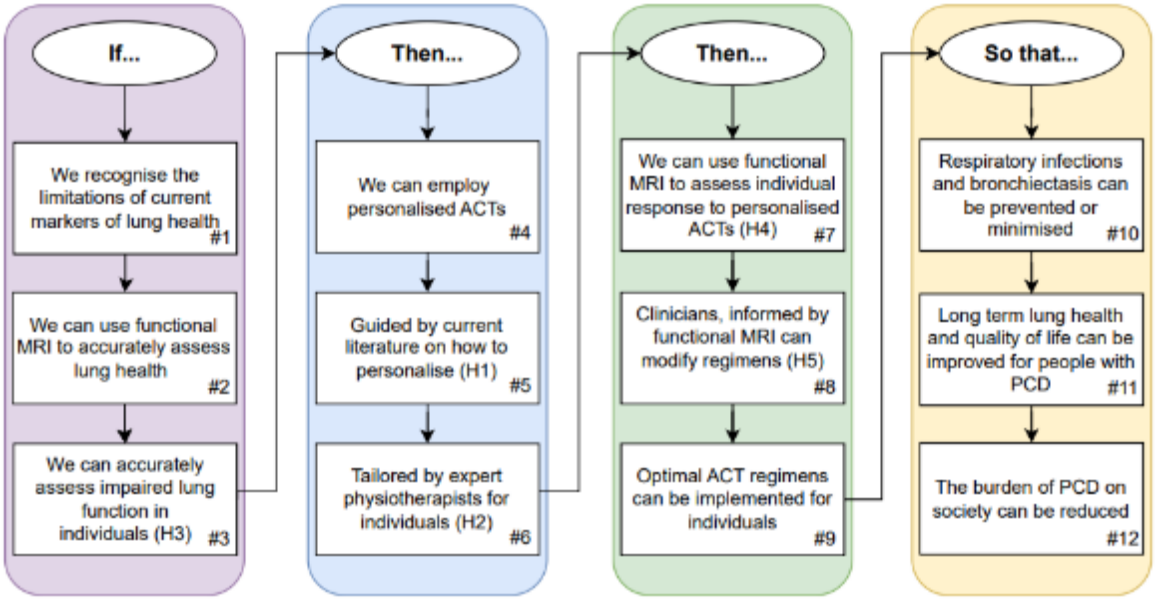


Figure 90: The thesis programme theory.

Chapter 7: Discussion

7.1 Statement of principal findings

This thesis approached four general scientific classes of problem in relation to the personalisation of ACTs for children with PCD: how we should personalise clinical care given different patient needs; how we actually do so; what the effects of personalised care are; and whether we might personalise care differently, given access to novel imaging techniques.

7.1.1 How we should personalise ACT regimens.

This thesis hypothesised there would be identifiable patterns in the literature on how to personalise ACTs for CSLDs (H1). Chapter 2 presented a scoping review that identified 62 publications pertaining to the methods of ACT personalisation. From these, 29 considerations for personalising ACT regimens were identified and subsequently grouped into 7 broad categories: patient physical and psychosocial factors; the intervention type procedure and dosage; patient response; provider. This confirmed that there were patterns in the factors which should be considered when personalising ACT regimens (H1). However, as introduced in Section 1.3.5, there was a lack of clarity on how ACTs are personalised, specifically how physiotherapists navigate through numerous factors to personalise ACTs. Recognising this uncertainty, the thesis presented an ACT personalisation model based on current literature (Section 2.3.3). This provided initial clarity on how ACTs should be personalised according to current literature: an iterative process of ongoing encounters in which the provider, informed by evidence considers the individuals physical and psychosocial needs, to adapt different components of the intervention, which is trialled, permitting the assessment of response. The scoping review also found a paucity of evidence on the effects of personalised ACT regimens, confirming there was a need to undertake this work.

7.1.2 How we do personalise ACT regimens.

Without explicit evidence of how physiotherapists do personalise ACT regimens for people with PCD, this thesis hypothesised there would be identifiable patterns in expert physiotherapists' decision-making when personalising ACTs for children and young people in practice (H2). Chapter 3 presented cognitive task analysis (CTA) interviews with expert physiotherapists, exploring a recent clinical scenario in which they personalised an ACT regimen for a recent non-typical case. It identified they commonly faced uncertainty and managed this by acquiring information through further assessment to establish the situation as certain. It confirmed there are patterns in how physiotherapists personalise ACT regimens (H3), for the first time making explicit: the

iterative process of ACT personalisation, which often involves numerous modifications; physiotherapists' consideration of patient cues, the intervention properties and the individual patient's response; ACT personalisation occurs in the context of the provider. Whilst the physiological principles underpinning ACTs are important in the personalisation of ACT regimens (Section 1.3.2), these findings elucidate the actual decision-making process specifically the clinicians balancing the various needs of the individuals to iteratively refine and optimise regimens.

7.1.3 Individuals with PCD do have different needs.

The assessment of patient needs is an important element of ACT personalisation; "clinical respiratory signs" such as disease severity were the most commonly cited patient factor in current literature on how ACTs should be personalised (Section 2.3.2). Clinical respiratory signs are cues such as spirometry, used by physiotherapists to assess patients and their ACT needs. Current evidence tells us clinical assessment tools are limited (Sections 1.4.1 and 1.4.3). $FEV_{1,}$ is the most commonly used marker of lung health and this thesis found it to be insensitive to assess individuals with mild PCD; 75% of children with PCD who had FEV_1 within normal limits had an abnormal^{129}Xe VDP. It was important to accurately assess respiratory abnormalities which indicate the need for ACTs in PCD. This thesis hypothesised lung health in PCD, as assessed by MRI-derived ventilation defect percentage (VDP) would be found to be heterogeneous (H4). The cross-sectional study (Chapter 4) found individuals with PCD with a broad range of ^{129}Xe VDP, confirming disease severity in PCD is varied. Whilst it the heterogeneity of disease prognosis in PCD was previously recognised (Section 1.2.5). this study has confirmed that unlike current clinical tools, ^{129}Xe MRI is able to assess the distribution of ventilation in children with PCD, providing not only a highly sensitive tool but also information of regional abnormalities which improves the level of detail available to inform clinical practice. The heterogeneity in ventilation abnormalities seen in PCD justifies the need for personalised ACTs in this population.

7.1.4 The effects of current personalised ACT regimens are varied.

This thesis hypothesised that there would be improvement in visual indicators of lung health, as measured, pre- and post-, by ^{129}Xe VDP, after personalised ACTs are completed (H4). Chapter 5 presented a before and after study, showing individual response to personalised ACT regimens is variable: some individuals showed improvement post-ACT, others showed worsening. This partially confirmed the hypothesis (H4) but also identified uncertainty over why ACT response varies. It identified variability in VDP over the day in those who do not complete an ACT. It

proposed that use of a standardised threshold to assess significant change is not appropriate in a condition with a heterogeneous baseline and regional assessment of change in ventilation may provide further information on the effects of ACTs. The use of relative change instead of absolute change has been adopted with FEV_1, although with recognised limitations when assessing populations with heterogeneous disease severity (289). As the study participants were using individually personalised regimens and improvement post-ACT was only seen in some cases, this confirms the limitations in the current tools used to assess the effects of ACT regimens (Sections 1.4.1 and 1.4.3) and shows the potential role of ^{129}Xe MRI in addressing the shortcomings.

7.1.5 We might personalise ACT regimens differently, given access to novel imaging techniques.

This thesis hypothesised that expert physiotherapists would see application of functional imaging to guide personalisation of ACTs for children with PCD (H5). Chapter 6 presented an integrated mixed methods study which discovered that in some cases information from ^{129}Xe MRI aligned with the existing clinical impression of the case and other cases it challenged physiotherapists and other clinicians' expectancies. It identified: cases where MRI findings aligned with the clinical picture and physiotherapists proposed ACT modifications often informed by MRI data; in cases where the MRI did not align with the clinical picture, the physiotherapists either proposed ACT modifications based on the MRI or planned to reassess the patient in light of the MRI. This partially supported the hypothesis that expert physiotherapists would see application of functional imaging to guide personalisation of ACTs for children with PCD (H5). These findings align with the complexity of personalising ACT regimens proposed in Section 1.7; "the practical problem, and *key uncertainty*, for physiotherapists is how to achieve consistent outcomes given that outcomes are affected by *context* (149), where context can be defined as settings, roles, relationships, interactions".

7.2 Strengths and limitations

7.2.1 Strength: philosophical pragmatism was an appropriate world-view through which to explore the personalisation of ACTs.

Pragmatism was chosen as the paradigm through which to explore the inquiry in this study (Section 1.7). This thesis aligns with the five steps of Dewey's systematic approach to inquiry as formulated by Morgan (314):

1. It has recognised the personalisation of ACTs as problematic: the daily completion of ACTs is burdensome for individuals with PCD (Section 1.2.6); whilst current evidence tells us ACTs should be personalised (Section 1.3.4), the tools to assess personalised regimens are limited (Sections 1.1.1 and 1.4.3).
2. It has considered defining the problem differently: it proposed using functional MRI to assess the effects of ACT regimens (Section 1.4.2); it has collated the current literature on how ACT regimens should be personalised, developed a model of ACT personalisation (Chapter 2); it has made the current decision-making of expert physiotherapists who personalise ACT regimens explicit (Chapter 3).
3. It has assessed the potential of ^{129}Xe MRI to inform ACT personalisation: it recognised the limitations of current measures of lung health and the potential of ^{129}XeMRI (Section 1.4); it has used ^{129}Xe MRI to assess baseline lung health in children with PCD and confirmed that ^{129}Xe MRI to be more sensitive than FEV_1 to detect abnormalities in children with PCD.
4. It has evaluated the potential of using functional MRI to assess the effects of ACT regimens (Chapter 5) and the likely consequence; the impact of functional MRI on ACT modifications (Chapter 6)**.**
5. As this work is exploratory and developmental, this inquiry continues. This chapter reflects on the work to date and proposes future research that are likely to address the remaining *uncertainties*.

This thesis has addressed an important *practical problem* faced by physiotherapists, personalising ACT regimens in the absence of suitable tools to assess lung health or the effects of ACT regimens (Section 1.7) and high-quality evidence showing personalised regimens are having the desired effects. PPI members want to understand more about the effects of their ACT regimens (Section 1.2.7).This study has shown ^{129}Xe MRI is a suitable tool to assess baseline lung health, to assess the effects of ACT regimens and that it does inform clinician decision-making in ACT personalisation. If this exploratory study is used to inform the research questions and study designs of future work, there is long-term potential to better optimise ACT regimens and improve care for individuals with PCD.

The appropriateness of a pragmatic approach to this inquiry is also evidenced by the study findings. How clinicians personalise ACT regimens aligns with the two pragmatic processes of interpretation summarised by Morgan (314); habit-based, and inquiry-based. Chapter 3 unpicked the tacit, habit-based decision-making used currently by physiotherapists the real-world; as they draw upon their previous experiences,

managing *uncertainty* to establish the clinical situation as familiar. Chapter 6, in contrast, found examples where physiotherapists moved to a more self-conscious inquiry-based decision-making process, when they were presented with findings from MRI which did not align with their existing clinical impression of the case.

Strength: employing the most suitable research methods

This study used a highly novel approach, employing a highly sensitive tool which can image the distribution of ventilation in the lungs to assess the effects of ACTs which manipulate ventilation. Currently clinical access to ^{129}Xe MRI is limited to a small number of centres and it is not used to inform physiotherapy practice. As such this study is experimental medicine, exploring a novel clinical application of ^{129}Xe MRI. The mixed methods approach in this study integrated novel MRI data into clinical practice, to gain a more comprehensive understanding than would have been possible with a single method. Over the course of this study a range of different methodologies were employed: scoping review, cognitive task analysis, cross-sectional study, before-and-after study, mixed methods case study. Using the *most appropriate research approach* for the inquiry, rather than a single method assumed to be the most valid, demonstrates commitment to pragmatism (315). Rather than adopting a controlled comparison study design, known to be challenging in this field (80), this study design was embedded in current clinical practice. By pragmatically assessing the effects of personalised ACT regimens routinely used by individuals, the findings reflect the *real-world context* of ACT interventions (Section 1.7). Using an experiment-like task and think aloud methods to feed the MRI findings back to physiotherapists and other MDT members, this study design mimicked the application of the novel tool to clinical practice and captured real time decision-making. The thesis aimed to integrate different forms of knowledge on ACT personalisation, including the theoretical physiology of ACTs, experiential knowledge of expert physiotherapists, empirical knowledge from MRI data to explore their *practical* relevance and role in the personalisation of ACT regimens. The approach was not only diverse but reflective and *flexible*, permitting *iterative* amendments to the proposed model of how physiotherapists personalise ACT regimens, rather than seeking a single, unified theoretical framework assumed to correspond to reality (315) (Section 1.7).

Strength: pragmatic flexibility

The approach used to produce the ACT personalisation model, which involved devising and revising the model with logical and intuitive thinking reflects the MRC complex intervention development framework (49). As current literature presented a large number of factors which should be considered when personalising ACT regimens but

lacked guidance on how to navigate through these factors, this study responded, providing an ACT personalisation model. Developed from the evidence base, instead of assuming this as truth, it was stress-tested and refined at a number of stages: with PPI input (Chapter 2); with CTA interviews and integrated with the recognition primed decision mode, an established model of decision-making (Chapter 3); with critical decision method (Chapter 6). The most recent version depicted in Figure 91 should continue to be *iteratively* developed (Section 1.7); tested and refined as needed through further work to establish if it is a useful model for understanding the personalisation of ACT regimens in CSLDs.

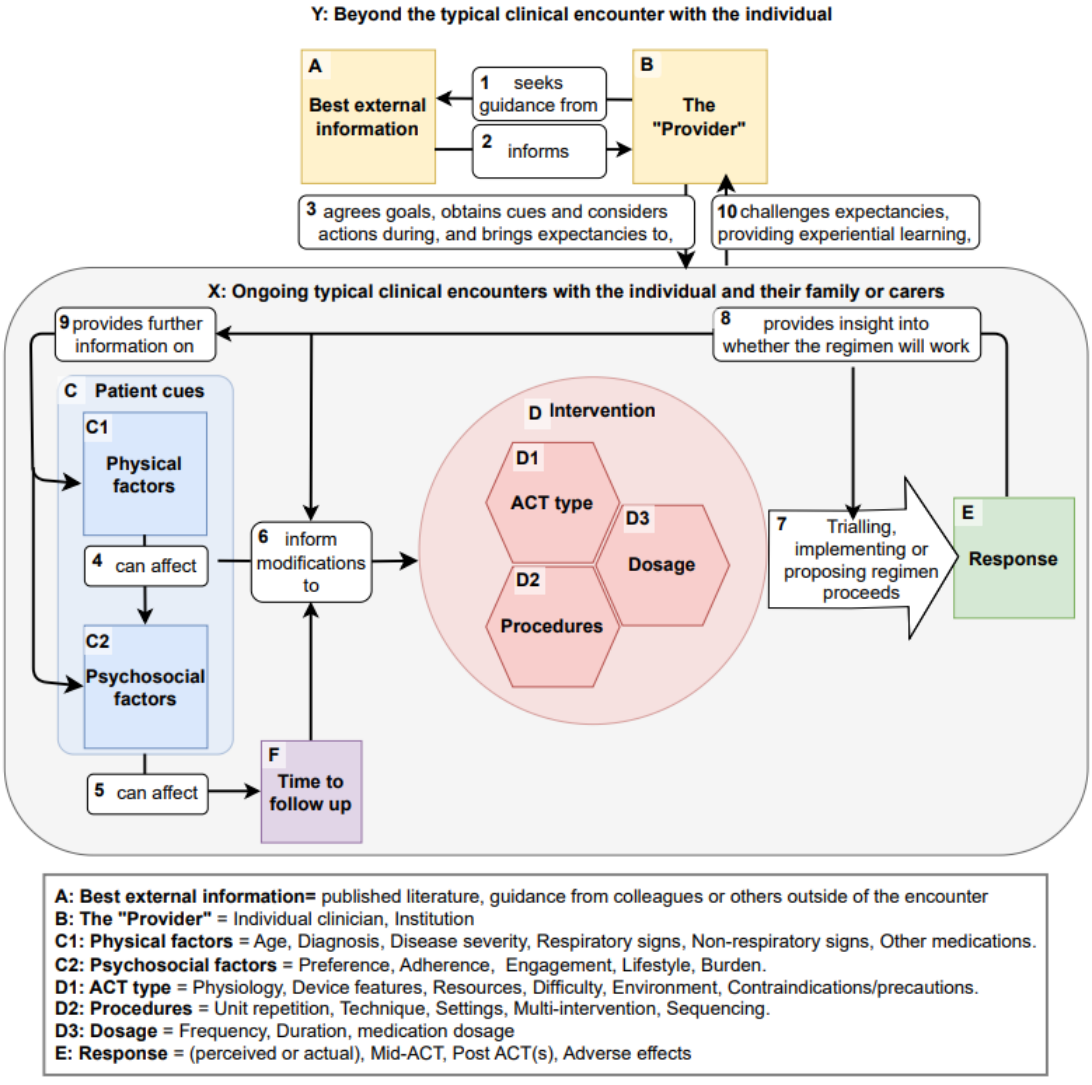


Figure 91: The ACT personalisation model, version 0.3.

A pragmatic approach allowed the researchers to be reflectively responsive. For example whilst the recognition primed decision model (RPDM) (218) was used for initial analysis of the CTA interviews (Chapter 3), reflection during the analysis identified limitations in the *context* of ACT personalisation. Responsively using the ACT

personalisation model for secondary analysis, this provided an opportunity to overcome the limitations of RPDM, and PPI feedback provided further opportunity for triangulation of the analysis findings.

Strength: stakeholder engagement

Pragmatism involves *commitment to democratic, community-engaged inquiry aimed at practical problem-solving* (Section 1.7), and a collaborative and participatory approach (316) was taken throughout this study. The lead researcher engaged key stakeholders relevant to the *context* of ACT personalisation of ACT regimen for children with PCD including patients, parents, physiotherapists, specialist nurses and medical consultants. Patient and public involvement (PPI) before the study embedded the research priorities of patients and parents in the study aims, regular PPI consultation during the study optimised success of the study, and further PPI work following the thesis is planned to disseminate the findings to the PCD community. The involvement of national expert physiotherapists and local physiotherapists who personalise ACT regimens as well as medics and nurses has drawn upon both the specialisms of PCD and paediatric care and MDT working.

7.2.2 Limitation: as a prospective development study, the findings are provisional and *context* specific.

A scoping review was selected as the appropriate method to explore the extent and range of current literature pertaining to the personalisation of ACT regimens. However, unlike systematic reviews, scoping reviews do not formally assess the quality of evidence quality in the field (146). As much of the current literature comprised review papers, a scoping review was indicated, however this scoping review did not make the quality of the studies explicit. The scoping review provided a novel and important contribution to the field, which may inform the design of a systematic review in the future, when there is indication in the field for this.

In the absence of same-day ^{129}Xe MRI repeatability day in people with PCD, the before-after study was powered based on the same-day repeatability of ^{129}Xe VDP in people with CF (Section 4.2.2). However, recognising this approach could be fallible, the study pragmatically included a small control group to explore same day variability in PCD. A number of study design limitations pertain to the control group including, the size of this group and methods of allocation to the group. With caution regarding withholding ACT regimens in research in CSLD's, the control group was intentionally small and there was no random allocation to the group. This study was not powered to assess the difference between the ACT and control groups but pragmatically employed

the use of data from the control group to assess the significance of outcomes following ACTs. Whilst the findings of this study are based on a small sample, they provided evidence of the need to further assess same-day variability of ^{129}Xe MRI markers in PCD rather than assuming confidence in the extrapolation of data from other lung conditions. This study did not follow the journey of patients beyond this MRI review to see if the modifications proposed by the physiotherapists in the TAPS interviews were implemented in practice, such as changing the ACT type to one felt indicated when reviewing the MRI scan. Whilst this was considered during the study, this additional data collection would have required an ethics approval amendment, work which was not possible during the time available.

The findings of the qualitative inquiries are *context* specific, with a small number of centres involved: in Chapter 3 physiotherapists' recruitment was limited to the English national paediatric PCD specialist centres; recruitment was limited to four centres in the North of England for patient participants (Chapters 4 and 5), and MDT clinicians (Chapter 6). Whilst the small number of centres was appropriate for this prospective development study, the personalisation of ACT regimens may be different in other contexts, for example, other locations, age groups and diseases, all of which are factors identified in the ACT personalisation model (Chapter 2). The ACT regimens used by study participants were prescribed by the individuals' local physiotherapists. As ACT regimens are known to vary depending on the location of the provider, the recruitment of patients from a small number of centres is likely to limit the application of the findings geographically. Additionally, whilst other ACTs are used by individuals with different conditions and different ages, it is important to recognise these findings as part of an ongoing process of inquiry, open to further refinement.

7.3 Strengths and weaknesses in the context of other studies

The research questions in this study were driven by the physiotherapy research priorities identified by children and young people with PCD and their parents (Section 1.2.7). As a recent study identified top research priorities for people with PCD found disease variability, prognosis and suitability of existing treatments all featured in the in top five (317) this study is highly relevant to people living with PCD.

This study presented a model of ACT personalisation: initially informed by the scoping review and PPI feedback (Chapter 2); refined by examples of physiotherapy clinical decision-making during ACT personalisation currently (Chapter 3) and with the introduction of MRI data (Chapter 6). This thesis compared the ACT personalisation model with more prescriptive algorithms of how ACTs should be personalised in

CSLDs (93, 213) (Section 2.4.1) and a conceptual model of acute cardiorespiratory decision-making (247) (Section 3.4.3). This thesis has reported the methods used to develop the ACT model for transparency (49). Whilst Volsko (93) provided a limited description of integrating findings from systematic reviews, expert opinions and clinical practice, Van Der Schans (213) provided no details of their algorithm development process. Similarity is seen between some features of the ACT personalisation model presented in this thesis and the alternatives presented by Volsko (93) and Van Der Schans (213): respiratory signs, assessment of response and an iterative process of personalisation (93, 213); age and engagement (93). Psychosocial factors are a core element of the newly developed ACT personalisation model, but patient preference is less apparent in Volsko's algorithm (93), and Van Der Schans (213) recommends increasing adherence to the prescribed regimen as opposed to rather than psychosocial factors prospectively influencing personalisation. Stress-testing our model with clinical decision-making showed psychosocial factors do inform ACT personalisation (Chapters 3 and 6) and as such, there was evidence for psychosocial factors to remain within the ACT personalisation model. Moving on to the acute cardiorespiratory physiotherapy decision-making model (247), initial contrasts were drawn in Section 3.4.3, as Thackray and Roberts (247) placed information processing, hypothesis testing and reflection centrally to their model. However, revisions to the ACT personalisation model in Chapter 6 have resulted in greater alignment with Thackray's model (247). Presenting physiotherapists with novel MRI data has highlighted differences in clinical decision-making during typical and non-typical clinical encounters. Revising the ACT personalisation model to incorporate where encounters are typical or non-typical (X and Y, Figure 91) flag these different decision-making processes. These changes again resonate with the central information processing component of the conceptual decision-making model (247). As, the physiotherapists reflected on their previous knowledge when MRI findings challenged their expectancies, this also resonated with the reflection component of the conceptual decision-making model. Whilst these comparisons affirm the similarities of the two models., difference remains in the *context* of their application; the broad context of decision-making in cardiorespiratory physiotherapy versus the more specific context of personalisation of ACTs in CSLDs.

This study used ^{129}Xe Ventilation MRI to assess lung health in children with PCD and provided comparison with tools which are currently available clinically, namely FEV_1. Finding ^{129}Xe VDP to be more sensitive to assess abnormalities than FEV_1, this study aligned with previous research in people with PCD (135, 276), CF (128, 131, 133, 271) and asthma (272). Assessing young people with PCD over the day without completion

of an ACT regimen, this study found greater variability in ^{129}Xe VDP over the day in individuals with PCD than has previously t seen in the CF population (Section 5.4.1). However, as previous research has shown high variance in lung health in FEV_1 in PCD during periods of condition stability (109) it is possible that greater natural variability is seen in PCD over the day. As multiple breath washout metric, the lung clearance index (LCI) has been shown to be more stable in PCD, sensitive to exacerbations (318), and is often used as an additional comparator (128, 133, 135, 271), this would have provided an additional valuable comparator.. LCI was excluded from the study protocol to ensure the study was feasible for young patients, however, as LCI is more sensitive to detect abnormalities than FEV_1, it may be beneficial to include LCI in future studies.

Whilst other studies have employed ^{129}Xe MRI to assess the effects of ACT regimens, the interventions they have used have been standardised (138-140, 142). As personalised ACT regimens are recommended across CSLDs (Chapter 2), this limits the relevance of the findings of these studies to current clinical practice. As the first study to assess the effects of personalised ACT regimens with ^{129}Xe MRI in any CSLD this thesis contributes important, novel, and clinically relevant work to this field. The mixed methods approach of this study for the first time integrated ^{129}Xe MRI data into clinical practice. Whilst previous studies have used Ventilation MRI to assess ACTs in CF (142) (138) and bronchiectasis (139), their findings have been purely quantitative. Integrating qualitative and quantitative research findings provided understanding of the circumstances in which MRI does inform ACT modifications, insights which would not have been possible using one approach in isolation.

This study captured the ACT regimen technique qualitatively, reflecting clinical practice. The ability to quantitatively assess elements of ACT regimen technique is a recent opportunity possible through novel remote monitoring technologies. Research in this area is allowing better understanding of the variation in patient techniques which may be sub-optimal (81, 288, 319). Research in people with CF using PEP and OPEP devices found despite standard instructions, the pressure, expiratory duration and when relevant oscillation amplitude varies between individuals and when unsupervised (81). In the current study whilst MDT clinicians used audible and visual cues from the ACT regimen video, such as expiratory duration, to assess the quality of patient participant techniques, in the absence of such ACT device data, it is not possible to quantitatively assess the impact of participant techniques on ACT treatment response.

The recruitment of patients to the study was challenging. As patient data collection took place in the period following the Covid-19 pandemic (April 2022 to September 2023), a number of parents declined participation due to the impact of their child taking a day of school or their capacity to take a day off, especially as children with PCD were advised

to shield at home during the pandemic period. Despite regular involvement of PPI members to review processes and opening a fourth participant identification site, the initial recruitment target of 43 patient participants was not met. As a rare disease, not only is the population of potential participants limited but the population is much less familiar with being approached for research participation. Other studies working with people with PCD have also struggled with participant recruitment, for example in recent study developing the parent proxy of the PCD quality of life questionnaire which did not meet the recruitment target (320, 321). With some parents citing travel concerns as a barrier to their child participating and in a number of cases having to shorten the study protocol when patients were delayed by transport, a larger data set may have been possible with the provision of taxis for participants.

7.4 Meaning of the study

7.4.1 Impact of the study

Knowledge translation and impact are key components of research and it is important to consider the impact of the findings appropriate for the stage of this study (86). This study has provided a novel contribution to the knowledge base, specifically pertaining to the personalisation of ACT regimens in PCD and more broadly in the CSLD population (Chapter 2). Throughout this project the lead researcher has been sharing information, through publication in a key peer-reviewed journal (322), presentations and posters at national and international meetings and conferences (323, 324). Full details of the outputs of this study which would be classified as diffusion knowledge translation (86) are provided in Appendix 12. As key stakeholders, the lead researcher is working with PPI members on content for knowledge dissemination to the PCD community in a number of formats: PCD live are webinars hosted by PCD support UK for the PCD community (325) and lead research will present the findings of this study in the near future; funding is in place for a research dissemination video, summarising key findings for young people with PCD; a lay summary of the findings will also be shared with study participants.

As a prospective development study, the main impact of this study will be informing future research. The following impacts of future studies are proposed.

1. Impacts on health and welfare: The current study aimed to understand how ACTs are personalised, what the effects of personalised ACT regimens are and how functional MRI may inform modifications to ACT regimens. These aims are key steps of an overarching aim to improve the personalisation of ACTs for

individuals with PCD. Improved clinical guidelines, treatment practices, or patient outcomes based on the findings of future research could be considered as an impact on health and welfare.

2. Impacts on practitioners and services: Recognising the role of the MDT in the management of PCD, the study current study engaged with physiotherapists, nurses, and medical doctors as research participants, and as mentors, supervisors, and project advisory group members. If future findings influence professional standards, guidelines, or training for delivering ACTs or assessing their effectiveness, it could be considered an impact on practitioners and services.
3. Impacts on public policy and services: This study has provided preliminary evidence that current personalised ACT regimens are not having a universal effect on lung health as assessed by Ventilation MRI. Whilst further research is required, in the longer-term these findings may inform future policy decisions or service recommendations related to managing PCD.
4. Impacts on the economy: As a long-term condition, PCD has an impact on the NHS and society. ACTs aim to facilitate secretion clearance, minimising the risk of repeated lower respiratory tract infections, airway inflammation and bronchiectasis. Therefore, if we can optimise ACTs for individuals, we have the potential to minimise the impact of this condition for people with PCD in the longer term. If we can reduce exacerbations, we can reduce the resulting time away from school and work and lower the economic impact of this condition.

However, further research is required to continue this work (Section 7.5) and the potential impacts described assume that the dissemination and integration of future research findings into clinical practice. In due course, appropriate evidence and indicators would need to be collected to prove impact. As assessed by the UK research excellence framework (326), these may include documented changes to guidelines, evidence of improved patient outcomes or experiences, or demonstrated influence on policy debates. The actual realisation of these impacts would depend on various factors beyond the scope of the thesis itself.

7.4.2 Researcher reflections

Personal reflections

As an experienced children's PCD physiotherapist often supporting individuals who were struggling with completing their ACT regimens every day I had regular contact with the treatment burden imposed by the recommendations I made to patients. I was aware of the limited evidence base to guide my practice and was motivated to build

research in this field by a moral obligation to ensure I was doing the right thing for the individuals with PCD I see in clinical practice. Working with PPI members to establish their research priorities, I was struck by the simplicity of their questions which I could not answer from current evidence: “what happens if I miss a session?”; “do “pats” (manual chest percussion) actually work?”; “Is PEP mask the most effective way of clearing mucus?”. It was clear that we needed an accurate tool to assess ACTs to begin answering these questions.

As preliminary work using ^{129}Xe MRI had identified ventilation abnormalities in children with PCD (135), I was optimistic about the potential role of ^{129}Xe MRI. One of the biggest challenges I faced was transitioning from a clinician, confident that the ACT regimens I recommended were effective, to adopting a position of equipoise as a researcher. In reality this transition occurred when some of the early patient participants had marked worsening in their ventilation post-ACT. As an experienced clinician this stimulated considerable reflection on my practice and the culture in which we grow as physiotherapists. The realisation that the ACT regimens were not having the effects I had expected led to a loss of trust in my own judgement. Working with PPI group, mentors and the project advisory group helped me to recalibrate my perspectives and to truly adopt a position of equipoise, allowing me to move forwards through the complexity of data.

Interpersonal reflections

As the MRI findings were complex, exploring clinical decision-making using MRI with experienced MDT clinicians provided opportunities to reflect on the data as it was evaluated by others in the field. However, as I had worked with all of the physiotherapists, nurses, and medical doctors previously, at times it was difficult to not influence or lead the discussion. Regular reflection and supervision allowed space for me to manage my interpretation of the data, to allow the MDT clinicians space to make their own judgements.

Methodological reflections

The study design is likely to have been influenced by my prior experiences. As my clinical role involves collaboration with the team at Sheffield Children’s Hospital who had experience of working with the University of Sheffield, POLARIS team, I had the opportunity to see the potential presented by ^{129}Xe MRI. When preliminary work with this team identified ventilation abnormalities in children with PCD (135), I was optimistic about using ^{129}Xe MRI to assess the effects of ACTs. Without these opportunities, I may have explored other avenues to further understand the effects of ACTs, however, as ACTs aim to manipulate ventilation in the lungs, I feel assured this was a logical

approach to the inquiry. Having previously led qualitative research exploring the lived experiences of children with PCD (40), I valued the possibilities provided by qualitative research to understand the real-world context of clinical problems. If conversely, I had experience of quantitative research, this study design could have been purely quantitative, with greater depth in a narrower inquiry. However, undertaking a mixed methods project has not only allowed me to approach this research pragmatically but also provided me with a broad range of research training opportunities. The breadth of this project has been challenging to manage at times, especially through the data analysis and write up. Rather than feeling a missed opportunity, this provides avenues for future work, some of which I hope to explore in the future.

Contextual reflections

Recognising the influence of provider location on the personalisation of ACT regimens (Chapter 2), having trained, and worked as a clinician only in the North of England, the experiences I have to draw upon are geographically limited. Within the fellowship, I have had the opportunity to visit hospitals in a number of cities in Sweden and Oslo, Norway, spending time with experienced clinicians who personalise ACT regimens in a different context. The practice in these countries differed from the clinical practice I was familiar with. The ACT regimens used in Sweden heavily featured: positive expiratory pressure (PEP) with minimal oscillatory PEP; breathing techniques using more active exhalation to lower lung volumes than familiar to my practice; upper limb focussed exercise. In Oslo, this differed again with less adjuncts and the specific cough technique (327) featuring which I have not seen in the UK. The difference of ACT approaches in different locations allowed me to see how diverse ACT personalisation can be, influenced by the provider. As clinicians we share a desire to optimise regimens for individuals, yet we approach this differently. Whilst this exploratory study resides in the context of the North of England as ACT personalisation does vary geographically, the context of this study does limit the generalisation of the specific findings.

7.5 Future research

This thesis contributes empirical knowledge to an ongoing inquiry of how we optimise personalised ACT regimens. As an exploratory study the study findings as provisional and context specific. The study could be considered as part of the 'development' phase of future work, with a longer-term overarching aim is to optimise the personalisation of ACTs in PCD. This study has established a number of uncertainties which provide areas for the next stage of future feasibility work:

- This study has developed an ACT personalisation model (Chapter 2), which has been tested through later work packages and refined (Chapters 3 and 6). It would be appropriate to test this model further in prospective studies exploring clinical decision-making in a broader context for example, within other CSLDs, with clinicians of different experience levels, and in other settings beyond the UK.
- Development of a personalised ACT regimen measure.
  This study has confirmed that ACT regimens are highly personalised (Section 5.3.3 and Chapters 2, 3 and 6) and as such it can be hard to effectively report the details of the regimens used in published literature. Therefore, it is important to be able to represent ACT regimens accurately for research studies and databases. The development of comprehensive measures of ACT personalisation would aid data collection in any research involving participants who are completing ACTs. This process would involve iterative development and validation of a new measure incorporating key dimensions and actions identified in the thesis, using qualitative feedback and quantitative psychometric testing. For this to be relative to a broad range of study settings, it likely this would require international collaboration.
  Establishing the clinimetric properties of ^{129}Xe VDP in people with PCD, including variability, repeatability and sensitivity. For example, whilst this study established disease severity as assessed by ^{129}Xe VDP is varied in a small population of individuals with PCD, it is unknown if this small group is representative of a broader PCD population. As such, there is warrant for further work to establish variability with a larger population. Assessing a broader population, from more centres and adults both within the same day and over a longer period of time would establish thresholds which could be used to assess the effects of interventions with ^{129}Xe MRI. It may also provide information on individual need for ACTs which has the potential to impact clinical recommendations.
- Assessing the effects of MRI informed personalised ACT regimens.
  Whilst we have established that MRI informs ACT regimen modifications in most cases, this work did not follow the decisions beyond the initial MRI data review. It is unknown if the proposed modification were implemented and what the impact of MRI informed modifications were. Future work could explore the effects of MRI informed ACT regimens, with assessment of the impact over a longer period of time. This work should include the assessment of important patient outcomes such as exacerbations requiring absence from school or work, antibiotics, and hospital admissions. It would

be important to be able to perform subgroup analysis within this study to explore the effects of different regimen components. As MRI is currently a novel tool, it would be key to include economic considerations of the role of MRI in the assessment of ACT regimens. If ^{129}Xe MRI informed ACT regimens are more effective, this potentially could influence clinical practice recommendations. Understanding if ACT regimens are having the intended effects over the longer term has potential to inform clinical training and practice.

As the current study focussed on the application of a ^{129}Xe imaging technology which is not widely available in clinical practice, to a common clinical problem, it focussed appropriately on the perspectives of physiotherapists. As this thesis recognises people with PCD and their caregivers as stakeholders in ACT research, it will be important to ensure future research actively involves these individuals. Work to develop a shared decision-making tool for ACT personalisation in bronchiectasis is ongoing (328), and one study which reported patient perspectives of ACTs recognised the importance of personalisation for patients (329). As such, the future work proposed should ensure the perspectives of patients and where appropriate carers are appropriately embedded within the study design. The proposed future work will require appropriate and effective knowledge translation to ensure findings are shared through diffusion, dissemination, and implementation, to ultimately influence policies which have the power to improve patient care.

7.6 Conclusion

Reflecting on the programme theory of this thesis (Figure 92): we have recognised the limitations of current markers of lung health (Chapter 2); used functional MRI to accurately assess lung health and impaired function in children and young people with PCD (Chapter 4); employed personalised ACT regimens (Section 5.3.3); guided by literature on how to personalise (Chapter 2); tailored by expert physiotherapists for individuals (Chapter 3); then we can use functional MRI to assess individual response to ACTs (Chapter 5); physiotherapists informed by functional MRI can modify regimens (Chapter 6). Further work can build on the findings of this study to assess if: MRI informed modifications are optimal for individuals (#9); so that respiratory infections and bronchiectasis can be prevented or minimised (#10); so that long term lung health and quality of life can be improved of people with PCD (#11); so that the burden of PCD on society can be reduced (#12).

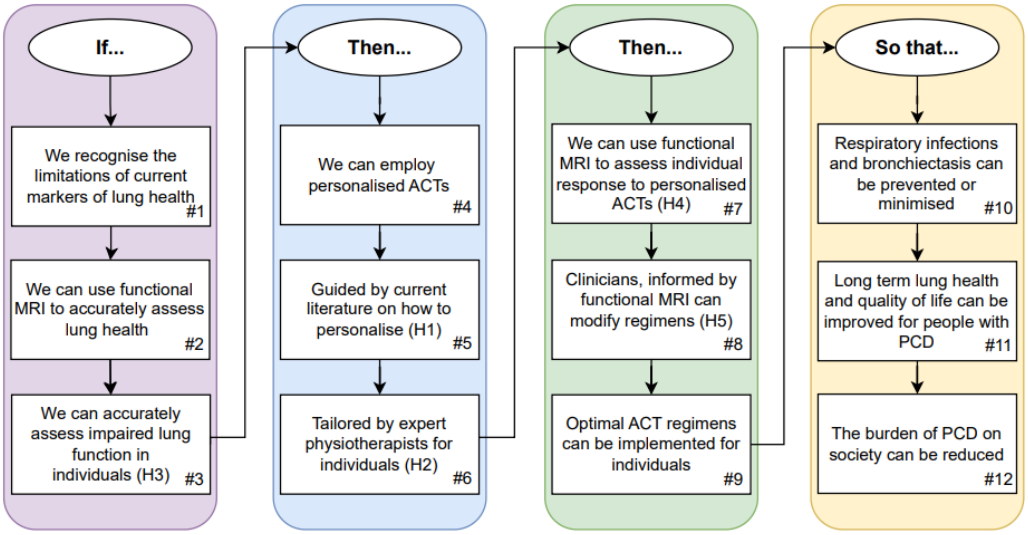


Figure 92: Programme theory for the thesis.

Chapter 8: References

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Appendix 1: Study protocol

1.1 Acronyms / Abbreviations

ACTs Airway clearance techniques

CF Cystic Fibrosis

PCD Primary Ciliary Dyskinesia

TLC Total Lung Capacity. An outcome marker measured from body plethysmography that describes how much gas is within the lung after a full inhalation.

FRC Functional Residual Capacity. An outcome marker measured from body plethysmography that describes how much gas is left within the lung after a normal exhalation.

HP MRI Hyperpolarised gas Magnetic Resonance Imaging. A specialised Imaging techniques involving the inhalation of a hyperpolarised noble gas, in this study either helium or Xenon.

^{1}H MRI Standard proton MRI

^{129}Xe MRI Hyperpolarised Xenon.

VV Ventilated volume. An outcome measure derived from HP MRI describing the percentage of the lung that is ventilated with hyperpolarised gas.

CV Co-efficient of Variance of inter-voxel pixel intensity. An outcome marker derived from HP MRI describing the degree of ventilation heterogeneity in the ventilated lung.

HRCT High resolution computed tomography. An imaging technique involving ionising radiation.

QOL-PCD The quality of life PCD questionnaire, a validated tool.

LTHT Leeds Teaching Hospitals NHS Trust

UoS University of Sheffield

Research Reference Numbers:

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FUNDERS Number: NIHR301558

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

Name (please print):

Position:

Chief Investigator:

Signature: Date:

Name: (please print):

1.2 Key study contacts

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Joint-sponsor(s)/co-sponsor(s)	Full contact details including phone, email and fax numbers of ALL organisations assuming sponsorship responsibilities as a joint- or co-sponsor/s (If applicable)
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1.3 Study summary

ACTs are recommended in Chronic Suppurative Lung Conditions. One such condition is PCD which is estimated to affect 5000 people in England. In PCD impaired mucociliary clearance causes retained mucus and airway obstruction leading to repeated infections, bronchiectasis and ultimately respiratory failure.

To maintain lung health, physiotherapists advise people with PCD to complete a personalised ACT regimen twice daily at home. It is important to ensure ACT regimens are effective, but current methods of assessing the effects of ACTs are limited.

This study will measure the effects of an ACT using HP MRI a highly sensitive tool and ^{1}H MRI, a potentially more widely available tool as a surrogate, to measure lung ventilation. Both types of MRI are radiation free, safe and well tolerated. HP MRI scans are abnormal in people with PCD even in mild disease.

This study will explore how physiotherapists make decisions about ACT regimen recommendations and if providing physiotherapists with the information from the MRI changes their recommendations. This research will provide, for the first time, accurate measurements of the short-term effects of ACTs and an understanding of how this information would influence clinical practice.

Study Title	Assessing the effects of personalised airway clearance regimens in young people with Primary Ciliary Dyskinesia.
Internal ref. no. (or short title)	Assessing Personalised Airway Clearance Techniques in PCD (ASPECT- PCD)
Study Design	Prospective convergent mixed methods
Study Participants	Physiotherapists and MDT clinicians working in PCD Children and young people with PCD
Planned Size of Sample	Patient participants 37 (ACT), 6 (non-ACT)
Follow up duration	N/A
Planned Study Period	20 months
Research Question/Aim(s)	1. What are the short-term effects of personalised ACT regimens on lung health in children and young people with PCD? 2. How do clinicians personalise ACT regimens and is this altered by the introduction of functional imaging?

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
HEE/ NIHR	Funding for the work is underwritten by HEE/NIHR Clinical Doctoral Research Fellowship of Miss Lynne Schofield, access to the imaging infrastructure and lung physiology lab is underwritten by the MRC POLARIS award and the NIHR research professorship award (Prof Wild).

1.4 Role of study sponsor and funder

This research project is sponsored by the Leeds Teaching hospitals NHS Trust. The sponsor is the organisation which is legally responsible for the organisation and management of the project.

This research project is funded by the NIHR CDRF grant for Miss Lynne Schofield ref: 301558 . This is the organisation which is providing the funding to support the research and will pay the Leeds Teaching Hospitals NHS Trust to ensure it is run and managed properly.

1.5 Roles and responsibilities of the study committee/management groups & individuals

Research team

The proposed research team comprises diverse expertise in clinical research, PCD, ACTs, mixed methods and qualitative research, and HP MRI. Each of the team holds Good Clinical Practice Certification.

Miss Lynne Schofield

Miss Schofield is a qualified respiratory physiotherapist with >16 years clinical experience in both adult and paediatric practice. She has been the lead physiotherapist in the North of England Paediatric PCD service since 2013. She has extensive experience in ACTs and physiotherapy reviews described in this proposal.

Prof Jim Wild

Prof Wild is a physicist with extensive experience in the use of hyperpolarised MRI techniques in lung imaging. He has GCP training and holds the position of MHRA Qualified Person for ^{129}Xenon polarisation.

Prof Dan Hind

Prof Hind is a Reader in Complex Interventions in the School of Health and Related Research. He is a graduate anthropologist with over ten years' experience of qualitative research. He is experienced in the use of cognitive task analysis methods and is currently preparing a systematic review of their use in healthcare contexts for publication.

Prof Sally Singh

Professor Singh is a leading respiratory physiotherapy clinical academic based between Coventry University and the University Hospitals of Leicester NHS Trust. As a respiratory physiotherapist, Professor Singh will bring valuable, experienced AHP insight to supervisory team, advising on the clinical interpretation and integration aspects of the study. Her guidance will also be key to successful dissemination and optimisation of impact.

Dr Noreen West

Dr West is a consultant paediatrician specialising in CF at Sheffield Children’s Hospital. She is the clinical lead for PCD at Sheffield and has experience of clinical use of HP MRI

Dr Eduardo Moya

Dr Moya is one of the lead consultants in the North of England Paediatric PCD Service at Leeds Teaching Hospitals in partnership with Bradford Teaching Hospitals.

Dr Evie Robson

Dr Robson is the lead consultants in the North of England Paediatric PCD Service at Leeds Teaching Hospital.

Dr Laurie Smith

Dr Smith is a research physiologist in the POLARIS team who has expertise of using HP MRI with young participants with PCD and CF.

Study Steering Groups

The study steering group will consist of the academic supervisors, at least one clinical supervisors and a member of the PPI group. Educational commitments and ill health may make attending every steering group meeting too onerous for one individual, as such, a rotational post system will be used allow any member of the PPI group to step in. Video conferencing may be used to minimising risks of cross infection.

Patient & Public Involvement Group

This study has originated from the research priority of a PPI focus group; "understanding and optimising the effects of ACTs in PCD", has provided the basis for my project and application. PPI members continue to support the project's use of MRI as a radiation free and sensitive tool and current clinical tools to assess the effects of ACT regimens. Miss Schofield has worked with PPI members throughout her application journey. Their guidance has been especially key on:

- Study design: concerns around exploring and managing the inclusion of a non-ACT group (recruitment, delay of airway clearance, participant perceived benefit compared to intervention).
- Duration of the study visit: felt to be acceptable for a single visit
- Guidance for participants on what to do between scan 2 and 3: key principles discussed and detail to be developed prior to phase 2 to optimise relevance.
- Recruitment: importance of educating potential participants and parents who may be unfamiliar with MRI to ensure they understand that the imaging method used in this project does not involve radiation exposure.

The PPI group includes young people with PCD and their parents and will meet at least biannually. Their advice will be sought on aspects including recruitment and participant

information. PPI members will be involved in dissemination through assisting with the content development and presentation of the research dissemination video. The PCD community will be updated on the study progress at their virtual meetings throughout the project.

Training will be provided for PPI members, with guidance and input from the “Leeds Young Research Owls” a young patient advisory group at Leeds Children’s Hospital and GenerationR, and the PCD family support group, to ensure the programme is comprehensive, timely, interactive and age-appropriate. This will include utilising resources from the testing treatments interactive website, interactive activities, peer support and an in-person/virtual visit the MRI unit in Sheffield to walk through the process and see examples of the POLARIS teams’ MR images. PPI members will be offered vouchers to acknowledge their time and input, those involved in data verification and video production will be offered appropriate publication co-authorship.

One young PPI member will also be involved in the verification of the qualitative data analysis, with additional appropriate training and recognition in the form of co-authorship will be offered for this. Following advice from my PPI group, the steering group will have rotational PPI member posts (both parent and young person) to allow participation of young members around their educational commitments. Additional support will be given to members in this role. I will regularly seek feedback through evaluations to shape and plan future meetings. Funding has been included to ensure PPI members can be reimbursed for their time, contributions and travel, or data reimbursement for virtual meetings.

Lucy Dixon, Chair of PCD Family Support Group feels this research is “extremely beneficial” to PCD patients, that it “fills an unmet need to better understand ACTs for PCD” and has the potential to impact other disease groups in the future.

Protocol contributors

The protocol has been written by Lynne Schofield with guidance from her supervisors Prof Wild and Prof Hind at the University of Sheffield and Anne Gowing, Research Governance Manager at Leeds Teaching Hospitals (sponsor).

The protocol has originated from the HEE/NIHR application of Lynne Schofield which was developed with her supervisory team. This application was reviewed by the HEE/NIHR panel.

Key words: PCD, airway clearance, MRI, physiotherapy

1.6 Study flow chart

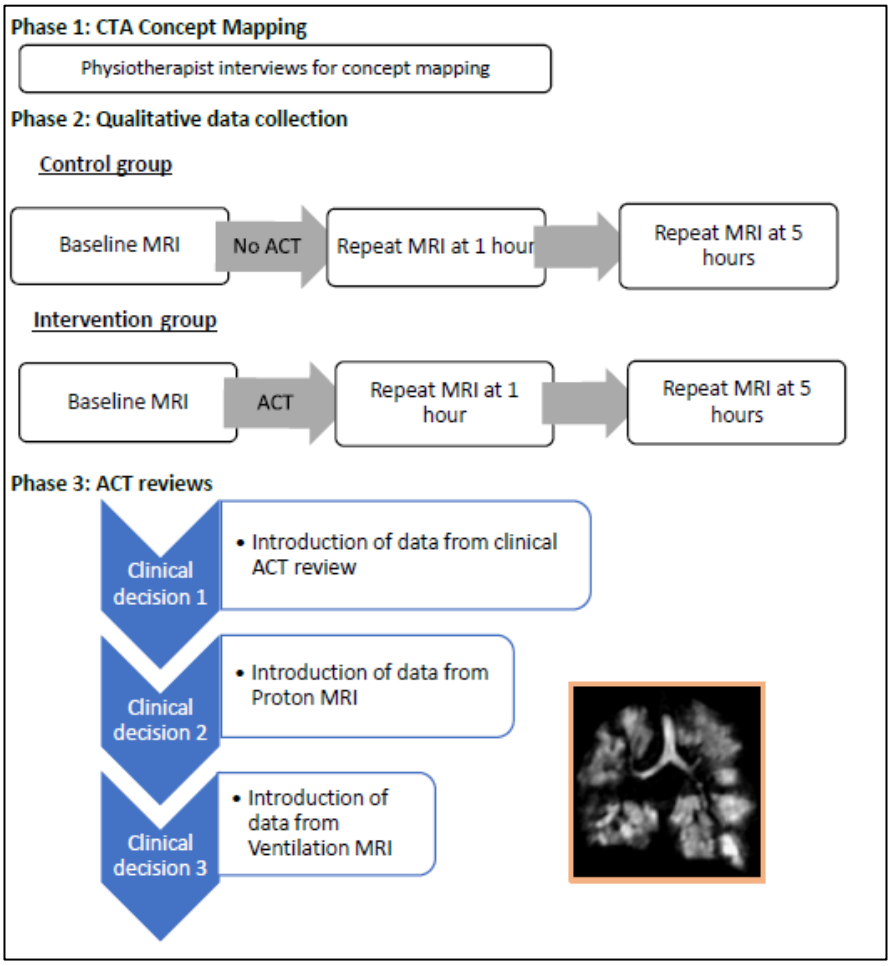

Figure 93: Study flow diagram

1.7 Study protocol

Full Project Title

Assessing the effects of personalised airway clearance regimens in young people with Primary Ciliary Dyskinesia.

1.7.1 Background

ACTs are commonly used interventions in Chronic Suppurative Lung Conditions. We currently have no reliable way of assessing if the regimens that physiotherapists advise patients to complete are improving their lung health.

Effective mucociliary clearance is essential to clear the respiratory tract of mucus and bacteria. Without this, retained mucus can plug small airways leading to repeated respiratory infections, bronchiectasis, and ultimately respiratory failure. Mucociliary clearance is impaired in chronic suppurative lung conditions including PCD, CF and Bronchiectasis.

PCD is estimated to effect over 5000 people in England. The importance of effective PCD management has been recognised by the NHS who funded the first national highly specialised PCD management service for children 8 years ago and recently for adults. In PCD, structural and functional abnormalities of the cilia cause impaired mucus clearance from birth, with symptoms including a persistent productive cough, rhinorrhoea, and recurrent lower respiratory tract infections. In PCD, bronchiectasis develops in childhood and progressive lung disease is seen; 80% of adults with PCD have bronchiectasis and 25% are in respiratory failure (requiring long-term oxygen or are listed for a lung transplant)[1]. Although further studies on long-term lung health in PCD are needed, the importance of effective management of PCD from an early age has been shown; an earlier diagnosis of PCD allowing for condition management to begin has been associated with a lower incidence of bronchiectasis and stabilisation of lung function[2].

A key component of managing conditions such as PCD are ACTs which aim to assist mucus clearance to prevent infections and maintain lung health. It is important to know if this major component of preventative care is achieving its objective. Additionally, my previous research affirmed that patients find undertaking ACT regimens twice-daily at home time-consuming and a psychological burden[3].

As it is now recognised that chronic suppurative lung conditions are diverse[4] and that no single ACT is superior[5] clinical practice has shifted from standardised to personalised ACT regimens[6]. ACT regimens are usually advised by physiotherapists with 3-monthly reviews to assess if the regimen is still suitable and effective[7]. However, there is a paucity of research into the effects of personalised ACT regimens and the tools commonly used to assess the effects of ACTs both in research and practice are limited. HRCT is the current gold standard for measuring structural lung disease progression but its use is limited due to ionising radiation exposure[8] which is especially an issue in the longitudinal assessment of children. HRCT is also limited to producing images which provide information on the structure rather than function of the lungs[4]. More commonly used tools are also limited; auscultation is subjective, chest X-rays and spirometry can be insensitive to changes in milder lung disease[4] and to treatment interventions[9].

1.7.2 Rationale

Firstly, this research will provide insight into the critical decision-making of clinicians who review and individualise patients ACT regimens. We will capture how experts use clinical cues, providing transparency to complex clinical decision-making, turning tacit knowledge into explicit knowledge.

Secondly, this research will provide accurate measurements of the short-term effects of personalised ACT regimens by sensitive structural and functional regional assessment of the two patho-physiological processes which they target; ventilation and mucus plugging[10]. We will also measure the same-day natural variation of lung function in PCD without an ACT intervention. This is a first in PCD and will provide repeatability data for this project and future research and will aid understanding of the potential reversibility of abnormalities seen in chronic suppurative lung diseases. To do this, functional HP MRI, a radiation-free, non-aerosol generating, well tolerated, functional, sensitive, and specific tool[11,12,13,14], will be used as a surrogate for gold standard HRCT. I will use two types of MRI, highly sensitive HP MRI will serve as the primary outcome measure and secondly, we will evaluate a free-breathing ^{1}H MRI method that is potentially a more widely available tool as a surrogate to measure lung ventilation. Parental input and opinion from my PPI work has specifically expressed support for using MRI as a radiation free outcome measure within research.

Finally, we will explore if providing clinicians with the findings of the MRIs changes their ACT regimen recommendations to patients. This project is highly relevant to other Chronic Suppurative Lung Conditions including CF. As ACTs are preventative self-management measures it aligns with the NHS 10-year plan.

1.7.3 Review of existing evidence

ACTs are very commonly advised to people with PCD[15], but a recent systematic literature search[16] identified only one published study pertaining to ACTs in PCD. Although a statistically significant improvement in lung function was demonstrated with two different ACTs[17] further evidence is needed.

The short-term benefits of completing an ACT compared to no-ACT have been demonstrated in CF[18], but the outcome of 5 Cochrane reviews have shown that no single ACT is universally superior[19] and personalisation is now seen in ACT regimens[6]. A framework for clinicians personalising ACTs has been developed from existing physiological evidence[20] and variation is seen in the ACTs patients use but the reasons for this variation remain unknown[6].

Clinical decision-making by physiotherapists is a recurrent, multifaceted and contextual process which incorporates biomedical and psychosocial elements[21]. Within respiratory physiotherapy research in this field is limited, with studies to-date focusing on acute inpatient settings rather than the long-term management of chronic suppurative lung conditions. This project will focus on the biomedical aspects of clinical decision-making which are relative to respiratory physiotherapy practice.

The IDEAL framework was proposed to improve the quality of research by providing a transparent method to introduce innovations and evaluate existing treatments[22]. As a stage 2a prospective development study, I will follow the principles of the IDEAL framework to provide transparency to the complex process of reviewing personalised ACTs allowing for iterative change and aiming towards and standardised processes for both future research and practice.

This study design has been shaped from knowledge of the constraints of existing ACT research; 4 recent large randomised controlled trials of ACTs have seen high dropout rates, standardised interventions and the outcome measures commonly used in ACT research have been insensitive to the effects of ACTs[23].

HP MRI can assess regional areas of ventilation and dynamically review changes in regional lung function in response to treatment in sequential scans. It has discriminatory power to detect disease and disease progression over time prior to routinely clinically used measures[11,12,13,14]. HP MRI is highly sensitive; in a pilot study collaboration between my host institutions, we showed for the first-time, signs of subclinical lung disease variation in the distribution of defects within the lungs using HP MRI in PCD patients with otherwise normal parameters[24]. Our pilot work with HP MRI, also showed ventilation defects in children with PCD that are not seen in healthy controls[24]. Although HP MRI repeatability data is available in the CF population[11,12,13,14], this work has not been done before in PCD. As such, the project will include a work-package on same-day repeatability of HP MRI in PCD to assess for natural variation without an airway clearance intervention (non-ACT group).

Changes in the homogeneity of ventilation following ACTs have been seen in work pioneered by my proposed host group using HP MRI following a single standardised ACT session in children with CF[25]. Similar findings have been demonstrated by other groups in children with CF[25,26], adults with COPD[27] and bronchiectasis[28], although these studies have used standardised ACT regimes.

^{1}H MRI is a more widely available tool which can provide both structural and some functional information from the lungs. Structurally, it has been shown to have performance outcomes similar to current clinical gold standard HRCT[4,29], with higher sensitivity to mucus plugging in paediatric non-CF bronchiectasis[30]. International trial databases show that no similar work is registered or currently being undertaken.

1.7.4 Research questions, aims and objectives

Research Questions

1. What are the short-term effects of personalised ACT regimens on lung health in children and young people with PCD?
2. How do clinicians personalise ACT regimens and is this altered by the introduction of functional imaging?

Aims

Quantitative research:

1. To measure lung health before and after airway clearance (compared to no intervention) in children and young people with PCD.
2. To compare the findings of two outcome metrics of lung ventilation pre and post airway clearance in children and young people with PCD.

Mixed methods research:

1. To explore how clinicians' make decisions when reviewing and personalising ACT regimens for children and young people with PCD.
2. To investigate how clinical decision-making changes with the introduction of functional imaging of the lungs.

Objectives

Quantitative:

1. To conduct a controlled before and after study to assess the short-term effects of an individualised airway clearance regimen on regional lung function versus no intervention over 4-hours using HP ventilation MRI and ^{1}H MRI in children and young people with PCD.
2. To assess the correlation and agreement between HP MRI and ^{1}H MRI pre and post ACT.

Mixed methods:

1. To undertake a knowledge elicitation exercise with physiotherapists using the critical decision method to produce a concept map to show how ACT regimens are personalised and assessed.
2. To carry out an experiment-like task using think aloud method to understand the clinical decision-making of clinicians when assessing the effects of personalised ACT regimens at three stages:

a) Watching a video-taped consultation of an ACT regimen review which provides data from existing clinical measures and tools.
b) With the introduction of proton MR images.

With the introduction of Ventilation MR images.

1.8 Plan of investigation

1.8.1 Study design

Quantitative:

The effects of ACTs on regional lung function will be accurately assessed using HP MRI. This component of the research will be a before and after study design with assessment pre-ACT (baseline), immediately post-ACT (1-hour post baseline) and at 5-hours post baseline. A non-ACT group will be used to assess lung health at the same time intervals to measure repeatability, assessing for any natural variability over time without an ACT.

Qualitative:

Semi structured interviews will be conducted in both phase 1 and phase 3:

- In phase 1, with paediatric PCD regional specialist physiotherapists, via Microsoft Teams
- In phase 3, with respiratory specialist physiotherapists and other members of PCD clinical care teams (e.g. consultants and nurse specialists) at 3 centres who provide care to children and young people with PCD. These interviews will either face to face or via Microsoft Teams as convenient to the participant.

For physiotherapists, the same participant may be interviewed in both phase 1 and 3 if they are in an appropriate clinical role.

Cognitive Task Analysis Methodology (CTA) is sometimes used in clinical settings[31] to uncover how experts make decisions in complex situations. This project will use a hybrid of three methods within the methodology of CTA; Critical Decision Method (CDM), Concept Mapping and Think Aloud Problem Solving[32] to turn tacit knowledge into explicit knowledge. Concept Mapping will be used to map clinicians' current cues for personalising ACT regimens. Think aloud methods will be supplemented with techniques from CDM including prompting and cues to identify points at which decisions pivot.

Mixed-methods:

This is a convergent mixed-methods, prospective development study with cases at the level of the individual patient, units of analysis being patient clinical data, physiotherapist reviews and MRI findings.

Eligibility criteria

Phase 1, Clinicians:

- Working in a highly specialised paediatric PCD service in the UK
- At least 5 years clinical experience, at least 2 years in respiratory.

Phase 2, People with PCD:

Inclusion criteria:

- Aged between 5 (the youngest age that a participant will be able to reliably lie still for the MRI) and 18 years.
- Confirmed PCD diagnosis as defined by the ERS Guidelines[33].
- Established on an ACT regimen for at least 3 months prior to recruitment.
- Under the clinical care of a PCD team at one of the participating centres (LTHT, BTH or SCH)

Exclusion criteria:

- A contraindication to MRI scanning (ferromagnetic metallic implants, pacemakers, pregnant) as per the MRI screening questionnaire.
- Resting oxygen saturation of <90% on air (using pulsed oximetry).
- Previous lung surgery.
- Those felt unable to follow the necessary steps required for HP MRI scans, for example, to hold their breath for 10 seconds.
- Currently being treated with antibiotics for a PCD exacerbation.

Phase 3, Clinicians:

- Working with people with PCD at one of the phase 2 recruitment centres (LTHT, BTH or SCH)
- At least 5 years clinical experience, at least 2 years in respiratory.

Sampling

Convenience sampling will be used for all phases of the study.

Sample size

Phase 1:

In phase 1, between 6 and 8 UK based PCD specialist physiotherapists will be recruited for in-depth knowledge elicitation interviews. As this is a homogenous group of experts this is an appropriate number for thematic saturation (235).

Phase 2:

For the purposes of sample size estimation, the primary outcome will be the change in lung function, as measured by the HP MRI image derived metric, the VV% area under the response curve from baseline to 5-hours post-baseline between the ACT group and the non-ACT group. As we have no information on the variability of this outcome measure in our proposed target population, calculations for the non-ACT group are based on unpublished work by the POLARIS group on reproducibility of ^{129}Xe MRI metrics (percentage lung ventilated volume – VV%) in patients of the same age with Cystic Fibrosis, where we established that a standardised difference or effect size of 1.6 or more is of clinical and practical importance. Thus with 37 subjects in the ACT group and 6 subjects in the non-ACT group we will have 90% power to detect a standardised difference or effect size of 1.6 or more between the ACT and non-ACT groups as statistically significant at the 5%-two-sided level.

Recruitment targets per centre:

Site	Number of patient participants
LTHT	18
BTHFT	17
SCH	8
Total	(37 ACT group, 6 no-ACT group)

Phase 3:

As ACTs are usually advised by physiotherapists, physiotherapist volunteers will be invited to participate in all phase 3 ACT reviews, with other MDT members invited to participate in two reviews each. Sample sizes of around 20 are appropriate for thematic saturation[34], with 37 data sets potentially available; cross-case analysis will be used to ensure thematic saturation is achieved.

Allocation to group (phase 2)

We will allocate patient participants to groups to similarly distribute confounding factors including: age, gender and disease severity indicated by number of exacerbations requiring antibiotics in the last 12 months. A self-audit process will be used during

recruitment and allocation to provide regulation to the process and allow adaptations as needed. Accurate reporting will be used to capture any necessary amendments.

Recruitment

Sample identification

Clinicians working PCD services will be identified through a professional network (phase 1) or clinical practice (phase 3) and invited to volunteer by an email distributed by LTHT's Research Governance Manager.

Potential patient participants will be identified during routine clinical practice. They or their parent/guardian (depending on their age), will be approached, and invited to participate by a member of their direct clinical care team.

Consent

All participants, and parents of potential participants aged under 16 will be provided with age-appropriate study information and ample time for questions will be provided. If they would like to take part, they will be invited to give consent, or assent as age appropriate, prior to their inclusion in the study. Language support will be available as required.

This will be documented on a paper consent form prior to starting the interview for those completed in person. For interviews completed via Microsoft Teams, consent will be taken via telephone or video, and recorded separately to the recording of the interview. Copies of completed telephone consent forms will be provided to each participant for their records.

1.9 Methodology

Phase 1, CTA Knowledge elicitation

The interview will use a four “sweep” method (see figure 2). Initially, the interviewee will be invited to suggest an appropriate example of where they have had to make a complex decision regarding the personalisation of an ACT regimen for a child or young person with PCD. This will form the basis of the rest of the interview, with the aim of eliciting information on how the clinician made this decision. The interviewee will be invited to provide an overview of the chosen example, which will be used in the subsequent sweeps to drill down into further detail.

The second sweep aims to provide a more detailed account of the chosen example, adding timelines, and identifying critical points within that timeline where the situation could have changed depending on the decision made at that time. If needed, during this second sweep, the interviewer will clarify points within the timeline so that this is a correct and detailed account ready for the next sweep.

The third sweep explores deeper into the chosen example, in terms of the interviewee's perceptions, expectations, goals, judgments and uncertainties about the example throughout the process, particularly at the critical points identified in the second sweep. The interviewee will be asked about the options they considered when making decisions, what information was needed in order to make this decision.

The final sweep asks questions such as "what if". This is an opportunity to take each point already discussed, and allow the interviewee to consider what they might have done differently, and if they had, what would have happened[32].

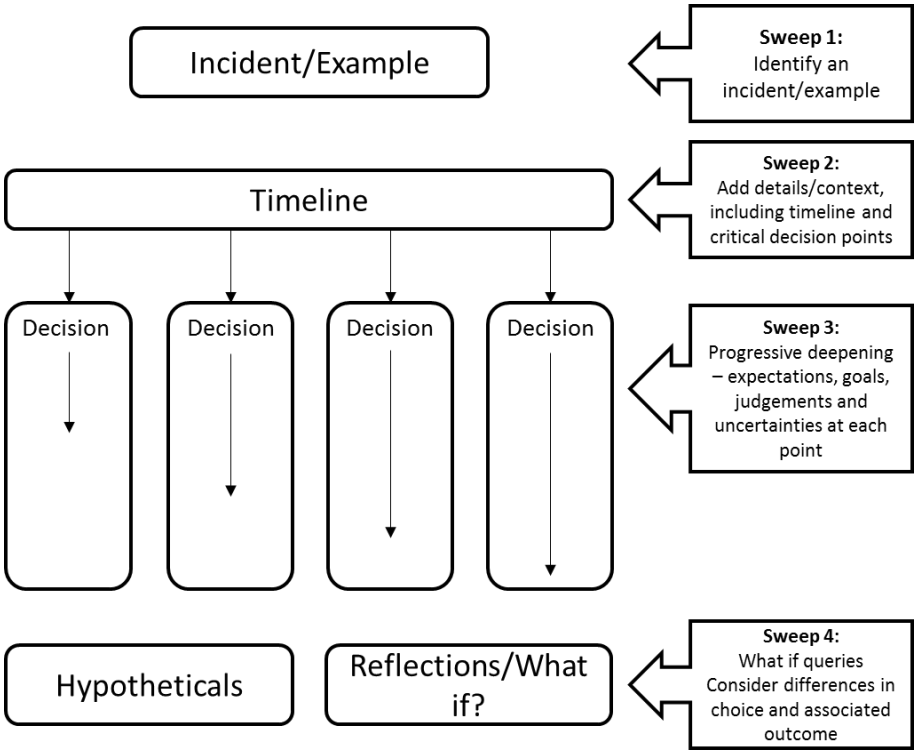

Figure 94: The Critical Decision Method procedure

Interviews will be recorded using an encrypted dictaphone, and clinician participants will be assigned a unique ID number, so that they are not identified by name on the recording. They will be made aware before beginning that it may be possible to identify them from some of the information that they give as part of the interview, but that data will be reported anonymously, and no identifiable information will be reported.

Interview schedule summary:

Sweep	Prompts
Introduction	Experience, professional training
1.Identify example	Overview case Decision to be made
2.Add details/context	Key decision shifts Cues What would newly qualified versus experienced physio notice?
3.Progressive deepening	Expectations Reminded of previous case? Goals Specifics and priorities Judgements Alternatives considered Uncertainties How right decision known?
4.What if queries	Differences and associated outcome If X changed what would outcome be? Anticipated novice errors.

A semi-structured interview script, or topic guide will be further developed and piloted with the help of Prof Hind and paediatric respiratory physiotherapist Dr Nicki Barker.

Demographic information will be collected for all participants and will include the following:

- Number of years of experience in respiratory care
- Number of PCD patients routinely under their care
- If they have a declared subspecialty interest in PCD

Interviews will be transcribed by the lead researcher, and will be imported into NVivo for processing and identification of themes. Transcripts will be coded and thematic analysis will be conducted. No identifiable information will be included in the transcripts, and participants will be identified on recordings by their study ID number only. Both transcripts and recordings will be stored in a locked cabinet, with recordings transferred to a password-protected, secure area of the University of Sheffield network drive. Transcripts will be anonymised and, in published material, vignettes that avoid speech mannerisms and context (through which participants may be identified) will be avoided. All transcripts and recordings will be stored securely by the researchers at the University of Sheffield for at least 5 years after publication.

The final output of the thematic analysis will be a concept map which will link, goals, cues, expectancies and actions.

Phase 2, Quantitative data collection – effects of intervention on lung function

All patient participants (from LTHT, BTH and SCH) will attend the MRI unit at the University of Sheffield (UoS).

All participants will have assessment by MRI at: baseline, 1-hour and 5-hours post baseline to measure the effects of ACTs immediately post ACT and at 4-hours post ACT based on the anecdotal recommended minimal interval between ACT regimens. Participants in the ACT group will complete their usual ACT regimen immediately after the baseline MRI scan. Those in the non-ACT group will be asked to not intentionally undertake any ACTs between the first and last MRI.

We will ask the referring clinician of all patient participants to provide clinical details from their history including details of their PCD diagnosis and recent health including lung function. Baseline spirometry and PCD-QOL will be performed at the study visit for to assist with defining the study population. As spirometry may cause inadvertent airway clearance it will be performed before the first MRI.

ACT group (n=37):

At the visit the following order of assessments will be used:

1. Height and weight
2. Baseline spirometry (lung function)
3. Oxygen saturations using an infrared light on a clip on their finger for approximately 30-60 seconds.
4. MRI-baseline (time 0 hours)
5. Physiotherapy ACT review and ACT completion
6. MRI- at 1 hour
7. QOL-PCD
8. MRI- at 5 hours

Non-ACT group (n=6):

At the visit the following order of assessments will be used:

1. Height and weight
2. Baseline spirometry (lung function)
3. Oxygen saturations using an infrared light on a clip on their finger for approximately 30-60 seconds.
4. MRI- baseline (time 0 hours)
5. MRI- at 1 hour
6. QOL-PCD
7. MRI- at 5 hours

Each MRI session will comprise of; 10-minute ^{129}Xe scan, 2-minute break, 20-minute ^{1}H scan. Participants will be free to move around between scan-sessions but will be asked to wear a simple pedometer to capture any unusual physical activity between

scans. A parent/guardian can come into the scanning room. The POLARIS team are experienced, having completed over 150 exams in children with CF with no adverse events, however the test will be terminated immediately if there is any subject distress.

Summary of imaging methods and quantitative metrics

The MRI scanning will take place on a whole body 1.5T MRI scanner equipped with transmit receive coils for ^{129}Xe Hyperpolarised gas MRI. The hyperpolarised gases will be manufactured under regulatory licence and administered via inhalation from a Tedlar plastic bag. The following images will be taken at each time point:

- ^{129}Xe HP breath-hold ventilation imaging of the lung performed at end inspiratory volume and at TLC using 3D steady state free precession sequences[37] with co-registered ^{1}H anatomical imaging[38].
- Structural proton ^{1}H MRI of the lung using a 3D gradient echo sequence acquired at two lung inflation levels FRC and TLC[36]
- Free breathing ^{1}H MRI using 75 seconds of free-breathing analysed using the PREFUL technique[39] including registration, low-pass filtering, and calculation of fractional ventilation.

The quantitative outcomes will include:

- From HP MRI:
    - Lung ventilated volume (^{129}Xe %VV)
    - The co-efficient of variance of ventilated image signal intensity (^{129}Xe CVmean).
- From free-breathing ^{1}H MRI:
    - Lung Ventilated volume (^{1}H %VV)
    - The co-efficient of variance of ventilated image signal intensity (^{1}H CVmean).

Airway clearance review

The participant will be asked to complete their usual airway clearance regime with the support of their parent or guardian. This may include taking a saline nebuliser, breathing techniques, the use of positive expiratory pressure device and coughing. The participant will be familiar with this routine as they will have been advised to complete it every day at home. - structure and content to be based on findings from phase 1 but anticipated to include; asking the participant questions about how they feel their ACT is working for them and auscultation palpation of chest wall. This assessment will be video recorded for phase 3.

Phase 3, CTA Experiment-like task

The process of clinicians observing a videoed ACT regimen review with the phased introduction of information from functional imaging is a familiar task with manipulated variables or an experiment-like task[32]. The stimulus, which more typically is a questionnaire will be structured with three stages of information introduction:

1. Video of ACT review and ACT completion
2. ^{1}H MR images
3. ^{129}Xe MR images.

The clinician will be asked to share their clinical decision-making using Think-Aloud Problem Solving (TAPS) during the session. The clinician participant will be invited to pause the video at any point and there will be a series of defined junctures after each new information introduction where the clinician will be invited to describe the clinical decision making that has been triggered. If sufficient time lapses without any comments whilst watching the video, standard prompts to keep talking will be given.

The interviews are anticipated to be all conducted as a 1:1. However for the 2 reviews per centre which are opened up to the wider MDT, clinician preference and convenience will be prioritised and as such these may potentially be conducted as an MDT group at the local centre. These interviews can be conducted either face to face or via Microsoft Teams dependent of participant preference and Covid-19 restrictions. Audio recordings and observational notes of all the reviews will be taken. Each clinician will observe only the reviews of patients under their care.

Data Analysis

Quantitative:

Primary outcome metrics will be derived from ^{129}Xe MR ventilation images which will be analysed using protocols developed locally to quantify the 3D images. Lung ventilated volume percentage (VV%) will be calculated by manual segmentation of the ^{129}Xe images using in-house tested and validated methods[40]. To measure ventilation heterogeneity, maps of coefficient of variation will be calculated as standard deviation/mean for an in-plane kernel of 3 x 3 pixels. Similar analysis will be applied to generate the ^{1}H MRI outcome measures from the surrogate maps of ventilation and perfusion derived from the ^{1}H PREFUL technique[39].

Correlation and agreement between the measures of ventilated volume at all three time points separately will be assessed using Spearman's rank-based correlation, and Bland-Altman plots of the difference in outcome versus the average analysis respectively. The inspiratory and expiratory ^{1}H anatomical images will be assessed for

mucus and air trapping by a paediatric radiologist (Dr Hughes) as a surrogate for structural CT

Qualitative:

Data for the concept maps will be managed using CmapTools[32]. Recordings from the clinical reviews will be transcribed and the qualitative data will be managed using NVivo software. A member of the PPI group will be invited to be involved in verification of the analysis. Transcripts will be coded and thematic analysis will be used to analyse the data. Analysis will be overseen by Professor Hind following the four-step Cognitive Task Analysis method[32].

1. Preparation: data is prepared, data records, review project issues and questions, plan first data sweep.
2. Structure data: data immersion and decomposition using coding, cataloguing, frequency counts and descriptive statistics.
3. Discover meaning: identify central issues and emergent threads of meaning using contrast and comparison of accounts, describing cues, questions, and emergent threads.
4. Identify/represent key findings: communicating findings through incident accounts, timelines, and concept maps.

A concept map will be produced to represent and convey the clinical cues that physiotherapists consider when personalising and reviewing an ACT regimen. This is anticipated to include baseline spirometry, auscultation, quality of life, exacerbation frequency and patient/parental perspectives, for example, “ease of sputum clearance”.

Integrated analysis:

Any iterative changes to the programme theory occurring during this prospective development study will be reflectively mapped[22], for example change to an ACTs regimen due to learning from earlier participants. A map of the crosswalking[42] between the units of analysis will be developed with data integrated using joint display tables[43,44] and a case-by-case structured final report.

1.10 Safety assessment and reporting

1.10.1 General MRI aspects

MRI studies are performed at our facility by a dedicated team of radiographers and MRI physicists for a variety of clinical and research indications. Subjects will be excluded if there are any concerns about the possible presence of MR incompatibility. This will be

assessed using a locally designed safety questionnaire and in accordance with local protocol.

A baseline oxygen saturation is recorded prior to and during the MRI to ensure the SpO2 remains at safe levels. The subject's heart rate and oxygen saturation will be monitored continuously during the MR studies using MR compatible monitoring equipment.

1.10.2 ^{129}Xe MRI

All persons handling these gases have held ethics approval for clinical lung imaging research with inhaled xenon and helium have had formal training in their use. Prof. Wild holds MHRA approval as a qualified person for the manufacture of both gases as IMPs and specials. In studies in over 1000 patients and volunteers over the last 14 years we have had no adverse events reported related to the use of either gas. In 2014 we received MHRA licence for manufacturing the gases for routine clinical imaging referral.

Minor side effects of xenon inhalation include transient euphoric symptoms, nausea and headache, lasting for few seconds. At the doses we plan to use the anticipated anaesthetic effect of Xenon is estimated to be negligible, as demonstrated in both volunteers and patients including children[45,46].

1.10.3 Infection prevention

Infection control requirements for all apparatus and personal protective equipment current guidance will be strictly adhered to, and no more than 1 PCD patient/family will be scheduled within a day.

1.10.4 Event reporting

A Serious Adverse Event (SAE) is defined as any adverse event or adverse reaction that:

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

SAEs will be reported to NHS REC, where in the opinion of the Chief Investigator the event was:

- “related”: that is, it resulted from administration of any of the research procedures; and
- “unexpected”: that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of SAEs that are both related and unexpected will be submitted to the NHS REC within 15 days of the CI becoming aware of the event, using the MHRA SAE Form. Reports of SAEs to the REC will be copied to the Sponsor R&D Coordinator.

Unexpected findings which are considered to have significant implications for safe clinical care of the subjects will be transmitted as soon as practical to the clinical team responsible for their usual clinical care, without waiting for completion of trial procedures.

1.10.5 Subject withdrawal, breaking the blind and trial stopping/discontinuation rules

This is not a blinded study. Subjects can withdraw from the study at any point. This will not affect their clinical care. An attempt to find a replacement subject will be made if the study remains within the recruitment window.

1.10.6 Quality control & assurance

Prof. Wild will oversee the collection and analysis of imaging data. Lynne Schofield will have overall responsibility for the study and will supervise, monitor, and review work undertaken, data collated and analysed.

Project plan

Our aim is to have recruited an initial two clinician participants within the first month of beginning the study and four patient participants in the first month of phase 2 (study month 4). 43 patient participants should be recruited by the end of the study enrolment period (16 months post study start date). If our recruitment falls short, a meeting will be held to discuss the feasibility of recruiting all subjects within the set time frame and either target number of subjects or dedicated clinic time may be revised accordingly.

Table 43: Study landmarks

Month	Target
0	Phase 1- Begin physiotherapy clinician recruitment
3	Phase 1- physiotherapist interviews completed
4	Phase 2 -Begin patient recruitment

Month	Target
6	Phase 3- clinician ACT reviews commenced
9	Phase 2 milestone- 18 Patients recruited
16	Phase 2 - pre and post ACT assessments completed
20	Phase 3- clinician ACT reviews completed
30	Write up complete and dissemination of research

1.11 Project management

Clinical fellow Lynne Schofield will take on the clerical tasks associated with the study with the help of a dedicated local MRI research administrative staff.

Dr's West, Moya and Robson will oversee the clinical care of patients in clinic and contribute towards identifying patients eligible for recruitment.

Prof Wild will oversee the MRI department gas polarisation and leads the POLARIS physics team involved with generating hyperpolarised xenon gas and acquiring the MR images. Miss Schofield as part of a team of imaging experts will be responsible for quantitative image analysis.

Experienced consultant respiratory radiologists will undertake the radiological reporting of the MRI scans. A paediatric specialist will report the paediatric images.

Prof Hind will provide additional academic supervision to Miss Schofield and guidance to the project and specifically to qualitative and mixed methods related matters.

The investigators will have regular meetings as a research team and a 12 weekly meeting of all investigators and research staff will be carried out.

Clinical fellow Lynne Schofield will have overall responsibility for the study and will supervise, monitor, and review work undertaken, data collated and analysed.

The study steering group will consist of the academic supervisors, at least one clinical supervisor and a member of the PPI group. Educational commitments and ill health may make attending every steering group meeting too onerous for one individual, as such, a rotational post system will be used allow any member of the PPI group to step in. Video conferencing may be used to minimising risks of cross infection. An advisory group will be met with as needed and update by written report biannually, including:

- Dr David Hughes, Radiologist at SCH with experience of the clinical interpretation of Lung MRI.
- Professor Stephen Walters, Professor of Statistics and Clinical Trials at UoS
- Dr Nielsen, Consultant Paediatrician, Danish National Paediatric Pulmonary Service
- Dr Nikki Barker, Specialist Paediatric Respiratory Physiotherapist at SCH

Leeds Teaching Hospitals experienced research finance department will oversee the financial management of the project, provide quarterly assessments and regular financial reports. I will also be guided and supported firstly by the R&I Manager of LTHT as needed.

The project progress, risks and success will be reviewed at each steering group meeting.

Risk	Probability 1=low 5=high	Severity 1=low 5=high	Risk score (Probability x Severity)	Mitigation
Recruitment	2	5	10	PPI advice on recruitment methods, age-appropriate information delivery and content. 3 recruitment sites to increase available population
Retention of clinicians	1	3	3	MRI training package for clinicians will be developed to minimise impact of introducing new clinicians
Study visit attendance	4	3	12	Transport to visits. Phone/text appointment reminders.
Time delays	4	3	12	Additional time and flexibility built into timetable
Equipment changes	1	2	2	Identical scanner at the Northern General Hospital run by the same team, as backup
Equipment failure	2	2	4	Additional time and flexibility built into timetable. Identical scanner at the Northern General Hospital available if needed
Data loss	2	1	2	Image data managed by university. Regular automated hard drive back-ups
PPI dropout	3	3	9	Proactive rolling programme planned. Recognition of contributions.

1.12 Ethical and regulatory considerations

1.13 Assessment and management of risk

MRI related

Risks involving MRI studies have been minimized and avoided where possible as per Section 5.15. Any subject who suffers a significant side event from the imaging modalities used will be withdrawn from further MRI studies.

The MRI is a non-routine imaging test and it is reiterated here that unexpected findings which are considered to have significant implications for safe clinical care of the subjects will be transmitted as soon as practical to the clinical team responsible for their usual clinical care, without waiting for completion of trial procedures.

Clinician participants

It is felt that there are no perceived risks involved in this research, to either the participants or the researchers in addition to usual job roles. Participants may be exploring potentially sensitive topics, where the decisions they made at that time are being discussed in relation to an outcome. However, all data will be anonymised and participants will not be identifiable in any publications from the responses they give.

Other considerations

Recruitment to a study through clinical pathways can lead to the conception that not taking part in the study may lead to poorer clinical care for the patient. We will stress in discussions with potential subjects that their clinical care will continue as normal, irrespective of their decision about whether to partake in the trial. This will be reflected in the participation information sheet. Potentially useful clinical information may be gained for those involved in the study which may allow care to be adjusted in light of the MRI findings.

It is hoped that this study will provide useful information for further research which may in the longer term provide valuable information on the efficacy of airway clearance interventions- a time consuming and key part of respiratory care.

Subjects will be inconvenienced by the time required for the scans and will be remunerated with travel and food expenses for each of their attendances.

1.14 Research ethics committee (REC) and other regulatory reviews & reports

Before the start of the study, a favourable opinion will be sought from a REC for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

Regulatory Review & Compliance

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. Different arrangements for NHS and non NHS sites are described as relevant.

Amendments

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

If applicable, other specialist review bodies (e.g. Confidentiality Advisory Group (CAG)) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

Amendments also need to be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

Any amendments will be guided by the CI, academic supervisors, and steering group. The CI will be responsible for the decision to make the amendment and if the amendment is substantial. Notification of any amendments will be made/approval sought to the relevant stakeholders including REC and R & D. Details of any amendments will be kept within the study documentation.

Peer review

This study has been peer reviewed as part of the NIHR CDRF application process of Miss Lynne Schofield

Protocol compliance

Prof Wild will oversee the MRI department gas polarisation and leads the POLARIS physics team involved with generating hyperpolarised xenon gas and acquiring the MR images. Miss Schofield as part of a team of imaging experts will be responsible for quantitative image analysis.

Experienced consultant respiratory radiologists will undertake the radiological reporting of the MRI scans. A paediatric specialist will report the paediatric images.

Prof Hind will provide additional academic supervision to Miss Schofield and guidance to the project and specifically to qualitative and mixed methods related matters.

Lynne Schofield will have overall responsibility for the study and her academic supervisors will oversee, monitor, and review work undertaken, data collated and analysed.

Data protection and patient confidentiality

Imaging will be stored in DICOM format. Data will be analysed on an imaging processing workstation within the University of Sheffield MRI unit which resides within the NHS network and is connected to the Sheffield Teaching Hospitals (STH) NHS trust PACS system. If files are transferred off these workstations, the images will be pseudo-anonymised and transferred in de-identified DICOM format to the POLARIS group XNAT server which resides on the UoS high performance computing cluster. The formats and software used will facilitate data sharing and compatibility both within the research team and any future collaborators to ensure long-term data validity. Derived data will be collated and stored in Mat lab, Microsoft Excel, Statistics Package for the Social Scientist (SPSS), Graph pad Prism and Microsoft Word files. We will use unique study identifiers to anonymised patient data.

Only information required for the study will be collected. Electronic data linking personal identifiable data and the pseudo-anonymisation key will be encrypted and stored only on the UoS computers within locked rooms of the UoS MRI Unit. Any hard-copies of data with personal identifiable information will be kept within the Study Site File, which will be kept securely within the department. Anonymised data may be shared and transferred within the research team electronically. All data stored on the University networked computers will be automatically backed up by the University servers and saved for a minimum of 10 years. Imaging data will be labelled with unique study identifiers and also backed up. Participants will be offered the option to be followed up beyond the one year follow up for future studies, though can withdraw their consent for follow up at any time.

1.15 Methods for disseminating research results

It is anticipated that this study will result in the generation of 2-4 high quality publications in the respiratory and MRI literature and conference abstracts at respiratory meetings (European Respiratory Society, American Thoracic Society).

Outputs during the fellowship:

- Abstracts, posters, and presentations at key international conferences such as ERS
- Articles in peer-reviewed journals such as Thorax and ERJ, with funding for open-access
- Presentations at NIHR trainee's meetings
- A specialised physiotherapists knowledge map
- A research video summary to raise the public profile of the study and engage audiences for future research.
- Articles and presentations through social media platforms, newsletters, and family days.
- Age-appropriate output guided by PPI work, for example, a participant blog.

1.16 Strategy for taking the work forward if the project is productive

This research will be the first phase of a larger package aiming to optimise the effects of ACTs and maintain long-term lung health. It will provide novel insight; for the first time, accurate measurements of the short-term effects of ACTs and an understanding of how this information would influence clinical practice. Subsequent steps will be based on the outcomes of this project and may involve:

- Assessing the longer-term effects of ACTs with both regionally specific and sensitive imaging and key clinical outcomes including Quality of Life, exacerbation rates, and hospital admissions.
- Comparison of imaging guided ACT regimen with standard ACT regimens.
- Comparison of the short-term effects of a single ACT versus an exercise session on regional ventilation and mucus clearance.

This work will have clinical potential in PCD and other Chronic Suppurative Lung Conditions, such as Cystic Fibrosis in which ACTs are commonly used.

HP MRI is a specialist tool, and phase 2 will enable understanding of the comparative role of surrogate methods for estimating lung ventilation from standard ^{1}H MRI. With new knowledge, any future clinical recommendations beyond this fellowship will require appreciate of costs, training requirements and availability of resources. In longer-term research beyond this project will involve health economists to assess the financial impact of any clinical recommendations.

Beyond this fellowship, this will be developed into a toolkit to guide less experienced clinicians and potentially patients through ACT personalisation Clinicians and patients will be consulted as stakeholders to find optimal dissemination pathways and to measure the impact of this educational material. Funding for this will be applied for towards the end of the fellowship.

1.17 Intellectual property arrangements

Intellectual property (IP) including publications, conference presentations, patient and public communications will be protected by automatic copyright. No commercial IP is anticipated to arise during this project. Should something arise related to the imaging technology it will reside with the POLARIS group at the UoS who have established successful systems for IP capture and management. If new IP is generated it will be captured via UoS Business Managers working alongside the University Commercialisation Team within Research & Innovation Services (R&IS).

1.18 References

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Appendix 2: NHS HRA approval letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Miss Lynne Schofield
2 Park Lane
2nd Floor (Paediatric Physiotherapy)
Leeds
LS3 1ES

Email: approvals@hra.nhs.uk

09 July 2021

Dear Miss Schofield

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Assessing the effects of personalised airway clearance regimens in children and young people with Primary Ciliary Dyskinesia.**
IRAS project ID:	**299027**
Protocol number:	**N/A**
REC reference:	**21/SC/0197**
Sponsor	**Leeds Teaching Hospitals**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Appendix 3: Scoping review search strategy

3.1 Medline

Performed 22/6/21

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to June 23, 2021>

1 *Lung/pp [Physiopathology] 11218

2 *Lung Diseases/th [Therapy] 2264

3 Bronchiectasis.ab,ti. 9846

4 *Bronchiectasis/ 5739

5 *Bronchi/ 26904

6 Cystic Fibrosis.ab,ti. 45733

7 *Cystic Fibrosis/ 30641

8 Primary Ciliary Dyskinesia.mp. 1486

9 *Ciliary Motility Disorders/ 898

10 Kartagener Syndrome/ 1393

11 ((chronic and suppurative) adj3 ((pulmonary or lung) adj2 disease*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 225

12 Impair* ciliary function.mp. 30

13 *Mucociliary Clearance/ 1465

14 Airway clearance.mp. 966

15 Respiratory Therapy/ 6809

16 Physical Therapy Modalities/ 38006

17 Chest Physiother*.ab,ti. 889

18 Respiratory Therap*.ab,ti. 2615

19 "Percuss*".ab,ti. 4055

20 "Vibrat*".ab,ti. 81208

21 "Oscillat*".ab,ti. 106395

22 "Manual technique*".ab,ti. 934

23 "Manual therap*".ab,ti. 2566

24 "Breathing technique*".ab,ti. 640

25 "Breathing exercise*".ab,ti. 1118

26 Active cycle*.ab,ti. 142

27 Autogenic Drainage.ab,ti. 62

28 Forced expiratory technique.ab,ti. 21

29 Positive expiratory Pressure.ab,ti. 349

30 OPEP.ab,ti. 64

31 Acapella.ab,ti. 43

32 Aerobika.ab,ti. 12

33 Cornet.ab,ti. 78

34 Flutter.ab,ti. 8922

35 Lung flute.ab,ti. 7

36 PEP.ab,ti. 8177

37 High frequency chest wall oscillation.ab,ti. 89

38 mucoactive.ab,ti. 177

39 mucolytic*.ab,ti. 1696

40 Precision Medicine/ 20720

41 (Personalis* or personaliz*).ab,ti. 57205

42 Deci*.ab,ti. 547024

43 (Individualis* or individualiz*).ab,ti. 69951

44 choice*.ab,ti. 351423

45 choose*.ab,ti. 47346

46 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 99218

47 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 258322

48 40 or 41 or 42 or 43 or 44 or 45 1008641

49 46 and 47 and 48 117

50 *Lung/pp [Physiopathology] 11218

51 *Lung Diseases/th [Therapy] 2264

52 Bronchiectasis.ab,ti. 9846

53 *Bronchiectasis/ 5739

54 *Bronchi/ 26904

55 Cystic Fibrosis.ab,ti. 45733

56 *Cystic Fibrosis/ 30641

57 Primary Ciliary Dyskinesia.mp. 1486

58 *Ciliary Motility Disorders/ 898

59 Kartagener Syndrome/ 1393

60 ((chronic and suppurative) adj3 ((pulmonary or lung) adj2 disease*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 225

61 Impair* ciliary function.mp. 30

62 *Mucociliary Clearance/ 1465

63 Airway clearance.mp. 966

64 Respiratory Therapy/ 6809

65 Physical Therapy Modalities/ 38006

66 Chest Physiother*.ab,ti. 889

67 Respiratory Therap*.ab,ti. 2615

68 "Percuss*".ab,ti. 4055

69 "Vibrat*".ab,ti. 81208

70 "Oscillat*".ab,ti. 106395

71 "Manual technique*".ab,ti. 934

72 "Manual therap*".ab,ti. 2566

73 "Breathing technique*".ab,ti. 640

74 "Breathing exercise*".ab,ti. 1118

75 Active cycle*.ab,ti. 142

76 Autogenic Drainage.ab,ti. 62

77 Forced expiratory technique.ab,ti. 21

78 Positive expiratory Pressure.ab,ti. 349

79 OPEP.ab,ti. 64

80 Acapella.ab,ti. 43

81 Aerobika.ab,ti. 12

82 Cornet.ab,ti. 78

83 Flutter.ab,ti. 8922

84 Lung flute.ab,ti. 7

85 PEP.ab,ti. 8177

86 High frequency chest wall oscillation.ab,ti. 89

87 mucoactive.ab,ti. 177

88 mucolytic*.ab,ti. 1696

89 Precision Medicine/ 20720

90 (Personalis* or personaliz*).ab,ti. 57205

91 Deci*.ab,ti. 547024

92 (Individualis* or individualiz*).ab,ti. 69951

93 choice*.ab,ti. 351423

94 choose*.ab,ti. 47346

95 "select*".ab,ti. 2027092

96 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 6199218

97 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 258322

98 89 or 90 or 91 or 92 or 93 or 94 or 95 2906679

99 96 and 97 and 98 313

3.2 Embase

Search performed 24/6/21

Embase <1974 to 2021 June 23>

1 *chronic lung disease/2554
2 *chronic obstructive lung disease/ 73077
3 *bronchiectasis/ 6476
4 *cystic fibrosis/ 49453
5 ciliary dyskinesia/ 2887
6 kartagener syndrome/1380
7 Bronchiectasis.ab. 14896
8 Cystic fibrosis.ab. 58218
9 Primary Ciliary Dyskinesia.mp. 2441
10 ((chronic and suppurative) adj3 ((pulmonary or lung) adj2 disease*)).mp. 339
11 Impair* ciliary function.mp. 40
12 *Mucociliary Clearance/ 1596
13 Airway clearance.mp. 2243
14 *Respiratory care/ 1498
15 *Physiotherapy/ 27160
16 Chest Physiother*.ab. 1397
17 Respiratory Therap*.ab. 4247
18 Percuss*.ab. 5611
19 "Vibrat*".ab. 67094
20 "Oscillat*".ab. 102773
21 "Manual technique*".ab. 1270
22 "Manual therap*".ab. 3198
23 "Breathing technique*".ab. 1005
24 "Breathing exercise*".ab. 1731
25 "Active cycle*".ab,ti. 242
26 "Autogenic Drainage".ab. 127
27 "Forced expiratory technique".ab. 30
28 "Positive expiratory Pressure".ab. 538

29 OPEP.ab. 103

30 Acapella.ab. 108

31 Aerobika.ab. 6

34 #33 AND #32 AND #31

1

32 Cornet.ab. 110

33 Flutter.ab. 12432

34 "Lung flute".ab. 23

35 PEP.ab. 10575

36 "high frequency chest wall oscillation".ab. 185

37 mucoactive.ab. 254

38 mucolytic.ab. 1678

39 personalized medicine/ 51608

40 (Personalis* or personaliz*).ab. 78064

41 deci*.ab. 724204

42 (Individualis* or individualiz*).ab. 97437

43 (choice* or choose*).ab. 492717

44 medical decision making/ 88785

45 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 164706

46 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 239184

47 39 or 40 or 41 or 42 or 43 or 44 1383273

48 45 and 46 and 47 394

3.3 Cochrane library

Search run 25/6/21 found 96

(Bronchiectasis OR "Cystic Fibrosis" or "Chronic suppurative lung disease" or "primary ciliary dyskinesia"):ab AND ("Airway clearance" or physiotherap* or "respiratory therap*"):ab AND (Personal* or individual* or deci* or choice* or choos*):ab

3.4 Web of science

Search run 25/6/21

33 #30 OR #29 OR #28

32 #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8

31 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

30 AB=(choice* OR choose*)

29 AB=(Individualis* or individualiz*)

28 AB=(Personalis* OR personaliz*)

27 AB=Mucolytic*

26 AB=Mucoactive

25 AB="High frequency chest wall oscillation"

24 AB="Lung flute"

23 AB=Cornet

22 AB=Aerobika

21 AB=Acapella

20 AB=OPEP

19 AB="Positive expiratory Pressure"

18 AB="Forced expiratory technique*"

17 AB="Autogenic Drainage"

16 AB="Active cycle*"

15 AB="Breathing exercise*"

14 AB="Breathing technique*"

13 AB="Manual therap*"

12 AB="Manual technique*"

11 TS="Respiratory Therap*"

10 TS=Chest Physiother*

9 TS="Airway clearance"

8 KP=Mucociliary Clearance

7 TS=Impair* ciliary function

6 TS="chronic suppurative lung disease*"

5 TS="chronic suppurative pulmonary disease*"
4 TS=Kartagener*
3 TS="Primary Ciliary Dyskinesia"
2 TS="Cystic Fibrosis"
1 TS=Bronchiectasis

3.5 Cinahl (EBSCO)

Search run 24/6/21

#	Query	Results
S43	(S35 OR S36 OR S37 OR S38 OR S39) AND (S40 AND S41 AND S42)	35
S42	S35 OR S36 OR S37 OR S38 OR S39	272,538
S41	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34	19,845
S40	(S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8)	9,910
S39	AB (choice* or choose*)	84,371
S38	AB (Individualis* or individualiz*)	25,181
S37	AB Deci*	164,663
S36	AB (Personalis* or personaliz*)	14,715
S35	(MH "Individualized Medicine")	5,735
S34	AB mucoactive	30
S33	AB mucolytic*	202
S32	AB High frequency chest wall oscillation	51
S31	AB lung flute	9
S30	AB Cornet	11
S29	AB flutter device	46
S28	AB Aerobika	8
S27	AB Acapella	27
S26	AB "PEP"	1,050
S25	AB OPEP	10
S24	AB positive expiratory pressure*	2,104
S23	AB forced expiratory technique	21

S22	AB autogenic drainage	31
S21	AB active cycle*	263
S20	AB breathing exercise*	1,011
S19	AB breathing technique*	625
S18	AB manual therap*	2,834
S17	AB manual techniq*	1,201
S16	AB oscillat*	4,592
S15	AB vibrat*	4,945
S14	AB percuss*	673
S13	AB respiratory physiotherap*	301
S12	AB chest physiotherap*	342
S11	AB airway clearance	597
S10	(MH "Mucociliary Clearance")	497
S9	(MH "Chest Physical Therapy")	533
S8	TX Impair* ciliary function	7
S7	AB chronic suppurative lung disease*	12
S6	AB ((chronic and suppurative) adj3 ((pulmonary or lung) adj2 disease*))	0
S5	TX kartagener syndrome	64
S4	TX primary ciliary dyskinesia	294
S3	AB Cystic Fibrosis	5,808
S2	AB Bronchiectasis	1,472
S1	(MH "Bronchiectasis") OR (MH "Ciliary Motility Disorders") OR (MH "Cystic Fibrosis/TH/RH") OR (MH "Lung Diseases, Obstructive/PP/TH/RH")	4,271

Appendix 4: Cognitive task analysis interview schedule

Sweep	Estimated time	Prompts	RPDM constructs	Crandall et al
Opening questions	5 minutes	This is about expert decision making. If we were to describe how we know you are an expert, would it be by years in a certain specialty, or are outcome rates measurable in your domain? E.g. number of cases.		
1 – Identify an incident/example	10 minutes	• Need to know if this is a routine/typical, challenging, or rare event/anomaly. • Choose a single episode with an appropriate timeframe, preferably not over a period of years • What was the decision to be made? • What was the desired endpoint? • Unstructured thoughts/overview of case “Tell us about….” • Would be of interest to know ultimately what happened with the patient.		
2 – Add details/context, including timeline and critical decision points	10 minutes	• Timeline – i.e. before, during, after consultation with patient • Go over the sequence of events “Do I have the sequence and the details right so far?” • Where would you say the key decisional shifts were? • Where were you looking at things that someone straight out of a		

		medical degree should have known? • Which cues would only be obvious to someone with a lot of experience?		
3 – Progressive deepening – expectations, goals, judgements and uncertainties	30 minutes	• What were you noticing?	Relevant cues	Cues
		• What information did you use in making this decision or judgment? • How and where did you get this information, and from whom? • What did you do with the information?		Information
		• Were you reminded of any previous experience? • What about that previous experience seemed relevant for this case?	Expectancies	Analogs
		• Does this case fit a standard or typical scenario? • Is it a type of event you were trained to deal with?	Are expectancies violated?	Standard operating procedures
		• What were your specific goals and objectives at the time? • What was most important to accomplish at this point in the incident?	Plausible goals	Goals and priorities
		• What other courses of action were considered or were available to you? • How was this option chosen or others rejected? • Was there a rule that you were following in choosing this option?	Actions	Options
		• What specific training or experience was necessary or helpful in making this decision?		Experience
		• Suppose you were asked to describe the situation to someone else at	Reassess	Assessment

		this point. How would you summarise the situation?	situation	
		• Did you imagine the possible consequences of this action? • Did you create some sort of picture in your head? • Did you imagine the events and how they would unfold?	Mental simulation of action	Mental models
		• What let you know that this was the right thing to do at this point in the incident? • How much time pressure was involved in making this decision? • How long did it take to actually make this decision?	Will it work?	Decision making
		• Did you seek any guidance at this point in the incident? • How did you know to trust the guidance you got?		Guidance
4 – "What-if" queries, Consider differences in choice and associated outcome	30 minutes	• If a novice had been in charge at this particular point in the incident, what type of error might she or he have made and why? • Would they have noticed what you noticed? • Would they have known to do X?		Expert-novice contrasts
		• If [key feature] of the situation had been different, what impact would it have had on your decision/assessment/actions/plan?		Hypotheticals
		• What training might have offered an advantage in this situation?		Experience
		• What knowledge, information, or tools/technologies could have helped?		Aids

Appendix 5: Participant study information sheets

5.1 Information for clinicians in phase 1 (cognitive task analysis interviews in Chapter 3)

NHS
The Leeds Teaching Hospitals
NHS Trust

The University Of Sheffield.

Patient Information Sheet: Clinicians in Phase 1

Title of project: Assessing personalised airway clearance techniques in PCD
Name of researcher: Lynne Schofield
Sponsor: LTHT

Study lead: Miss Lynne Schofield
Address, Paediatric Physiotherapy, 2 Park Lane, 2nd Floor, Leeds LS31ES
Phone number: 0113 3920609, email lynneschofield@nhs.net

You can keep this Information Sheet and if you take part you will be given a copy of the informed consent form to keep.

Introduction

You are being asked to take part in a research study. Before you decide whether to give consent for this it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Discuss it with your colleagues if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

What is the purpose of the study?

This research aims to investigate how complex clinical decisions are made by physiotherapists who are experienced in working with people with PCD when considering airway clearance treatment options for children and young people with PCD. We hope that through interviews with approximately 6 PCD Physiotherapy Specialists, we can generate an account of how experts make decisions under conditions of uncertainty.

This would help others to understand what cues experts use in clinical decision making around personalisation of airway clearance regimens, potentially assisting with future decision making, the design of future research, and the production of clinical guidance.

This research is being undertaken as part completion of the lead researcher's Doctorate.

Why have I been invited to take part?

You have been asked to take part because you work as a physiotherapist with children or young people with PCD.

Do I have to take part?

No. It is up to you to decide whether you agree to take part, and you can change your mind at any time, without any repercussion and without giving a reason. If you choose to withdraw after you have completed the interview, either in part, or in full, the interview recording and transcript will be destroyed and will not be used in the final write-up.

IRAS number 299027
Version 0.2
Date 21/06/2021

Who is organising the study?
Lynne Schofield is a physiotherapist working in the North of England PCD service at Leeds Teaching Hospitals, and a clinical doctoral research fellow. She is working with Leeds Teaching Hospitals and the University of Sheffield MRI unit to performing this research. This study has been reviewed by the South Central - Oxford B Research Ethics Committee.

What will happen to me if I agree to take part?
If you do decide to take part, you will be invited to attend an interview with Lynne, which will last up to 2 hours. This interview will take place via Microsoft Teams. Once the interview is scheduled, you will be asked to give your formal consent to take part. If this is done via telephone or Microsoft Teams, the audio consent process will be recorded separately to the interview. You will be asked whether you prefer to be sent a copy of your consent form by post or email. The interview will involve you identifying a particular occasion where you have made a complex clinical decision regarding the airway clearance regimen of a specific patient with PCD The methods used in the interview will involve going over this example a total of four times, each time in greater detail. After identifying the example, you will be asked to add context to this, providing a timeline, and noting critical points in the decision process. You will also be asked to consider at each of these critical points, whether a different decision could have been made at that time, and what the consequences might have been. It is hoped that exploring specific examples in this way will help the researchers to understand how complex clinical decisions are made, and how this information could help to inform future similar decisions.

What are the potential risks and benefits of taking part?
There are no anticipated risks associated with participation in this research. However, the topics discussed may potentially be sensitive due to the detailed discussion and analysis of particular clinical decisions you have made in the past. If at any point during the interview you feel uncomfortable, please let the researcher know, and the interview can end at any point.
Whilst there are no immediate benefits for those people participating in the research, it is hoped that this work will establish some conclusions and recommendations to help clinicians with future clinical decision making, both for patients within the subgroups investigated, but also in other areas.

Will my taking part in this project be kept confidential?
All the information that we collect from you during the course of the research will be kept strictly confidential and will only be accessible to members of the research team. You will not be identifiable in any reports or publications unless you have given your explicit consent for this. When the interview is recorded, you will be assigned a research ID number, so the researchers can identify you throughout the study, but your identifiable information is not available alongside your interview data. Copies of consent forms will be stored in a locked cabinet in a locked room, separately to any

interview recordings or transcripts. Some basic demographic information will also be collected from you, but this will also be stored separately, and will not be linked to your interview responses in any publications. Copies of consent forms, paper demographics forms, and interview recordings will be destroyed at the end of this research. Interview transcripts and electronic demographics database will be stored securely for as long as required, but for at least 5 years, before being destroyed.

What will happen to the results of the research project?
The results of the research may be published in journals and presented at conferences. This work may also be used to inform a larger study using similar methods. Any direct quotes used in publications will not be traceable to a particular individual or NHS Trust.

Will I be recorded, and how will the recorded media be used?
The audio recordings from the interviews will be used only for analysis and inclusion in publications and other outputs arising from this research. They will not be used for any other purpose without your written permission, and no-one outside of the research team will have access to the original recordings. They will be securely recorded on an encrypted Dictaphone, before being transferred to a university network drive, only accessible by the researchers.

How will we use information about you?
We will need to use information from your interview for this research project.
Parts of your data such as your consent form will include your:

- Name and initials
- Contact details

People will use this information to do the research or to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.
Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, the interview recording and transcript will be destroyed and will not be used in the final write-up.

Where can you find out more about how your information is used?
You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/

- our information on our website https://www.leedsth.nhs.uk/patients-visitors/patient-and-visitor-information/how-we-use-your-data/
- by asking one of the research team
- by sending an email to Leedsth-tr.informationgovernance@nhs.net
- by ringing us on 0113 2433144 and ask for the Data Protection Officer

Who is responsible for this research?
This research is being carried out by researchers at Leeds Teaching Hospitals (the sponsor) and the University of Sheffield.

Who has reviewed the study?
This study has been reviewed by the South Central - Oxford B Research Ethics Committee.

What if something goes wrong?
If you are harmed by taking part in this research project, there are no special compensation arrangements, but if you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of the study you should contact the Chief Investigator (Lynne Schofield, *Leeds Teaching Hospitals lynneschofield@nhs.net)*. Alternatively, the normal National Health Service *(via letter to The Chief Executive, Leeds Teaching Hospitals, Leeds General Infirmary, Great George Street, Leeds LS1 3EX)* or the normal University complaints mechanisms are available *(via letter to the University of Sheffield Registrar and Secretary, Firth Court, Western Bank, Sheffield. S10 2TN)*.

What if I have any other concerns?
If you have any problems, concerns, complaints, or other questions about this study, you should preferably contact the investigator, (Lynne Schofield, Leeds Teaching Hospitals, lynneschofield@nhs.net*)*. Alternatively, you may contact Leeds Teaching Hospitals or the University of Sheffield, via the addresses listed under the heading 'What if anything goes wrong?' above. You can keep this information sheet and will be given a copy of the signed consent form to keep.

Thank you for taking the time to read this information.

5.2 Information for parents of patient participants

NHS
The Leeds Teaching Hospitals
NHS Trust

Patient Information Sheet for Parents/Guardians

Title of project: Assessing personalised airway clearance techniques in Primary Ciliary Dyskinesia (PCD)

Name of researcher: Lynne Schofield

Sponsor: LTHT

Study lead: Miss Lynne Schofield
Address, Paediatric Physiotherapy, 2 Park Lane, 2nd Floor, Leeds LS31ES
Phone number: 0113 3920609, email lynneschofield@nhs.net

You can keep this information sheet and if you take part, you will be given a copy of the informed consent form to keep.

Introduction

Your child is being asked to take part in a research study. Before you decide whether to give consent for this it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Discuss it with your child and your family if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish for your child to take part.

What is the purpose of the study?

Airway clearance techniques (also known as "chest physio") are used to move and clear mucus from the lungs in conditions where normal mucus clearance is impaired. One such condition is Primary Ciliary Dyskinesia (PCD). The measures currently available to assess the effects of airway clearance techniques are limited.

This study will, for the first time, measure the short-term effects of airway clearance techniques with a sensitive tool. It will use a new, safe technique; Magnetic Resonance Imaging (MRI) to take pictures of air inside the lungs before and after an airway clearance technique.

The new technique uses a gas called Xenon, and this has made it possible to take pictures of the lungs using MRI to measure how the lungs work. MRI is harmless, does not require X-rays, and is performed in many millions of people each year. Xenon is well known to us and Xenon MRI studies have already been carried out in hundreds of people. The gases are scentless, so-called "inert" gases which means they do not combine with things chemically. This means they do not produce poisonous things that could cause side effects, though Xenon does have mild anaesthetic effects when inhaled in large quantities. Using this new technique, we are obtaining new, detailed information on how the lung functions, in particular how different areas of the lung are affected.

The MRI pictures can inform clinicians about patients' lung health. This study will find out how specialist PCD physiotherapists currently decide what airway clearance

techniquesregimen they recommend to patients and explore if providing clinicians with the information from the MRI changes their recommendations.

Study design:
This study has 3 stages, or phases. This information explains how, if you wish to take part, your child will be involved in one study visit (in Phase 2) and the information from their study visit will be shared with members of the PCD team who look after your child at your local hospital (in Phase 3).

- Phase1: Finding out how clinicians currently decide what airway clearance regimen to recommend to children and young people with PCD.
- Phase 2: Assessing the effects of an airway clearance regimens in children and young people with PCD using a standard clinical review and MRI.
- Phase 3: Understanding how the information from MRI scans influences the decisions that health care professionals make about airway clearance regimens.

This research is being undertaken as part completion of the lead researcher's Doctorate.

Who is organising the study?

Lynne Schofield is a physiotherapist working in the North of England PCD service; you will have met Lynne in clinic previously. She is working with scientists in the University of Sheffield MRI unit and doctors who look after young people with PCD (Dr Robson from Leeds, Dr Moya from Bradford, and Dr West from Sheffield) to performing this research as a team. This study has been reviewed by the South Central - Oxford B Research Ethics Committee.

Why has my child been chosen?

Your child has been chosen because they have been diagnosed with PCD and is under the care of one of the centres taking part in this study (Leeds Teaching Hospitals, Bradford Teaching Hospitals or Sheffield Children's Hospital).

If your child takes part in the research, this may provide information about how their lungs respond to an airway clearance session, but we cannot be certain that this will change or improve their treatment. It is hoped that this research will help us to understand more about the effects of airway clearance techniques which may help guide physiotherapists and other health professionals. It may also provide knowledge that can help plan future studies which may be larger and include people with other lung conditions.

Does my child have to take part?
No, this is completely voluntary. We will explain the study to you and your child and go through this information sheet. If you wish for your child to take part, we will ask you to sign a consent form and if your child is old enough, we will ask them to fill in a form to say if they are happy to take part. Your child will be free to withdraw at any stage, even during the study day itself. You do not have to give reasons if your child does withdraw or chooses not to take part, without this having any effect on your child's future health care.

Are there any reasons why my child should not take part?

When you arrive, Lynne and the team at the University of Sheffield MRI unit will check you and your child do not have any significant medical problems that would affect your safety.

There is no financial reward or payment for taking part in this study. We will cover the cost of your travel to the MRI unit and provide reimbursement for refreshments.

What will happen to my child if they take part?

Before the study

We will need to check that MRI is a safe procedure for your child. If they have a pacemaker, had previous brain surgery, might be pregnant or have suffered an injury to the eye (metal splinter) or have an implanted hearing device you should inform us so we may check this before the MRI takes place. We can also check similarly if you have any reasons that you would not be able to enter the scanning room at this point. We will also contact you to make sure your child is not currently taking any antibiotics for a chest infection, if they are, we will rearrange their appointment for when they have finished the antibiotics.

You will receive a letter containing details of the study visit appointment, including where the appointment is and parking details. If the appointment falls on a school day, it may be useful to show the appointment letter to school to support your child's absence for the study visit day.

A short video of the scanning process can be found using this link:
https://drive.google.com/file/d/1iKdd1J9Y-E5IIJ7Ep39VpP05Bz4Gi09J/view?usp=sharing

If you would prefer to receive this link by text or e-mail, please let the research team know.

What will happen on the study day?

Order of events (further details below)

1. Safety check before entering the MRI unit.
2. Going over the information, any questions and signing the consent form
3. Look round MRI unit and see the scanner.
4. Check their height and weight.
5. Complete lung function (like completing lung function in clinic)
6. MRI scan number 1
7. Physiotherapy assessment
8. Complete airway clearance regimen
9. MRI scan number 2
10. Fill in a questionnaire about how having PCD affects your child in day-to-day life.
11. Break for approximately 3-4 hours- you can both leave the MRI unit during this time.
12. MRI scan number 3

If your child takes part, they will need to come to the University of Sheffield MRI Unit, Royal Hallamshire Hospital for one appointment. The study visit will last approximately 7 hours in total, but there is a long break where you both can leave the unit and then come back for the final part of the study a few hours later.

When you arrive, Lynne and the team at the University of Sheffield MRI unit will check you and your child do not have any significant medical problems that would affect your safety.

There is no financial reward or payment for taking part in this study. We will cover the cost of your travel to the MRI unit and provide reimbursement for refreshments.

What will happen to my child if they take part?

Before the study

We will need to check that MRI is a safe procedure for your child. If they have a pacemaker, had previous brain surgery, might be pregnant or have suffered an injury to the eye (metal splinter) or have an implanted hearing device you should inform us so we may check this before the MRI takes place. We can also check similarly if you have any reasons that you would not be able to enter the scanning room at this point. We will also contact you to make sure your child is not currently taking any antibiotics for a chest infection, if they are, we will rearrange their appointment for when they have finished the antibiotics.

You will receive a letter containing details of the study visit appointment, including where the appointment is and parking details. If the appointment falls on a school day, it may be useful to show the appointment letter to school to support your child's absence for the study visit day.

A short video of the scanning process can be found using this link:
https://drive.google.com/file/d/1iKdd1J9Y-E5IIJ7Ep39VpP05Bz4Gi09J/view?usp=sharing

If you would prefer to receive this link by text or e-mail, please let the research team know.

What will happen on the study day?

Order of events (further details below)

1. Safety check before entering the MRI unit.
2. Going over the information, any questions and signing the consent form
3. Look round MRI unit and see the scanner.
4. Check their height and weight.
5. Complete lung function (like completing lung function in clinic)
6. MRI scan number 1
7. Physiotherapy assessment
8. Complete airway clearance regimen
9. MRI scan number 2
10. Fill in a questionnaire about how having PCD affects your child in day-to-day life.
11. Break for approximately 3-4 hours- you can both leave the MRI unit during this time.
12. MRI scan number 3

If your child takes part, they will need to come to the University of Sheffield MRI Unit, Royal Hallamshire Hospital for one appointment. The study visit will last approximately 7 hours in total, but there is a long break where you both can leave the unit and then come back for the final part of the study a few hours later.

With the first scan we are assessing your child's lungs when they have not done any airway clearance, so we ask on the day of the appointment that they withhold from taking any saline (salt) nebulisers, using their airway clearance devices, or exercising for 8 hours before the appointment. It is ok if they need to cough, we are just asking for them to not specifically undertake activities or treatments which they normally usually use to clear their mucus. We will ask you to bring anything your child uses for airway clearance with you, including your nebuliser equipment.

When you arrive, we will check you understand the study and answer any extra questions, before asking you to sign a form agreeing to go ahead.

We will show you both around the University MRI department and the MRI scanner. You and your child will only be allowed to enter the MRI scanner room after filling in a standard questionnaire which is to double check that it is safe for your child to have an MRI scan and for you to join them in the MRI scanning room.

We will explain about how to breathe in the gas during the scan. The gases are brought into the scanning room in a sealed plastic bag with a tube like a straw. Your child will be asked to breathe in, hold their breath for a short while, then breathe out again on a few occasions. This needs to be coordinated with taking pictures but is an easy test to do.

Each scanning session takes around 20 minutes. During the time in the scanner, your child will be asked to lie very still. We will check their health using simple equipment to measure their heart rate and blood oxygen level. During this process, you will hear some noise from the MR scanner, so we will provide some earplugs you can both wear to reduce the noise.

After the first scan, we will ask you both to move into a different room for the airway clearance/physiotherapy part of the visit. Lynne will complete an airway clearance assessment, like when your child sees a physio in clinic. The exact content of this assessment will be decided from the earlier part of the research (Phase 1), but it is expected to include:

- Questions about their airway clearance regimen, such as, what routine they normally use at home and how you feel this is working.
- Examination including listening to your child's chest with a stethoscope and placing hands on their ribs to see how well their ribs expand when they breathe.

Lynne will then ask your child to complete their usual airway clearance regimen, just as they would do at home. Lynne may ask some additional questions during or after the airway clearance, such as if the session is clearing the same amount of secretions as it would normally.

All of this session, including the assessment and airway clearance technique will be video recorded. This video will be used in phase 3 of the research. It will be shown to the physiotherapist(s) who are involved in your child's care at your local hospital and possibly by other members of the PCD team such as the doctor or nurse who is involved in their care. The video will only be used for this purpose and will be destroyed when the research finishes

After finishing the airway clearance session there will be 2 further sets of MRI scans- one straight away and the final one is 4 hours later. This is to allow us to see the effects of the airway clearance technique over this period of time.

A small number of people taking part will be asked to be part of what is called a control group. This is where we are assessing what happens to the lungs during the day when an airway clearance technique is not completed. We will let you know if your child is in this group. Your child will have the same MRI scans at the same time points but will not ask them to complete their airway clearance technique or have a physiotherapy review between the 1st and 2nd scans. Facilities will be available so that when the 3rd (final) scan has finished your child can then complete their airway clearance before you go home if they wish to.

Between the second and third MRI scan you will have plenty of time and can leave the MRI unit if you wish. This may be a good time to go for lunch; we will provide re-imbursement for lunch costs along with covering your travel costs. We will offer you some information on what is available in the local area as we know you may be new to Sheffield. We will ask your child to wear a simple pedometer to measure how many steps you take during the break; we want you forget they are wearing this and be as active as they would usually be. We will ask you to ensure you are back in plenty of time for the final scan as it is important that we perform the scans at the right time.

We will ask your PCD team for some information about your child's PCD from their hospital records. This will include details about when they were diagnosed with PCD, and the results of any recent tests such as lung function.

What are the possible risks of taking part?

The MRI scanner is tunnel shaped and during the scan your child will lie in the tunnel section of the scanner. Some people may find the space around them feels quite small during the scan. The Sheffield team are very experienced with scanning children and very few children have not been able to tolerate going in the scanner. The team will take time to explain everything to both you and your child to make sure you both feel comfortable before they get into the scanner. If at any time your child wants to stop the scan and get out, the team can quickly stop the scan and bring them out of the scanner. If this happens, the team will ask if they want to have a break and continue or if you wish to withdraw from the study.

Xenon gas has been used a lot to help CT scanning. In these cases, the amount of gas used is often much more than we will be using. Xenon is very safe. However, your child may have a temporary slight decrease in blood oxygen levels, together with some light-headedness from the mild anaesthetic effect of Xenon. In this research, we will only ask your child to hold their breath for a short period of time (less than 20 seconds). To be on the safe side, we will monitor your child's oxygen levels with a finger probe throughout the investigation. If their blood oxygen saturation does not return to its usual level in a short time or your child experiences any other side effects, we will record the events with a written letter to your GP or take any other action necessary. However, oxygen levels have always gone back to their usual levels in all the patients that we have scanned so far.

In the unlikely event that your child experiences any other side effects that might be related to any of the tests (scans or breathing tests) we will arrange extra check-ups, as necessary.

We will ask your child to delay their usual airway clearance session in the 8 hours before the tests. This could make them feel a little more congested but as they will complete the delayed airway clearance session at the appointment this should not be a problem.

Are there any possible benefits of taking part?

This is a research study. It is carried out to learn things in general and is not designed to provide information for your child's personal benefit. However, if by chance we happen to find something important for their health we will let your family doctor or own specialist know as soon as possible so they can make sure everything necessary is done for their health.

What will we do with the measurements we take?

All recorded information (data) will be held in a locked room in the University of Sheffield MRI unit. The images taken from the MRI scan will be stored on University of Sheffield computers and will be looked at so that we can understand the changes in your child's lungs in terms of passage of air and blood through the lungs. We will also see if we can measure other things, such as the size of the air spaces within the lung. We will make comparisons between different areas of their lungs and compare their measurements before and after their airway clearance session.

All the data will by anonymised; that means it will not be labelled with your child's name. We will use a code so people do not know your child's data is about them.

The only exception to this is the information we will share with your local PCD care team in Leeds, Bradford, or Sheffield. We will send the scans through a secure electronic system back to your care teams so they can be part of your child's medical records.

We will also share your child's data with the PCD health professionals who look after your child. Your child's physiotherapist, and possibly other members of the PCD team including their doctor or specialist, will see the video (of the airway clearance review and your child completing their physio) and information from their scans. This is for the final part of the research where we are looking to understand how the MRIs inform decisions health care professionals make about airway clearance. Only members of the research team and people who directly look after your child will be involved in reviewing their information and your child's information will only be used for this purpose.

What will happen to the information resulting from the study?

The primary aim of the study is scientific and clinical understanding of the effects of airway clearance techniques in children and young people with PCD. We will let other doctors and scientists know about the results by explaining them at meetings and writing articles for scientific journals. We will also share findings from the study with the PCD and wider community, for example through PCD Support UK. Your child's identity will never be revealed in this process.
We also plan to make a short video explaining what the research has found. If you would like to receive a link to the video or would be interested in seeing copies of any scientific papers that we produce, please let us know whether to send this to you by post or email, and we will let share these with you as they become available.

How will we use information about your child?

We will need to use information from your study visit and information about your child sent by their PCD team for this research project.
This information will include:

- Your child's name and initials
- Their NHS number
- Your name
- Your contact details.

People will use this information to do the research or to check your child's records to make sure that the research is being done properly.
People who do not need to know who your child is will not be able to see their name or contact details. Their data will have a code number instead. We will keep all information about your child safe and secure.
Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that your child took part in the study.
If you give us permission, we will tell your child's GP about the study and let them know that they have taken part.

What are your choices about how your child's information is used?

- Your child can stop being part of the study at any time, without giving a reason, but we will keep information about them that we already have.

- If you agree for your child to take part in this study, you will have the option to take part in future research using their data saved from this study. **Where can you find out more about how your information is used?**

You can find out more about how we use your child's information:

- at www.hra.nhs.uk/information-about-patients/
- our information on our website https://www.leedsth.nhs.uk/patients-visitors/patient-and-visitor-information/how-we-use-your-data/
- by asking one of the research team
- by sending an email to Leedsth-tr.informationgovernance@nhs.net
- by ringing us on 0113 2433144 and ask for the Data Protection Officer

Confidentiality - who will see my records and know about my child taking part?

The information collected about your child during the consent for the research will be kept confidential. Their records will only be looked at by researchers who need to do so to get specific information. Once they have got that information, they will record it without labelling it with your child's name. They will label it using a code. It will be kept in a locked office to be certain it is kept private. No names will be mentioned in any reports of the study and care will be taken so that individuals cannot be identified from details in reports of the results of the study. There will be no way in which anyone will be able to identify your child from any publications or reports arising from the study. Research is sometimes checked to ensure it is carried out properly and reliably. This is so the results can be trusted, and to check that your child has been treated safely and properly. This checking may be carried out by members of Sheffield Teaching Hospitals, University of Sheffield, statutory review bodies.

What if something goes wrong?

If your child is harmed by taking part in this research project, there are no special compensation arrangements, but if they are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you or your child has been approached or treated during the study you should contact the Chief Investigator (Lynne Schofield, *Leeds Teaching Hospitals lynneschofield@nhs.net)*. Alternatively, the normal National Health Service *(via letter to The Chief Executive, Leeds Teaching Hospitals, Leeds General Infirmary, Great George Street, Leeds LS1 3EX)* or the normal University complaints mechanisms are available *(via letter to the University of Sheffield Registrar and Secretary, Firth Court, Western Bank, Sheffield. S10 2TN)*.

What if I have any other concerns?

If you have any problems, concerns, complaints, or other questions about this study, you should preferably contact the investigator, (Lynne Schofield, Leeds Teaching Hospitals, lynneschofield@nhs.net*)*. Alternatively, you may contact Leeds Teaching Hospitals or the University of Sheffield, via the addresses listed under the heading 'What if anything goes wrong?' above. You can keep this information sheet and will be given a copy of the signed consent form to keep.

Thank you for taking the time to consider entering this study.

5.3 Information for patients aged 5-7

NHS
The Leeds Teaching Hospitals
NHS Trust

The University Of Sheffield.

Patient Information Sheet: Age 5-7

Research is a type of exploring. We want to ask if you would like to join in our research.

You can choose if you want to join in. We are doing this research because we want to learn more about PCD.

We want to take pictures of the lungs of kids with PCD. We want to take these pictures before and after they have a done their airway clearance (you may call this doing physio) to see how the lungs change.

We can take pictures of the lungs using a special machine called an MRI machine. When we are taking the pictures, you would need to wear a special jacket and lie still to make sure the pictures are good.

You would also have to breathe in a special gas from a bag using a tube like a straw. The gas doesn't taste of anything and won't hurt you.

On the day you will come to Sheffield with your Mum or Dad. Before you come for the scan you will miss your physio at home, but you would bring all your physio kit with you.

We will show you the MRI scanner and explain what happens before we start. We will ask you and your Mum or Dad some questions.

We will check your height and weight and do your blows like when you come to clinic.

Then, we will do scan number 1.

The MRI machine can be noisy so we will give you some headphones to wear. Your Mum or Dad can sit near you when you have your scan. Someone will stand next to you while you have the scan to keep talking to you about what is happening.

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Version 0.2
Date 17/05/2021

Next, Lynne will talk to you about your physio. She will listen to your chest, this bit will be like when you go to clinic but it will be recorded on a video.

Then we will ask you to do your airway clearance, just like you would do at home. This will be video recorded too.

We will then do scan number 2 and ask you a few more questions.

There will be a break, you can go outside with your Mum or Dad and eat your lunch.

Then we just need to do scan number 3 before you go home.

A few people will be asked to not do their physio until all the tests are finished. This is to help us see what happens inside the lungs when people don't do their physio.

We will ask your Mum/Dad if it is ok for you to join in our research. If you don't want to do it, that is ok. It is also ok if you want to ask another adult, like your Mum or Dad. It is important that you only say yes if feel happy about doing this study.

When we have finished all the scans we might write a story or make a poster about the scans. Only the physios who look after you will know that the pictures are of your lungs. Anyone else who sees your pictures will not know that they are of your lungs.

If you don't understand anything about the project, ask your mum or dad. You can also ask Lynne or your doctor.

Thank you for reading this!

5.4 Information for patients aged 8-10

NHS
The Leeds Teaching Hospitals
NHS Trust

The University Of Sheffield.

Patient Information Sheet: Age 8-10

To be shown and read by parent/carer if required. You can keep this information sheet.

Study title

Taking special pictures of your lungs to see the differences after you have done your physio.

1. What is research?

Research is a way to find out the answers to questions.

2. Why is this project being done?

We want to take pictures of the lungs of young people with PCD before and after they have a done their physio to find out more about what happens to the lungs when they do their physio.

3. Why have I been asked to take part?

You have been chosen because you have PCD and you can help us find some answers that will help us understand PCD and physio better.

4. Who checked that it's ok to do the study?

Before any research is allowed to happen, it has to be checked by a group of people called a Research Ethics Committee. They make sure that the research is fair.

5. Do I have to take part?

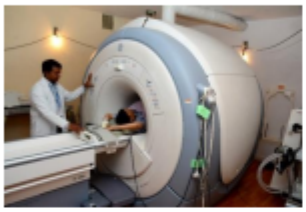
No you do not! It is up to you. We would like you to read this information sheet. If you agree to take part, we would like you to write your name, if you can, on two forms. We will also ask your mum, dad or carer to write their name on the forms and give one back to us. You can still change your mind later. If you don't want to take part, just say no!

6. What will happen to me if I take part in the research?

On the day you would come to Sheffield with your Mum or Dad. This is where the special scanner is. On the day you would not do your physio at home, but you would bring all your physio kit with you, including your nebuliser and medication.

MRI scan:

To take pictures of the lungs we will use a special machine called an MRI scanner. We will show you the MRI scanner and explain what happens before we start.



We will ask you and your parent some questions to make sure you are ok to have a scan.

When the scanner is taking the pictures, you would need to wear a special jacket and lie still to make sure we get good pictures. We will ask you to breath in special gas from a bag using a tube like a straw. We will ask you to hold your breath for about 10 seconds while we take the pictures. This helps us to see the lungs better. The gas doesn't taste of anything and won't hurt you.

The MRI machine can be noisy so we will give you some headphones to make it quieter. Your parent can come into the scanning room with you. Someone from the MRI team will stand next to you while you have the scan to keep talking to you about what is happening, we'll make sure you can hear them.

Physio:

Lynne will ask you some questions about your physio. She will listen to your chest like when you go to clinic. We will video record this.

Lynne will ask you to do your physio, just in the same way that you would do at home. We will video record this too.

A few people will be asked not to do their physio until all of the tests are finished. This is to help us see if your pictures change during the day if you don't do any physio.

Order of the tests:

- Height and weight
- Lung function (doing your blows)
- First set of pictures in the scanner
- Asking questions and listening to your chest
- Physio (just like you do at home)
- Second set of pictures in the scanner
- Filling in some questions

- Break
- Third set of pictures in the scanner
- Finished!!!

A little while after your visit, Lynne will show the physios, doctors and nurses the video of you doing your physio and your scan pictures. She will ask them if they think your physio is doing what they think it should be doing. Only people who look after you will see your video and your scan.

7. What happens if I say no?

You can decide if you want to do the study or not. It is ok if you don't want to. You will still be treated the same when you go to your clinic appointments for check- ups or treatments.

8. Might anything else about the research upset me?

We don't expect that the research will be upsetting. As you won't have seen one of the MRI scanners before we will show you it before we start any of the tests. You will have to spend most of one day at the unit where the scanner is in Sheffield. When there is a break between the scans you can go outside and eat your lunch. The scans are very safe and have been done on lots of people before.

If we find out something that we think is important about your PCD, we will talk to your mum, dad or carer and ask them if they want you to be checked again at the hospital.

9. Will joining in help me?

We cannot promise the study will help you but the information we get might help treat children and young people with PCD with better physio in the future.

10. What happens when the research stops?

It will take time to get the full information from the pictures and do the next bits of the research. We will show you and your Mum/Dad your pictures when they are ready and when you are in clinic.

You will just carry on your physio as normal at home after the scan. We may learn more about how the physio helps your lungs so we may change a few things once we have seen your scans to make sure your physio routine is right for you.

We will collect all the information together and understand what it tells us about how we can manage PCD better in the future.

11. What if something goes wrong during the project?

Your mum, dad or carer will be able to talk to someone who will be able to tell them what they need to do about it.

12. Will my medical details be kept private if I take part? Will anyone else know I'm doing this?

The people in our research team will know you are taking part. The physio, doctor and nurse who look after you for your PCD will also know. No one else will know because we will not use your name or address. You will get a number which will be used instead.

If you agree we will also tell your family doctor (your GP).

13. What if I don't want to do the research anymore?

If at any time you don't want to do the research any more, just tell your parents, doctor, nurse or physio. They will not be cross with you.

14. What if something goes wrong?

If there is something you don't feel happy about to do with the study you or your mum, dad or carer can talk to Lynne Schofield. You Mum or Dad can also complain to the hospital.

15. What happens to what the researchers find out?

When we collect your information we will make sure it is stored in a safe place and only the people doing the research study can look at it.

We will use the information to teach physios about how to treat PCD and put it in medical magazines and on websites that physios and doctors read.

No-one will know you were in the study.

16. How can I find out more about this study?

Your mum, dad, carer or other grownup you trust may be able to answer your questions. The doctors, nurses and physios looking after you can also help you find out more about the study.

Thank you for taking the time to read this – please ask any questions if you need to.

5.5 Information for patients aged 11-15

NHS
The Leeds Teaching Hospitals
NHS Trust

Patient Information Sheet: Age 11-15

Title of project: Assessing personalised airway clearance techniques in Primary Ciliary Dyskinesia (PCD)

Name of researcher: Lynne Schofield

You can keep this information sheet.

Introduction

We are asking if you would join in a research project to find the answer to two questions:

- *What happens to the lungs when people with PCD do their physio?*
- *If we give physiotherapists, doctors, and nurses new information about what happens when people with PCD do their physio, does this change what advice they give?*

Before you decide if you want to join in, it is important to understand why the research is being done and what it will involve for you. So please consider this leaflet carefully. Talk to your family, friends, doctor, or nurse if you want to.

Part 1 – to give you an overview of the project

1. Why are we doing this research?

Young people with PCD are asked to do their physio every day but at the moment there isn't very much information on what happens in the lungs when someone does their physio. We want to look at the lungs of young people with PCD before and after they have done their physio using a special type of Magnetic Resonance Imaging (MRI) scan. We also want to understand more about what these scans tell physiotherapists, doctors, and nurses about the lungs and if it changes what the physiotherapist, and possibly the doctor and nurse, advises you to do.

2. What is the medicine, device or procedure that is being tested?

We will be assessing the physio or airway clearance routine that you normally do at home. This may be using your nebuliser and then blowing into something like an Acapella, Aerobika or PEP mask.

We can use a special type of scan to take pictures of gas inside the lungs and will take these pictures before a physio session, straight after and then a few hours later to see if there are any differences.

We have to use a special type of scanner called an MRI. Lots of people have MRI scans every year and they are safe. To be able to see the lungs well we ask people in the scanner to breath in a special gas, called Xenon. You may have heard of the gas at school - these gases do not smell, and they are not harmful to you.

3. Why have I been invited to take part?

You have been chosen because you have PCD, and you go to one of the hospitals involved in the study for your PCD care. The hospitals taking part are in:

- Leeds
- Bradford
- Sheffield

4. Do I have to take part?

No, you don't have to, it is up to you. We will ask if you agree to take part- this is called assent. If you want to take part, we will ask if you would sign a form. We will give you a copy of this information sheet and your signed form to keep.

You are free to stop taking part at any time during the research without giving a reason. If you decide to stop or choose not to take part, this will not affect the care you receive.

5. What will happen to me if I take part?

We will ask for you to come to one appointment in Sheffield, with your parent or guardian. This appointment will last most of the day. During the appointment we will ask you to take part in some tests and to complete your physiotherapy, just like you would do at home. Once the appointment is finished, you can head home.

Before the study

We will need to check that it is safe for you to have an MRI scan. If you have had certain operations before, if you might be pregnant, have hurt your eye or have certain types of hearing device you should tell us so we can check this before the MRI scan takes place.

What will happen on study day?

On the day of the appointment, we will ask that you do not take your nebuliser or do your airway clearance or exercise for 8 hours before the appointment. It is ok if you need to cough though. We will ask you to bring anything you use for airway clearance with you, including nebuliser equipment.

When you arrive, we will check with you and your parent/guardian to ensure that you understand the study and answer any extra questions you may have, before asking you to sign a form agreeing to go ahead.

We will then take you through the following tests:

- Height and your weight
- Lung function (measuring your blows, like in clinic)
- MRI scan session number 1
- Physiotherapy assessment
- Complete your airway clearance

- MRI scan session number 2
- Fill in a questionnaire about PCD
- Break for approximately 3-4 hours
- MRI scan session number 3
- Finished!!!

You will have 3 MRI scanning session in total. Each scanning session involves: a 10-minute scan, a five-minute break then a 20-minute scan.

More information about what happens:

The MRI scan:

An MRI is a special type of scanner. Before we go into the area near the scanner, we will ask some questions to make sure it is safe for you to go into the scanner. When you are ready to have your MRI, we will show you the scanner and explain what we will ask you to do. The MRI scanner can be noisy while it is working so we will give you some earplugs to make it a bit quieter. Your parent or guardian should be able to stay with you in the scanner room.

When you have the scan, we will ask you to breathe in the special gases from a bag through using a tube like a straw. The gas doesn't taste of anything and is safe. You will have to breathe in, hold your breath for a short time, then breathe out again. We will ask you to do this a few times while we take the picture of your lungs. During the time in the scanner, you will be asked to lie very still and to wear a special jacket; this is to help the scanner to take clear pictures. We will check your heart rate and oxygen level using a clip on your finger.

Physio:

Once you have finished the first MRI scan, Lynne will do a physio assessment-like when you see the physio in clinic. She will ask you some questions about how your physio has been going when you are at home. She will also examine you- listening to your chest and putting her hands on each side of your chest to see how well it moves when you breathe.

Lynne will ask you to then do your airway clearance routine, just as you would do at home. She may ask you a few extra questions while you are doing this.

Lynne will video this part of the day- the physio assessment and you completing your airway clearance. This is to show the physiotherapists, doctors, and nurses in the next part of the research project. They will be shown the video and then they will see your scans to help understand if the new information from the scans changes what they think about how well your airway clearance routine is working. Only people who look after you for you will see your video and your scan.

A small number of people taking part will be asked to not do any physio until all of the scans have been done. This is to help us understand if there is a change the lungs during the day when physio is not done. We will let you know if you are someone we

will ask not to do physio. You will be able to do your physio when the final scan has been finished before you go home.

6. What are the possible side effects of the scan?

The special gas that will be used is safe. We will keep the oxygen saturation finger clip on your finger while you have the scan to make sure your oxygen levels stay at similar numbers while you are breathing the gas.

7. Is there anything else to be worried about if I take part?

We will ask you to not do your usual airway clearance session before the scan but as you will then do this a bit later at the appointment this should not cause you any problems.

If we find out something that we think is important about your PCD, we will talk to your parent or guardian and ask them if they want to have you checked again at the hospital.

8. What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get might help treat children and young people with PCD with better physio in the future.

9. Contact for further information

If you would like any further information about this study you could contact the study lead:

Name: Miss Lynne Schofield
Designation: Physiotherapist and Research Fellow
Hospital/Department: Children's Physiotherapy, Leeds General Infirmary
Tel: 0113 3920609

Thank you for reading so far - if you are still interested, please go to Part 2:

Part 2 - more detail – information you need to know if you want to take part.

10. What happens when the research project stops?

We will be able to show you and your parent/guardian your pictures when you come to clinic but there may be a bit of a delay while we complete the next step of the research.

You will just carry on your physio as normal at home after the scan. We may learn more about how the physio helps your lungs so we may change a few things once we have seen your scans to make sure your physio routine is right for you.

We will collect all the information together and we will decide if it is useful in telling us if the physios can manage PCD better in the future.

11. What if there is a problem or something goes wrong?

Tell us if there is a problem and we will try and sort it out straight away. You and your parent or guardian can either contact the project coordinator:

Name: Miss Lynne Schofield
Designation: Physiotherapist and Research Fellow
Hospital/Department: Children's Physiotherapy, Leeds General Infirmary
Tel: 0113 3920609

12. Will anyone else know I am doing this?

We will keep your information in confidence. This means we will only tell those who have a need or right to know. The PCD team at your hospital will know, as they will see your scans. Whenever possible, instead of using your name, we will use a number to make sure other people do not know that your information belongs to you.

If you agree we will also tell your family doctor (GP) that you are doing the study.

13. What will happen to my scans?

We will keep any information with your name on it very safe, so only people involved in the study can see it. Again, whenever possible, instead of using your name, we will use a number to make sure other people do not know that your information belongs to you.

14. Who is organising and funding the research?

The research is being organised by Leeds Teaching Hospitals, the University of Sheffield and paid for by grants from the National Institute for Health Research.

15. Who has reviewed the study?

Before any research goes ahead it has to be checked by a Research Ethics Committee. They make sure that the research is fair. This study has been checked by <name of> Research Ethics Committee.

It has also been checked by the Research Department at this hospital.

Thank you for reading this – please ask any questions if you need to.

5.6 Information for patients aged 16-18

NHS
The Leeds Teaching Hospitals
NHS Trust

The University Of Sheffield.

Patient Information Sheet: Age 16-18

Title of project: Assessing personalised airway clearance techniques in Primary Ciliary Dyskinesia (PCD)

Name of researcher: Lynne Schofield

Sponsor: LTHT

Study lead: Miss Lynne Schofield
Address, Paediatric Physiotherapy, 2 Park Lane, 2nd Floor, Leeds LS31ES
Phone number: 0113 3920609, email lynneschofield@nhs.net

You can keep this Information Sheet and if you take part, you will be given a copy of the informed consent form to keep.

Introduction

You are being asked to take part in a research study. Before you decide whether to give consent for this it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Discuss it with your friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

What is the purpose of the study?

Airway clearance techniques (also known as "chest physio") are used to move and clear mucus from the lungs in conditions where normal mucus clearance is impaired. One such condition is Primary Ciliary Dyskinesia (PCD). The measures currently available to assess the effects of airway clearance techniques are limited.

This study will, for the first time, measure the short-term effects of airway clearance techniques with a sensitive tool. It will use a new, safe technique; Magnetic Resonance Imaging (MRI) to take pictures of air inside the lungs before and after an airway clearance technique.

The new technique uses a gas called Xenon, and this has made it possible to take pictures of the lungs using MRI to measure how the lungs work. MRI is harmless, does not require X-rays, and is performed in many millions of people each year. Xenon is well known to us and Xenon MRI studies have already been carried out in hundreds of people. The gases are scentless, so-called "inert" gases which means they do not combine with things chemically. This means they do not produce poisonous things that could cause side effects, though Xenon does have mild anaesthetic effects when inhaled in large quantities. Using this new technique, we are obtaining new, detailed information on how the lung functions, in particular how different areas of the lung are affected.

The MRI pictures can inform clinicians about patients' lung health. This study will find out how specialist PCD physiotherapists currently decide what airway clearance technique regimen they recommend to patients and explore if providing clinicians with the information from the MRI changes their recommendations.

Study design:
This study has 3 stages, or phases. This information explains how, if you wish to take part, you will be involved in one study visit (in Phase 2) and the information from your study visit will be shared with members of the PCD team who look after you at your local hospital (in Phase 3).

- Phase1: Finding out how clinicians currently decide what airway clearance regimen to recommend to children and young people with PCD.
- Phase 2: Assessing the effects of an airway clearance regimens in children and young people with PCD using a standard clinical review and MRI.
- Phase 3: Understanding how the information from MRI scans influences the decisions that health care professionals make about airway clearance regimens.

This research is being undertaken as part completion of the lead researcher's Doctorate.

Who is organising the study?

Lynne Schofield is a physiotherapist working in the North of England PCD service; you will have met Lynne in clinic previously. She is working with scientists in the University of Sheffield MRI unit and doctors who look after young people with PCD (Dr Robson from Leeds, Dr Moya from Bradford, and Dr West from Sheffield) to performing this research as a team. This study has been reviewed by the South Central - Oxford B Research Ethics Committee.

Why have I been chosen?

You have been chosen because you have been diagnosed with PCD and are under the care of one of the centres taking part in this study (Leeds Teaching Hospitals, Bradford Teaching Hospitals or Sheffield Children's Hospital).

If you do take part in the research, this may provide information about how your lungs respond to an airway clearance session, but we cannot be certain that this will change or improve your own treatment. It is hoped that this research will help us to understand more about the effects of airway clearance techniques which may help guide physiotherapists and other health professionals. It may also provide knowledge that can help plan future studies which may be larger and include people with other lung conditions.

Do I have to take part?
No, this is completely voluntary. We will explain the study to you and go through this information sheet. If you wish to take part, we will ask you to sign a consent form. You will be free to withdraw at any stage, even during the study day itself. You do not have to give reasons if you do withdraw or choose not to take part and this will not affect your future healthcare.

Are there any reasons why I should not take part?

On your first visit Lynne and the team at the University of Sheffield MRI unit will check you do not have any significant medical problems that would affect your safety.

There is no financial reward or payment for taking part in this study. We will cover the cost of your travel to the MRI unit and provide reimbursement for refreshments.

What will happen to me if I take part?

Before the study

We will need to check that MRI is a safe procedure for you. If you have a pacemaker, had previous brain surgery, might be pregnant or have suffered an injury to the eye (metal splinter) or have an implanted hearing device you should inform us so we may check this before the MRI takes place. We will also contact you to make sure you are not currently taking any antibiotics for a chest infection, if you are, we will rearrange your appointment for when you have finished the antibiotics.

You will receive a letter containing details of the study visit appointment, including where the appointment is and parking details. If the appointment falls on a day when you would be at school, college, or work, it may be useful to show the appointment letter to your school/college/employer to support your absence for the study visit day.

A short video of the scanning process can be found using this link:
https://drive.google.com/file/d/1iKdd1J9Y-E5IIJ7Ep39VpP05Bz4Gi09J/view?usp=sharing

If you would prefer to receive this link by text or e-mail, please let the research team know.

What will happen on the study day?

Order of events (further details below)

1. Safety check before entering the MRI unit.
2. Going over the information, any questions and signing the consent form
3. Look round MRI unit and see the scanner.
4. Check your height and your weight.
5. Complete lung function (like completing lung function in clinic)
6. MRI scan number 1
7. Physiotherapy assessment
8. Complete airway clearance regimen
9. MRI scan number 2
10. Fill in a questionnaire about how having PCD affects you in day-to-day life.
11. Break for approximately 3-4 hours- you can leave the MRI unit during this time.
12. MRI scan number 3

If you take part you will need to come to the University of Sheffield MRI Unit, Royal Hallamshire Hospital for one appointment. The study visit will last approximately 7 hours in total, but there is a long break where you can leave the unit and then come back for the final part of the study a few hours later. You can bring someone with you on the day of the scan.

With the first scan we are assessing your lungs when you have not done any airway clearance, so we ask on the day of the appointment that you withhold from taking any saline (salt) nebulisers, using their airway clearance devices, or exercising for 8 hours before the appointment. It is ok if you need to cough, we are just asking for you to not specifically undertake activities or treatments which you normally usually use to clear your mucus. We

will ask you to bring anything you use for airway clearance with you, including your nebuliser equipment.

When you arrive, we will check you understand the study and answer any extra questions, before asking you to sign a form agreeing to go ahead.

We will show you around the University MRI department and the MRI scanner. You and your family member/friend will only be allowed to enter the MRI scanner room after filling in a standard questionnaire which is to double check that it is safe for you to have an MRI scan and for your family member/friend to join you in the MRI scanning room.

We will explain about how to breathe in the gas during the scan. The gases are brought into the scanning room in a sealed plastic bag with a tube like a straw. You will be asked to breathe in, hold your breath for a short while, then breathe out again on a few occasions. This needs to be coordinated with taking pictures but is an easy test to do.

Each scanning session takes around 20 minutes. During the time in the scanner, you will be asked to lie very still. We will check your health using simple equipment to measure your heart rate and blood oxygen level. During this process, you will hear some noise from the MR scanner, so we will provide some earplugs you can wear to reduce the noise.

After the first scan, we will ask you both to move into a different room for the airway clearance/physiotherapy part of the visit. Lynne will complete an airway clearance assessment, like when you see a physio in clinic. The exact content of this assessment will be decided from the earlier part of the research (Phase 1), but it is expected to include:

- Questions about your airway clearance regimen, such as, what routine you normally use at home and how you feel this is working.
- Examination including listening to your chest with a stethoscope and placing hands on your ribs to see how well your ribs expand when you breathe.

Lynne will then ask you to complete your usual airway clearance regimen, just as you would do at home. Lynne may ask some additional questions during or after the airway clearance, such as if the session is clearing the same amount of secretions as it would normally.

All of this session, including the assessment and airway clearance technique will be video recorded. This video will be used in phase 3 of the research. It will be shown to the physiotherapist(s) who are involved in your care at your local hospital and possibly by other members of the PCD team such as the doctor or nurse who is involved in your care. The video will only be used for this purpose and will be destroyed when the research finishes.

After finishing the airway clearance session there will be 2 further sets of MRI scans- one straight away and the final one is 4 hours later. This is to allow us to see the effects of the airway clearance technique over this period of time.

A small number of people taking part will be asked to be part of what is called a control group. This is where we are assessing what happens to the lungs during the day when an airway clearance technique is not completed. We will let you know if you are in this group. You will have the same MRI scans at the same time points, but will not ask you to complete your airway clearance technique or have a physiotherapy review between the 1st and 2nd

scans. Facilities will be available so that when the 3rd (final) scan has finished you can then complete your airway clearance before you go home if you wish to.

Between the second and third MRI scan you will have plenty of time and can leave the MRI unit if you wish. This may be a good time to go for lunch; we will provide re-imbursement for lunch costs along with covering your travel costs. We will offer you some information on what is available in the local area as we know you may be new to Sheffield. We will ask you to wear a simple pedometer to measure how many steps you take during the break; we want you forget you are wearing this and be as active as you would usually be. We will ask you to ensure you are back in plenty of time for the final scan as it is important that we perform the scans at the right time.

We will ask your PCD team for some information about your PCD from your hospital records. This will include details about when you were diagnosed with PCD, and the results of any recent tests such as lung function.

What are the possible risks of taking part?

The MRI scanner is tunnel shaped and during the scan you will lie in the tunnel section of the scanner. Some people may find the space around them feels quite small during the scan. The Sheffield team are very experienced with scanning people and very few people have not been able to tolerate going in the scanner. The team will take time to explain everything to you and to make sure you feel comfortable before you get into the scanner. If at any time you want to stop the scan and get out, the team can quickly stop the scan and bring you out of the scanner. If this were to happen, the team will ask if you want to have a break and continue or if you wish to withdraw from the study.

Xenon gas has been used a lot to help CT scanning. In these cases, the amount of gas used is often much more than we will be using. Xenon is very safe. However, you may have a temporary slight decrease in blood oxygen levels, together with some light-headedness from the mild anaesthetic effect of Xenon. In this research, we will only ask you to hold your breath for a short period of time (less than 20 seconds). To be on the safe side, we will monitor your oxygen levels with a finger probe throughout the investigation. If your blood oxygen saturation does not return to its usual level in a short time or you experience any other side effects, we will record the events with a written letter to your GP or take any other action necessary. However, oxygen levels have always gone back to their usual levels in all the patients that we have scanned so far.

In the unlikely event that you experience any other side effects that might be related to any of the tests (scans or breathing tests) we will arrange extra check-ups, as necessary.

We will ask you to delay your usual airway clearance session in the 8 hours before the tests. This could make you a little more congested but as you will complete the delayed airway clearance session at the appointment this should not be a problem.

Are there any possible benefits of taking part?

This is a research study. It is carried out to learn things in general and is not designed to provide information for your personal benefit. However, if by chance we happen to find something important for your own health we will let your family doctor or own specialist know as soon as possible so they can make sure everything necessary is done for your own health.

What will we do with the measurements we take?

All recorded information (data) will be held in a locked room in the University of Sheffield MRI unit. The images taken from the MRI scan will be stored on University of Sheffield computers and will be looked at so that we can understand the changes in your lungs in terms of passage of air and blood through the lungs. We will also see if we can measure other things, such as the size of the air spaces within the lung. We will make comparisons between different areas of your lungs and compare your measurements before and after your airway clearance session.

All the data will by anonymised; that means it will not be labelled with your name. We will use a code so people do not know your data is about you.

The only exception to this is the information we will share with your local PCD care team in Leeds, Bradford, or Sheffield. We will send the scans through a secure electronic system back to your care teams so they can be part of your medical records.

We will also share your data with the PCD health professionals who look after you. Your physiotherapist, and possibly other members of the PCD team including your doctor or specialist, will see the video (of the airway clearance review and you completing your physio) and information from your scans. This is for the final part of the research where we are looking to understand how the MRIs inform decisions health care professionals make about airway clearance. Only members of the research team and people who directly look after you will be involved in reviewing your information and your information will only be used for this purpose.

What will happen to the information resulting from the study?

The primary aim of the study is scientific and clinical understanding of the effects of airway clearance techniques in children and young people with PCD. We will let other doctors and scientists know about the results by explaining them at meetings and writing articles for scientific journals. We will also share findings from the study with the PCD and wider community, for example through PCD Support UK. Your identity will never be revealed in this process.

We also plan to make a short video explaining what the research has found. If you would like to receive a link to the video or would be interested in seeing copies of any scientific papers that we produce, please let us know whether to send this to you by post or email, and we will let share these with you as they become available.

How will we use information about you?

We will need to use information from your study visit and information about you sent by your PCD team for this research project.
This information will include your:

- Name and initials
- NHS number
- Contact details.

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.
Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.
If you give us permission, we will tell your GP about the study and let them know that you have taken part.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

Where can you find out more about how your information is used?

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- our information on our website https://www.leedsth.nhs.uk/patients-visitors/patient-and-visitor-information/how-we-use-your-data/
- by asking one of the research team
- by sending an email to Leedsth-tr.informationgovernance@nhs.net
- by ringing us on 0113 2433144 and ask for the Data Protection Officer

Confidentiality - who will see my records and know about my taking part?

The information collected about you during the consent for the research will be kept confidential. Your medical records will only be looked at by researchers who need to do so to get specific information. Once they have got that information, they will record it without labelling it with your name. They will label it using a code. It will be kept in a locked office to be certain it is kept private. No names will be mentioned in any reports of the study and care will be taken so that individuals cannot be identified from details in reports of the results of the study. There will be no way in which anyone will be able to identify you from any publications or reports arising from the study. Research is sometimes checked to ensure it is carried out properly and reliably. This is so the results can be trusted, and to check that you have been treated safely and properly. This checking may be carried out by members of Sheffield Teaching Hospitals, University of Sheffield, statutory review bodies.

What If Something Goes Wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements, but if you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the study you should contact the Chief Investigator (Lynne Schofield, *Leeds Teaching Hospitals lynneschofield@nhs.net)*. Alternatively, the normal National Health Service *(via letter to The Chief Executive, Leeds*

Teaching Hospitals, Leeds General Infirmary, Great George Street, Leeds LS1 3EX) or the normal University complaints mechanisms are available *(via letter to the University of Sheffield Registrar and Secretary, Firth Court, Western Bank, Sheffield. S10 2TN)*.

What if I have any other concerns?

If you have any problems, concerns, complaints, or other questions about this study, you should preferably contact the investigator, (Lynne Schofield, Leeds Teaching Hospitals, lynneschofield@nhs.net). Alternatively, you may contact Leeds Teaching Hospitals or the University of Sheffield, via the addresses listed under the heading 'What if anything goes wrong?' above. You can keep this information sheet and will be given a copy of the signed consent form to keep.

Thank you for taking the time to consider entering this study.

5.7 Information for clinicians in phase 3 (ACT data reviews, Chapter 6)

NHS
The Leeds Teaching Hospitals
NHS Trust

The University Of Sheffield.

Patient Information Sheet: Clinicians in Phase 3

Title of project: Assessing personalised airway clearance techniques in PCD
Name of researcher: Lynne Schofield
Sponsor: LTHT

Study lead: Miss Lynne Schofield
Address, Paediatric Physiotherapy, 2 Park Lane, 2nd Floor, Leeds LS31ES
Phone number: 0113 3920609, email lynneschofield@nhs.net

You can keep this Information Sheet and if you take part you will be given a copy of the informed consent form to keep.

Introduction

You are being asked to take part in a research study. Before you decide whether to give consent for this it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Discuss it with your colleagues if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

What is the purpose of the study?

This study is split into 3 phases, this information sheet relates to Phase 3:

1. *Exploring how clinicians' make decisions when reviewing and personalising ACT regimens for children and young people with PCD.*
2. *Assessing the short term effects of personalised airway clearance techniques in children and young people with PCD*
3. ***To investigate how clinical decision-making changes with the introduction of functional imaging of the lungs.***

This part of the research (phase 3) aims to investigate how clinical decisions about airway clearance regimens are made by health care professionals experienced in PCD. We will look at clinical decision making with information from current clinical sources and subsequently with new information from functional imagining that has been generated in phase 2. We plan to feed information back about patients who have taken part in phase 2 to the clinicians involved in their PCD management. As airway clearance is predominantly reviewed by physiotherapists:

- We will ask physiotherapists to complete this interview review process for each patient in phase 2 who is under their care.
- We will ask other members of the MDT to review the information for 2 patients in phase 2 under their care.

We hope that through interviews with clinicians from 3 different centres, we can generate an account of how the new information from imaging may influence the clinical decision making of experts .

This would help others to understand the role of functional imaging in clinical practice, specifically in decision making around the personalisation of airway clearance regimens potentially assisting with the design of future research, and the production of clinical guidance.
This research is being undertaken as part completion of the lead researcher's Doctorate.

Why have I been invited to take part?
You have been asked to take part because you are a clinician working with children or young people with PCD.

Do I have to take part?
No. It is up to you to decide whether you agree to take part, and you can change your mind at any time, without any repercussion and without giving a reason. If you choose to withdraw after you have completed the interview, either in part, or in full, the interview recording and transcript will be destroyed and will not be used in the final write-up.

Who is organising the study?
Lynne Schofield is a physiotherapist working in the North of England PCD service at Leeds Teaching Hospitals, and a clinical doctoral research fellow. She is working with Leeds Teaching Hospitals and the University of Sheffield MRI unit to performing this research. This study has been reviewed by the South Central - Oxford B Research Ethics Committee.

What will happen to me if I agree to take part?
If you do decide to take part, you will be invited to attend a series of interviews with Lynne, each will last up to 1 hour. The interviews can take place face-to-face at a mutually convenient location, or via Microsoft Teams if that is not possible. We anticipate that all of the interviews will take place on a 1:1 basis. However, for the 2 cases where the wider MDT is involved, if it is more convenient for this take place as a group interview, the convenience of the MDT will be prioritised.

For physiotherapists, the number of interviews will depend on the number of patients under their care who have participated in phase 2 with one interview required per patient. This is anticipated numbers for each area are: Leeds 15, Bradford 16, Sheffield 6. The interviews will take place at times convenient for you, a 12 month period has been allocated in which to complete the clinician interviews. For non-physiotherapist health care professionals this will be 2 interviews only.

You will be asked to give your formal consent to take part. If this is done via telephone or Microsoft Teams, the audio consent process will be recorded separately to the interview. You will be asked whether you prefer to be sent a copy of your

consent form by post or email. If face to face, you will be asked to sign a copy of the consent form prior to starting the interview.

As you are unlikely to have seen Ventilation MR images in clinical before, we will provide you with training which covers essential information needed when looking at the images from these scans before you take part in your first interview. The training will take no more than 1 hour and is most likely to be virtual.

Each interview will involve you reviewing the following items for phase 2 participant under your care:

- A video recording of:
  - an airway clearance technique review
  - the patient will then completing their airway clearance regimen
- Images from two types of MRI
  - Proton MRI
  - Ventilation MRI

The methods used in the interview will involve you "thinking aloud" whilst you review the information and Lynne will prompt you to keep talking. It is hoped that exploring specific examples in this way will help the researchers to understand how complex clinical decisions are made, and how this information could help to inform future similar decisions.

What are the potential risks and benefits of taking part?

There are no anticipated risks associated with participation in this research. However, the topics discussed may potentially be sensitive due to the detailed discussion and analysis of particular clinical decisions about patients you work with. If at any point during the interview you feel uncomfortable, please let the researcher know, and the interview can end at any point.

Whilst there are no immediate benefits for those people participating in the research, it is hoped that this work will establish some conclusions and recommendations to help clinicians with future clinical decision making, both for patients within the subgroups investigated, but also in other areas.

Will my taking part in this project be kept confidential?

All the information that we collect from you during the course of the research will be kept strictly confidential and will only be accessible to members of the research team. You will not be identifiable in any reports or publications unless you have given your explicit consent for this. When the interview is recorded, you will be assigned a research ID number, so the researchers can identify you throughout the study, but your identifiable information is not available alongside your interview data. Copies of consent forms will be stored in a locked cabinet in a locked room, separately to any interview recordings or transcripts. Some basic demographic information will also be collected from you, but this will also be stored separately, and will not be linked to

your interview responses in any publications. Copies of consent forms, paper demographics forms, and interview recordings will be destroyed at the end of this research. Interview transcripts and electronic demographics database will be stored securely for as long as required, but for at least 5 years, before being destroyed.

What will happen to the results of the research project?
The results of the research may be published in journals, and presented at conferences. This work may also be used to inform a larger study using similar methods. Any direct quotes used in publications will not be traceable to a particular individual or NHS Trust.

Will I be recorded, and how will the recorded media be used?
The audio recordings from the interviews will be used only for analysis and inclusion in publications and other outputs arising from this research. They will not be used for any other purpose without your written permission, and no-one outside of the research team will have access to the original recordings. They will be securely recorded on an encrypted Dictaphone, before being transferred to a university network drive, only accessible by the researchers.

How will we use information about you?
We will need to use information from your interview for this research project.
Parts of your data such as your consent form will include you're:

- Name and initials
- Contact details

People will use this information to do the research or to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.
Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, the interview recording and transcript will be destroyed and will not be used in the final write-up.

Where can you find out more about how your information is used?
You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- our information on our website https://www.leedsth.nhs.uk/patients-visitors/patient-and-visitor-information/how-we-use-your-data/

- by asking one of the research team
- by sending an email to Leedsth-tr.informationgovernance@nhs.net
- by ringing us on 0113 2433144 and ask for the Data Protection Officer

Who is responsible for this research?
This research is being carried out by researchers at Leeds Teaching Hospitals (the sponsor) and the University of Sheffield.

Who has reviewed the study?
This study has been reviewed by the South Central - Oxford B Research Ethics Committee.

What If Something Goes Wrong?
If you are harmed by taking part in this research project, there are no special compensation arrangements, but if you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of the study you should contact the Chief Investigator (Lynne Schofield, *Leeds Teaching Hospitals lynneschofield@nhs.net)*. Alternatively the normal National Health Service *(via letter to The Chief Executive, Leeds Teaching Hospitals, Leeds General Infirmary, Great George Street, Leeds LS1 3EX)* or the normal University complaints mechanisms are available *(via letter to the University of Sheffield Registrar and Secretary, Firth Court, Western Bank, Sheffield. S10 2TN)*.

What if I have any other concerns?
If you have any problems, concerns, complaints or other questions about this study, you should preferably contact the investigator, (Lynne Schofield, Leeds Teaching Hospitals, lynneschofield@nhs.net*)*. Alternatively you may contact Leeds Teaching Hospitals or the University of Sheffield, via the addresses listed under the heading 'What if anything goes wrong?' above. You can keep this information sheet and will be given a copy of the signed consent form to keep.

Thank you for taking the time to read this information.

Appendix 6: MRI safety screening form

THE UNIVERSITY OF SHEFFIELD ACADEMIC DEPARTMENT OF RADIOLOGY

Magnetic Resonance Imaging Unit at the Royal Hallamshire Hospital

PATIENT & VOLUNTEER SCREENING FORM

Please complete this form prior to having your scan. Please circle the appropriate answer.

Surname _____

First names _____

Date of Birth _____

Address _____

Home Tel _____ Work Tel _____

Have you ever had any surgery to your heart or chest e.g. cardiac pacemaker, replacement valves, stents or filters inserted?	Yes	No
Have you ever had any operation to your brain, e.g. aneurysm clips or shunts inserted?	Yes	No
Have you **EVER** had any metal fragments in your eyes?	Yes	No
Are you or could you be pregnant?	Yes	No
Do you have an electronic or breast implant in your body?	Yes	No
Have you had any surgery of any type in the last 2 months?	Yes	No

YOU MUST RING THE UNIT IF YOU HAVE ANSWERED 'YES' TO ANY OF THE ABOVE QUESTIONS. FAILURE TO DO SO MAY MEAN THAT YOU CANNOT BE SCANNED. TELEPHONE No. 0114 215 9595

Do you suffer from any heart disease or rhythm disorder?	Yes	No
Do you have any hearing problems, e.g. tinnitus?	Yes	No
Do you have any kidney problems?	Yes	No
Do you wear any removable metal dental work?	Yes	No
Do you suffer from epilepsy or diabetes?	Yes	No
Do you have any allergies?	Yes	No
Do you have any other metallic object in your body, e.g. metal fragments or surgical clips?	Yes	No

If so, please specify _____

Please remove all credit cards and loose metallic objects, e.g. watches, wallets, keys, money, glasses, jewellery (including body piercing), hearing aids, hair clips and skin patches.

Lockers for your valuables are provided in the waiting area.

How much do you weigh? _____

If you have read and understood the above restrictions please sign below.

Signature _____ Date _____

or signature of consenting adult

Appendix 7: Quality of life questionnaire, QOL-PCD

Provided are three versions of the QOL-PCD: for children aged 6-12 years; for adolescents aged 13-17 years; parent proxy. A version for adults is also available but

as the oldest participant was 17 years old, this was not used in the study. Participants and their parents completed the questionnaires via on online platform as depicted in , the content of the online questionnaires is as per Figure 95 the questionnaires provided in appendices 7.1 to 7.3.

Figure 95: Screenshot taken from the electronic child QOL-PCD (320). Reproduced with permission from L.Behan.

7.1 QOL-PCD child version

QOL-PCD QUESTIONNAIRE

Children Ages 6-12 years

These questions are for children like you who have PCD. Your answers will help us understand what this disease is like and how your treatments help you. So, answering these questions will help you and others like you in the future.

Please answer all the questions. There are no right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Notes for physicians and researchers:

This questionnaire can only be used with agreement of the consortium of developers. The developers request that all data generated by use of the questionnaire contributes to the further validation of the instrument. Data relating to this questionnaire cannot be published in any form until the results of the validation study by the consortium of developers are published.

For further details and permissions please contact:

- North America: Prof Quittner email aquittner@miami.edu
- Europe and other regions outside North America: Prof Jane Lucas jlucas1@soton.ac.uk

QOL-PCD QUESTIONNAIRE

Children Ages 6-12 years

Please check the box matching your response.

In the past **week**:	Very True	Mostly True	A little bit True	Not at all True
1. You were able to walk as fast as others	☐	☐	☐	☐
2. You were able to climb stairs as fast as others	☐	☐	☐	☐
3. You were able to run, jump, and climb as you wanted	☐	☐	☐	☐
4. You were able to run as quickly and as long as others	☐	☐	☐	☐
5. You were able to do sports that you enjoy (e.g., soccer, dancing or others)	☐	☐	☐	☐

Please check the box matching your response.

And during this past **week**, indicate how often:	Always	Often	Sometimes	Never
6. You felt mad	☐	☐	☐	☐
7. You felt grumpy	☐	☐	☐	☐
8. You felt worried about getting sick	☐	☐	☐	☐
9. You felt sad	☐	☐	☐	☐
10. You felt frustrated about doing your daily treatments	☐	☐	☐	☐
11. You had to stop having fun to do your treatments	☐	☐	☐	☐

QOL-PCD QUESTIONNAIRE Children Ages 6 to 12 years

Please check the box matching your response.

During the past **week**:	Very True	Mostly True	A little bit True	Not at all True
12. You were late or missed school because of PCD	☐	☐	☐	☐
13. You had enough time to do all of your treatments	☐	☐	☐	☐
14. Doing treatments in front of your friends bothers you	☐	☐	☐	☐
15. You spent a lot of time with your friends	☐	☐	☐	☐
16. You missed going to after-school activities because of PCD	☐	☐	☐	☐
17. You were teased by other children because your nose was runny	☐	☐	☐	☐
18. Others were afraid you would get them sick	☐	☐	☐	☐
19. You had trouble hearing (if you wear hearing aids: you had trouble hearing without your aids)	☐	☐	☐	☐
20. Doing your treatments bothered you	☐	☐	☐	☐
21. Your ears felt blocked up	☐	☐	☐	☐

Please check the box matching your response.

Let us know how often in the past **week**:	Always	Often	Sometimes	Never
22. You coughed during the day	☐	☐	☐	☐
23. Your ears hurt	☐	☐	☐	☐
24. You woke up during the night because you were coughing	☐	☐	☐	☐
25. You had to cough up mucus (even if you swallow it)	☐	☐	☐	☐

QOL-PCD QUESTIONNAIRE Children Ages 6 to 12 years

Let us know how often in the past **week**:	Always	Often	Sometimes	Never
26. You had trouble breathing	☐	☐	☐	☐
27. You had liquid coming out of your ears	☐	☐	☐	☐
28. You woke up during the night because your nose was blocked up	☐	☐	☐	☐
29. Your chest hurt	☐	☐	☐	☐
30. You had mucus stuck in your chest	☐	☐	☐	☐
31. You had a runny nose	☐	☐	☐	☐
32. Your head hurt (near your eyes or in your forehead)	☐	☐	☐	☐
33. Your nose felt blocked up	☐	☐	☐	☐
34. You felt snot (stuff) dripping down your throat	☐	☐	☐	☐

Please be sure all the questions have been answered.

THANK YOU

7.2 QOL-PCD adolescent version

QOL-PCD QUESTIONNAIRE

Adolescents Ages 13 to 17 years

Understanding the impact of your illness and treatments on your everyday life can help your healthcare team keep track of your health and adjust your treatments. For this reason, this questionnaire was specifically developed for people who have primary ciliary dyskinesia (PCD). Thank you for your willingness to complete this form.

Instructions

The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Notes for physicians and researchers:

This questionnaire can only be used with agreement of the consortium of developers. The developers request that all data generated by use of the questionnaire contributes to the further validation of the instrument. Data relating to this questionnaire cannot be published in any form until the results of the validation study by the consortium of developers are published.

For further details and permissions please contact:

- North America: Prof Quittner email aquittner@miami.edu
- Europe and other regions outside North America: Prof Jane Lucas jlucas1@soton.ac.uk

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QOL-PCD QUESTIONNAIRE

Adolescents Ages 13 to 17 years

Section I. Quality of Life

Please check the box indicating your answer.

***During the past week**, to what extent have you had difficulty:*	**A lot of difficulty**	**Some difficulty**	**A little difficulty**	**No difficulty**
1. Performing activities such as running or playing sports	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Climbing stairs as fast as others	☐	☐	☐	☐

***During the past week**, indicate how often:*	**Always**	**Often**	**Sometimes**	**Never**
4. You felt well	☐	☐	☐	☐
5. You felt worried about getting sick	☐	☐	☐	☐
6. You felt happy	☐	☐	☐	☐
7. You felt tired	☐	☐	☐	☐
8. You felt energetic	☐	☐	☐	☐
9. You felt exhausted	☐	☐	☐	☐
10. You felt sad	☐	☐	☐	☐
11. Your treatments for PCD got in the way of your activities	☐	☐	☐	☐
12. Doing your treatments frustrated you	☐	☐	☐	☐

*Thinking about the state of your health over the last **week**:*

13. How difficult is it for you to fit in your treatments (including medications) each day?

1. Not at all
2. A little
3. Moderately
4. Very

QOL-PCD QUESTIONNAIRE

Adolescents Ages 13 to 17 years

Please select a box indicating your answer.

Thinking about your health ***during the past week****, indicate the extent to which each sentence is true or false for you.*	Very True	Mostly True	Somewhat True	Not At All True
14. I have trouble recovering after physical effort	☐	☐	☐	☐
15. I have to limit activities such as running or playing sports	☐	☐	☐	☐
16. I feel comfortable discussing my illness with others	☐	☐	☐	☐
17. I feel comfortable blowing my nose in front of friends	☐	☐	☐	☐
18. People are afraid I might get them sick	☐	☐	☐	☐
19. I think my coughing bothers others	☐	☐	☐	☐
20. It is difficult to make plans for the future (for example, going on in school, getting a job, etc.)	☐	☐	☐	☐

Section II. School, Work, or Daily Activities

21. How often were you absent from school, work, or unable to complete daily activities during the past week because of your illness or treatments?

☐ Always ☐ Often ☐ Sometimes ☐ Never

22. To what extent does PCD get in the way of meeting school, work, or your own goals?

☐ A lot ☐ Moderately ☐ A little ☐ Not at all

QOL-PCD QUESTIONNAIRE

Adolescents Ages 13 to 17 years

Section III. Symptoms

Please select a box indicating your answer.

*Indicate how you have been feeling during the past **week**.*	**A great deal**	**Somewhat**	**A little**	**Not at all**
23. Have you been congested in the chest?	☐	☐	☐	☐
24. Have you been coughing during the day?	☐	☐	☐	☐
25. Have you had to cough up mucus (including swallowing it)?	☐	☐	☐	☐ **If not at all go to Question 27**

During the past week:

26. Has your mucus been mostly: ☐Clear ☐Clear to yellow ☐Yellowish-green ☐Greenish ☐Green with traces of blood ☐Don't know

	A great deal	**Somewhat**	**A little**	**Not at all**
27. You had fluid coming out of your ears	☐	☐	☐	☐
28. You had trouble hearing (if you wear hearing aids: you had trouble hearing without your aids)	☐	☐	☐	☐
29. You felt snot dripping down your throat	☐	☐	☐	☐

During the past week, indicate how often:	**Always**	**Often**	**Sometimes**	**Never**
30. Your breathing has been noisy (whistling, wheezy chest)	☐	☐	☐	☐
31. You had a stuffy nose	☐	☐	☐	☐
32. You had difficulty sleeping because of your chest	☐	☐	☐	☐
33. You had trouble breathing	☐	☐	☐	☐
34. Your ears hurt	☐	☐	☐	☐
35. You had a runny nose	☐	☐	☐	☐
36. You had difficulty sleeping because your nose was blocked up	☐	☐	☐	☐
37. Your ears were blocked up	☐	☐	☐	☐
38. You had a headache	☐	☐	☐	☐

QOL-PCD QUESTIONNAIRE

Adolescents Ages 13 to 17 years

Please be sure you have answered all the questions.

THANK YOU

7.3 QOL-PCD parent proxy version

QOL-PCD QuestionnaireParents/Caregivers (Children Ages 6 to 12)

Understanding the impact of your child's illness and treatments on his or her everyday life can help your healthcare team keep track of your child's health and adjust his or her treatments. For this reason, we have developed a quality of life questionnaire specifically for parents of children with PCD. We thank you for your willingness to complete this questionnaire.

Instructions: The following questions are about the current state of your child's health, as **he or she** perceives it. This information will allow us to better understand how **he or she feels** in everyday life.

Please answer all the questions. There are no right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your child's situation.

Notes for physicians and researchers:

This questionnaire can only be used with agreement of the consortium of developers. The developers request that all data generated by use of the questionnaire contributes to the further validation of the instrument. Data relating to this questionnaire cannot be published in any form until the results of the validation study by the consortium of developers are published.

For further details and permissions please contact:
North America: Prof Quittner email aquittner@miami.edu
Europe and other regions outside North America: Prof Jane Lucas jlucas1@soton.ac.uk

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QOL-PCD QuestionnaireParents/Caregivers (Children Ages 6 to 12)

Section I. Quality of Life

Please indicate how your child has been feeling during the past week by checking the box matching your response.

To what extent has your child had difficulty:	**A lot of difficulty**	**Some difficulty**	**A little difficulty**	**No difficulty**
1. Performing vigorous activities, such as running or playing sports	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Climbing stairs as fast as others	☐	☐	☐	☐
4. Climbing several flights of stairs	☐	☐	☐	☐

*During the past **week**, indicate how often your child:*	**Always**	**Often**	**Sometimes**	**Never**
5. Seemed happy	☐	☐	☐	☐
6. Seemed worried about his/her illness	☐	☐	☐	☐
7. Seemed tired	☐	☐	☐	☐
8. Seemed well	☐	☐	☐	☐
9. Seemed energetic	☐	☐	☐	☐
10. Was absent or late for school or other activities because of his/her illness or treatments				
11. Was frustrated by doing his/her treatments	☐	☐	☐	☐

Please check the box that matches your response to these questions.

*Thinking about your child's state of health during the past **week**, indicate the extent to which each sentence is true or false for your child:*

	Very true	**Mostly true**	**Somewhat True**	**Not at all True**
12. My child had trouble recovering after physical effort	☐	☐	☐	☐
13. Mealtimes were a struggle	☐	☐	☐	☐
14. My child's treatments got in the way of his/her activities	☐	☐	☐	☐
15. My child felt healthy	☐	☐	☐	☐
16. My child got enough help in his/her classroom to perform well (e.g., sitting up front, time to make up homework when sick)	☐	☐	☐	☐
17. My child was able to keep up with his/her school work or outdoor activities	☐	☐	☐	☐
18. My child spent a lot of time on his/her treatments everyday	☐	☐	☐	☐

QOL-PCD QuestionnaireParents/Caregivers (Children Ages 6 to 12)

Please circle the number indicating your answer. Please choose only one answer for each question.

19. How difficult is it for your child to fit in his/her treatments (including medications) each day?

1. Not at all
2. A little
3. Moderately
4. Very

20. How do you think your child's health is now?

1. Excellent
2. Good
3. Fair
4. Poor

Section II. Symptoms

Please indicate how your child has been feeling during the past week.

	A great deal	Somewhat	A little	Not at all
21. My child had trouble gaining weight	☐	☐	☐	☐
22. My child's ears hurt	☐	☐	☐	☐
23. My child's chest was congested	☐	☐	☐	☐
24. My child coughed during the day	☐	☐	☐	☐
25. My child had to cough up mucus (including swallowing it)	☐	☐	☐	☐
26. My child had a runny nose	☐	☐	☐	☐
27. My child felt mucus dripping down his/her throat	☐	☐	☐	☐

QOL-PCD QuestionnaireParents/Caregivers (Children Ages 6 to 12)

*During the past **week:***	**Always**	**Often**	**Sometimes**	**Never**
28. My child had trouble hearing (if aided, he/she had trouble without aids)	☐	☐	☐	☐
29. My child had fluid draining from his/her ears	☐	☐	☐	☐
30. My child had a sinus headache	☐	☐	☐	☐
31. My child had trouble breathing	☐	☐	☐	☐
32. My child woke up during the night because he/she was coughing	☐	☐	☐	☐
33. My child had a stuffy nose	☐	☐	☐	☐
34. My child's chest hurt	☐	☐	☐	☐
35. My child had a poor appetite	☐	☐	☐	☐

Please ensure you have answered all of the questions

THANK YOU FOR YOUR COOPERATION!

Appendix 8: Clinical data collection template

Session date	
Age	
Sex	
Clinical history	
PCD diagnosis and relevant PCD history	
Other medical conditions	
Regular medications	
No of exacerbations or antibiotics in previous 12 months	
Lung function	
Recent imaging	
Physio reviews	
ACT regimen advised	
When started	
Social history	
Subjective	
Current health	
Physio routine being done at home	
History of regimen	
Independence	
Nasal symptoms	
Physical activity	
Continence/MSK symptoms	
Objective pre-ACT	
Ausc	
Palpation/expansion	
Huff/cough	
Sputum	
SpO2	
Objective- post-ACT	
Step count/information from break	
Observation	
Ausc	
Palpation	
Expansion	
Huff/cough	

Sputum		
SpO2 (if indicated)		
QOL-PCD score	Patient	Parent (if applicable)
Physical functioning		
Emotional functioning		
Treatment burden		
Role		
Social functioning		
Vitality		
Upper respiratory symptoms		
Lower respiratory symptoms		
Hearing symptoms		
Eating and weight		
Health perception		

Appendix 9: Individual case graphs of change over time

9.1 ^{129}Xe VDP

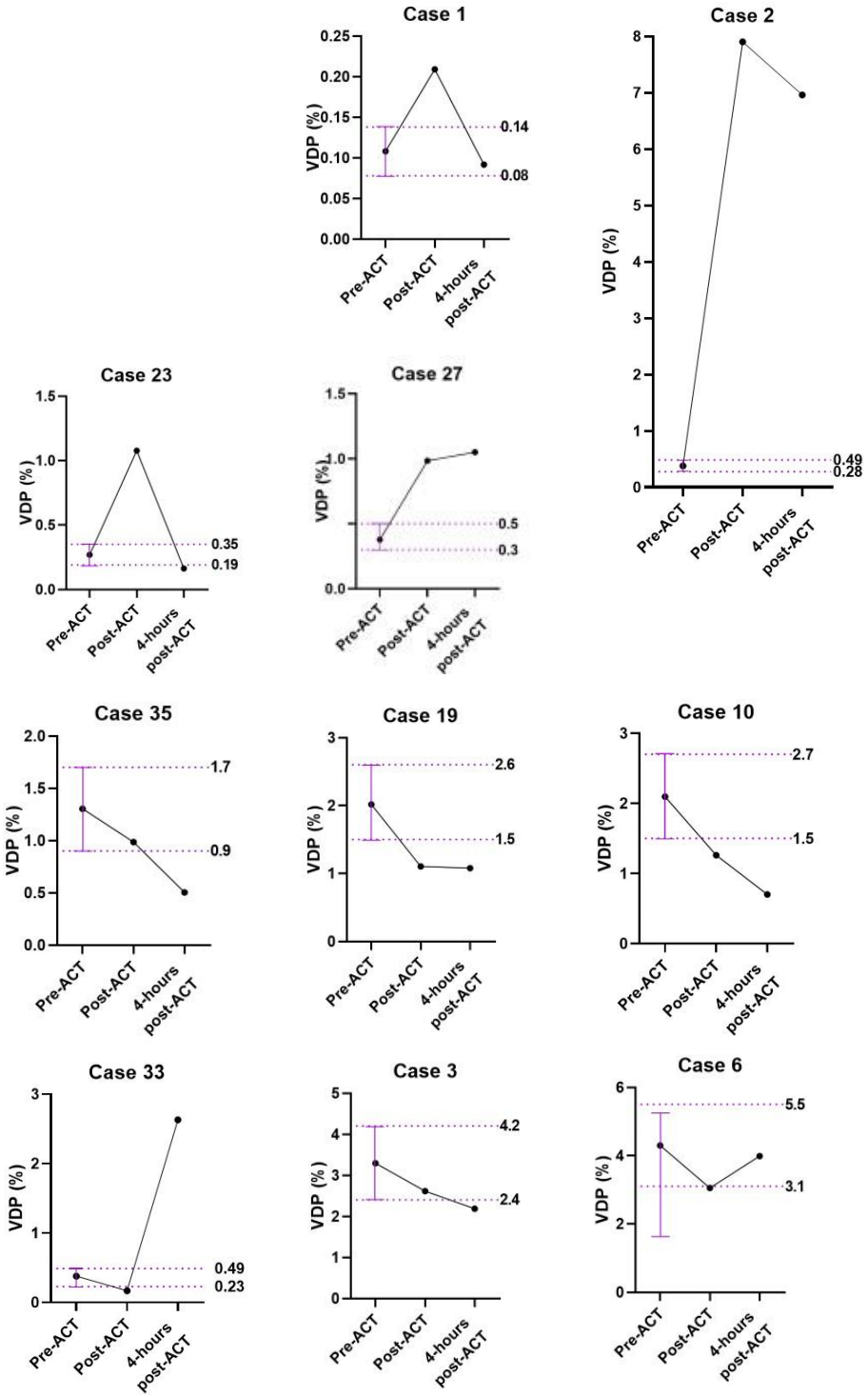


Figure 96: (1 of 3) The assessment change in ^{129}Xe VDP over time for each individual case, in the context of individual coefficient of variance (CoV) parameters calculated from the control group. The purple bars depict the range of variability over time anticipated for each individual case, calculated from the same day variability in the no-ACT group. The purple dotted lines depict the upper and lower CoV values for each case at ±28% of pre-ACT VDPI.

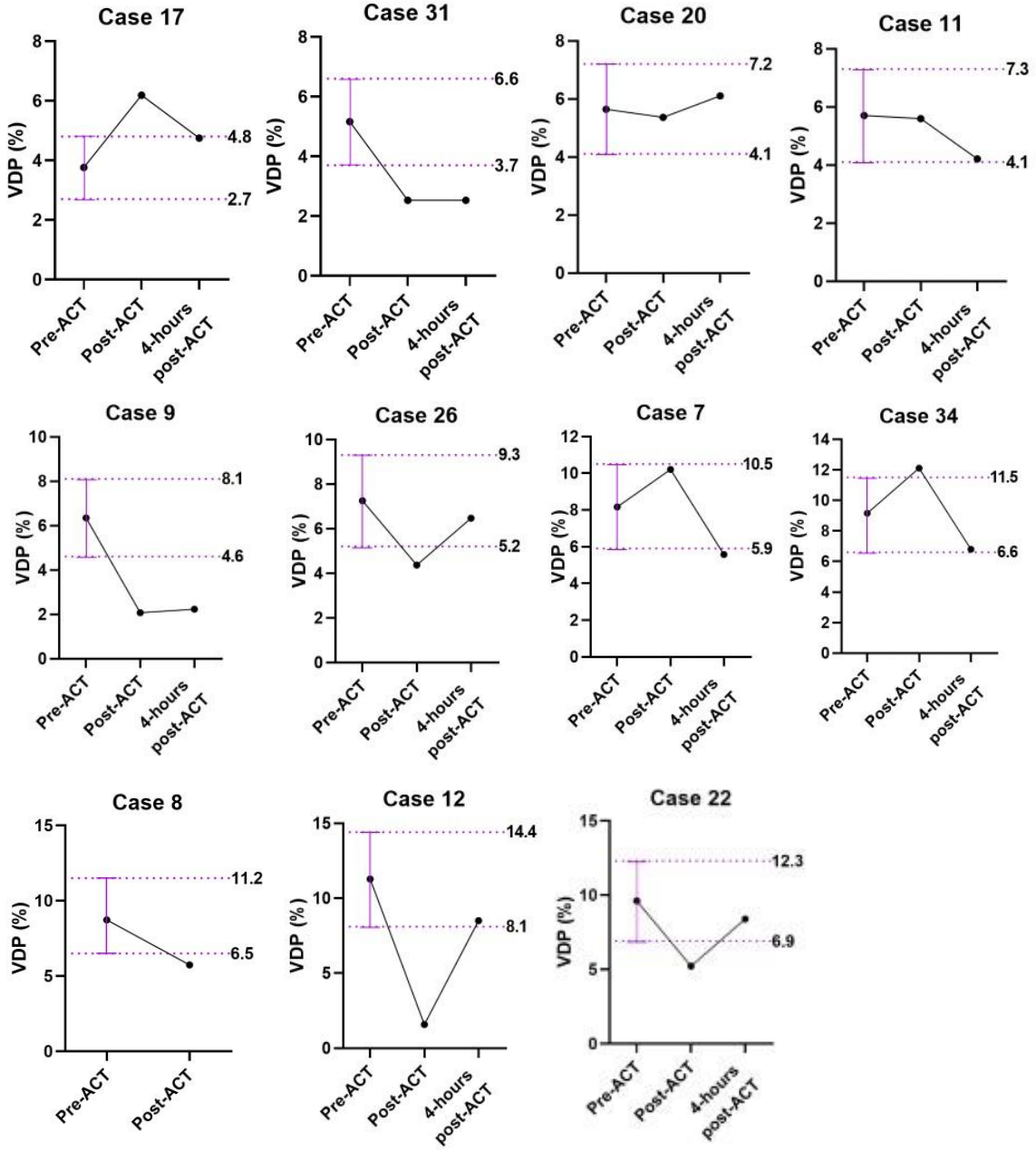


Figure 97: (2 of 3) The assessment change in ^{129}Xe VDP over time for each individual case, in the context of individual coefficient of variance (CoV) parameters calculated from the control group. The purple bars depict the range of variability over time anticipated for each individual case, calculated from the same day variability in the no-ACT group. The purple dotted lines depict the upper and lower CoV values for each case at ±28% of pre-ACT VDPI.

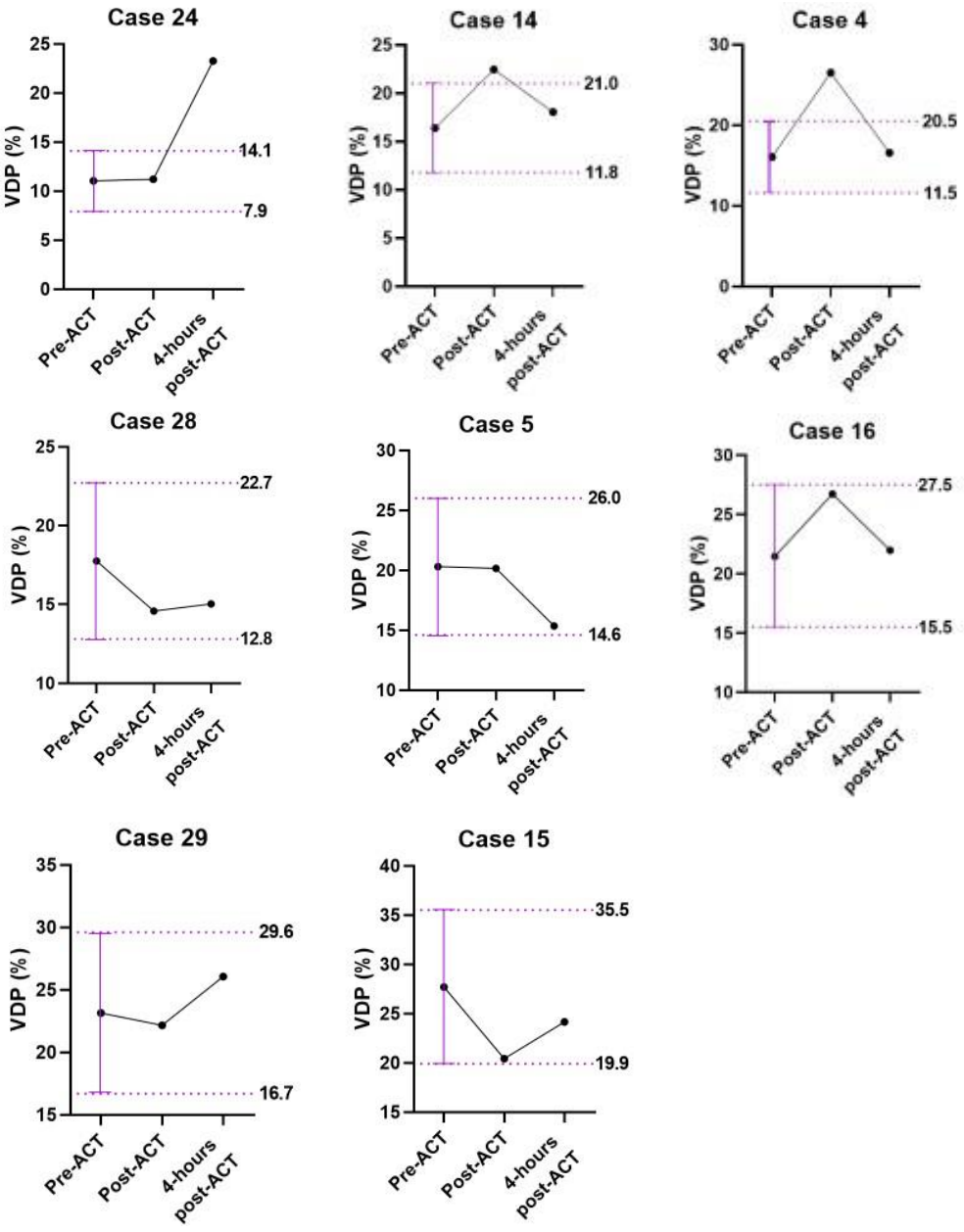


Figure 98: (3 of 3) The assessment change in ^{129}Xe VDP over time for each individual case, in the context of individual coefficient of variance (CoV) parameters calculated from the control group. The purple bars depict the range of variability over time anticipated for each individual case, calculated from the same day variability in the no-ACT group. The purple dotted lines depict the upper and lower CoV values for each case at ±28% of pre-ACT VDPI.

9.2 ^{129}Xe VHI

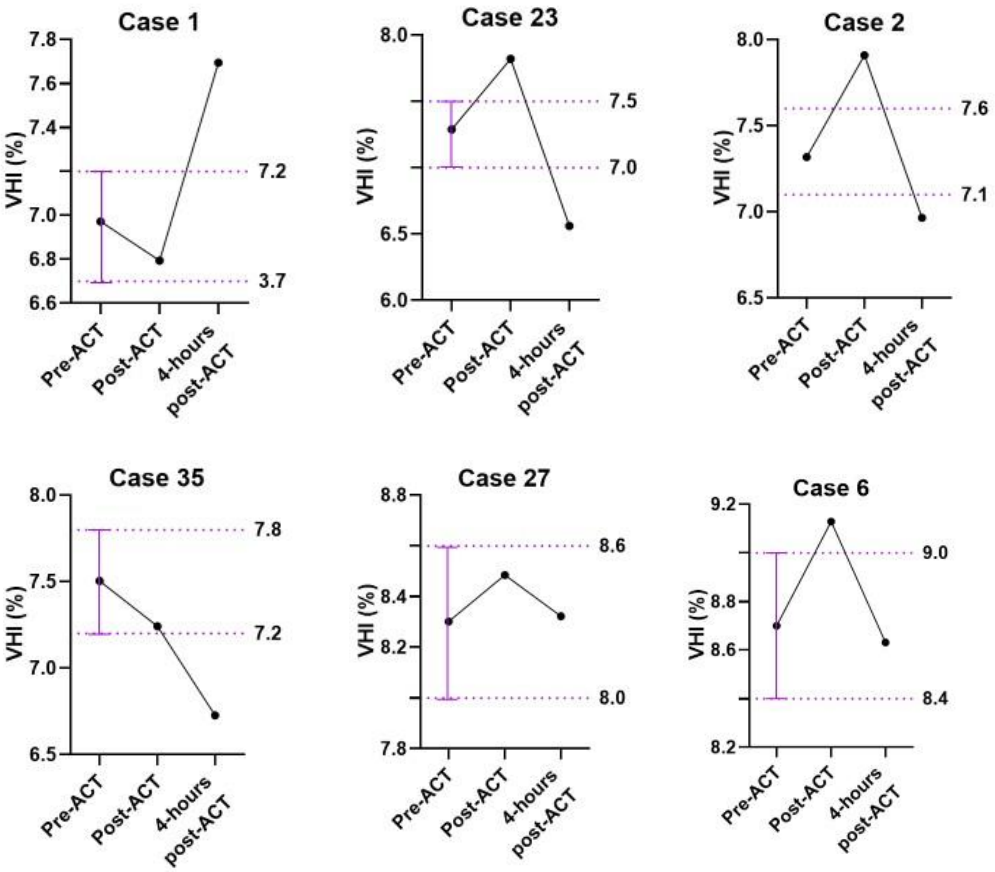


Figure 99 (1 of 3) The assessment change in ^{129}Xe VDP over time for each individual case, in the context of individual coefficient of variance (CoV) parameters calculated from the control group. The purple bars depict the range of variability over time anticipated for each individual case, calculated from the same day variability in the no-ACT group. The purple dotted lines depict the upper and lower CoV values for each case at ±3.6 of pre-ACT VHI.

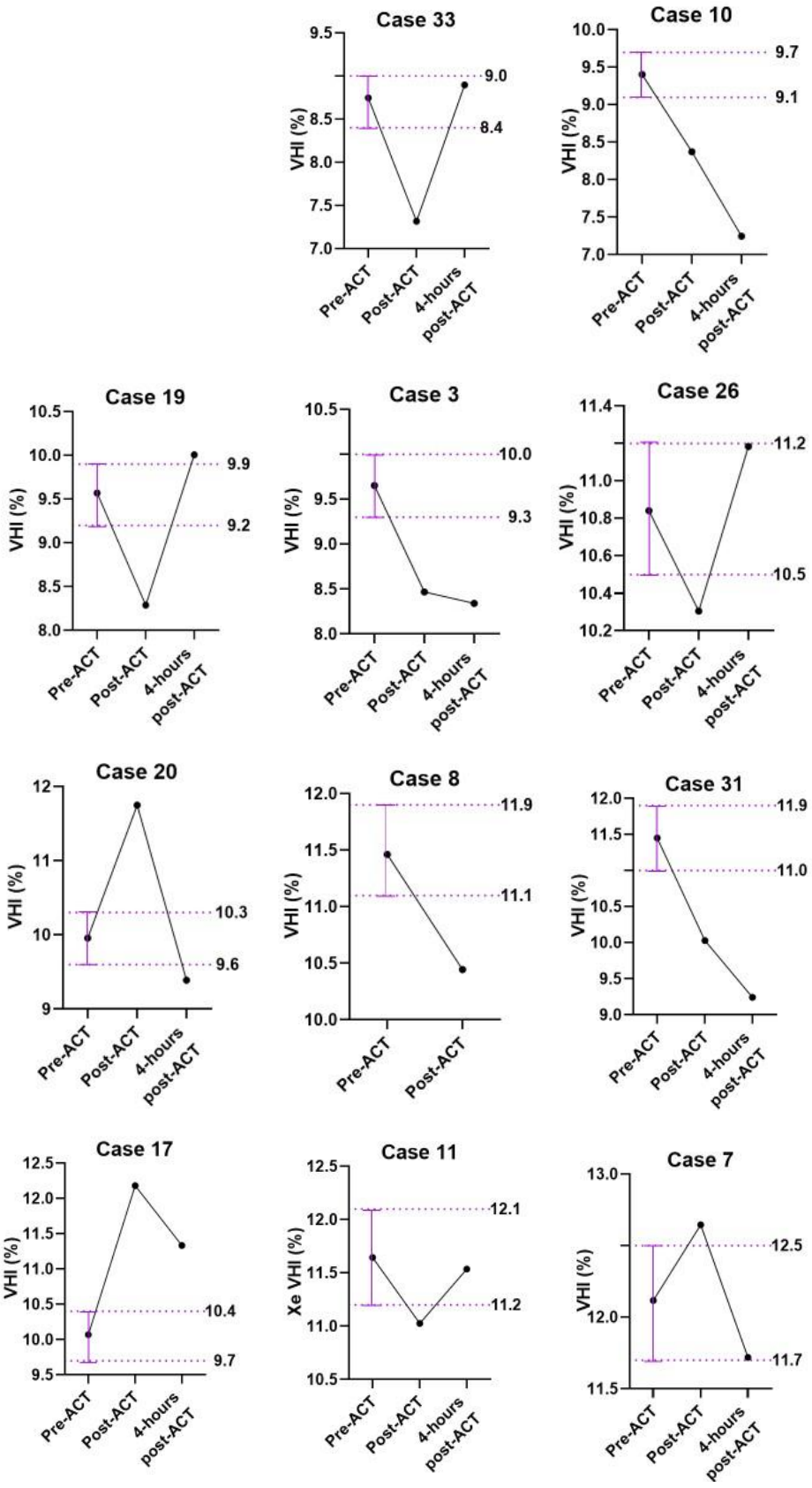


Figure 100: (2 of 3) The assessment change in ^{129}Xe VDP over time for each individual case, in the context of individual coefficient of variance (CoV) parameters calculated from the control group. The purple bars depict the range of variability over time anticipated for each individual case, calculated from the same day variability in the no-ACT group. The purple dotted lines depict the upper and lower CoV values for each case at ±3.6 of pre-ACT VHI.

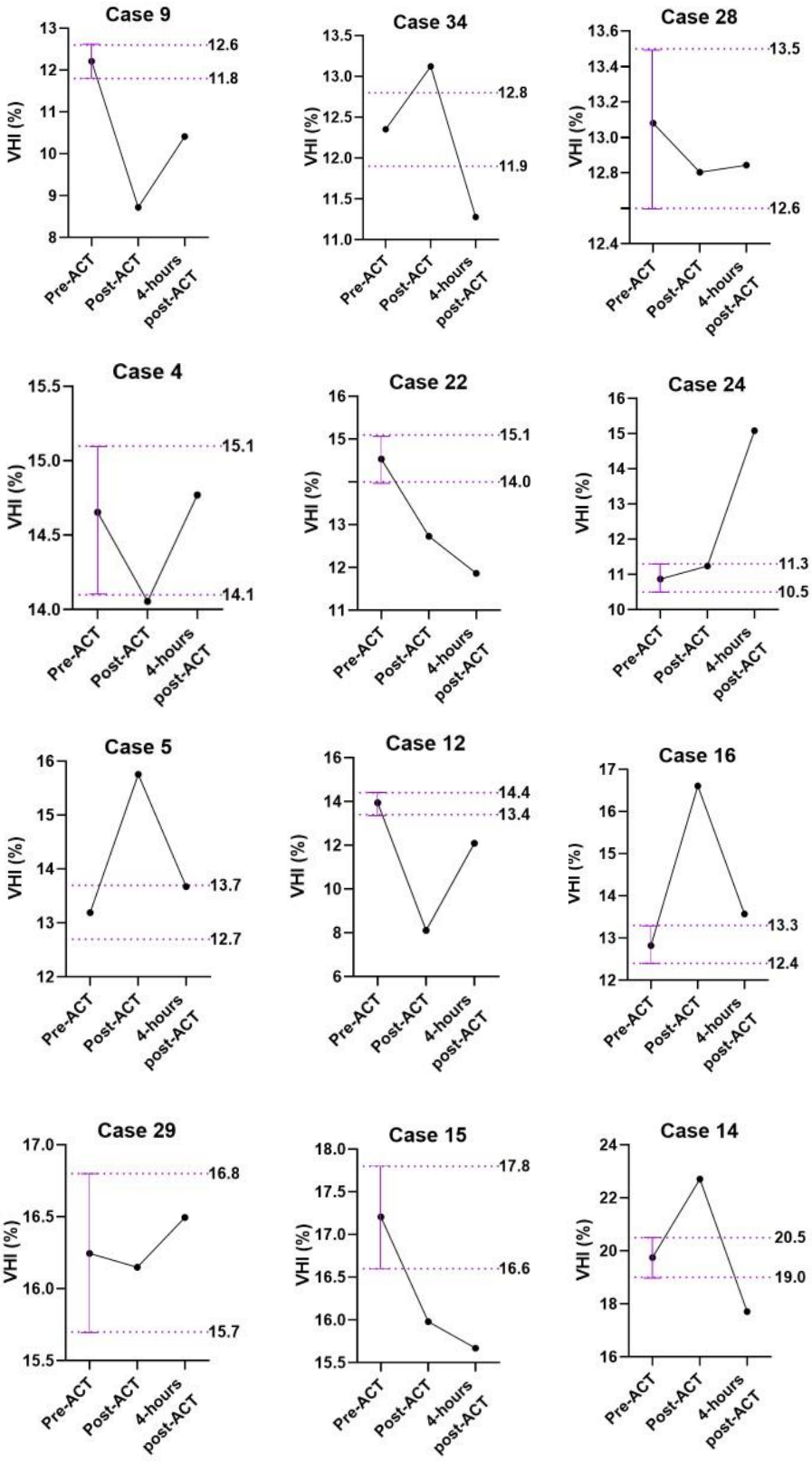


Figure 101: (3 of 3) The assessment change in ^{129}Xe VDP over time for each individual case, in the context of individual coefficient of variance (CoV) parameters calculated from the control group. The purple bars depict the range of variability over time anticipated for each individual case, calculated from the same day variability in the no-ACT group. The purple dotted lines depict the upper and lower CoV values for each case at ±3.6 of pre-ACT VHI.

9.3 ^{1}H (PREFUL) VDP

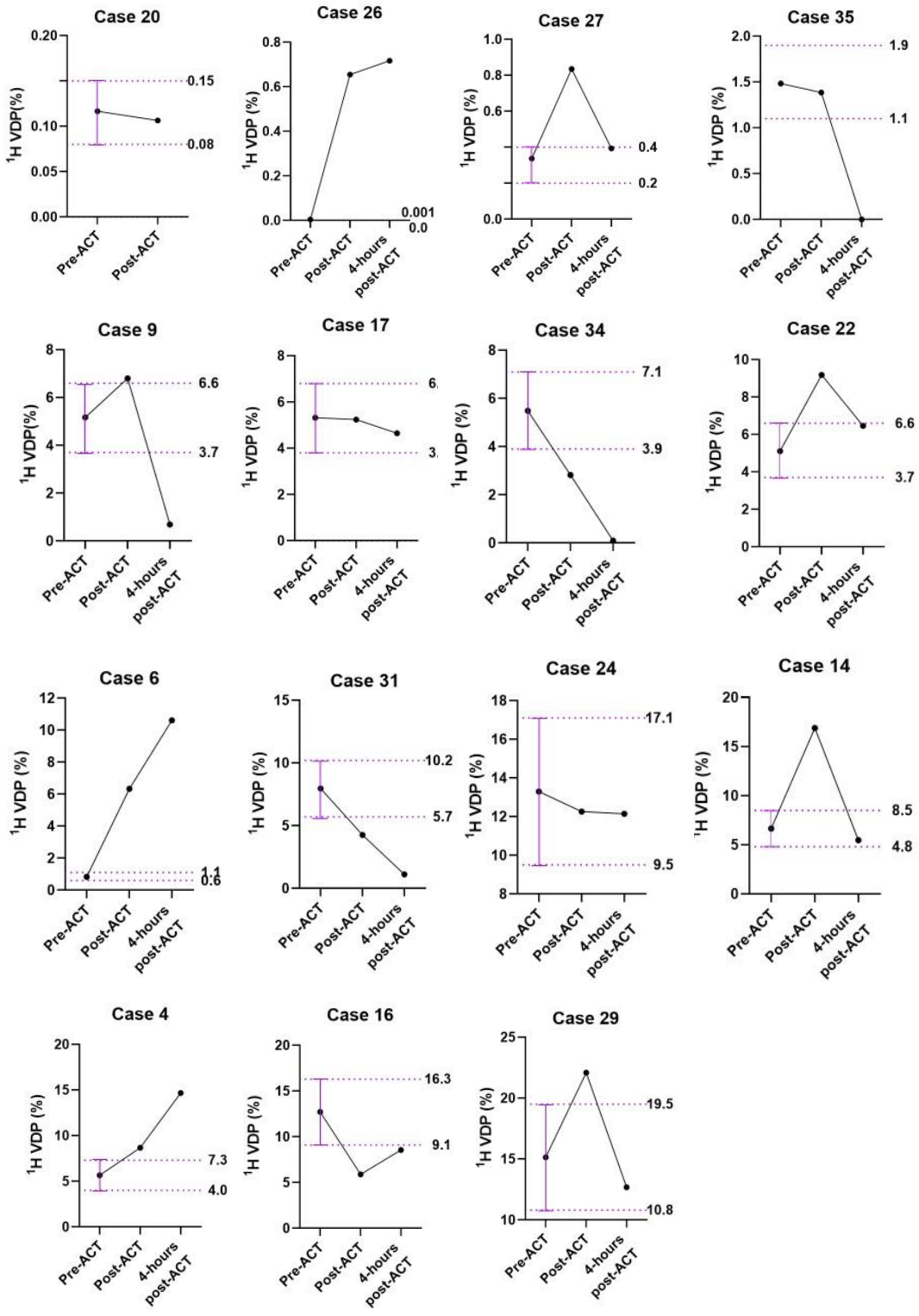


Figure 102: The assessment change in ^{1}H VDP over time for each individual case, in the context of individual coefficient of variance (CoV) parameters calculated from the control group. The purple bars depict the range of variability over time anticipated for each individual case, calculated from the same day variability in the no-ACT group. The purple dotted lines depict the upper and lower CoV values for each case at ±28% of pre-ACT ^{1}H VDP.

Appendix 10: CTA interview schedule

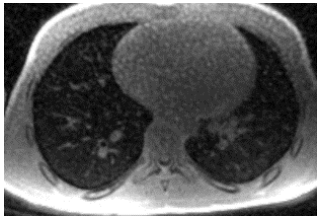
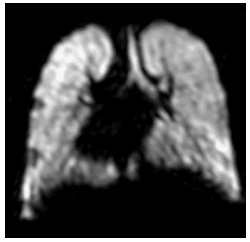
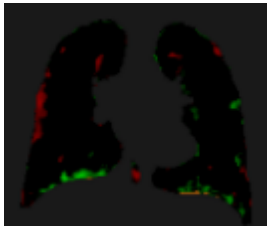
Cue category	Cue	Prompts	RPDM	ACT model
Information which would be available clinically	Summary of clinical history	Keep talking Is this in keeping with their usual clinical picture? Do you know how they came to be on this regimen?	Cues Expectancies	Cues Intervention
	Video of ACT review	Keep talking Is this similar to how they are in clinic?	Cues	Cues
	Video of ACT completion	Keep talking Do you think it is working for them? What would it look like if it was? If they were coming to see you in clinic next week what would your plan be? When would you like to see them next?	Cues Will it work? Modify? Implement	Cues Trial of intervention Response Will it work Time to follow up
Structural imaging	RV image from pre-ACT	Keep talking Does this fit with the clinical picture?	Information Cues Expectancies	Cues
	UTE from pre-ACT	Does this fit with the clinical picture? If they were coming to see you in clinic next week what would your plan be in terms of their	Information Cues Expectancies	Cues Time to follow up

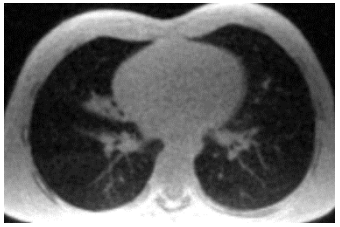
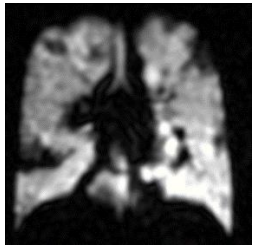
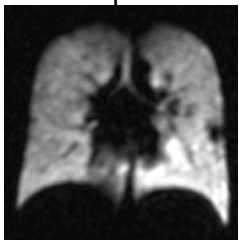
		ACT regimen? When would you like to see them next?		
	Any other 1H images which are indicated for the case or arising from the discussion	As above		
Ventilation imaging	Pre ACT Xe EITV (raw images, report including binning map and metrics)	Keep talking	Cues Expectancies Goals Actions	Cues ? experiential learning
	Post-ACT Xe EITV (raw images, report including binning map and metrics)	Keep talking		Response Further cues
	Pre-post TRM	Keep talking		Response
	4hour post-ACT (raw images, report including binning map and metrics)	Keep talking		Response Further cues
	Pre-4hour TRM	Keep talking	Response	Response
	Pre, post and 4hours post-ACT at TLC (report including binning maps and metrics, raw images if indicated)	Keep talking	Response	Response Further cues
Preful imaging	Pre, post and 4hours post-ACT at TLC (report including binning maps and metrics)	Keep talking	Cues Expectancies Goals Actions	Response Further cues

Appendix 11: Case summaries from the joint display tables

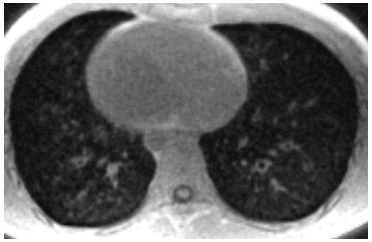
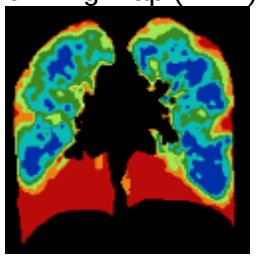
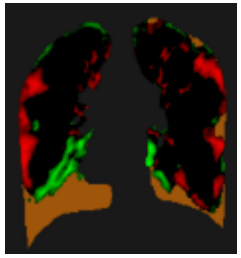
11.1 Cases classified as Case type X

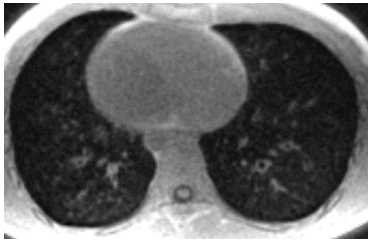
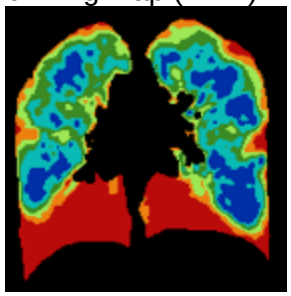
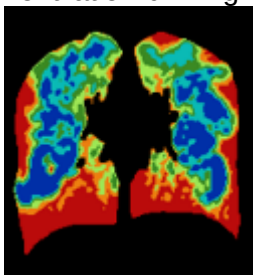
Table 44: Excerpts from the joint display tables used to integrate the quantitative and qualitative data for cases classified as Case type X. Full details are not provided to ensure anonymity of both the patient and clinician participants. For each case, spirometry (FEV_1 % predicted), frequency of prescribed ACTs and self-reported frequency are provided as selected clinical information from the available clinical data. Cue indicates the information being reviewed by the clinician at the time of the except below. Model links to the constructs from the ACT personalisation model. Unless specified, ^{129}Xe images were acquired at end inspiratory tidal volume. BD= twice daily, OD= once daily, 6 or 7% NaCl = nebulised 6 or 7% sodium chloride, PEP= positive expiratory pressure, ASL= alternate side lying UTE= ultrashort echo. TRM= treatment response map.

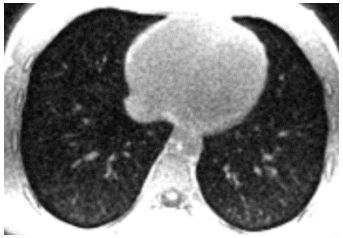
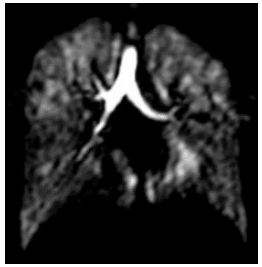
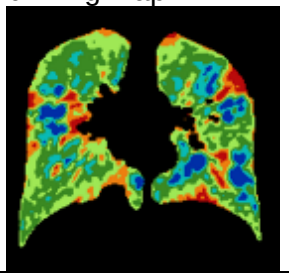
Case 10 **X1** **Physio**	**Clinical information** FEV_1 107% predicted, prescribed ACT BD, completes 4-5 times/week.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =2.1, post= 1.3, 4-hours post =0.7.	**Case classification point**
Cue	Observation of ACT regimen (7% NaCl with Aerobika in sitting prone and ASL)	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	Post-ACT Xe TRM 

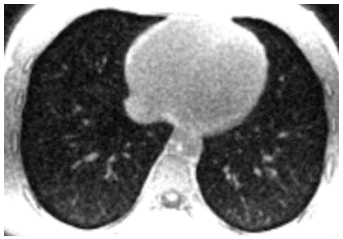
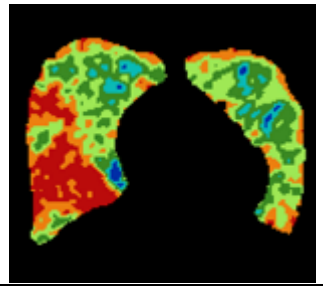
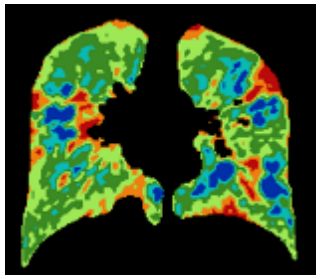
Excerpt	*(The video) made me think more about going through the neb... as well as separating the two to see if you could increase... the...time the hypertonic was down before we started clearing it because he has obviously got quite sticky secretions*	*I thought he might look a bit better than this…exercise… doesn't replace airway clearance, but you expect an element of that to help him. But…you wonder whether that masks his true respiratory health.*	*That's normal….it doesn't look bad….it is probably more what I thought it would look like, it's better than I thought*	*I don't know that there is tons we need to change, maybe it is just about going back to that video and refining his technique and…maximising his breath control during exercise...and making sure we were maximising the frequency that he does do his physio.*
Model	Response provides further information on psychosocial factors. Response informs modification to procedures.	MRI, as a physical factor, challenges expectancies.	MRI as a physical factor aligns with expectancies.	MRI as response provides insight into whether the regimen will work and informs modifications to procedures and dosage.
Case 12 **X1** **Physio**	**Clinical information** FEV_1 72% predicted, prescribed ACT OD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =11.3, post= 1.6, 4-hours post =8.5.	**Case classification point**
Cue	Observations of ACT regimen (Salbutamol, 7% NaCl, Acapella in supine, prone and ASL) and prior knowledge of the case.	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	4-hours post-ACT ^{129}Xe MRI 

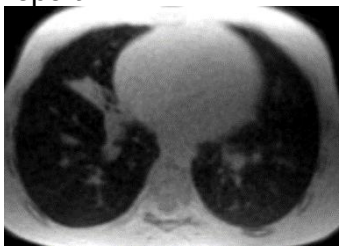
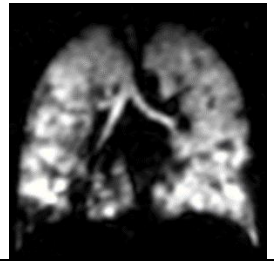
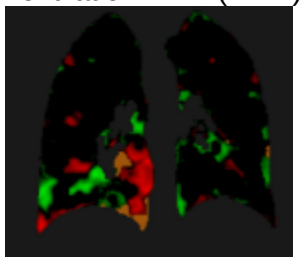
Excerpt	*If it's taking him this long, he's puffing his cheeks out and getting tired, whether you reduce it and make it more effective... I don't think the acapella was working very well in the postural drainage position…I'd just give him the Aerobika… his inhaler technique making sure he's shaking it between doses, taking nice long deep breaths with the spacer. Same with the nebuliser would he have better technique with a mask.*	*You can see that wedge of that segment there, that right mid lobe… it's chronically collapsed, and I know we should still try to promote it opening but it's whether it would…if he's losing concentration …whether he…starts with that position so he does it well rather than rushing through it…is his acapella working properly…by having more time the better PEP…would you recruit those areas that don't have air trapping to move the mucus.*	*There's little pockets all over where he's got defects… doing different position for drainage is indicated…he doesn't do anything in sitting…it would be interesting to see what he's like after physio.*	*He needs to do twice daily physio, because we can see…it's having short term effects but they're not lasting for a full 24 hours…what he has been doing is effective…but we need to do it more often and see if we can make it shorter so it's more manageable…if he's gone swimming, he does his neb when he gets back and some big huffs and coughs, if we can juggle it that way.*
Model	Response provides insight into whether the regimen will work, which informs modifications to ACT type and procedures.	Considers goals and cues, MRI as physical factor informs modifications to procedures.	Physical factor informs modifications to procedures. Awaits response.	MRI as response provides insight into whether the regimen will work and along with psychosocial factors, informs modifications to dosage
Case 16 X1 Physio	**Clinical information** FEV_1 67% predicted, prescribed ACT BD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =21.5, post= 26.7, 4-hours post =22.0.	**Case classification point**

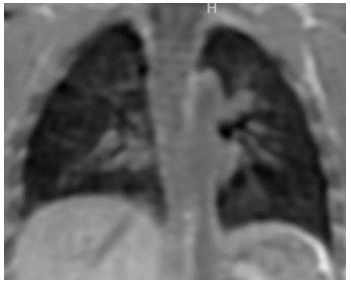
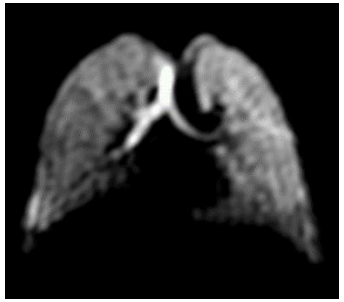
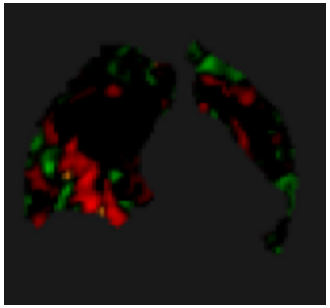
Cue	Prior knowledge of the Case and observation of ACT regimen (7% NaCl, Aerobika in prone and ASL).	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI ventilation binning map (EITV) 	Post-ACT Xe TRM 
Excerpt	*I am happy with his physio and what he has got, I would just increase his time doing it and the amount times he did it during the day.*	*His secretion load is so big that…doing one good physio session I don't think it is enough to change his scans … that is probably what I already thought before I saw them.*	*There is not one specific area…that I could…work on because it is pretty much all through both lungs…looking at him doing his physio before and knowing him, I think…if he does his physio, I don't think it is very effective.*	*On one hand…because he does cough quite a lot of secretions up…you…expect them to be…clear lungs but…I know his adherence to his physio is poor and he does have loads of secretions, so…to think that they would change after one session would be silly, I think…it takes longer than that.*
Model	Response provides insight into whether the regimen will work. Psychosocial factors inform modifications to dosage.	MRI and other prior physical factors. Anticipates psychosocial factor will limit response.	MRI as physical factor, anticipates psychosocial factor will limit response.	Provider brings expectancies to encounter. Response provides insight into whether regimen will work.
Case 16 Medic	**Clinical information** FEV_1 67% predicted, prescribed ACT BD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =21.5, post= 26.7, 4-hours post =22.0.	**Case classification point**

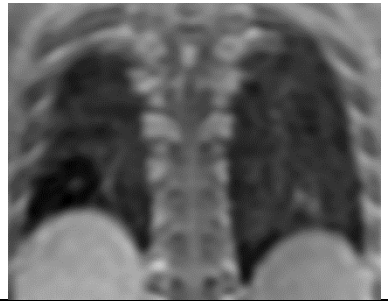
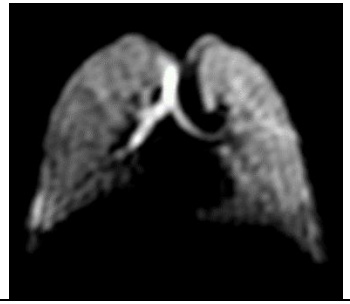
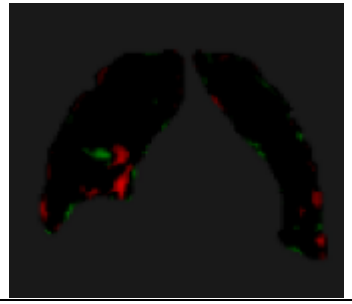
Cue	Prior knowledge of the Case and observation of ACT regimen (7% NaCl, Aerobika in prone and ASL).	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI ventilation binning map (EITV) 	4-hours post-ACT ^{129}Xe MRI ventilation binning map (TLC) 
Excerpt	*I was expecting more to come out, knowing how bad his bronchiectasis is… but again I don't think he's putting in much effort.*	*He's not following the routine that he's been advised to do… you can see lots of areas of mucus plugging and you could argue that could improve with effective chest physiotherapy as well as the areas of air trapping.*	*I expected it would be at least this bad…because I have memory of his CT scan and I know how non-complaint he is and how productive he is and how unhelpful his spirometry is.*	*He…has got severe lung disease…well established bronchiectasis, he is very productive, he is not very compliant, if he was compliant, you would expect an improvement in his overall condition and improvement on his images…I think that he may improve further with salbutamol.*
Model	Provider brings expectancies to encounter that procedures affect response.	Provider brings goals when considering MRI as physical factor	Provider brings expectancies to review MRI as physical factor.	Provider brings expectancies to review MRI response. Response provides insight into whether regimen will work and informs modifications to ACT type.
Case 20 X2 Physio	**Clinical information** FEV_1 111% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =5.6, post= 5.4, 4-hours post =6.1.	**Case classification point**

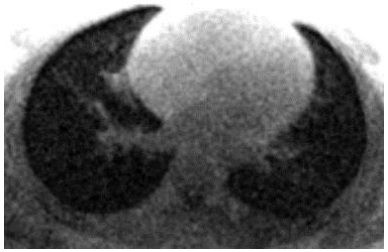
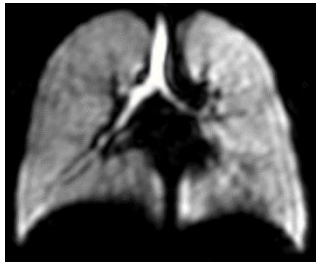
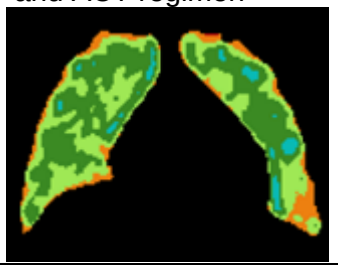
	Observation of ACT regimen (Salbutamol, 7% NaCl, Aerobika in supine, prone and ASL).	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	Post-ACT ^{129}Xe ventilation binning map 
Excerpt	*I think that looked fairly good… it's quite a good technique. I wouldn't think you'd have to tweak masses with it.*	*I can't see anything massive.*	*It's better than I expected…given how symptomatic he can be and how poor his compliance is at times…it correlates with him having a good lung function.*	*If you did 4 puffs (of salbutamol) would that mean that he was…less bronchoconstricted and allow him to clear his secretions more, even more centrally and maximise his physio.*
Model	Response provides insight into whether the regimen will work.	MRI as physical factor.	MRI as physical factor correlates with other physical factors.	Response provides insight into whether the regimen will work and informs modifications to ACT type.
Case 20 X Medic	**Clinical information** FEV_1 111% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =5.6, post= 5.4, 4-hours post =6.1.	**Case classification point**

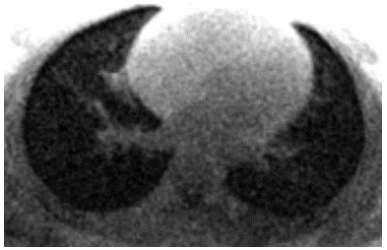
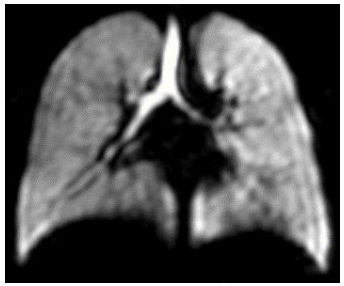
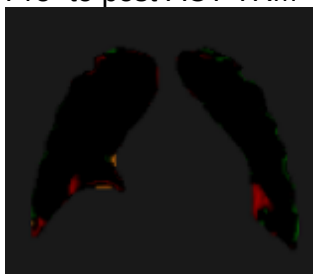
Cue	Observation of ACT regimen (Salbutamol, 7% NaCl, Aerobika in supine, prone and ASL).	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI ventilation binning map (EITV) and VDP=5.4% 	4-hours post-ACT ^{129}Xe MRI ventilation binning map (EITV) 
Excerpt	*I think if he's getting a really good wobble then you've got as good a chance as any of clearing secretions.*	*I think that looks ok. Although there's, I think there's probably…quite a bit of mucus-y plugging…centrally on both sides.*	*It doesn't seem that bad to me but I don't know…I don't know whether it would be worth doing more… of his oscillating device…to get a little bit more in the peripheries but certainly more on the right.*	*I can't work out whether different positions would make any difference…it doesn't feel like it would to me I just wonder whether you just need a little bit longer to clear a little bit more mucus rather than it just continuing to stick and wedge.*
Model	Response provides insight into whether the regimen will work.	MRI as physical factor.	MRI as physical factor informs modifications to dosage.	MRI response provides insight into whether the regimen would work, less confident decisional shift.
Case 26 X1 Physio	**Clinical information** FEV_1 113% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =7.3, post= 4.4, 4-hours post =6.5.	**Case classification point**

Cue	Observation of ACT regimen (Salbutamol, 7% NaCl Aerobika complex positioning) and prior knowledge of the Case.	Pre-ACT UTE and previous CT report 	Pre-ACT ^{129}Xe MRI 	4-hours post-ACT ^{129}Xe MRI ventilation TRM (EITV) 
Excerpt	*His Aerobika technique is a bit different from what I would recommend, I've tried to change it a few times…he probably rushes it a bit…taking his time and slowing down, recognising…does he need to do a long slow huff or is it higher up in his throat. And if he would be reasonable to try the Aerobika in a different way.*	*We know about the right middle change and were trying to target that with physio, which he does his position every time, potentially could do his neb in that position… I don't think I'd change anything.*	*He's got quite good aeration throughout he's just got little pockets…mainly in that right mid area…he's already got lengthy treatment session, so I don't want to add more positions… he does rush and doesn't always go to full capacity or definitely with his neb, he could do a much better technique with that…recruit his airways before his airway clearance before…his Aerobika.*	*It'd be interesting just to see what he would be like with ACBT…almost incorporate it into his neb kind of routine at the start…with him not recruiting collateral ventilation in his bases…with his Aerobika what he does…that forced…he's almost collapsing his distal smaller airways and not, he's opening them up and closing them again.*
Model	Response provides insight into whether the regimen will work and informs modifications to procedure.	MRI as physical factor.	MRI as physical factor informs modification to procedure.	MRI as response provides insight into whether the regimen will work and informs modifications to ACT type.
Case 27 X1 Physio	**Clinical information** FEV_1 104% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =0.4, post= 1.0, 4-hours post =1.1.	**Case classification point**

Cue	Observation of ACT regimen (7% NaCl, Aerobika in sitting and ASL).	Pre-ACT RV 	Pre-ACT ^{129}Xe MRI and VDP=0.4% 	4-hours post-ACT ^{129}Xe MRI ventilation TRM 
Excerpt	*He definitely benefits in changing positions…his technique is really, really good, I…probably wouldn't change masses.*	*It probably backs up his physio routine I don't think it would make me change anything.*	*I wouldn't change anything…I probably wouldn't nag him too much about his hypertonic either…I would want him to do it at least every other day…if he felt he had more symptoms to increase it to at least once a day, if not twice a day if he really felt unwell.*	*Maybe doing some breaths in supine…because actually the rest of his lung fields…look a bit more green, so it must be that anterior bit that has got worse.*
Model	Response provides insight into whether the regimen will work.	MRI as physical factor.	MRI as physical factor informs modifications to dosage.	MRI as response provides insight into whether the regimen will work and informs modifications to procedure.
Case 27 X Medic	**Clinical information** FEV_1 104% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =0.4, post= 1.0, 4-hours post =1.1.	**Case classification point**

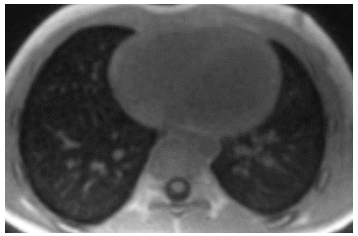
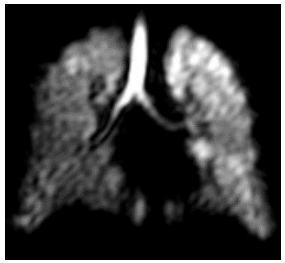
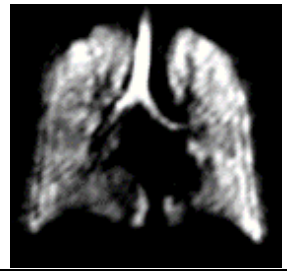
Cue	Observation of ACT regimen (7% NaCl, Aerobika in sitting and ASL).	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI and VDP=0.4% 	4-hours post-ACT ^{129}Xe MRI ventilation TRM 
Excerpt	*I don't think I'd change what he does, maybe he doesn't do his huffs as well as he could.*	*There's probably more air trapping further down posterior, I think there's more anterior on the right… no consolidation type bronchial thickening…you have to take into clinical context…I wouldn't change something based on just something I can see.…I don't think I would change anything based on that alone.*	*it's a good scan really… he's normally really well so it is what I expected.*	*There's something happening in the right mid…we know that that's a persistent chronic thing… if it's worse 4 hours after…he's definitely doing some shifting but not clearing it. I don't really know what that means though… I'm not really sure I'd change his routine.*
Model	*Response provides insight into whether the regimen will work and informs modifications to procedure.*	*MRI as physical factor*	*MRI as physical factor aligns with other physical factors.*	*MRI as response provides insight into whether the regimen will work.*
Case 35 X1 Physio	**Clinical information** FEV_1 92% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =1.3, post= 1.0, 4-hours post =0.5.	**Case classification point**

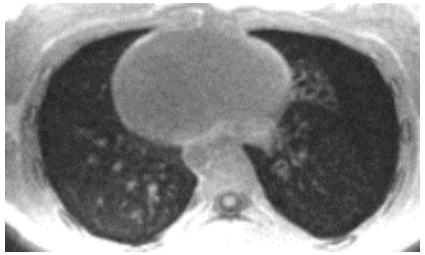
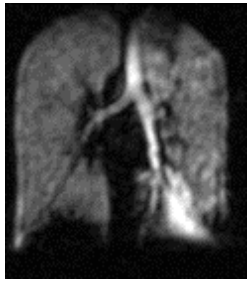
Cue	Observation of ACT regimen (Aerobika in sitting, prone, ASL and patient led supine).	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	Pre-4-hours post-ACT BINNING MAP and ACT regimen 
Excerpt	*I think that's what he should be doing, considering how well he is I think that's an appropriate thing to do in his physio*	*I don't think it would change masses of what I do….That scan doesn't make me think anything*	*It reenforces that I want to say well done…that area on that right middle…it's a chronic collapse…you're not going to change it by changing something immediate and it's been there a long time so I'm not too stressed about it.*	*He could feel…something fluttering in that left base…I would say to him that if you think that you've identified some secretions and you think you then move it, do another cycle…try and do a variety of positions during your sessions that focus on where you think you need it most.*
Model	Response insight into whether the regimen will work.	MRI as physical factor.	MRI as physical factor.	Response insight into whether the regimen will work and informs modifications to dosage.
Case 35 X Nurse	**Clinical information** FEV_1 92% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =1.3, post= 1.0, 4-hours post =0.5.	**Case classification point**

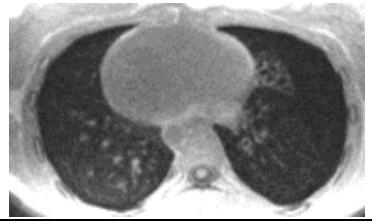
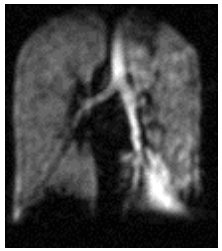
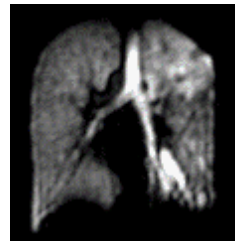
Cue	Clinical history (started 7% NaCl since MRI) and observation of ACT regimen. (Aerobika in sitting, prone, ASL and patient led supine).	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	Pre- to post-ACT TRM 
Excerpt	*To carry on…he's definitely worth trying…hypertonic… because he's so dry it might just help to cough up a bit more…would it be helpful to go on his tummy as well to see if it cleared round the back as well as the side, but he is quite attuned to his chest which I think is really good for his age.*	*he's…concentrating on where he can hear it…but actually it's the other side, he needs to be working harder on to clear those.*	*He's ventilating well there's just these areas that…you'd want to work on…the left… he probably needs to be altering position…I'm totally guessing this, but does he need to be breathing longer slower breaths…. because, maybe he's not filling…and clearing the whole of his lungs.*	*I think you'd talk to him about how good it was … that he can feel on that left side…he needs to do something on the right as well for these bases, and it's still just needs to kind of try and get secretions mobilised from those difficult areas.*
Model	Response insight into whether the regimen will work and informs modifications to procedure and provides further information on psychosocial factors.	MRI as physical factor informs modifications to procedure.	MRI as physical factor informs modifications to procedure	Response provides insight into whether the regimen will work and informs modifications to procedure.

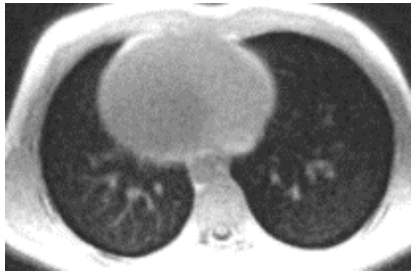
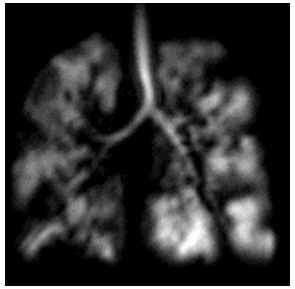
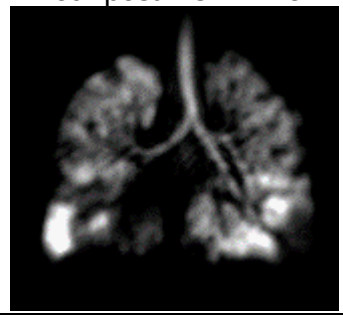
11.2 Cases classified as Case type Y1 and Y2

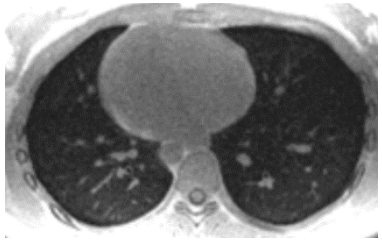
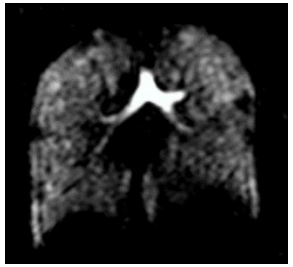
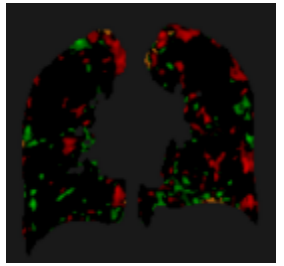
Table 45: Excerpts from the joint display tables used to integrate the quantitative and qualitative data for cases classified as Case types Y1 and Y2. Full details are not provided to ensure anonymity of both the patient and clinician participants. For each case, spirometry (FEV_1 % predicted), frequency of prescribed ACTs and self-reported frequency are provided as selected clinical information from the available clinical data. Cue indicates the information being reviewed by the clinician at the time of the except below. Model links to the constructs from the ACT personalisation model. Unless specified, ^{129}Xe images were acquired at end inspiratory tidal volume. BD= twice daily, OD= once daily, 6 or 7% NaCl = nebulised 6 or 7% sodium chloride, PEP= positive expiratory pressure, ASL= alternate side lying UTE= ultrashort echo. TRM= treatment response map.

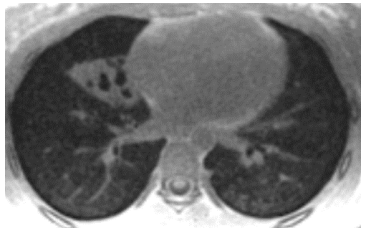
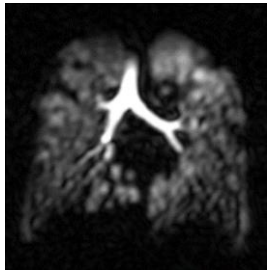
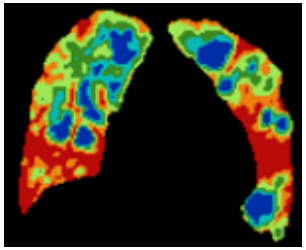
Case 2 Y1 Physio	**Clinical information** FEV_1 unreliable, prescribed ACT BD, completes once weekly.	**Structural MRI**	Functional MRI ^{129}Xe VDP (%) pre =0.4 post= 7.9, 4-hours post =7.0.	**Case classification point**
Cue	Observation of ACT regimen (7% NaCl via mask, Aerobika in ASL and sitting)	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI ventilation 	Post-ACT ^{129}Xe MRI ventilation 
Excerpt	*Mum says he does cough phlegm up but…it's just coming from his nose...we don't have lots of children with PCD that don't have any secretions…it's whether he needs the hypertonic…or whether he can just use the Aerobika…I'm not sure… his chest doesn't seem to have secretions…or is it because he never does his physio.*	*We can't hear any secretions and he's not clearing anything from hypertonic and from MRI scan we can't see any areas from sputum plugging or secretions then why are we using hypertonic, so I would probably take that away and make sure he's still having some PEP and obviously the oscillation.*	*When I see him, he's dry, but mum's saying he's got a wet cough and he has lots and lots of oral antibiotics, but actually, he's got really good ventilation….it makes you look at it differently…on one hand…do we just throw everything at him and in case he does a little bit…or…does he even need to do physio at all?*	*I…thought we'd find all sorts of atelectasis and sputum plugging…because he doesn't do any physio, he doesn't do any exercise and these reports of having lots of chesty and phlegmy coughs and things…I thought they were going to be worse than that.*

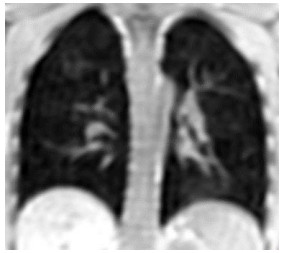
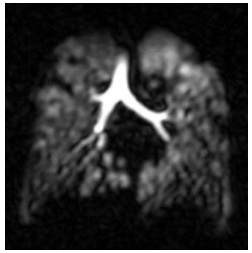
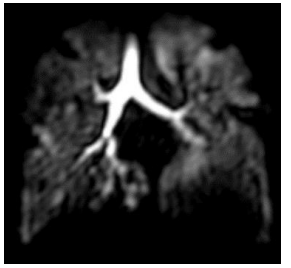
Model	Response provides insight into whether the regimen will work, less confident decisional shift	Response provides further information on physical factors, MRI as physical factor informs modification to ACT type	(Divergent) physical factors, MRI aligns with some physical factors, challenges expectancies	MRI response provides experiential learning, more confident to agree action.
Case 6 Y1 Physio	**Clinical information** FEV_1 88% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =4.3 post= 3.1, 4-hours post =4.0.	**Case classification point**
Cue	Observation of ACT regimen (Salbutamol, 7% NaCl via Pari PEP for Hi-PEP regimen in ASL and prone.	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	4-hours post-ACT TRM 

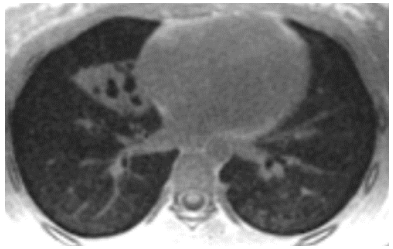
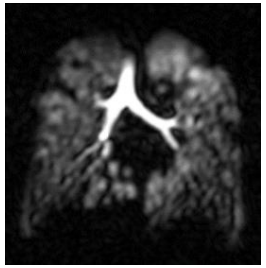
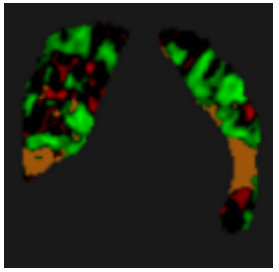
Excerpt	*It's obviously effective because she's clearing after every cycle… I'm just wondering whether she needs some oscillation just to help with the pluggy bits*	*I don't think I would really change it apart from potentially needing that oscillation because her phlegm is sticky.*	*It's mainly just the left base…we could potentially look at working on her left…more so we can get more phlegm away, which could potentially help with her ventilation, but I think that would be it really.*	*I just can't quite get my head round…why it's…better…ventilation…but then there's areas that are much worse...I don't know what I can do about those images specifically… we could potentially do prone with a little pillow under her left side that might help from a ventilation point of view, left base… I think we're doing everything else we can really from a secretion point of view she just needs to increase to 90 breaths or more if she can.*
Model	Response provides insight into whether the regimen will work, less confident decisional shift.	MRI as physical factor.	MRI as physical factor informs modifications to procedures.	MRI as response provides insight into whether the regimen will work, informs modifications to procedures.
Case 6 Y Nurse	**Clinical information** FEV_1 88% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =4.3 post= 3.1, 4-hours post =4.0.	**Case classification point**
Cue	Observation of ACT regimen (Salbutamol, 7% NaCl via Pari PEP for Hi-PEP regimen in ASL and prone.	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	Post-ACT 

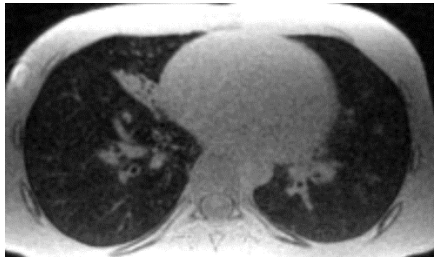
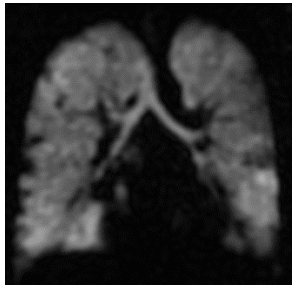
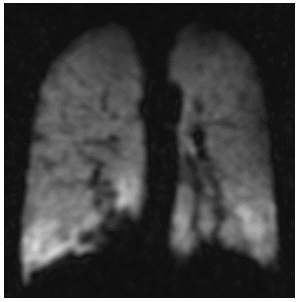
Excerpt	*I want to make sure she's taking…her inhalers correctly so I'm definitely going to do that next time I see her…having an experienced physio…going through (her ACT regimen) with her then I think she could probably be even better.*	*I were perhaps expecting to see more than what I'm seeing in terms of abnormalities…she's a lot better…she's not taking her inhalers properly…I don't think she's quite following what the physios want her to do. But overall, I think we'd be relatively positive with them.*	*Given…the past I'd have maybe thought that would have been worse… there's obviously room for improvement in some areas, maybe that would be down to us or physio to look at those particular areas that maybe could be better.*	*I was expecting to go "wow look at the difference" so it's maybe not quite what I was expecting it was going to show.*
Model	Response provides insight into whether the regimen will work, informs modifications to technique.	MRI as physical factor.	MRI as physical factor.	MRI as response.
Case 14 Physio Y1	**Clinical information** FEV_1 88% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =16.1 post= 26.5, 4-hours post =16.6.	**Case classification point**
Cue	Observation of ACT regimen (Salbutamol, 7% with Aerobika in supine, prone and ASL) and prior knowledge of case.	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	4-hour post-ACT ^{129}Xe MRI 

Excerpt	*He's obviously very used to doing it and just yet, he needs that prompting to actually slow down and take really nice deep breaths.*	*I feel like I've had a complete mind blank.*	*He has a lot of areas of poor ventilation and associated with high ventilation next to it…it's worse than what I expected for him.*	*They probably look slightly worse than I would have hoped for…you do wonder if he would benefit form that second dose of hypertonic in the day… I think more focus on consistency…slow deep breath counting rather than rushing.*
Model	Response provides insight into whether the regimen will work: provides further information on psychosocial factors; informs modifications to procedures.	Nil	MRI as physical factor.	MRI as response, provides insight into whether the regimen will work, inform modifications to dosage and procedures.
Case 17 Y1 Physio	**Clinical information** FEV_1 97% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =3.8, post= 6.2, 4-hours post =4.7.	**Case classification point**
Cue	Observation of ACT regimen (7% NaCl via Pari PEP in sitting, prone and ASL) and prior knowledge of case.	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	Pre-to Post-ACT TRM 

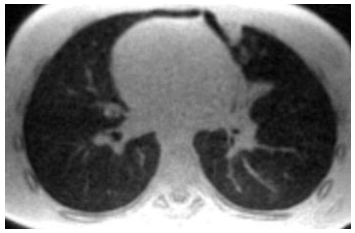
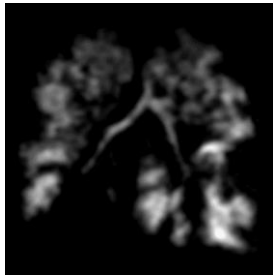
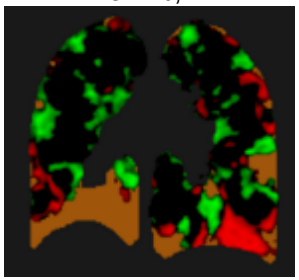
	You cleared…3 sticky plugs…because she was doing a good technique. *…she doesn't do it often and doesn't do it very well…we could…give her the hypertonic through a Pari mask…and her huffing technique…* *potentially…manual therapy…because it's really sticky*	*There wasn't anything that jumped out at me…for example sputum trapping, bronchiectasis, or anything like that.*	*There's parts of her lungs that are potentially not being ventilated so; I think that would be where the hypertonic's not necessarily getting to…you can't see what the reason is…it's more peripheral…just wondering whether that's her technique in taking a deep breath*	*I didn't expect it, I mean she cleared more secretions as well…It's not made the ventilation any better from the images, it looks like they're all worse…I don't know why…the likelihood is this percentage would be better after a week rather than just after one session.*
Model	Response provides insight into whether the regimen will work and informs modifications to ACT type and procedure.	MRI as physical factor.	MRI as physical factor, less confident decisional shift.	MRI as response challenges expectancies.
Case 22 Y1 Physio	**Clinical information** FEV_1 94% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =9.6, post= 5.2, 4-hours post =8.4.	**Case classification point**
Cue	Observation of regimen (Salbutamol, 6% NaCl, Pari PEP in ASL, supine and sitting clearance). Auscultation findings.	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	Pre-ACT ^{129}Xe binning map and VDP =9.6% 

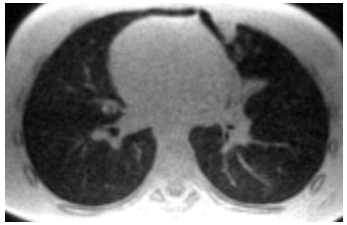
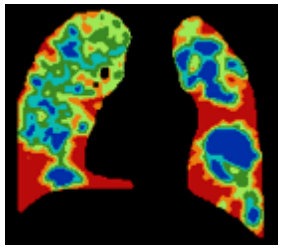
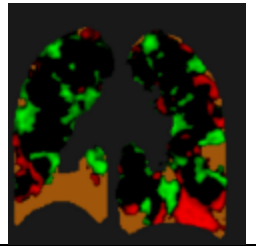
Excerpt	*She has good observable improvement…I think her huffs are pretty ineffective at times and perhaps that would help her… I'd also just make sure she's doing what she's supposed to be.*	*She has clearly got a patch on that right hand side. So, making sure that's she is doing it in left side…if she is doing slightly less sets than she would normally do.*	*I thought it would show…a ventilation defect where the patch is but actually it's more widespread isn't it? So…doing it in multiple positions rather than singling out…that right mid patch… doing some prone in because of her posterior defect.*	*They're worse than I thought they would be…. clinically, she doesn't present as if she would have as significant a quantity of defects as she does and probably to me highlights the importance of sorting her physio routine out.*
Model	Response provides insight into whether the regimen will work and informs modifications to procedure.	MRI as physical factor informs modifications to procedures.	MRI as physical factor challenges expectancies and informs modifications to procedures.	MRI as physical factor challenges expectancies.
Case 22 Y1 Medic	**Clinical information** FEV_1 94% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =9.6, post= 5.2, 4-hours post =8.4.	**Case classification point**
Cue	Observation of regimen (Salbutamol, 6% NaCl, Pari PEP in ASL, supine and sitting clearance) and engagement with regimen.	Pre-ACT RV 	Pre-ACT ^{129}Xe VDP =9.6% 	Post-ACT ^{129}Xe VDP =5.2% 

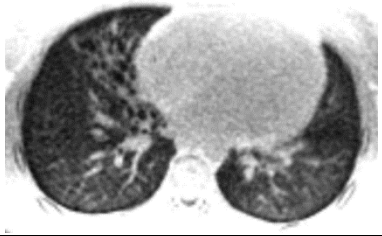
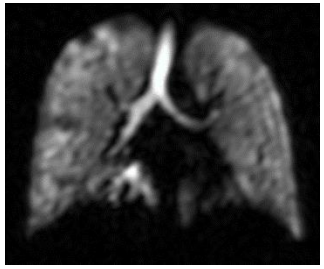
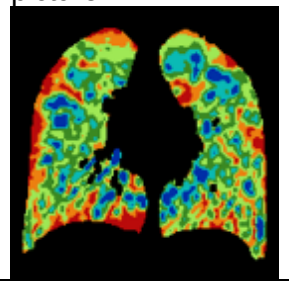
Excerpt	*I don't think it's working well for her at all… her secretions are thick, and she's not fully engaged with the process.*	*the lungs look a little bit varied in their appearance… suggesting some air trapping or inadequate ventilation...those secretions are…not really shifting…it probably illustrates what you can hear and see when she's doing physio on the video.*	*there's big areas she's not ventilating…this is worse than I expected…because she's not symptomatic although I know she's wet and secretions are there and she probably not very compliant… maybe talking her through this and encouraging her to comply a bit better…would be a good start.*	*9.6% so that seems pretty significant and not what you expect from a CT scan. Initially she was worse than I would have expected…her post physio images are where I expected her to be as a baseline.*
Model	Response provides insight into whether the regimen will work and provides further information on psychosocial factors.	MRI as physical factor.	MRI as physical factor challenges expectancies.	MRI as response provides further information on physical factors.
Case 22 Y1 Nurse	**Clinical information** FEV_1 94% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =9.6, post= 5.2, 4-hours post =8.4.	**Case classification point**
Cue	Observation of regimen (Salbutamol, 6% NaCl, Pari PEP in ASL, supine and sitting clearance) and engagement with regimen.	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	Post-ACT TRM 

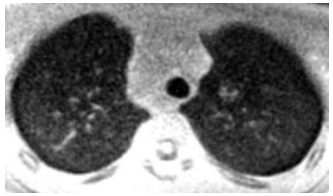
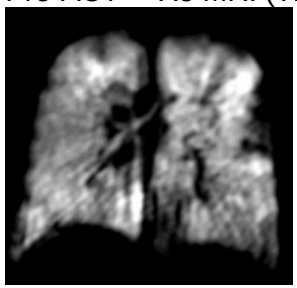
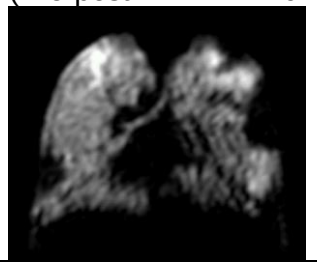
Excerpt	*She is obviously not doing…the different positions that we are saying for her to do… she's…obviously got some really troublesome thick secretions and that obviously feels normal for her because…she said she coughed the same amount up that she...normally does on physio sessions so.*	*There is definitely something going on with the right side…I don't know if lying on your left-hand side so then it opens up the right side…so yeah it would influence the physio.*	*There is quite a lot of defect on both sides of the lung, particularly to the lower left lobe and then there is this area that middle of the right lobe…but there's areas throughout…it's…showing that there is an issue.*	*That's surprising really because…I think there is probably more areas of green where things are better than red.*
Model	Response provides insight into whether the regimen will work.	MRI as physical factor which informs modifications to procedure.	MRI as physical factor.	MRI as response challenges expectancies.
Case 24 Y1 Physio	**Clinical information** FEV_1 73% predicted, prescribed ACT OD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =11.0, post= 11.2, 4-hours post =23.3	**Case classification point**
Cue	Observation of ACT regimen (Salbutamol, 7% NaCl, Aerobika in supine and ASL with self-overpressures).	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI (EITV) VDP=11.0% 	Post-ACT ^{129}Xe MRI (TLC) 

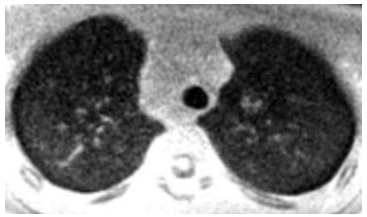
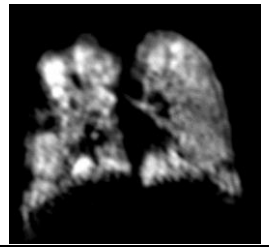
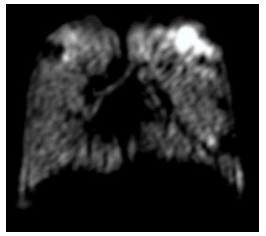
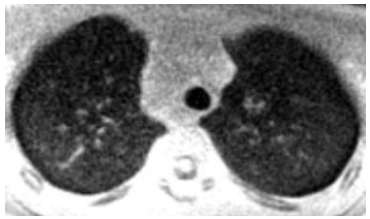
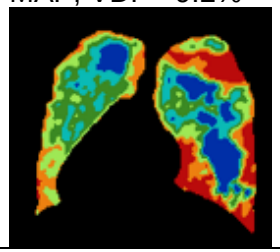
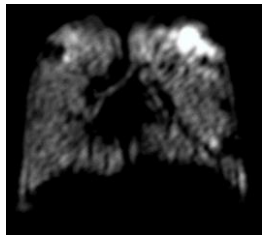
Excerpt	*He can judge where his secretions are and obviously, he's adding in like over pressures and vibs manually himself, his technique is good, nebuliser intake was good…I would like him to do it more…because he's not done it for 2 days.*	*He doesn't do any…positioning to target that right middle lobe, it's whether he has in the past done it and he's just chosen not to… adding some right middle lobe postural drainage…some time in prone*	*He's doing that really like squeezed exhale, so is he actually collapsing down his distal areas…I would see if he can clear as effective without being as forceful…he might just be able to clear it with huffs rather than as forced with the Aerobika… we'll see what he's like post.*	*Is the really forced exhale for his Aerobika actually benefiting him…is he recruiting his lower lobes…Is the oscillation helping to splint them open…Is he spending enough time at a fixed PEP…how can we recruit his bases; from positioning, deeper breath on his nebuliser, deeper breath on his Aerobika…not to encourage him to do that forced exhale…look at those things first and then…a few more cycles…a few more on his tummy.*
Model	Response provides further information on psychosocial factors.	MRI as physical factor informs modifications to procedure	MRI as physical factor informs modifications to procedure. Response awaited.	MRI as response provides insight into whether the regimen will work, provides experiential learning, protracted decisional shift.
Case 29 Y1 Physio	**Clinical information** FEV_1 40% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =23.1, post= 22.2, 4-hours post =26.1	**Case classification point**

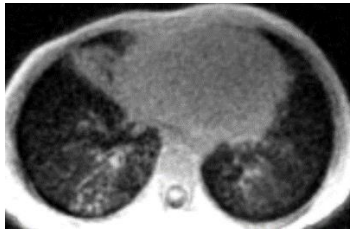
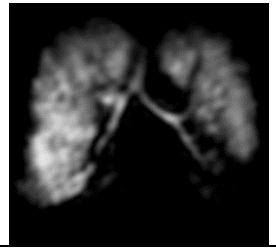
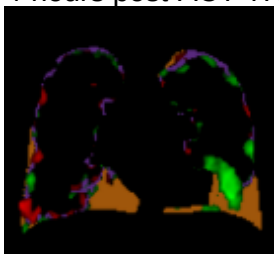
Cue	Clinical history and observation of ACT regimen (Salbutamol, 7% NaCl, Aerobika in sitting and ASL).	Post-ACT UTE and previous CT report 	Pre-ACT ^{129}Xe MRI 	4-hours post-ACT TRM and VDP= 26.1%, 
Excerpt	*he's optimised from a nebuliser perspective… but not fully clearing… does he need a longer treatment or a change in treatment potentially?... I'd probably do more Aerobika cycles.*	*I'd be more targeted with postural drainage, and I'm sure in the past, yeah sometimes completes in right side ¼ turn if not clearing effectively…prone and supine.*	*it's quite patchy throughout… he is really wet and productive, so I'd imagine he does have a lot of mucus plugging effecting flow of ventilation…there's room for improvement…I don't think in terms of changing adjunct because he's on an oscillatory PEP adjunct.*	*He needs to be admitted with those numbers if they're really bad. And like, physio review regularly on the ward…I'd see what works as an inpatient first.*
Model	Response provides insight into whether the regimen will work and informs modifications to dosage.	MRI as physical factor informs modifications to procedure.	MRI as physical factor, provider agrees goals.	MRI as response provides further information on physical factors and can affect time to follow up. Protracted decisional shift.
Case 29 Y Medic	**Clinical information** FEV_1 40% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =23.1, post= 22.2, 4-hours post =26.1	**Case classification point**

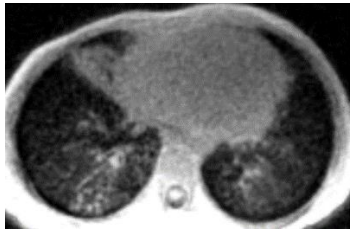
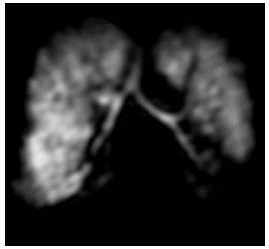
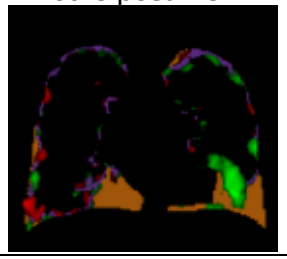
Cue	Prior knowledge of the Case and observation of ACT regimen.	Post-ACT UTE 	Pre-ACT ^{129}Xe MRI binning map 	4-hours Post-ACT Xe TRM 
Excerpt	*I'd be wondering about a period of admission, in which we checked he wasn't growing anything else, gave him some IV's, a bit of inpatient physiotherapy*	*It gives me a little bit of reassurance…because…things aren't massively significantly worse when he last had a CT scan.*	*I'm not at all surprised he's got a big black hole in the left middle lobe because that's been…developing bronchiectasis for 11 years. But…all this in the right lower zone that isn't borne out by the structural imaging…. I don't know how much that should be influencing my treatment in the face of structural things that don't look different.*	*What strikes me at looking at those images is how much of it is orange as if nothing is really different at all, particularly the bits like that right lower zone where if I we were only using CT's and x-rays and even structural images, I'd say there's no problem…I would want to be asking…the PCD consultants and the other PCD experts' advice.*
Model	Response provides further information on physical factors.	MRI as physical factor.	MRI as physical factor challenges expectancies.	MRI as response provides further information on physical factors and challenges expectancies. Protracted decisional shift.
Case 31 Y1 Physio	**Clinical information** FEV_1 82% predicted, prescribed ACT BD, completes BD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =5.2, post= 2.5, 4-hours post =2.5.	**Case classification point**

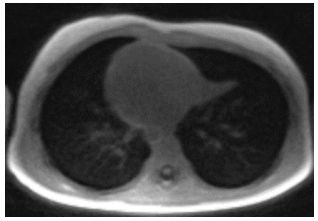
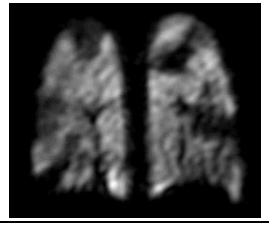
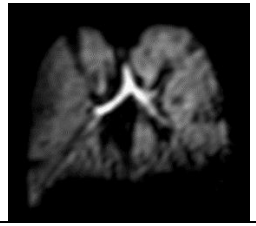
Cue	Observation of ACT regimen (Salbutamol, 6% NaCl and Aerobika 10 x 10 in supine, side lying, sitting up.)	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	Pre-ACT ^{129}Xe MRI and clincial picture 
Excerpt	*We probably need to look at the Mucoclear…not necessarily take it out, but how we can adapt that to see whether we can make it work better for her…she's doing it together with the Aerobika, but I think the Aerobika is having more effect than the Mucoclear is on its own*	*That's probably what I expected to be fair.*	*Given her lung function and how she presents as from a symptom point a view… the patches there you see on that central image; they correlate with what you can see on the, on the structural one but I think I still anticipated she would have more peripheral defects…I'd be tempted to do more treatment in right side lying to increase the ventilation in that left side*	*You anticipated that if you've got lung function on a good day of 81, 82% then you're, you'll have, you've got more peripheral destruction because you're not seeing that on the lung function until it gets below a certain point are you…there's things that we can improve on, but we've got perhaps more to work with than I'd anticipated.*
Model	Response provides insight into whether the regimen will work and informs modifications to procedure.	MRI as physical factor.	MRI as physical factor challenges expectancies, informs modifications to procedure.	MRI as response challenges expectancies, provides insight into whether the regimen will work.
Case 34 Y1 Physio	**Clinical information** FEV_1 103% predicted, prescribed ACT BD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =9.2, post= 12.1, 4-hours post =6.8.	**Case classification point**

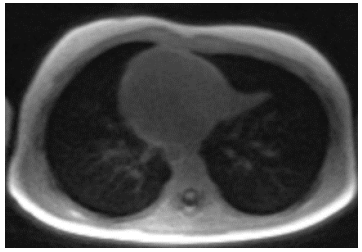
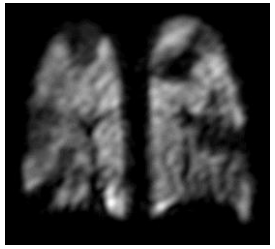
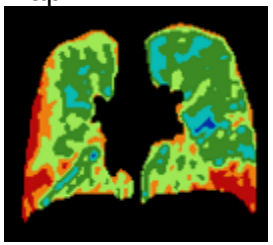
Cue	Clinical history and observation of ACT regimen (Aerobika in sitting).	Post-ACT UTE 	Pre-ACT ^{129}Xe MRI (TLC) 	Post-ACT ^{129}Xe MRI (EITV) (Pre-post ∆VDP=+ 2.9%) 
Excerpt	*He does only do physio once a day but he's so active and generally so well and he's grown like nothing, he's had hardly any exacerbations this year, that we've just left him at that because it seems to be managing him ok….(His) huffs and coughs, they leave a bit to be desired…but I think generally his technique's pretty reasonable.*	*It looks pretty reasonable.*	*Clinically I'm surprised at how many defects and how significant they are looking at those images…perhaps he does need a more structured routine, perhaps needs to look at doing things in different positions…would he be better with a PEP or something similar where you've got a bit more control over inspiration and whether that would give you better resolution from a ventilation point of view.*	*Watching his physio routine, I would have thought…that was effective…but looking at his images I think he's… adjusting his ventilation slightly…looking at the numbers it's not improving…which probably implies that he doesn't ventilate very well during his physio…I would look at doing treatment in different positions and I think given what his TLC looks like I'd probably swap him to something different.*
Model	Response provides insight into whether the regimen will work.	MRI as physical factor.	MRI as physical factor challenges expectancies, informs modifications to ACT type.	MRI as response provides insight into whether the regimen will work which challenges expectancies, informs modifications to ACT type.
Case 34 X Medic	**Clinical information** FEV_1 103% predicted, prescribed ACT BD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =9.2, post= 12.1, 4-hours post =6.8.	**Case classification point**

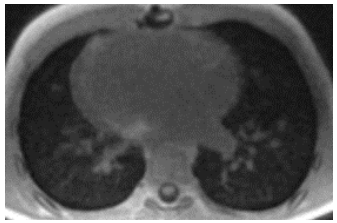
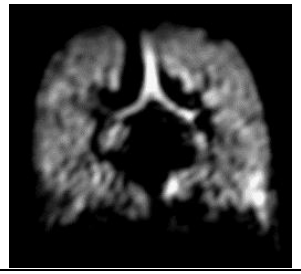
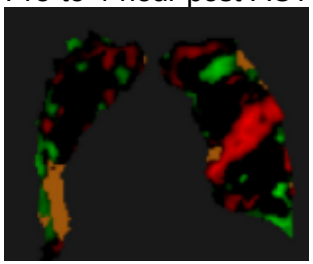
Cue	Prior knowledge of the Case and observation of ACT regimen (Aerobika in sitting).	Post-ACT UTE 	Pre-ACT ^{129}Xe MRI 	4-hours Post-ACT Xe 
Excerpt	*It is effective isn't it, he brought something up, and he got drier as the session went on as well.*	*He had cultured something a few years ago…but he has also been incredibly well…* *I would be happy that things seem to be working for him.*	*It is not outside of what I would expect but I am not sure I am experienced enough to say whether it is good or bad or exactly as I would expect It to be for him.*	*There was probably that more down there than I realised at the time…maybe…he also clears more passively with whatever he did in the four hours than just with a physio session…I wouldn't feel that we dramatically needed to do anything differently for him.*
Model	Response provides insight into whether the regimen will work.	MRI as physical factor.	MRI as physical factor.	MRI as response challenges expectancies.
Case 34 X Nurse	**Clinical information** FEV_1 103% predicted, prescribed ACT BD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =9.2, post= 12.1, 4-hours post =6.8.	**Case classification point**
Cue	Prior knowledge of the Case and observation of ACT regimen.	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI BINNING MAP, VDP= 9.2% 	4-hours Post-ACT Xe 

Excerpt	*I'm wondering about the quality of it sometimes because you have to be constantly correcting him and keeping him on task.*	*He tends to be quite well, not someone we have a lot of worries about, so we assume, I assume his relatively good lung health and there aren't any big issues.*	*He's got more defects than what you'd expect…I'm surprised about that I thought he would be nearer normal.*	*I thought things might completely resolve…but I suppose you're never going to achieve that are you… I'd ask an expert physio.*
Model	Response provides insight into whether the regimen will work.	MRI as physical factor	MRI as physical factor challenges expectancies.	MRI as response challenges expectancies and provides experiential learning. Provider seeks best external information.
Case 5 Y2 Physio	**Clinical information** FEV_1 60% predicted, prescribed ACT BD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =20.3, post= 20.2, 4-hours post =15.4.	**Case classification point**
Cue	Observation of ACT regimen (7%NaCl, Aerobika in ASL and prone).	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	4-hours post-ACT TRM 

Excerpt	*She's getting breathless… she's not been able to do a very good technique …you don't know how much you're clearing from the bottom…I'd probably want her to be reviewed …because that's not her normal ...we could potentially go down to…3% erm, but …I would probably just do the 7% with some hands on.*	*If this was clinic, we would admit her... she needs the oscillation and the PEP…because she's got sticky secretions, but at this point …she's not…able to complete the physio. I would … do some percussions to try and help shift it… I don't think the 7 (%saline) is necessarily irritating her airways I think it's just being effective and moving her phlegm which is making her cough.*	*I said to you about pulling away …but…there's obviously lots and lots of defects…we have to work on…but… what would I even do because…the defects are all over…to get better ventilation we need to clear her secretions… Aerobika in supine for these anterior parts…the wedges are on both sides… alternate side lying and target those areas. Then hopefully, if you clear those, your ventilation may be more normal.*	*With this patient …I don't think there's…specifically a right or wrong thing to do, you're obviously thinking about the scans but also the patient's wellbeing…it'd be hard to do a long-term management plan from that one encounter and I would probably be quite worried to change something from a clinical point of view and not reassess it quite quickly.*
Model	Response provides insight into whether the regimen will work and informs modifications to ACT type.	MRI as physical factor informs modifications to ACT type.	MRI as physical factor informs modifications to procedure.	MRI as response provides insight into whether the regimen will work, further information on physical factors which can affect time to follow up.
Case 5 Y Nurse	Clinical information FEV_1 60% predicted, prescribed ACT BD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =20.3, post= 20.2, 4-hours post =15.4.	**Case classification point**
Cue	Observation of ACT regimen (7%NaCl, Aerobika in ASL and prone).	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	4-hours post-ACT TRM 

Excerpt	*It's…probably not working as it should but I think that's because of adherence at home…the routine you've got although it looks really hard for her to carry out because it makes her cough so much, but I don't know what else you'd do…if they can… be more consistent she probably won't always react like that to physio because she will hopefully have less secretions to clear.*	*She's probably got loads and loads of mucus down there, so trying to be consistent with airways clearance I think the hypertonic is probably super useful… she should probably keep trying with the DNase…I know in other cases… you might have…used high PEP…I don't know if something like that would be appropriate for her, the whole thing makes me feel really worried about her.*	*You can…see the bits we were seeing on the right-hand side, here …what looked like collapse…but I am a bit surprised at how poorly the left lower lobe is ventilated. But…she's getting more ventilation in the right side…which is not what I was expecting…I don't think…we can say what you're doing right now is fine…I mean at home because I don't think they're doing it and I think this is really good evidence for that.*	*I thought they'd look better which is why when I looked at that one initially this doesn't kind of make sense to me…when you look at how much you cleared, I'd have thought oh right this is going to improve everything straight away but then when you look at it here you can see the difference from this to this so something happening so it makes me think it is working but it's a sustained thing.*
Model	Response provides insight into whether the regimen will work.	MRI as physical factor and considers modifications to ACT type.	MRI as physical factor.	MRI as response provides insight into whether the regimen will work, challenges expectancies and provides experiential learning.
Case 7 Y2 Physio	**Clinical information** FEV_1 59% predicted, prescribed ACT BD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =8.2, post= 10.2, 4-hours post =5.6.	**Case classification point**
Cue	Observation of ACT regimen (Salbutamol, 7%, Cornet in sitting).	Post-ACT UTE 	Pre-ACT ^{129}Xe MRI 	Pre-ACT ^{129}Xe image and VDP =5.6% 

Excerpt	*Ideally you would want to put your hands on… try and slow it down…and do some relaxed breathing.*	*It tracks quite a long way down that wedge of collapse...I am thinking…to do some real focused stuff on that left side…make sure he is doing his nebuliser and his physio twice a day…three cycles of sitting and…right side lying…may be more achievable in the short term…it is not ideal but trying to make the best of the situation.*	*This isn't as one sided as I think his other scans look... He's…flummoxed me a little bit…In an ideal world, with a very compliant patient, I would want to make sure they were doing enough cycles in each position so doing some in supine, prone and alternate side lying.*	*I don't know. He really does need to be targeting different areas of his lungs doesn't he… there are focal areas of dense poor ventilation on both sides…I would…arrange a home visit to see him doing it in his own environment.*
Model	Response provides insight into whether the regimen will work and informs modifications to procedure.	MRI as physical factor informs modifications to procedure and dosage.	MRI as physical factor, combined with psychosocial factors cause protracted decisional shift.	MRI as response provides insight into whether the regimen will work and cause protracted decisional shift.
Case 7 Y Nurse	**Clinical information** FEV_1 59% predicted, prescribed ACT BD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =8.2, post= 10.2, 4-hours post =5.6.	**Case classification point**
Cue	Observation of ACT regimen (Salbutamol, 7%, Cornet in sitting).	Post-ACT UTE 	Pre-ACT ^{129}Xe MRI 	4-hours post-ACT ^{129}Xe binning map 

Excerpt	*His nebuliser didn't seem to move a lot of stuff... he probably needs to get into different positions to clear different parts…he just needs to be slower and concentrate.*	*That area of collapse, who knows whether that's going to open up…but he's definitely not effectively doing physio…he needs to be doing… different positioning…on the left…on your tummy, on your front so you're trying to open those bits… there's quite significant areas that needing attention.*	*Worse…than I would have expected…I think positioning, and good exercise that's making him breathless…they just need to up their treatments, or…do some treatment.*	*I'm afraid physio, physio, physio but effective physio, it's got to be targeted on the areas it needs to work, I mean obviously it's got to work everywhere but I think it needs more specific, targeted.*
Model	Response provides insight into whether the regimen will work and informs modifications to procedure.	MRI as physical factor informs modifications to procedure.	MRI as physical factor informs modifications to dosage.	MRI as response provides insight into whether the regimen will work and informs modifications to procedure.
Case 11 Y2 Physio	**Clinical information** FEV_1 70% predicted, prescribed ACT BD, completes OD.	**Structural MRI**	**Functional MRI** ^{129}Xe VDP (%) pre =5.7, post= 5.6, 4-hours post =4.2.	**Case classification point**
Cue	Observation of ACT regimen (7%, Aerobika in sitting prone and ASL) and prior knowledge of case.	Pre-ACT UTE 	Pre-ACT ^{129}Xe MRI 	Pre-to 4-hour post-ACT TRM 

Excerpt	*I think it was effective… I'd…think about… salbutamol before and see if that… made it easier to clear the secretions… I'd probably…chat with doctors about…DNase… because it's quite pluggy and difficult to clear but I'd probably want to start with salbutamol first*	*I don't necessarily think the scans would give me anything different from what I've thought before*	*I'd probably try…doing some hands-on thoracic expansion …to try and… ventilate the bottom because that's the main area these pictures…. I don't really know how to target it (anterior defect)…we could do some more in left side lying to target more on the right, on that right side but I wouldn't really know position to specifically get that area.*	*From looking at the scans it looks like from doing her physio her bases… look better ventilated… I don't know why it's got worse anteriorly….maybe there's just some area of sticky phlegm where DNase might help or maybe a bronch or something like that maybe there's just a big area of something. But I couldn't really see anything specific on the scans before.*
Model	Response provides insight into whether the regimen will work and informs modifications to ACT type.	MRI as physical factor.	MRI as physical factor informs modifications to procedures, less confident decisional shift.	MRI as response provides insight into whether the regimen will work and further information on physical cues. Less confident decisional shift.

Appendix 12: Research outputs

12.1 Publications during PhD

- **Schofield, L.M.,** Singh, S.J., Yousaf, Z., Wild, J.M. and Hind, D., 2023. Personalising airway clearance in chronic suppurative lung diseases: a scoping review. *ERJ Open Research*, *9*(3).
- Driessens, C., Carr, S., Clough, E., Copeland, F., Dell, S., Dixon, L., Harris, A., Knibb, R., Leigh, M., Narayanan, M. Redfern, B., Robson, E., Sawras, M., **Schofield, L.,** Sullivan, K., Tipping, M., Tran, N., Waler, W., Lucas, J., and Behan, L. 2022. The impact on parents of diagnosing PCD in young children. *Journal of Clinical Medicine*, *11*(16), p.4774.
- Driessens, C., Carr, S., Clough, E., Copeland, F., Dell, S., Dixon, L., Harris, A., Knibb, R., Leigh, M., Narayanan, M. and Redfern, B., Robson, E., Sawras, M., **Schofield, L.,** Sullivan, K., Tipping, M., Tran, N., Waler, W., Lucas, ., and Behan, L 2024. Experiences of parents whose young child has been diagnosed with primary ciliary dyskinesia. *Authorea Preprints*.
- Goutaki, M., Lam, Y.T., Anagiotos, A., Armengot, M., Burgess, A., Campbell, R., Carlier, M., Caversaccio, N., Chadha, N.K., Demir, B. and Dheyauldeen, S.A.D., Gunaydin, O., Harris, A., Hayn, I., Inal-Ince, D., Levi, E., Lopez Fernandez, T., Lucas, J.S., Maitre, B., Poirrier, A.M.L., **Schofield, L.,** Takeuchi, K., van Gogh, C., Wolter, N.E., Papon, J. 2024. Definition of sinonasal and otologic exacerbation in patients with primary ciliary dyskinesia-an expert consensus. medRxiv, pp.2024-03.

12.2 First author conference presentation or meetings

- Schofield, L., Biancardi, A., Smith, L., Marshall, H., Hughes, D., Capener, D., Bray, J., Fazal, S., Zalewska, A., Norquay, G., Munro, R., Rodgers, O., Armstrong, L., Rodgers, J., Shanks, S., Hind, D., Moya, E., Robson, E., Shawcross, A., Singh, S.J. West, N., & Wild, J.M. 2024. ^{129}Xe-MRI to assess regional airway clearance in children with primary ciliary dyskinesia. Selected for presentation at the European respiratory society international congress.
- Schofield, L., Biancardi, A., Smith, L., Marshall, H., Hughes, D., Capener, D., Bray, J., Fazal, S., Zalewska, A., Norquay, G., Munro, R., Rodgers, O., Armstrong, L., Rodgers, J., Shanks, S., Hind, D., Moya, E., Robson, E., Shawcross, A., Singh, S.J. West, N., & Wild, J.M. 2024. ^{129}Xe-MRI to assess regional airway clearance in children with primary ciliary dyskinesia. Presented at the University of Sheffield School of population health meeting.

- Schofield, L., Biancardi, A., Capener, D., Hughes, D., Marshall, H., Moya, E., Robson, E., Shawcross, A., Shanks, S.J. Smith, L., West, N., S., Singh, Wild, J.M. & Hind, D., 2024. Can 129Xe ventilation MRI guide personalisation of airway clearance regimens in children with Primary Ciliary Dyskinesia? Presented at the University of Sheffield School of population health meeting.
- Schofield, L., Smith, L., Biancardi, A., Marshall, H., Hughes, D., Shanks, S., Shawcross, A., Robson, E., Moya, E., West, N., Singh, S.J. Hind, D. & Wild, J.M. 2024. Assessing the effects of personalised airway clearance techniques in children with Primary Ciliary Dyskinesia, a mixed method study employing ^{129}Xe ventilation MRI. Platform presentation at the King John Price Paediatric Respiratory Conference.
- Schofield, L., Smith, L., Biancardi, A., Robson, E., Marshall, H., Capener, D., Bray, J., Armstrong, L., Rodgers, J., Munro, R., Norquay, G., Rodgers, O., Fazal, S., Zalewska, A., . Hughes, D., Shanks, S., Hind, D., Moya, E., Singh, S.J. West, N., & Wild, J.M. 2023. Assessing personalised airway clearance techniques in Primary Ciliary Dyskinesia with 129Xe ventilation MRI. Top posters at ERS flash presentation at the BEAT-PCD international meeting.
- Schofield, L., Smith, L., Biancardi, A., Robson, E., Marshall, H., Capener, D., Bray, J., Armstrong, L., Rodgers, J., Munro, R., Norquay, G., Rodgers, O., Fazal, S., Zalewska, A., . Hughes, D., Shanks, S., Hind, D., Moya, E., Singh, S.J. West, N., & Wild, J.M. 2023. Can Ventilation MRI provide insight into the effects of airway clearance techniques in PCD? Platform presentation at the Association of physiotherapists in respiratory care conference.
- Schofield, L.M., Singh, S.J., Yousaf, Z., Wild, J.M. & Hind D. 2023. Scoping the literature, how should airway clearance techniques be personalised in CSLDs? Flash presentation at the Association of physiotherapists in respiratory care conference.
- Schofield, L.M. & Swingwood, E. 2023. How do we really embed research into physiotherapy practice? Selected symposium at the Association of physiotherapists in respiratory care conference.

12.3 First author conference poster presentations

- Schofield, L., Biancardi, A., Capener, D., Hughes, D., Marshall, H., Moya, E., Robson, E., Shawcross, A., Shanks, S.J. Smith, L., West, N., S., Singh, Wild, J.M. Hind, D., 2024. Can ^{129}Xe ventilation MRI guide personalisation of airway clearance regimens in children with Primary Ciliary Dyskinesia? Selected for presentation at the European respiratory society international congress.

- Schofield, L., Smith, L., Biancardi, A., Robson, E., Marshall, H., Capener, D., Bray, J., Armstrong, L., Rodgers, J., Munro, R., Norquay, G., Rodgers, O., Fazal, S., Zalewska, A., . Hughes, D., Shanks, S., Moya, E., Singh, S.J. West, N., Hind, D., & Wild, Assessing the effects of personalised airway clearance techniques in children with PCD, a mixed methods study employing ^{129}Xe MRI, Leeds teaching hospitals research and innovation conference, 2024.
- Schofield, L., Smith, L., Biancardi, A., Robson, E., Marshall, H., Capener, D., Bray, J., Armstrong, L., Rodgers, J., Munro, R., Norquay, G., Rodgers, O., Fazal, S., Zalewska, A., . Hughes, D., Shanks, S., Hind, D., Moya, E., Singh, S.J. West, N., & Wild, J.M. 2023. Assessing personalised airway clearance techniques in Primary Ciliary Dyskinesia with 129Xe ventilation MRI. European Respiratory Journal 62 (67).
- Schofield, L.M., Singh, S.J., Wild, J.M. & Hind D. 2023. Personalising airway clearance in PCD, exploring expert physiotherapist decision making. European Respiratory Journal 60 (Suppl 66).
- Schofield, L.M. Brooks, K & Brooks, O. 2022. Involving Children and Young People with Primary Ciliary Dyskinesia in Research. Presented at the NIHR academy member's conference.

12.4 Presentations as an invited speaker

- Assessing Personalised Airway Clearance Techniques in Primary Ciliary Dyskinesia, International PCD physiotherapy network webinar, March 2024.
- Assessing Personalised Airway Clearance Techniques in Primary Ciliary Dyskinesia, Association of chartered physiotherapists in cystic fibrosis non-medical prescribers study day, November 2023.
- Can Ventilation MRI provide insight into the effects of airway clearance techniques in PCD? Newcastle physiotherapy research meeting, October 2023.
- ASPECT PCD study, summary of findings to date, national PCD medical board meeting, May 2023.
- Assessing personalised airway clearance techniques in PCD, Leicester physiotherapy research meeting, May 2023.
- Assessing Personalised Airway Clearance Techniques in Primary Ciliary Dyskinesia, Nordic Cystic fibrosis meeting, Lund, Sweden September 2022.
- "Chest physio twice a day"...an insight into PCD airway clearance regimens, PCD live session hosted by PCD support UK, July 2022.

12.5 Awards

- Best abstract finalist, Leeds teaching hospitals research and innovation conference, 2024. Assessing the effects of personalised airway clearance techniques in children with PCD, a mixed methods study employing ^{129}Xe MRI.
- Best poster, NIHR academy conference, 2022: 2022. Involving Children and Young People with Primary Ciliary Dyskinesia in Research.