The University Of Sheffield.

Full Project Title:

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

Shortened Project Title:

Assessing Personalised Airway Clearance Techniques in PCD (ASPECT- PCD)

Protocol Version Number: 0.6 **Date:** 14/05/2021

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

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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 Key Study Contacts

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2 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).

3 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.

4 Roles and Responsibilities of study management committees/groups & individuals.

4.1 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.

4.2 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.

4.3 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

5 Study Flow Chart

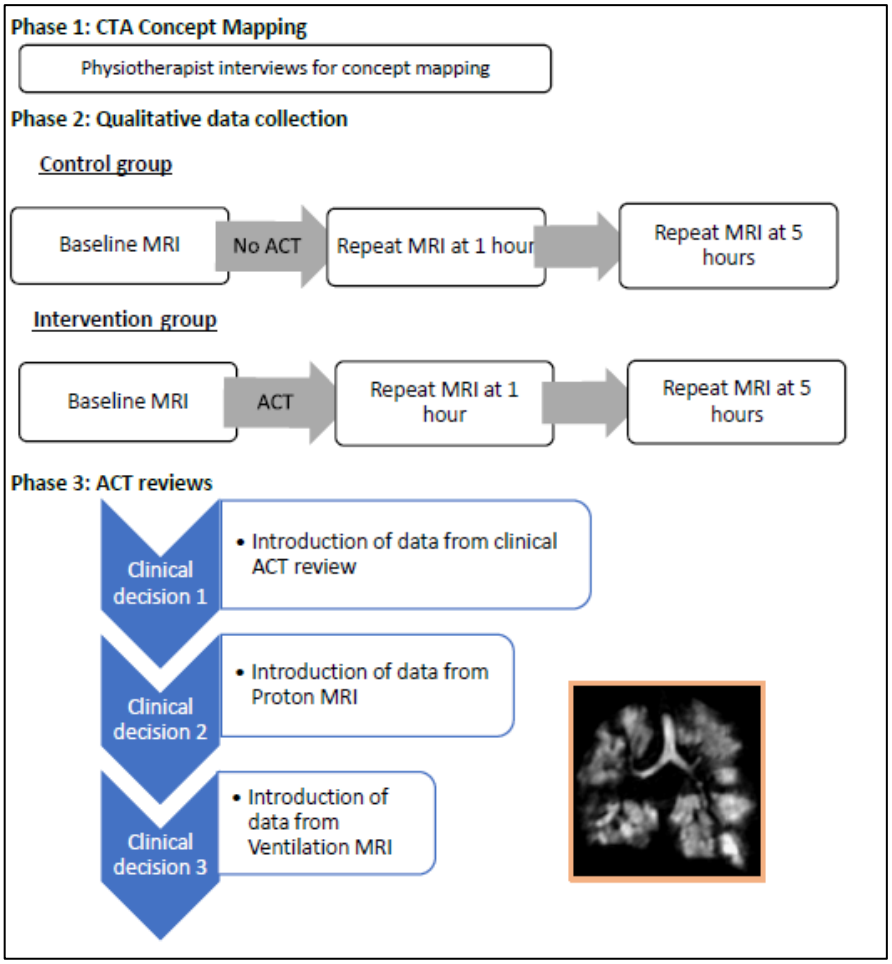

Figure 1: Study flow diagram

1. Full Project Title:

Assessing the effects of personalised airway clearance regimens in young people with Primary Ciliary Dyskinesia.

2. 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].

3. 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.

4. 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.

5. Research questions, aims and objectives

5.1. 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?

5.2. 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.

5.3. 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.
    c) With the introduction of Ventilation MR images.

6. Plan of investigation

6.1. Study design

<u>Quantitative:</u>

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.

<u>Qualitative:</u>

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.

6.2. Sample and Recruitment

6.2.1. 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.

6.2.2. Sampling

Convenience sampling will be used for all phases of the study.

6.2.2.1. 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(Guest 06- ref to be inserted).

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	43 (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.

6.2.3. 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.

6.3. Recruitment

6.3.1. 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.

6.3.2. 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.

6.4. Methodology

6.4.1. 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].

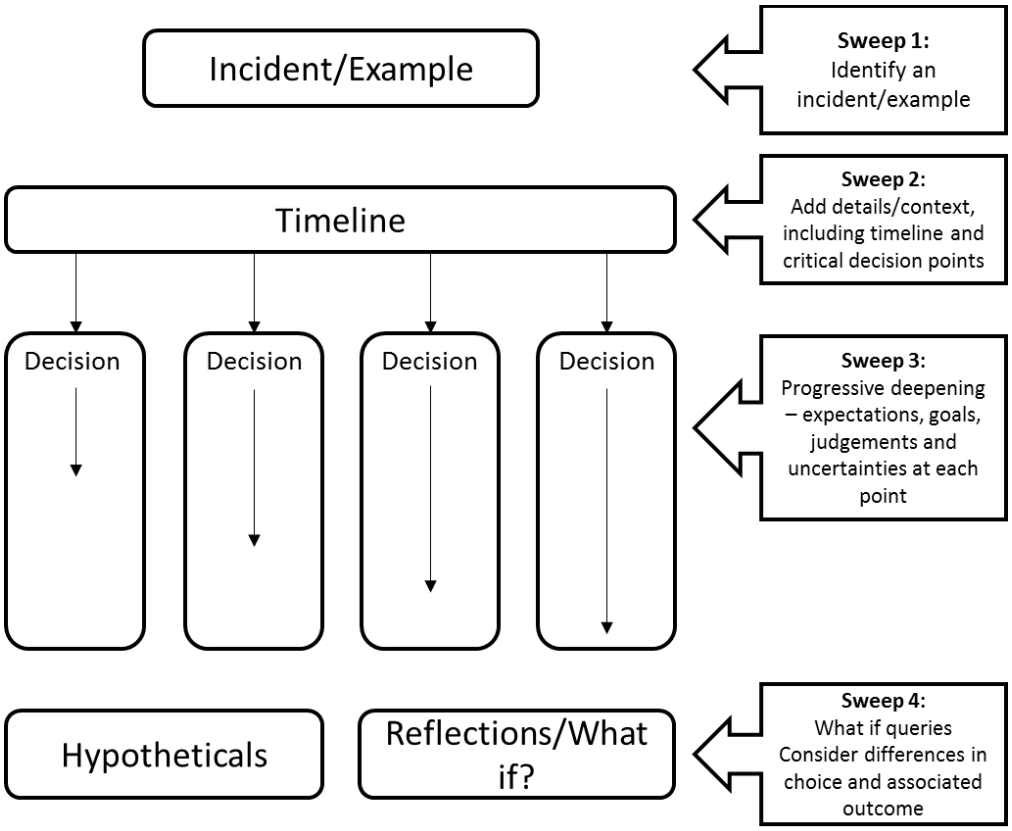

Figure 2: The Critical Decision Method procedure

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.

6.4.2. 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.

6.4.3. 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.

6.5. 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:

6.6. 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.

7. Safety assessments and Reporting

7.1. 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.

7.2. ^{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].

7.3. 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.

7.4. 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.

7.5. 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.

7.6. 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.

7.7. 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.

Month	Target
0	Phase 1- Begin physiotherapy clinician recruitment

Month	Target
3	Phase 1- physiotherapist interviews completed
4	Phase 2 -Begin patient recruitment
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

Table 2: Study landmarks

8. 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.

9. Ethical and regulatory considerations

9.1. Assessment and management of risk

9.1.1. 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.

9.1.2. 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.

9.1.3. 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.

9.2. Research Ethics Committee (REC) and other Regulatory review & 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.

9.2.1. 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.

9.2.2. 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.

9.2.3. Peer review

This study has been peer reviewed as part of the NIHR CDRF application process of Miss Lynne Schofield

9.2.4. 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.

9.2.5. 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.

10. 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.

11. Strategy for taking the work forward if the research 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.

12. 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).

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