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Feasibility study of paediatric regional lung function assessment via X-ray Velocimetry (XV) imaging in children with normal lungs and in children with cystic fibrosis

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Protocol: Feasibility study of paediatric regional lung function assessment via X-ray Velocimetry (XV) imaging in children with normal lungs and in children with cystic fibrosis

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Abstract:

Introduction: Cystic fibrosis (CF) is a life-limiting autosomal recessive genetic condition. It is caused by mutations in the gene that encodes for a chloride and bicarbonate conducting transmembrane channel. X-ray Velocimetry (XV) is a novel form of X-ray imaging that can generate lung ventilation data through the breathing cycle. XV technology has been validated in multiple animal models, including the □-ENaC mouse model of cystic fibrosis lung disease. It has since been assessed in early-phase clinical trials in adult human subjects, however there is a paucity of data in the paediatric cohort, including in CF. The aim of this feasibility study is to conduct a single-centre cohort study in paediatric patients with CF and in those with normal lungs, to demonstrate the appropriateness of proceeding with further studies of XV in these cohorts.
Methods and analysis: This is a prospective, single-centre, feasibility cohort study. It will recruit children aged 3 to 18 years to have XV lung imaging performed, as well as paired pulmonary function testing. The study will aim to recruit 20 children without cystic fibrosis with normal lungs, and 20 children with cystic fibrosis. The primary outcome will be the feasibility of recruiting children and performing XV testing. Secondary outcomes will include comparisons between XV and current assessments of pulmonary function and structure.
Ethics and dissemination: This project has ethical approval granted by The Women's and Children's Hospital Human Research Ethics Committee. (HREC ID 2021/HRE00396). Findings will be disseminated through peer-reviewed publication and conferences.

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Strengths and limitations of this study

- This is the first study to investigate the use of X-ray Velocimetry in a paediatric Cystic Fibrosis cohort
- This is a new technology which could have significant benefits in this patient group if it is found to be feasible and becomes a clinically-validated tool
- As a pilot study the sample size is small, and the aim and design is well suited to assessment of the feasibility of future XV studies in paediatrics and cystic fibrosis.
- The small study size means that secondary assessments and comparisons of XV and lung function tests may be underpowered

Keywords: Cystic fibrosis, X-ray Velocimetry, ventilation heterogeneity

Word count: 3553

Introduction

Cystic fibrosis

Cystic fibrosis is a life-limiting autosomal recessive genetic condition, with an incidence of approximately 1 in 2500 in the Caucasian population[1, 2]. It is caused by mutations in the gene that encodes for the cystic fibrosis transmembrane conductance regulator (*CFTR*), affecting chloride as well as bicarbonate ion transmembrane channel activity[1, 3]. Cystic fibrosis is a multi-system disorder, with CFTR dysfunction causing issues in the lung, pancreas, liver, bowel, sweat glands and vas deferens, amongst others.

There have been significant advances in the care of cystic fibrosis. In the 1950's median life expectancy was only a few months, with mortality mainly due to meconium ileus and malnutrition secondary to exocrine pancreatic insufficiency[1]. There has been a progressive increase in life expectancy over the past six to seven decades, with multidisciplinary care advances and more recently the introduction of highly effective modulator therapies. In Australia, the median survival is now over 50 years of age[2].

With improved treatment of early complications and the use of pancreatic enzyme replacement, the primary morbidity and mortality is now related to pulmonary pathology, including bronchiectasis, small airway obstruction and progressive respiratory failure[1, 4].

Pulmonary exacerbations

Pulmonary pathology is predominantly driven by inflammation, caused by the inability to clear micro-organisms. CFTR dysfunction causes impaired mucociliary clearance secondary to reduced hydration of the airway surface liquid. However, multiple other factors likely contribute, including mucus tethering and function, impaired innate immunity and increased intrinsic cellular inflammation[1, 5-7]. CF lung disease is heterogenous, both phenotypically between patients and within individual patients[8]. It is difficult to predict the progression and disease manifestation within an individual[8, 9].

Those affected by cystic fibrosis have recurrent exacerbations of disease. Pulmonary exacerbations are defined symptomatically by increased cough and sputum production and may be associated with respiratory distress, fatigue and reduced exercise tolerance[10, 11]. Investigations including pulmonary function tests, chest imaging, sputum culture and blood inflammatory markers may assist with the clinical decision for treatment initiation and duration[1, 4, 10-12].

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Pulmonary assessment and monitoring

There are multiple methods available to assess pulmonary status in CF, including both functional and structural aspects. There are also developments being made in functional lung imaging, with new imaging modalities able to give visual and quantitative assessments of regional lung ventilation.

Pulmonary function testing

The most commonly used pulmonary function test in CF is spirometry. Spirometry is a quick, non-invasive way to assess for airway obstruction or restriction. It requires significant respiratory effort and appropriate technique, meaning it is unsuitable for children less than 5-6 years of age. Reduced forced expiratory volume in 1 second (FEV1) is used as the main indicator of airway obstruction, indicating disease progression or pulmonary exacerbation[13, 14]. Body plethysmography can also be used to measure total lung capacity (TLC) and residual volume (RV), which can give an indication of gas trapping associated with airway obstruction. These assessments provide a global assessment of lung function. When there is ventilation inhomogeneity, they cannot identify whether there is potentially a compensated abnormality present[15].

Multiple breath washout (MBW) is another method of assessing pulmonary function. It has the benefit of being able to be performed in a younger age group due to less dependence on technique[16]. The lung clearance index (LCI) is the most commonly utilised outcome and reflects the global ventilation inhomogeneity. It has been shown to be associated with evidence of structural lung disease in patients with CF[17]. However, while it is associated with structural disease, it is not able to identify the location of any abnormality.

Structural lung assessment

Structural assessment of the lungs in CF is generally performed through chest X-ray, computed tomography (CT) or magnetic resonance imaging (MRI).

Chest X-ray (CXR) is a quick and commonly used imaging technique. It can assess anatomical changes in the lungs and is generally recommended to be performed annually as part of routine CF care[14]. However, it is limited by low resolution and is not sensitive enough to detect early structural lung changes associated with CF.

High Resolution Computed Tomography (HRCT) is the gold standard for identifying structural lung disease in CF[18]. There have been several scoring systems developed for CF lung disease, aimed at identifying evidence of structural damage including bronchiectasis, mucus plugging, bronchial wall thickening and atelectasis. The Perth-Rotterdam Annotated Grid Morphometric Analysis method (PRAGMA-CF) is a scoring system developed by Rosenow, et al, which showed improved correlation between neutrophilic inflammation and CT scores compared to previous methods, as well as stronger relationships between structural changes and trapped air progression[18]. It was also designed to provide reliable quantitative estimates of lung disease in young children, whereas previous methods were predominantly focused on older children and adults. While CT is the gold standard, it is associated with a higher ionising radiation dose than CXR.

MRI of the lung has traditionally been limited, largely due to the technical difficulties produced by low proton density (required for MRI to acquire an appropriate resonance signal) and artefact created by respiratory and cardiac motion[19]. There have been advances in MRI technology to improve lung image quality, with novel MR sequences able to depict some structural changes in CF. However, it is still limited by longer acquisition times and higher expense.

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Functional lung imaging

4D computed tomography

4D computed tomography has a diverse range of methods described in the literature. However, to calculate ventilation metrics they generally undergo three computational steps, including lung volume delineation, measurement of lung motion and algorithmic calculation of surrogate measures for regional ventilation[20, 21]. The most common algorithms are evaluation of lung volume changes using CT intensity or Hounsfield Unit values and deformation vectors[20].

Xenon computed tomography

Xenon is an inert, noble gas. It has been used an inhalational contrast agent for functional lung imaging due to its x-ray absorption characteristics, being similar to iodine[20, 22]. Xenon CT involves a wash-in phase, where the subject inhales a xenon and oxygen mixture, followed by a period of wash-out, where they inhale a high oxygen concentration while the radioisotope is exhaled or absorbed. Images captured by CT are subsequently processed into three-dimensional distribution maps, where ventilation can be qualitatively and quantitatively assessed[20, 23].

Hyperpolarised gas magnetic resonance imaging

Hyperpolarised gas MRI allows an evaluation of both pulmonary anatomy and function, by the visualisation of dynamic ventilation over the course of a respiratory cycle. The use of noble gas contrast agents, such as helium-3 or xenon-129, allows the circumvention of the traditional lack of proton signal in the lung and better image capture[19, 20, 24]. Ventilation imaging can provide information about defects (including calculation of the ventilation defect percentage, VDP, the percentage of lung with ventilation below 60% of the mean), and diffusion weighted imaging can be utilised to calculate the apparent diffusion coefficient to differentiate between normal and enlarged airspaces[20]. The primary limitations to uptake of hyperpolarised gas MRI is access to expensive hyperpolarising equipment, in addition to an MRI machine and the technical expertise required for testing.

X-ray Velocimetry

X-ray Velocimetry (XV) is a novel form of X-ray imaging that was designed to collect lung ventilation data. The clinical implementation of this technique uses information collected via X-ray fluoroscopy to track the motion of the distinctive speckle pattern that is created by overlapping alveoli within the lung. In the current clinically available assessments in adults, single breath cine-scans using existing fluoroscopic imaging equipment are captured at 5 different angles during tidal breathing. When combined with a thoracic CT, the scans are used to construct a four-dimensional map (i.e. the 3-D volume changes, tracked over time) of regional lung tissue displacement during the breath[25, 26]. This enables creation of a visual map of regional ventilation, derived from the quantitative measures of airflow, and provides metrics such as mean specific ventilation, ventilation heterogeneity (VH) and ventilation defect percentage (VDP)[25].

XV technology has been validated in multiple animal models, including the □-ENaC mouse model of CF lung disease, in which XV was able to visualise the patchy lung disease and identify regions of reduced airflow[26-28]. The technique has also shown a strong correlation with direct measurements using pneumotachography and plethysmography in a mouse model of bleomycin-induced pulmonary fibrosis[29], and been used to map airflow during high-frequency ventilation[30, 31]. It has since been assessed in early-phase clinical trials in adult human subjects[32]. The first clinical validation was performed in a cohort of patients undergoing radiation therapy for various thoracic cancers, excluding lung cancer[33]. Regional lung ventilation was quantified and compared to spirometry and CT findings at baseline, 4 and 12 months after radiotherapy. Analysis showed

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correlation between XV ventilation data and both spirometry and CT. XV was also shown to be more sensitive in measuring alterations in regional lung function over time. Changes detected at 4 months via XV were not reflected in spirometry metrics at that time point, but became evident at 12 months post-radiotherapy[33].

While XV imaging utilises X-rays, at the current stage of development it also requires a CT of the chest to provide a structural framework and boundaries for the software. The CT is not required for assessment of ventilation or parenchymal data. With further development the technique is aimed to no longer require any CT input and acquire all relevant information from fluoroscopy only.

Aim

The aim of this study is to conduct a single-centre cohort feasibility study in paediatric patients with CF and in those with normal lungs. Before a statistically powered cohort study is undertaken to establish both a normative reference range and a CF diagnostic reference range, a feasibility study was deemed necessary to determine if a properly powered study was possible, and to outline the optimal design features.

Methods and analysis

Study design overview

This is a prospective, single-centre, feasibility cohort study. It will recruit children aged 3 to 18 years (inclusive) to have XV lung imaging performed. The study will recruit children without CF with healthy/normal lungs, and children with CF. Patients in both cohorts will be required to have had a CT scan within the last 6 months (or as per clinical judgement) or scheduled to have had a CT scan in an upcoming appointment as part of their normal clinical care.

Patients will be recruited at the Women's and Children's Hospital, North Adelaide, Australia. They will undergo a clinical assessment with history and physical exam, undertake an XV scan, and perform at least one of spirometry, plethysmography and diffusing capacity, or multiple breath washout. Those with CF will also complete the CFQ-R Cystic Fibrosis questionnaire. The CFQ-R will be applied regularly in a follow-up longitudinal study. Investigators will not be blinded to cohort allocation.

Patient and public involvement

Patients and public were not involved in the design of this study. Separate to this study, a qualitative assessment of XV will be undertaken and results used to guide future, larger studies.

Ethical approval

Ethical approval has been granted by The Women's and Children's Hospital Human Research Ethics Committee. (HREC ID 2021/HRE00396)

All participants will provide written consent, either individually or by legal guardian if 16 or older, or by their legal guardian if younger than 16.

Study registration

The study has retrospective registration with the Australian New Zealand Clinical Trial Registry (ANZCTR): 1262000109606 and the Universal Trial Number (UTN): U1111-1287-9096.

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Sample selection

20 patients will be recruited to both the healthy lung (control) and CF cohorts. A sample size of n=20 is within the range recommended for pilot studies to be able to detect adequate effect sizes as would be seen in comparative studies[34, 35].

For each study arm, potential participants will be identified from medical record reports identifying young people aged 3-18 years who may meet our inclusion criteria. Reports of children who have had a CT scan of their chest within the past 3 months will be compiled by hospital administrators or data custodians of individual departments records for assessment by the study team for potential inclusion in the study.

Arm 1

Arm 1 will include those children with normal lungs. Given children will be required to have a chest CT, specific patient groups have been targeted. These include new-diagnosis oncology patients prior to treatment, physical trauma patients without evidence of lung injury, and rheumatology patients without evidence of pulmonary disease. Other patients identified as potentially suitable will be considered on a case-by-case basis.

Arm 2

Arm 2 will include those patients with CF. The inclusion and exclusion criteria are the same as for Arm 1, with the exception of the inclusion of a confirmed diagnosis of cystic fibrosis.

Inclusion criteria

- Aged 3-18 years inclusive at time of consent
- CT scan performed within the last 6 months (or as per clinical judgement), or scheduled to have a CT in an upcoming appointment

Exclusion criteria

- Pre-existing lung disease in Arm 1, including asthma, interstitial lung disease etc.
- Currently receiving mechanical ventilation, intensive or critical care
- Contraindication to ionising radiation
- Urgent clinical treatment precluding the addition of XV imaging
- Inability to comply and remain still for period of XV image acquisition
- Inability to perform at least one of the pulmonary function tests listed previously.

Intervention

Clinical assessment

Patients will undergo a clinical review and physical examination.

X-ray Velocimetry scan

An XV scan will be performed in The Women's and Children's Hospital Radiology Department. The XV scan involves fluoroscopic imaging of tidal breathing from 5 different angles (AP, +/- 36°, +/- 60°). The images will be sent to 4DMedical, Melbourne, and a report generated via their X-ray Velocimetry Lung Ventilation Analysis Software (XV LVAS) platform. Tissue expansion is calculated to assess ventilation at a regional level within the lung. Ventilation is determined by measuring the change in volume of a specific lung region during inhalation and dividing it by the volume of that same region at the end of exhalation. This calculation generates a unit called specific ventilation (SV), which quantifies volume changes in mm^3 for each individual lung region. Regions that inflate more have higher SV. The SV measurements are presented as a coloured contour image map of the lungs illustrating the spectrum of ventilation measurements during breathing.

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XV LVAS report metrics include:

- Tidal Volume (TV) – the volume of air inhaled from start of inspiration to peak inspiration
- Mean Specific Ventilation (MSV) – the mean of specific ventilation across all regions of the lung
- Ventilation Defect Percentage (VDP) – measures the percentage of lung volume that is below 60% of the mean specific ventilation
- Ventilation Heterogeneity (VH) – measures the overall variability of ventilation across the lung

Pulmonary function testing

Pulmonary function testing will be performed in the Women's and Children's Hospital Lung Laboratory, a nationally accredited pulmonary function testing centre, under the auspices of the Thoracic Society of Australia and New Zealand.

Multiple breath washout

Eco Medics Exhalyser D equipment will be used to perform nitrogen multiple breath washout testing to generate the Lung Clearance Index.

Spirometry and body plethysmography

Spirometry and DLCO tests will be performed on a Medisoft Spiro Air, as per ERS/ATS standards[36, 37]. Plethysmography testing will be performed using Medisoft bodybox, also as per ERS/ATS standard[38].

Outcome measures

Primary

The primary outcome measure from this feasibility study is to learn how long it will take to recruit 20 children without CF and 20 children with CF to complete an XV scan and the other assessments listed above.

This data will determine if a larger, statistically-powered study can be undertaken at this site to evaluate the diagnostic capabilities of XV imaging, which may be able to better measure lung health compared to existing methods.

Secondary

Appropriateness of XV LVAS technology as a clinical assessment for lung function, compared to standard and specialised pulmonary lung function techniques

This will be measured by comparisons of XV-LVAS report metrics to report metrics of existing pulmonary function testing, including spirometry, plethysmography and diffusion capacity, and lung clearance index.

Appropriateness of XV LVAS technology as a clinical assessment for structural lung disease, compared to CT imaging

XV LVAS report metrics will be compared to CT chest evidence of structural lung disease, assessed via PRAGMA-CF scoring.

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Identify which participant characteristics should be considered to clinically evaluate lobar ventilation distribution, ventilation heterogeneity and expiratory time constant

This will be determined through visual inspection of characteristic data and identification of potential factors that may influence report metrics. Factors will be considered where correlation trends are observed in continuous and dichotomous variables.

Identify if ongoing assessment of ventilation distribution, ventilation heterogeneity and expiratory time constant is safe and clinically appropriate

This will be determined through a retrospective evaluation of CT scan frequency among the young people with CF, identification of any adverse events during and immediately following XV imaging and preliminary appropriateness of XV LVAS testing.

Data analysis

The XV, lung function and CT outcome data obtained from this study will be described by group, using descriptive statistics. Continuous variables will be described using mean and standard deviation, or median and interquartile range if the distribution is asymmetric. Categorical variables will be presented as numbers and percentages. Demographic variables age, sex, height and weight will also be described by group. Statistical association between outcome measures will be assessed graphically and described using correlation coefficients.

Data storage

All data for an individual participant will be collected by the principal investigator or their delegated nominees and recorded in the patient record. Participant identification will be through their unique participant study number. All clinical data will be stored as per SA Health data storage guidelines.

Standard clinical lung function data will be collected and stored securely as per WCH guidelines. Each participant's lung function data will be identified by hospital unique record number (URN) initially, then de-identified using a numerical code before being sent to statisticians for analysis.

Pre-existing radiological data (i.e., CT chest) will continue to be stored as per routine clinical data in the WCH Radiology Department, using secure WCH server and SA Health computers.

De-identified XV LVAS data will be stored in the WCH Respiratory and Sleep Department using the WCH SA Health Network server. Data will be stored for a minimum of 30 years, according to WCH data-retention requirements.

At the conclusion of the study, all hard copy case report forms, signed consent forms and trial data will be archived according to the Respiratory Clinical Trial Unit's Archiving SOP at Iron Mountain.

Adverse events and analysis

Lung function testing entails standard procedures that are well established. The testing staff are trained and experienced in recognising and dealing with potential risks, as a normal part of routine testing. Some procedures require special breathing efforts. Known risks are:

- Dizziness
- Feeling short of breath
- Coughing
- Asthma attack precipitated by deep inhalation

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XV imaging protocol involves exposure to ionising radiation. The radiation dose in the research portion of the study is low, estimated to between 0.52 – 0.83 mSv, equivalent to between 2-5 standard chest X-rays. As such, there is minimal risk to participants.

Sponsorship

This study is supported by 4DMedical, who will provide the XV LVAS reports for patients undergoing XV imaging. 4DMedical have no input into study design, outcome analyses, or study conclusions.

Challenges in study design

To allow for appropriate XV LVAS mapping and report, a chest CT is currently required to provide the anatomical framework. Given the radiation dose required for CT of the chest region, it is not ethically appropriate to perform a chest CT in children, in addition to that required for routine clinical care. This is particularly the case in those with healthy lungs where a chest CT assessment is not clinically indicated. This limits the eligible normal lung patient cohort considerably, given the relative clinical reluctance to perform CT in children compared to adults. Some potential cohorts of eligible patients, for example oncology patients, have routine CT. They also, however, frequently receive agents with known pulmonary side effects. A further limitation is that it will be common to be unable to perform the additional XV imaging and pulmonary function tests on a child in the emotionally difficult period between an oncological diagnosis with routine screening CT and subsequent rapid initiation of treatment.

Pulmonary function testing is dependent on compliance and technique. Children less than 5-6 years of age will be unable to undergo spirometry and plethysmography. In the cohort 5 years and over there can still be technique issues affecting accurate results. This may affect the ability to compare XV imaging with standard lung function metrics in some younger children, however this will not affect the primary study outcome of feasibility.

Future trial considerations

A feasibility study design is necessary to determine if it is possible to recruit and test children without CF with healthy lungs as well as those with CF to participate in an XV imaging study. This is an important first step towards establishing a statistically-powered cohort study. Such a study would evaluate XV LVAS outcomes in children with normal lung function and anatomy that can be used to provide normal reference range data sets against which putative disease states can be examined.

Since XV is a new lung function imaging technology, studies to establish a reference range are a prerequisite before clinical adoption of the technique for diagnosis and monitoring of children with lung pathology.

Article summary

This is one of the first studies to investigate XV imaging in a paediatric cohort. Enrolment of participants is ongoing in 2023 and final results are expected by the end of 2024.

Author contributions:

MB: Recruitment, draft and review/editing of final manuscript. AT, TG: concept, study design, ethics submission and approval, recruitment and review/editing of final manuscript. MD: concept, study design and review/editing of final manuscript. KCC: concept, design and review/editing of final

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manuscript. DP: concept, study design, ethics submission and approval, review/editing of final manuscript. JP: recruitment and review/editing of final manuscript.

Acknowledgments:

Nil additional

Conflicts of interest:

DP has received renumeration for research advice from 4DMedical. DP and MD have both purchased shares in 4DMedical Ltd

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

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Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	9
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a

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Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	1-3
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			

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Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final	7

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		value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that	n/a

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		is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description	7

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		of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7-8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			

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Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	5
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5

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Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	5
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8

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Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	1
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	7
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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Protocol: Pilot study of paediatric regional lung function assessment via X-ray Velocimetry (XV) imaging in children with normal lungs and in children with cystic fibrosis

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Protocol: Pilot study of paediatric regional lung function assessment via X-ray Velocimetry (XV) imaging in children with normal lungs and in children with cystic fibrosis

Authors:

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Abstract:

Introduction: Cystic fibrosis (CF) is a life-limiting autosomal recessive genetic condition. It is caused by mutations in the gene that encodes for a chloride and bicarbonate conducting transmembrane channel. X-ray Velocimetry (XV) is a novel form of X-ray imaging that can generate lung ventilation data through the breathing cycle. XV technology has been validated in multiple animal models, including the □-ENaC mouse model of cystic fibrosis lung disease. It has since been assessed in early-phase clinical trials in adult human subjects, however there is a paucity of data in the paediatric cohort, including in CF. The aim of this pilot study is to investigate the feasibility of performing a single-centre cohort study in paediatric patients with CF and in those with normal lungs, to demonstrate the appropriateness of proceeding with further studies of XV in these cohorts.
Methods and analysis: This is a cross-sectional, single-centre, pilot study. It will recruit children aged 3 to 18 years to have XV lung imaging performed, as well as paired pulmonary function testing. The study will aim to recruit 20 children without cystic fibrosis with normal lungs, and 20 children with cystic fibrosis. The primary outcome will be the feasibility of recruiting children and performing XV testing. Secondary outcomes will include comparisons between XV and current assessments of pulmonary function and structure.
Ethics and dissemination: This project has ethical approval granted by The Women's and Children's Hospital Human Research Ethics Committee. (HREC ID 2021/HRE00396). Findings will be disseminated through peer-reviewed publication and conferences.

Trial registration number (ACTRN12623000109606)

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Strengths and limitations of this study

- As a pilot study the sample size is small, and the aim and design is well suited to assessment of the feasibility of future XV studies in paediatrics and cystic fibrosis.
- The cohorts targeted for recruitment have undertaken CT as part of their routine clinical care, limiting the amount of radiation required to undergo XV imaging
- The small study size means that secondary assessments and comparisons of XV and lung function tests may be underpowered

Keywords: Cystic fibrosis, X-ray Velocimetry, ventilation heterogeneity

Word count: 3673

Introduction

Cystic fibrosis

Cystic fibrosis is a life-limiting autosomal recessive genetic condition, with an incidence of approximately 1 in 2500 in the Caucasian population[1, 2]. It is caused by mutations in the gene that encodes for the cystic fibrosis transmembrane conductance regulator (*CFTR*), affecting chloride as well as bicarbonate ion transmembrane channel activity[1, 3]. Cystic fibrosis is a multi-system disorder, with CFTR dysfunction causing issues in the lung, pancreas, liver, bowel, sweat glands and vas deferens, amongst others.

There have been significant advances in the care of cystic fibrosis. With improved treatment of early complications and the use of pancreatic enzyme replacement, the primary morbidity and mortality is now related to pulmonary pathology, including bronchiectasis, small airway obstruction and progressive respiratory failure[1, 4].

Pulmonary exacerbations

Pulmonary pathology is predominantly driven by inflammation, caused by the inability to clear micro-organisms. CFTR dysfunction causes impaired mucociliary clearance, however, multiple other factors also contribute, including mucus tethering and function, impaired innate immunity and increased intrinsic cellular inflammation[1, 5-7].

Those affected by cystic fibrosis have recurrent exacerbations of disease. Pulmonary exacerbations are defined symptomatically by increased cough and sputum production and may be associated with respiratory distress, fatigue and reduced exercise tolerance[8, 9]. Investigations including pulmonary function tests, chest imaging, sputum culture and blood inflammatory markers may assist with the clinical decision for treatment initiation and duration[1, 4, 8-10].

Pulmonary assessment and monitoring

There are multiple methods available to assess pulmonary status in CF, including both functional and structural aspects. There are also developments being made in functional lung imaging, with new imaging modalities able to give visual and quantitative assessments of regional lung ventilation.

Pulmonary function testing

The most commonly used pulmonary function test in CF is spirometry. Spirometry is a quick, non-invasive way to assess for airway obstruction or restriction. It requires significant respiratory effort and appropriate technique, meaning it is unsuitable for children less than 5-6 years of age. Reduced forced expiratory volume in 1 second (FEV1) is used as the main indicator of airway obstruction, indicating disease progression or pulmonary exacerbation[11, 12]. Body plethysmography can also

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be used to measure total lung capacity (TLC) and residual volume (RV), which can give an indication of gas trapping associated with airway obstruction. These assessments provide a global assessment of lung function. When there is ventilation inhomogeneity, they cannot identify whether there is potentially a compensated abnormality present[13].

Multiple breath washout (MBW) is another method of assessing pulmonary function. It has the benefit of being able to be performed in a younger age group due to less dependence on technique[14]. The lung clearance index (LCI) is the most commonly utilised outcome and reflects the global ventilation inhomogeneity. It has been shown to be associated with evidence of structural lung disease in patients with CF[15]. However, while it is associated with structural disease, it is not able to identify the location of any abnormality.

Structural lung assessment

Structural assessment of the lungs in CF is generally performed through chest X-ray, computed tomography (CT) or magnetic resonance imaging (MRI).

Chest X-ray (CXR) is a quick and commonly used imaging technique. It can assess anatomical changes in the lungs and is generally recommended to be performed annually as part of routine CF care[12]. However, it is limited by low resolution and is not sensitive enough to detect early structural lung changes associated with CF.

High Resolution Computed Tomography (HRCT) is the gold standard for identifying structural lung disease in CF[16]. There have been several scoring systems developed for CF lung disease, aimed at identifying evidence of structural damage including bronchiectasis, mucus plugging, bronchial wall thickening and atelectasis. The Perth-Rotterdam Annotated Grid Morphometric Analysis method (PRAGMA-CF) is a scoring system developed by Rosenow, et al, which showed improved correlation between neutrophilic inflammation and CT scores compared to previous methods, as well as stronger relationships between structural changes and trapped air progression[16]. It was also designed to provide reliable quantitative estimates of lung disease in young children, whereas previous methods were predominantly focused on older children and adults. While CT is the gold standard, it is associated with a higher ionising radiation dose than CXR.

MRI of the lung has traditionally been limited, largely due to the technical difficulties produced by low proton density (required for MRI to acquire an appropriate resonance signal) and artefact created by respiratory and cardiac motion[17]. There have been advances in MRI technology to improve lung image quality, with novel MR sequences able to depict some structural changes in CF. However, it is still limited by longer acquisition times and higher expense.

Functional lung imaging

4D computed tomography

4D computed tomography has a diverse range of methods described in the literature. However, to calculate ventilation metrics they generally undergo three computational steps, including lung volume delineation, measurement of lung motion and algorithmic calculation of surrogate measures for regional ventilation[18, 19]. The most common algorithms are evaluation of lung volume changes using CT intensity or Hounsfield Unit values and deformation vectors[18].

Xenon computed tomography

Xenon is an inert, noble gas. It has been used an inhalational contrast agent for functional lung imaging due to its x-ray absorption characteristics, being similar to iodine[18, 20]. Xenon CT involves a wash-in phase, where the subject inhales a xenon and oxygen mixture, followed by a period of wash-out, where they inhale a high oxygen concentration while the radioisotope is exhaled or

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absorbed. Images captured by CT are subsequently processed into three-dimensional distribution maps, where ventilation can be qualitatively and quantitatively assessed[18, 21].

Hyperpolarised gas magnetic resonance imaging

Hyperpolarised gas MRI allows an evaluation of both pulmonary anatomy and function, by the visualisation of dynamic ventilation over the course of a respiratory cycle. The use of noble gas contrast agents, such as helium-3 or xenon-129, allows the circumvention of the traditional lack of proton signal in the lung and better image capture[17, 18, 22]. Ventilation imaging can provide information about defects (including calculation of the ventilation defect percentage, VDP, the percentage of lung with ventilation below 60% of the mean), and diffusion weighted imaging can be utilised to calculate the apparent diffusion coefficient to differentiate between normal and enlarged airspaces[18]. The primary limitations to uptake of hyperpolarised gas MRI is access to expensive hyperpolarising equipment, in addition to an MRI machine and the technical expertise required for testing.

X-ray Velocimetry

X-ray Velocimetry (XV) is a novel form of X-ray imaging that was designed to collect lung ventilation data. The clinical implementation of this technique uses information collected via X-ray fluoroscopy to track the motion of the distinctive speckle pattern that is created by overlapping alveoli within the lung. In the current clinically available assessments in adults, single breath cine-scans using existing fluoroscopic imaging equipment are captured at 5 different angles during tidal breathing. When combined with a thoracic CT, the scans are used to construct a four-dimensional map (i.e. the 3-D volume changes, tracked over time) of regional lung tissue displacement during the breath[23, 24]. This enables creation of a visual map of regional ventilation, derived from the quantitative measures of airflow, and provides metrics such as mean specific ventilation, ventilation heterogeneity (VH) and ventilation defect percentage (VDP)[23].

XV technology has been validated in multiple animal models, including the □-ENaC mouse model of CF lung disease, in which XV was able to visualise the patchy lung disease and identify regions of reduced airflow[24-26]. The technique has also shown a strong correlation with direct measurements using pneumotachography and plethysmography in a mouse model of bleomycin-induced pulmonary fibrosis[27], and been used to map airflow during high-frequency ventilation[28, 29]. It has since been assessed in early-phase clinical trials in adult human subjects[30]. The first clinical validation was performed in a cohort of patients undergoing radiation therapy for various thoracic cancers, excluding lung cancer[31]. Regional lung ventilation was quantified and compared to spirometry and CT findings at baseline, 4 and 12 months after radiotherapy. Analysis showed correlation between XV ventilation data and both spirometry and CT. XV was also shown to be more sensitive in measuring alterations in regional lung function over time. Changes detected at 4 months via XV were not reflected in spirometry metrics at that time point, but became evident at 12 months post-radiotherapy[31].

While XV imaging utilises X-rays, at the current stage of development it also requires a CT of the chest to provide a structural framework and boundaries for the software. The CT is not required for assessment of ventilation or parenchymal data. With further development the technique is aimed to no longer require any CT input and acquire all relevant information from fluoroscopy only.

Aim

The aim of this study is to investigate the feasibility of performing X-ray Velocimetry in paediatric patients with CF and in those with normal lungs. Before a statistically powered cohort study is

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undertaken to establish both a normative reference range and a CF diagnostic reference range, a pilot study was deemed necessary to determine if a properly powered study was possible, and to outline the optimal design features.

Methods and analysis

Study design overview

This is a cross-sectional, single-centre, pilot study. It will recruit children aged 3 to 18 years (inclusive) to have XV lung imaging performed. The study will recruit children without CF with healthy/normal lungs, and children with CF. Patients in both cohorts will be required to have had a CT scan within the last 6 months (or as per clinical judgement) or scheduled to have had a CT scan in an upcoming appointment as part of their normal clinical care.

Patients will be recruited at the Women's and Children's Hospital, North Adelaide, Australia. They will undergo a clinical assessment with history and physical exam, undertake an XV scan, and perform at least one of spirometry, plethysmography and diffusing capacity, or multiple breath washout. Those with CF will also complete the CFQ-R Cystic Fibrosis questionnaire. The CFQ-R will be applied regularly in a follow-up longitudinal study. Investigators will not be blinded to cohort allocation.

Patient and public involvement

Patients and public were not involved in the design of this study. Separate to this study, a qualitative assessment of XV will be undertaken and results used to guide future, larger studies.

Ethics and dissemination

Ethical approval has been granted by The Women's and Children's Hospital Human Research Ethics Committee. (HREC ID 2021/HRE00396)

All participants will provide written consent, either individually or by legal guardian if 16 or older, or by their legal guardian if younger than 16.

Findings from this study will be disseminated through peer-reviewed publication and conferences.

Study registration

The study has retrospective registration with the Australian New Zealand Clinical Trial Registry (ANZCTR): 1262000109606 and the Universal Trial Number (UTN): U1111-1287-9096.

Sample selection

20 patients will be recruited to both the healthy lung (control) and CF cohorts. A sample size of n=20 is within the range recommended for pilot studies to be able to detect adequate effect sizes as would be seen in comparative studies[32, 33].

For each study arm, potential participants will be identified from medical record reports identifying young people aged 3-18 years who may meet our inclusion criteria. Reports of children who have had a CT scan of their chest within the past 3 months will be compiled by hospital administrators or data custodians of individual departments records for assessment by the study team for potential inclusion in the study.

Arm 1

Arm 1 will include those children with normal lungs. Given children will be required to have a chest CT, specific patient groups have been targeted. These include new-diagnosis oncology patients prior

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to treatment, physical trauma patients without evidence of lung injury, and rheumatology patients without evidence of pulmonary disease. Other patients identified as potentially suitable will be considered on a case-by-case basis.

Arm 2

Arm 2 will include those patients with CF.

Inclusion criteria

- Aged 3-18 years inclusive at time of consent
- CT scan performed within the last 6 months (or as per clinical judgement), or scheduled to have a CT in an upcoming appointment

Exclusion criteria

- Pre-existing lung disease in Arm 1, including asthma, interstitial lung disease etc.
- In Arm 2, a current or recent (within the past 4-6 weeks) pulmonary exacerbation as diagnosed by CF physician
- Currently receiving mechanical ventilation, intensive or critical care
- Contraindication to ionising radiation
- Urgent clinical treatment precluding the addition of XV imaging
- Inability to comply and remain still for period of XV image acquisition
- Inability to perform at least one of the pulmonary function tests listed previously.

Intervention

Clinical assessment

Patients will undergo a clinical history and physical examination. The clinical history will include past medical history, current medications and current symptomatology. Physical examination will measure clinical observations and include examination of the cardiac, respiratory and gastrointestinal systems.

X-ray Velocimetry scan

An XV scan will be performed in The Women's and Children's Hospital Radiology Department. The XV scan involves fluoroscopic imaging of tidal breathing from 5 different angles (AP, +/- 36°, +/- 60°). The images will be sent to 4DMedical, Melbourne, and a report generated via their X-ray Velocimetry Lung Ventilation Analysis Software (XV LVAS) platform. Tissue expansion is calculated to assess ventilation at a regional level within the lung. Ventilation is determined by measuring the change in volume of a specific lung region during inhalation and dividing it by the volume of that same region at the end of exhalation. This calculation generates a unit called specific ventilation (SV), which quantifies volume changes in mm^3 for each individual lung region. Regions that inflate more have higher SV. The SV measurements are presented as a coloured contour image map of the lungs illustrating the spectrum of ventilation measurements during breathing.

XV LVAS report metrics include:

- Tidal Volume (TV) – the volume of air inhaled from start of inspiration to peak inspiration
- Mean Specific Ventilation (MSV) – the mean of specific ventilation across all regions of the lung
- Ventilation Defect Percentage (VDP) – measures the percentage of lung volume that is below 60% of the mean specific ventilation
- Ventilation Heterogeneity (VH) – measures the overall variability of ventilation across the lung

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Pulmonary function testing

Pulmonary function testing will be performed in the Women's and Children's Hospital Lung Laboratory, a nationally accredited pulmonary function testing centre, under the auspices of the Thoracic Society of Australia and New Zealand.

Multiple breath washout

Eco Medics Exhalyser D equipment will be used to perform nitrogen multiple breath washout testing to generate the Lung Clearance Index.

Spirometry and body plethysmography

Spirometry and DLCO tests will be performed on a Medisoft Spiro Air, as per ERS/ATS standards[34, 35]. Plethysmography testing will be performed using Medisoft bodybox, also as per ERS/ATS standard[36].

Outcome measures

Primary

The primary outcome measure from this study is to investigate the feasibility of recruiting 20 children without CF and 20 children with CF from our centre to complete an XV scan and the other assessments listed above.

This data will determine if a larger, statistically-powered study can be undertaken at this site to evaluate the diagnostic capabilities of XV imaging, which may be able to better measure lung health compared to existing methods.

Secondary

Appropriateness of XV LVAS technology as a clinical assessment for lung function, compared to standard and specialised pulmonary lung function techniques

This will be measured by comparisons of XV-LVAS report metrics to report metrics of existing pulmonary function testing, including spirometry, plethysmography and diffusion capacity, and lung clearance index.

Appropriateness of XV LVAS technology as a clinical assessment for structural lung disease, compared to CT imaging

XV LVAS report metrics will be compared to CT chest evidence of structural lung disease, assessed via PRAGMA-CF scoring.

Identify which participant characteristics should be considered to clinically evaluate lobar ventilation distribution, ventilation heterogeneity and expiratory time constant

This will be determined through visual inspection of characteristic data and identification of potential factors that may influence report metrics. Factors will be considered where correlation trends are observed in continuous and dichotomous variables.

Identify if ongoing assessment of ventilation distribution, ventilation heterogeneity and expiratory time constant is safe and clinically appropriate

This will be determined through a retrospective evaluation of CT scan frequency among the young people with CF, identification of any adverse events during and immediately following XV imaging and preliminary appropriateness of XV LVAS testing.

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Data analysis

The XV, lung function and CT outcome data obtained from this study will be described by group, using descriptive statistics. Continuous variables will be described using mean and standard deviation, or median and interquartile range if the distribution is asymmetric. Categorical variables will be presented as numbers and percentages. Demographic variables age, sex, height and weight will also be described by group. Statistical association between outcome measures will be assessed graphically and described using correlation coefficients.

Data storage

All data for an individual participant will be collected by the principal investigator or their delegated nominees and recorded in the patient record. Participant identification will be through their unique participant study number. All clinical data will be stored as per SA Health data storage guidelines.

Standard clinical lung function data will be collected and stored securely as per WCH guidelines. Each participant's lung function data will be identified by hospital unique record number (URN) initially, then de-identified using a numerical code before being sent to statisticians for analysis.

Pre-existing radiological data (i.e., CT chest) will continue to be stored as per routine clinical data in the WCH Radiology Department, using secure WCH server and SA Health computers.

De-identified XV LVAS data will be stored in the WCH Respiratory and Sleep Department using the WCH SA Health Network server. Data will be stored for a minimum of 30 years, according to WCH data-retention requirements.

At the conclusion of the study, all hard copy case report forms, signed consent forms and trial data will be archived according to the Respiratory Clinical Trial Unit's Archiving SOP at Iron Mountain.

Adverse events and analysis

Lung function testing entails standard procedures that are well established. The testing staff are trained and experienced in recognising and dealing with potential risks, as a normal part of routine testing. Some procedures require special breathing efforts. Known risks are:

- Dizziness
- Feeling short of breath
- Coughing
- Asthma attack precipitated by deep inhalation

XV imaging protocol involves exposure to ionising radiation. The radiation dose in the research portion of the study is low, estimated to between 0.52 – 0.83 mSv, equivalent to between 2-5 standard chest X-rays. A detailed analysis of the expected radiation exposure has been undertaken by the assessors in the South Australian Medical Imaging Department prior to study commencement. As per the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) Code of Practice for the Exposure of Humans to Ionizing Radiation for Research Purposes, the radiation exposure is classified as category IIa or "very-low risk"[37]. The radiation dose administered during XV imaging will be monitored and recorded. Exposure settings of the XV scans will be adjusted to administer the lowest practicable dose while still achieving technically useable results.

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Sponsorship

This study is supported by 4DMedical, who will provide the XV LVAS reports for patients undergoing XV imaging. 4DMedical have no input into study design, outcome analyses, or study conclusions.

Challenges in study design

To allow for appropriate XV LVAS mapping and report, a chest CT is currently required to provide the anatomical framework. Given the radiation dose required for CT of the chest region, it is not ethically appropriate to perform a chest CT in children, in addition to that required for routine clinical care. This is particularly the case in those with healthy lungs where a chest CT assessment is not clinically indicated. This limits the eligible normal lung patient cohort considerably, given the relative clinical reluctance to perform CT in children compared to adults. Some potential cohorts of eligible patients, for example oncology patients, have routine CT. They also, however, frequently receive agents with known pulmonary side effects. A further limitation is that it will be common to be unable to perform the additional XV imaging and pulmonary function tests on a child in the emotionally difficult period between an oncological diagnosis with routine screening CT and subsequent rapid initiation of treatment.

Pulmonary function testing is dependent on compliance and technique. Children less than 5-6 years of age will be unable to undergo spirometry and plethysmography. In the cohort 5 years and over there can still be technique issues affecting accurate results. This may affect the ability to compare XV imaging with standard lung function metrics in some younger children, however this will not affect the primary study outcome of feasibility.

Future trial considerations

A feasibility study design is necessary to determine if it is possible to recruit and test children without CF with healthy lungs as well as those with CF to participate in an XV imaging study. This is an important first step towards establishing a statistically-powered cohort study. Such a study would evaluate XV LVAS outcomes in children with normal lung function and anatomy that can be used to provide normal reference range data sets against which putative disease states can be examined.

Since XV is a new lung function imaging technology, studies to establish a reference range are a prerequisite before clinical adoption of the technique for diagnosis and monitoring of children with lung pathology.

Article summary

This is one of the first studies to investigate XV imaging in a paediatric cohort. Enrolment of participants is ongoing in 2023 and final results are expected by the end of 2024.

Author contributions:

MB: Recruitment, draft and review/editing of final manuscript. AT, TG: concept, study design, ethics submission and approval, recruitment and review/editing of final manuscript. MD: concept, study design and review/editing of final manuscript. KCC: concept, design and review/editing of final manuscript. DP: concept, study design, ethics submission and approval, review/editing of final manuscript. JP: recruitment and review/editing of final manuscript.

Acknowledgments:

Nil additional

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Conflicts of interest:

DP has received renumeration for research advice from 4DMedical. DP and MD have both purchased shares in 4DMedical Ltd

Funding:

This project is supported by a seed grant from 4DMedical

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

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Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	9
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a

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Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	1-3
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			

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Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final	7

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		value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that	n/a

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		is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description	7

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		of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7-8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			

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Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	5
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5

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Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	5
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8

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Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	1
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	7
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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