PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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	Bruorton, Matthew; Donnelley, Martin; Goddard, Thomas; O'Connor, Antonia; Parsons, David; Phillips, Jessica; Carson-Chahhoud, Kristin; Tai, Andrew

VERSION 1 – REVIEW

REVIEWER	Mroueh, Salman American University of Beirut, Pediatrics and Adolescent Medicine
REVIEW RETURNED	05-Oct-2023

GENERAL COMMENTS	The study population includes children 3 to 18 years of age, some of which may not be able to perform well in pulmonary function testing, and therefore may not contribute the secondary outcome measures as stated. Another concern is the time of performance of the studies; patients with cystic fibrosis are prone to exacerbations, which will affect their pulmonary functions, and presumably the results of the X-ray velocimetry study. Should this be accounted for by making the exclusion criteria more specific? There is also a concern about exposing children to unnecessary ionizing radiation, as minimal as it can be. Finally, the major concern is about conflict of interest: the study is sponsored by 4DMedical and 2 of the authors have a financial relationship with 4DMedical, which has to gain by having this technology promoted.

REVIEWER	Carr, Siobhan Royal Brompton Hospital, Paediatric Respiratory
REVIEW RETURNED	22-Oct-2023

GENERAL COMMENTS	bmjopen-2023-080034 This is well written, easy to read and understand. There are really nice summaries of the different types of scans that can be used to assess lung structure from new techniques such as Xenon CT to hyperpolarised MRI, there is no mention of radio-isotope ventilation scans in the background information, although they are not quantitative. This section does have some reference to the radiation burden of the XV in this protocol (I note the long term aim is to not need a CT) but some comparison of the radiation for CT, 4D CT, the CT+XV might be helpful.

	I realise this is approved by an ethics committee already however I would worry that the exclusion criteria of anyone unable to perform at least one of the 3 lung function tests (LCI, spirometry, plethysmography) may limit sample size even more. However, as stated it is a feasibility study so will give us the answer. I also wonder if the numbers of children that have CT scans routinely in the hospital in the year prior to the study opening that fall into Arm 1 or 2 have been looked at to add strength to the argument that recruitment will be possible in a single site. There is a minor point in the abstract in that the conversion into the PDF has meant that β-ENaC has come out with a box instead of β-.

REVIEWER	Nathan, Anna university of Malaya
REVIEW RETURNED	23-Oct-2023

GENERAL COMMENTS	1. The introduction is too long: details regarding what CF is, the lung pathology and the traditional lung function tests should all be summarised. Instead of talking about the function of 4D CT, Xenon CT, MRI-these should've compared with x-ray velocimetry. 2. Aim: This is not well written; The aim of the study is not to " conduct a single-centre cohort feasibility study...it does not mention anything about the XV. Page 6 line 16-21 3. Is this a corss sectional or prospective study? sounds more like a cross sectional study. Page 6 line 27 3. Will the controls be age- matched with patients? 4. The authors should collect data regarding the exclusion criteria listed 5 and 6th bullet as this contributes to the feasibility of this test. 5. Authors should describe what clinical assessment/examination will be undertaken.(page 6, line 35 and line 46) 6. The primary outcome is to measure the ?feasibility" or how long it will take to recruit 20 children .....to complete an XV scan. Page 7 line 33 Are there other determinants defining " feasibility", which the author should define besides " how long" The author should reduce the number of words of this document.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Salman Mroueh, American University of Beirut
Comments to the Author:
The study population includes children 3 to 18 years of age, some of which may not be able to perform well in pulmonary function testing, and therefore may not contribute the secondary outcome measures as stated.
• Thank you for your comments. This is a well known limitation of pulmonary function testing in the paediatric cohort. While it is our intention to gather all the stated pulmonary function tests in all recruited patients, we are aware this will likely not be possible due to age and/or technique and

compliance. For those patients younger than 5, we will only feasibly be able to perform multiple breath washout. This is something we acknowledge may limit the strength of secondary outcome measures, and is, in part, why the comparison between XV and PFT's are a secondary aim. However, it will not affect our primary aim of investigating the feasibility of performing XV testing in children and the potential for future, larger studies of XV in paediatric cohorts.

Another concern is the time of performance of the studies; patients with cystic fibrosis are prone to exacerbations, which will affect their pulmonary functions, and presumably the results of the X-ray velocimetry study. Should this be accounted for by making the exclusion criteria more specific?
• This is a good point, one we have taken into account clinically, but it was not explicitly stated in the exclusion criteria. Patients with CF who have been diagnosed with a pulmonary exacerbation are not eligible until at least 4-6 weeks post recovery. The submission text exclusion criteria have been updated accordingly.
o "In Arm 2, a current or recent (within the past 4-6 weeks) pulmonary exacerbation as diagnosed by CF physician"

There is also a concern about exposing children to unnecessary ionizing radiation, as minimal as it can be.
• We acknowledge the importance of limiting radiation exposure, particularly in a paediatric cohort. There obviously needs to be an acceptable balance between the risks of ionising radiation exposure and the benefit that can arise from its use, which is inherent in any X-ray based procedure. This has been carefully considered by the Human Research Ethics Committee at the hospital prior to approval of the study. Part of the consideration included a detailed analysis of the radiation exposure and a designation of the risk level by the experienced assessors in the South Australian Medical Imaging department. The radiation exposure is designated as category IIa or "very-low risk" 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 dose administered is being monitored as part of the study. The 4DMedical team have also worked with the WCHN Radiology team to adjust exposure settings to administer the lowest practicable dose that can still achieve technically useable results.
• We have added in this information to the manuscript to better explain the process.
o "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"{Prof Richard Smart, 2005 #98}. 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."

Finally, the major concern is about conflict of interest: the study is sponsored by 4DMedical and 2 of the authors have a financial relationship with 4DMedical, which has to gain by having this technology promoted.
• This concern has also been raised by the HREC of the hospital prior to study approval. We have been certain to ensure there is full disclosure of the COI during each stage of this study. Two members of the research team (A/Prof Parsons, A/Prof Donnelley) have purchased shares in 4DMedical, the company that performs the XV analysis. None of the Clinical Investigators or the Study Coordinator are shareholders in 4DMedical. A/Prof Parsons and Donnelley helped develop the XV technology over the past 15 years and are part of the study to continue to contribute their expert knowledge in technique development and analysis. They could expect financial gains from their shareholding if the results of the study are favourable. Their involvement is limited to helping with

design of the study and in interpreting and publishing of results. They will not be involved in recruiting participants, conducting study visits, or in lung function or XV testing. This study is supported, in part, by a grant from 4DMedical, who are analysing XV scans at no cost and supplying statistical support but have no other role in or influence on the study. Participants receive this COI information as part of their written information sheet. We believe the above ensures full disclosure to participants (and in any publications) enabling those taking part and/or viewing and assessing the findings best use of our team's XV expertise while ensuring that any potential financial motivations are also clear.

Reviewer: 2
Dr. Siobhan Carr, Royal Brompton Hospital, Imperial College London
Comments to the Author:bmjopen-2023-080034
This is well written, easy to read and understand.
There are really nice summaries of the different types of scans that can be used to assess lung structure from new techniques such as Xenon CT to hyperpolarised MRI, there is no mention of radio-isotope ventilation scans in the background information, although they are not quantitative.
• Thank you for your comments. The functional lung imaging methods described were chosen as examples of currently available methods that can give quantitative assessment of lung ventilation, similar to the metrics we expect to obtain from XV imaging. While radio-isotope imaging certainly has a role in pulmonary imaging, as you state it does not provide a quantitative metric. For this reason we have not included it in the background information.

This section does have some reference to the radiation burden of the XV in this protocol (I note the long term aim is to not need a CT) but some comparison of the radiation for CT, 4D CT, the CT+XV might be helpful.
• Thank you. There have been similar questions about radiation raised previously, as well as by another reviewer. We have amended our "adverse events and analysis" section to include some more background about the radiation assessments undertaken prior to study approval by our HREC.
o "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"{Prof Richard Smart, 2005 #98}. 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."
• In terms of directly comparing the radiation exposure between the modalities, this can quickly become quite convoluted. We are able to give the estimated effective dose of the XV scans in mSv, however when making comparisons to CT and 4DCT there are wide ranges in the estimated effective dose depending on scan protocols, age ranges and the form of imaging itself. As such we kept the XV summary relatively simple and used CXR as a comparator, rather than expand more significantly into the various imaging modalities.

I realise this is approved by an ethics committee already however I would worry that the exclusion criteria of anyone unable to perform at least one of the 3 lung function tests (LCI, spirometry, plethysmography) may limit sample size even more. However, as stated it is a feasibility study so will give us the answer.
• Assessment of pulmonary function in younger children is a challenging area. We acknowledge that by excluding participants who can't perform lung function it will limit potential recruitment. However, having metrics for comparison is an important consideration when looking forward to future, larger studies which may aim to validate XV against standard pulmonary function tests in various age groups. If XV imaging is identified as a clinically accurate and useful tool in these younger cohorts, it

would be a technically easier way to assess lung function than the currently available tests with the associated technique and compliance dependent limitations.

I also wonder if the numbers of children that have CT scans routinely in the hospital in the year prior to the study opening that fall into Arm 1 or 2 have been looked at to add strength to the argument that recruitment will be possible in a single site.
• This approach was a key part of the establishment of the study. Data from the hospital's radiology department was reviewed, in particular for the number of, and indication for, CT chest imaging. This has also helped guide the authors in targeting cohorts of patients who may be appropriate for the control arm.

There is a minor point in the abstract in that the conversion into the PDF has meant that β-ENaC has come out with a box instead of β-.
• Noted, thank you.

Reviewer: 3
Prof. Anna Nathan, university of Malaya
Comments to the Author:
1. The introduction is too long: details regarding what CF is, the lung pathology and the traditional lung function tests should all be summarised. Instead of talking about the function of 4D CT, Xenon CT, MRI-these should've compared with x-ray velocimetry.
• Thank you for your comments. The introduction has been shortened to provide more of a summary.
• It is difficult to make comparisons between the functional lung imaging modalities. The aim of describing them was to highlight the differences in how they are performed or achieve the metrics they report. To perform and compare the different metrics of the imaging methods is outside the scope of the feasibility study, but we expect it will be an important part of future studies in XV imaging. Being able to report the similarities or differences between these modalities and how they compare to current lung function assessment will also guide clinicians and researchers in how XV imaging can improve our assessment of lung function in children.

2. Aim: This is not well written; The aim of the study is not to " conduct a single-centre cohort feasibility study...it does not mention anything about the XV. Page 6 line 16-21
• Thank you, this has been reworded to be more representative
o "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"

3. Is this a cross sectional or prospective study? sounds more like a cross sectional study. Page 6 line 27
• On further discussion, yes, this is a cross-sectional study. We are aiming to collect the data from a single time point and make comparisons. There will likely be further, prospective studies focusing on the CF cohort in particular, however this study itself is purely cross-sectional. The wording has been amended.
o "This is a cross-sectional, single-centre, pilot study"

3. Will the controls be age- matched with patients?
• The controls will also be paediatric in the same age-group of 3-18. The recruitment will not be more specifically age-matched than this, limited both by the small numbers we aim to recruit in this pilot study as well as the method of recruitment, ie recruiting those that have already had CT chest imaging. However, there may be an opportunity to analyse age sub-groups.

4. The authors should collect data regarding the exclusion criteria listed 5 and 6th bullet as this contributes to the feasibility of this test.

• The screening process and data recorded includes explanations for those that are excluded during the subject screening process. Such exclusions may be due to inability to comply with either XV or pulmonary function testing (for example, severe autism spectrum disorder). Similarly, those that have been recruited but are then unable to complete testing are also clearly recorded.

5. Authors should describe what clinical assessment/examination will be undertaken.(page 6, line 35 and line 46)
• This has been expanded with more detail
o “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.”

6. The primary outcome is to measure the ?feasibility" or how long it will take to recruit 20 children .....to complete an XV scan. Page 7 line 33 Are there other determinants defining " feasibility", which the author should define besides " how long"
• Thank you for highlighting this. Yes, there are multiple other variables other than time taken, including the ability to recruit at our centre in general and the ability to complete testing once recruited. This has been re-worded to more accurately reflect this.
o “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”

The author should reduce the number of words of this document.
• Thank you, this has been taken into account.

VERSION 2 – REVIEW

REVIEWER	Mroueh, Salman American University of Beirut, Pediatrics and Adolescent Medicine
REVIEW RETURNED	04-Jan-2024

GENERAL COMMENTS	The authors have addressed my concerns to my satisfaction.

REVIEWER	Carr, Siobhan Royal Brompton Hospital, Paediatric Respiratory
REVIEW RETURNED	29-Dec-2023

GENERAL COMMENTS	The authors have responded to the reviewers comments. As stated the protocol already has ethics approval.