Monitoring Asthma in School-aged Children using the Forced Oscillation Technique

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by

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Abstract

Background: Diagnosing asthma in school-aged children can be difficult, as spirometry can be challenging and even when successful is often normal when the patient is stable. Forced Oscillation Technique (FOT) could offer a rapid, non-invasive alternative test that reflects the resistance and reactance of the lungs during spontaneous breathing, requiring minimal patient cooperation.

Aims: To assess FOT measurements in children with acute, stable and uncontrolled asthma before and after bronchodilator administration (BDR), while also comparing the FOT to other lung function tests.

Methods: Children aged 5–16 years with stable controlled or uncontrolled asthma or doctor-diagnosed asthma attacks were eligible. A control group of healthy children in the same age range was also included. After obtaining informed consent, we assessed FOT using waveforms of 5–37 Hz and 7–41 Hz, before and after bronchodilation with salbutamol inhalation in asthma patients only. We reported, each at 5 or 7 Hz, the (i) resistance (Rrs5 or Rrs7), (ii) differences in resistance over the frequency range to 20 Hz (Rrs5-20 or Rrs7-20), (iii) reactance (Xrs5 or Xrs7) and (iv) area under the reactance curve (AX).

Results: FOT was feasible in cases of stable controlled and uncontrolled asthma and in children with asthma attacks. Of the reported parameters, AX best discriminated between asthmatic and healthy children. FOT measurements were more sensitive in children with stable asthma with diagnoses confirmed by objective tests than in those with incomplete or no evidence. In addition, FOT measurements at 5–37 Hz and 7–41 Hz showed significant airway improvements following bronchodilator in children with acute and uncontrolled asthma, with no significant differences between measurements at different frequencies.

Conclusion: FOT measurements, including the assessment of BDR, are feasible in school-aged children with asthma. FOT is a useful method that could be applied alongside additional objective testing methods in asthmatic children.

To My Father (Saleh)
and
My Mother (Mahasen)

Acknowledgments

I would like to start by thanking God for the opportunity, determination and countless blessings to pursue a PhD and achieve my goals. Without God, it would not be possible to complete my research study and the thesis.

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Statement of author's contribution to this thesis

All the work presented in my thesis was performed under the supervision of my supervisors, and my personal record of contribution is as follows:

I had major involvement in preparing the documents needed for ethical approval, the ethics application and the amendments. I was also involved in developing the study protocol, the parent and patient information sheets and the consent and assent forms.

I was personally responsible for recruiting the participants, contacting the families, having the consent form signed by the parents and the participants and collecting the data. All the forced oscillation technique measurements were collected by me, with the exception of a very low number (five participants) that were collected by another investigator. I was then responsible for the review and analysis of the collected data. The majority of the spirometry, multiple breath nitrogen washout and fractional exhaled nitric oxide measurements in the study were performed by me, with a small number performed by the respiratory physiologist. However, all the spirometry under the audit section was performed by the respiratory physiologist. In addition, I was personally responsible for fitting the smart inhalers for the participants involved in the study. I was also in charge of contacting the companies for technical support and ordering the supplies required for the study.

I entered all the data into the database. I also took the primary role in interpreting the data and performing the statistical analysis, as well as preparing and presenting the work at various meetings and seminars.

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Publications

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Alshlowi M, Devani P, **Alraimi A**, Beardsmore C, Gaillard E. Pre- and post-bronchodilator Forced Oscillation Technique in preschool children with acute wheeze in the emergency department. ERS 2022 International Congress

Alshlowi M, Devani P, **Alraimi A,** Beardsmore C, Gaillard E. Feasibility of Airwave Oscillometry in Preschool Children with Acute Wheeze in the Emergency Department. ERS 2022 International Congress

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Covid-19 impact on PhD study progress statement

Between March 2020 and May 2021, a total of 15 months, I was not able to recruit any participants due to the universal crisis of the pandemic. This unfortunately impacted my data collection and the intended number of participants that was planned to be reached by the end of the study. My aims in the study were to perform and compare different lung function testing techniques. However, performing respiratory tests early in the pandemic was impossible, particularly because my target population was children with respiratory problems. There were a number of reasons for this. First, the clinic visits were cancelled during that period and appointments were conducted through phone calls. This impacted the progress of my project, since it was required for the patients to attend visits and perform several lung function manoeuvres for the project. Although the participants had the opportunity to go to the hospital in some cases, families were understandably concerned about involving their children in any breathing test. Additionally, during that period, the ethical committee raised concerns regarding the COVID-19 pandemic and requested various adjustments to the ethical application to fulfil the new requirements of dealing with patients during the pandemic, which delayed the ethical approval until May 2021. Additionally, Leicester University stopped in-person clinical studies and classes for more than a year and replaced it with online methods. This made it even more difficult to collect patient data. During this period, I intended to analyse some data that I had gathered before the COVID pandemic (under the UHL audit), but unfortunately, access to the hospital records required VPN, and my UHL access was blocked. This was a further challenge. Thus, not obtaining the ethical approval at the expected time, in addition to the other reasons mentioned above, including the issue of technical accessibility, prevented further progress.

After the ethical approval process, the regulations for performing procedures were more conservative, especially for respiratory tests. For instance, aerosol generating tests must be performed under maximum care and in a safe environment. For example, after running each test, the area in which the test was performed had to be ventilated for 30 to 60 minutes. These new processes also impacted the workflow and decreased the number of participants who could be tested each day. Even after obtaining the ethical approval, we could not collect data upon returning to the clinical field until all these issues were sorted out within different departments of the hospital. With all the restrictions due to COVID in these areas, it was difficult to recruit participants from the emergency department (ED) and the clinics. Furthermore, doctor appointments with patients were still conducted through phone calls, without the patients coming to the hospital in person. This made it difficult to recruit participants for the healthy control group without respiratory problems, as they

rarely came to the hospital. The lack of data collection and analysis also prevented me from participating in, presenting at and publishing some results or abstracts at different conferences.

Various adjustments were made to the test procedures to facilitate data collection and maximise the benefit of the procedures performed in reaching the study objectives. Some of the procedures were removed from the protocol or adjusted because we were not able to perform them due to COVID. An example of an adjustment made to the protocol is minimising the contact with the patient by filling out the questionnaire and the required paper documents through phone calls.

Due to this matter, I applied for an extension to compensate for the year 2020–2021 and the effects of not proceeding with the research within the expected time frame and to expand the time for data collection. The limited time and the shortage in the number of the participants may have impacted the ability to achieve the main aims of the study. However, I modified some of the procedures and adjusted several sections of my thesis to comply with the changes required due to the COVID pandemic. A systematic review on asthma diagnosis was performed and added to the thesis, which may support the main aims and the objective of the study. Moreover, additional analysis has been performed on some of the data that I had collected before the COVID pandemic under the UHL audit. However, despite reductions in the amount of data in one or more chapters of the thesis, the final output is expected to be similar.

List of Abbreviations

ACT	Asthma control test
AOS	Airway Oscillometry
Ar	Argon
ATS	American Thoracic Society
AUC	Area under the curve
AX	Reactance area/Area under the reactance curve
β2	Beta 2
BDR	Bronchodilator reversibility
CEV	Cumulative expired volume
CINAHL	Cumulative Index to Nursing and Allied Health Literature
cmH_20	Centimeter of water
Crs	Respiratory system compliance
ERS	European Respiratory Society
f	Frequency
$FEF_{25–75}$	Maximal expiratory flow between 25% and 75% of forced vital capacity
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FOT	Forced oscillation technique
FVC	Forced vital capacity
FRC	Functional residual capacity
Fres	Resonance frequency
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
He	Helium
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IOS	Impulse oscillometry
ISAAC	International Study of Asthma and Allergies in Childhood
kPa	Kilopascal
L	Liter
LCI	Lung clearance index
MBW	Multiple breath washout

MBNW	Multiple breath nitrogen washout
µg	Microgram
ms	Millisecond
N_2	Nitrogen
NHLBI	National Heart, Lung, and Blood Institute
NICE	National Institute for Health and Care Excellence
NO	Nitric oxide
p	Pressure
PEF	Peak expiratory flow
POPS	Paediatric Observation Priority Score
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies
r	Correlation coefficient
RAST	Radioallergosorbent test
ROC	Receiver operating characteristic
Rrs	Resistance
Rrs5	Resistance at 5 Hz
Rrs7	Resistance at 7 Hz
Rrs5-20	The resistance at 5 Hz minus the resistance at 20 Hz
Rrs7-20	The resistance at 7 Hz minus the resistance at 20 Hz
R0	Resistance at zero Hz
Raw	Airway resistance
Rcw	The resistance of the chest wall and the diaphragm
Rm	Mean reactance
Rtis	The resistance of the lung tissue and the parenchymal component
sec	Second
S	Slope of the resistive component of the impedance
S_{acin}	Ventilation heterogeneity in the acinar airways
SBW	Single breath washout
S_{cond}	Ventilation heterogeneity in the conductive airways
SD	Standard deviation
SF_6	Sulfur hexafluoride
TO	Lung turnover
UHL	University Hospitals of Leicester

$\dot{v}$	Flow
Xrs	Reactance
Xrs5	Reactance at 5 Hz
Xrs7	Reactance at 7 Hz
Zrs	Impedance
Z-score	Standard score

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CHAPTER 1 INTRODUCTION AND LITERATURE REVIEW

1.1 Overview

Asthma is a chronic respiratory disorder and the most common condition affecting the paediatric population. It is characterized by reversible airflow obstruction and is linked with airway inflammation and remodelling. Clinical symptoms, such as wheezing, coughing, shortness of breath, and chest tightness, are associated with asthmatic patients (1-3).

The entire respiratory system, including the central and peripheral airways, is affected in asthma (4). However, the evaluation of the small airways in asthma is debatable (5). Various studies in the field have addressed several methods and parameters that could be used to reflect the pathological presentation of the small airways in asthma. However, no gold standard is accepted and used widely to represent the small airway disease in lung function laboratories (4-6).

The forced oscillation technique (FOT) is a non-invasive method used to reflect breathing mechanics by applying external pressure waves to the lung while the patient is breathing spontaneously. The relationship between external pressure waves and their developed flow is responsible for reflecting lung parameters. Impedance measurements, including resistance and reactance derived from the FOT, are used to reflect the central and peripheral airways (7). It is suggested that these impedance measurements of resistance at 5 Hz (Rrs5), resistance of 5−20 Hz (Rrs5-20), reactance at 5 Hz (Xrs5), and reactance area (AX) represent small airway impairment. Impedance is also used in the assessment of asthma exacerbation and the effect of the inhaled treatment on the small airways (7-9)

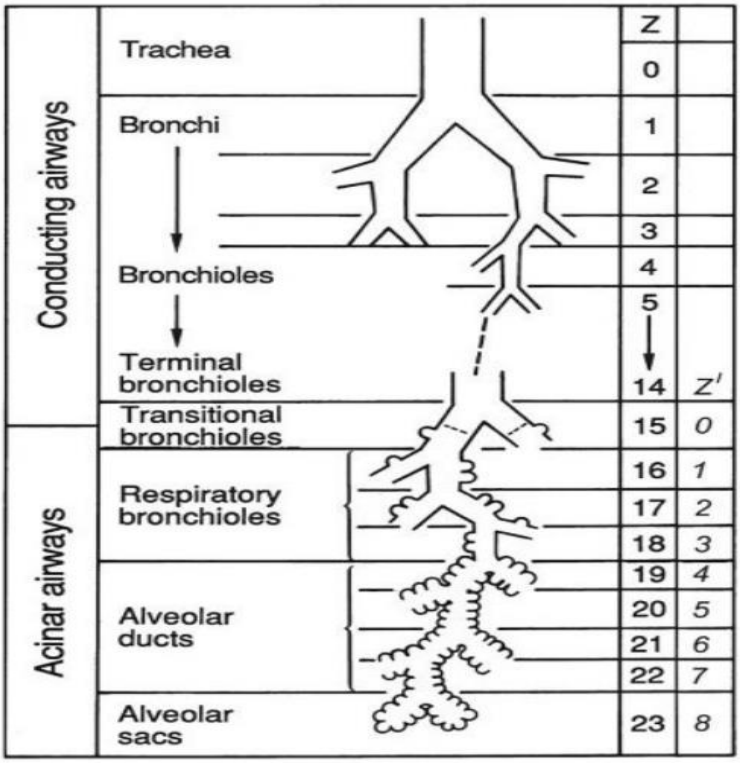
This introduction focuses on the physiology of the small airways. In addition, it presents an overview and the pathophysiology of asthma, followed by different methods used to diagnose and monitor asthma.

1.2 Physiology of small airways

The trachea separates into the main right and left bronchi. Although some branching patterns are asymmetrical, the bronchial tree branches mainly into large and small peripheral airways, and the length and diameter of these airways decrease as the airways divide and the number of branches of the airways increases. Each bronchus divides into smaller bronchioles, which comprise 23 generations that further divide into 300 million alveoli in the human lung. The

branches of the airways start at the trachea (generation 0), followed by the conducting airways—the bronchi, bronchioles, and terminal bronchioles (generations 1–14) which lead to generation 15, the transitional airway, followed by generations 16–23, which represent the acinar area that terminates in the alveolar ducts and alveolar sacs (10-12)(Figure 1.1). The airway tree is responsible for ventilation and gas exchange. The tree is designed in a way that fulfils the role of ventilation through different physical strategies. The central airways are mainly responsible for convection at the level of generations 15–18, and then gas transport by diffusion is mainly performed by the peripheral airways at the level of the alveoli, where gas exchange occurs (13,14).

Figure 1.1: Schematic structure of the airways



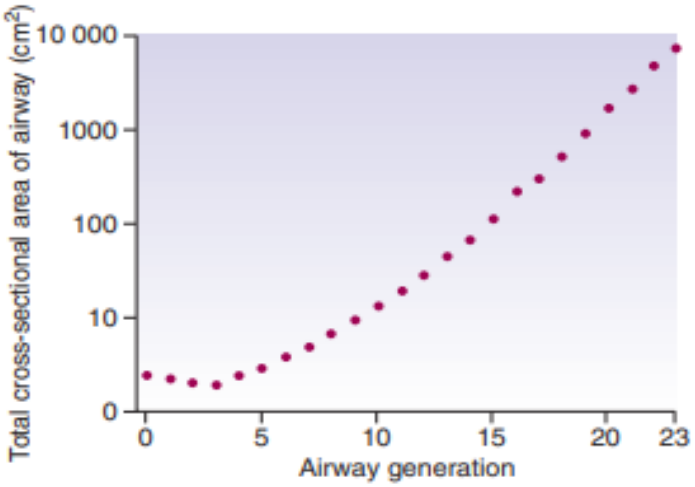
Legend: Schematic structure representing the airways' branches and generations (Figure adopted from [Wiebel, 2005]) with permission

The small airways start at generation 8 and continue to the alveoli level, where they are less than 2 mm in diameter and lack cartilage in their walls (15,16). The cross-sectional area of the small airways is larger than the cross-sectional area of the large airways because of the structural difference between the small and large airways. In the large airways, the velocity of the flow is high, and the gas flow is turbulent. By contrast, in small airways, the laminar flow is a

result of considerably lower gas velocity compared with that in the large airways. For this reason, the resistance in the large airways is affected by the gas density; however, the gas density has very minimal to no effect on the small airways' resistance (17).

Although the resistance in a single small airway is higher than that in a single large airway, the total resistance to airflow depends on the total number of airways. Because the small airways are numerous compared with the large and the medium airways, the total cross-sectional area is higher in the small airways, resulting in lower resistance in the small airways compared with that in the large airways (14) (Figure 1.2). In healthy patients with normal lungs, the contribution of the small airways' resistance to the total resistance is low. However, the peripheral airway resistance is considered a main site of resistance in unhealthy lungs. This was demonstrated in a study by Yanai et al. in which a catheter-tipped micromanometer was inserted into the right lobe of conscious humans to reflect central and peripheral airway resistance in different groups of patients; the results revealed that peripheral airway obstruction significantly increased in patients with emphysema, chronic bronchitis, and bronchial asthma with airflow obstruction (18).

Figure 1.2: Airway cross sectional area and airway generation



Legend: The relationship between the total cross-sectional area and airway generation is represented in this figure. The cross-sections (in cm^2) become large as the airways approach to the peripheral airways (figure adopted from [Lumb, 2016]) with permission

Airway inflammation and remodelling occurs not only in the central airway but also in peripheral airways, and it spreads to the lung parenchyma (19). In asthma, this occurs because the accumulation of macrophages, T lymphocytes, neutrophils, and eosinophils leads to airway

obstruction (20). Brown, Woolcock, et al. assessed the effect of obstruction in small and central airways; they used large and small beads to artificially obstruct the airways of excised lobes in dog and pig lungs. The vital capacity in pigs dropped to 50%, unlike in dogs, in which the small airway obstruction had very minimal effect on the vital capacity. This is due to the lack of collateral ventilation in pigs, whereas dogs have collateral channels (21). For this reason, in humans, who have collateral ventilation, the disease could present with no or little effect on the spirometry (16,22).

Despite the importance of different methods used to assess the airways and their clinical significance in the field, assessing new techniques and methods are still valuable. Within this thesis, a newly suggested non-invasive method is used to assess the small airways; this method will be discussed further.

1.3 Asthma overview

1.3.1 Definition

Asthma is a serious health problem worldwide and affects different age groups. The prevalence of asthma is increasing, especially among children (23). It is the most common chronic disease of childhood, affecting approximately 1.1 million children in the UK, and can result in considerable morbidity and mortality (24). Asthma, especially paediatric asthma, also impacts the health care system and productivity in workplaces and society (23).

Because of the complexity of the disease, numerous definitions of asthma were found in the literature. However, the most updated definition from the Global Initiative for Asthma (GINA) report (2020 update) states: "Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation" (25).

The clinical presentation of asthma depends on and differs according to the underlying mechanism; some of the asthma phenotypes are easily identified according to the clinical presentation. On the other hand, some phenotypes are challenging to distinguish. Childhood asthma is typically associated with eczema, food allergies, rhinitis, a family history of asthma, and viral infection with coughing and wheezing (26). Approximately one-third of children with wheezing retain this symptom into adulthood. The likelihood of the deterioration and persistence of asthma rises with exposure to smoking and allergen sensitivity in the early stages of life (27). When children with severe asthma reach adulthood, they are likely to have airflow limitation

and worse lung function (28). Non-allergic asthma involves respiratory infection and can occur at any age; in children, it typically resolves in adolescence (26,29). In some cases, exercise-induced bronchoconstriction may be the only symptom of asthma, especially in those who perform high-level aerobic workouts, are exposed to cold air, or swim in chlorinated pools (30). Previously, airway inflammation was the main feature of asthma, and exercise-induced bronchoconstriction was primarily used to diagnose asthma. Nevertheless, today, different symptoms and airflow limitations are assigned with the definition of asthma (26).

The majority of the children have good asthma control while using low to medium doses (<500 µg /day fluticasone equivalents) of inhaled corticosteroids (ICS) (31). However, in children with severe asthma, the disease remains uncontrolled, with abnormal lung function, exacerbations, and persistence of symptoms even with optimal treatment using high doses of ICS or oral corticosteroids. This group represents approximately 5% of the cases of asthma in children. Severe asthma is categorized into two categories: difficult-to-treat asthma and severe therapy-resistant asthma. Difficult-to-treat asthma is asthma with poor control due to different factors, such as inappropriate diagnosis, poor adherence, and comorbidities. However, treatment-resistant asthma is defined as asthma that remains severe even with optimal control of the mentioned factors (1,26,31).

Approximately 20% to 36% of patients with asthma develop asthma exacerbations (32). Asthma exacerbation, also known as an asthma attack or flare-up, is a result of an acute or subacute increase in symptoms. Flare-ups suggest a change of the asthma nature, and at this point, adjusting or changing the treatment is required (26). An increase in shortness of breath, chest tightness, cough, wheezing, and deterioration of lung function are characteristics associated with exacerbations (33). The onset can be sudden in children. Asthma exacerbation influences quality of life, and it is also considered a lethal disease (26,34,35).

Poor adherence to the treatment of asthma is one of the recognised problems in children and adolescents with asthma. Poor adherence could lead to poor control and may result in asthma attacks (36,37). There is no gold standard to report adherence in patients with asthma (37). However, reporting the adherence using electronic monitoring has been shown to be more accurate than reporting by patients (38).

1.3.2 Pathophysiology of small airways in asthma

Asthma is a chronic variable respiratory disease characterized by airway inflammation, remodelling, and airflow obstruction (1,39,40). Different studies have demonstrated that inflammation in asthma is localized not only in the trachea and bronchi but also spreads to the terminal bronchioles (41). Additionally, some investigators revealed the presence of inflammatory cells in the parenchyma (41).

Comparing asthmatic patients to non-asthmatic controls using various methods, such as bronchoscopy, bronchoalveolar lavage and bronchial biopsy, to assess the inflammation in the airways revealed that the airways in patients with asthma are swollen and erythematous (41). This inflammation in the lower airways possibly occurs because of both genetic and environmental factors. Most patients with asthma had type 2 inflammation, which is named for type 2 lymphocytes. Type 2 inflammation is linked with a specific cytokine profile and certain inflammatory cells (immunoglobulin E [IgE], mast cells, eosinophils, basophils, activated macrophages, and type 2 T helper lymphocytes) (41,42).

The pathological alternation in the lower airways in both the mucosa and the submucosa is referred to as tissue remodelling. It includes changes in the metaplasia of goblet cells, epithelial hyperplasia, muscle hypertrophy, and an increase in mucus production. Changes in the tissue result in airway remodelling (42,43). Airway remodelling can occur at early stages in childhood, although it is not purely an outcome of inflammation (44,45). Another characterization of airway remodelling leads to the thickening of the airways, luminal narrowing, destruction of small airways, and mucus plugging (26).

The strongest predictor of airflow limitation is the smooth muscles mass. However, other attributes can affect airflow, as damage to epithelial cells, thickening of the lamina and the basement membrane, and goblet cells hyperplasia. In addition, an increase of the smooth muscle mass, vascularity, subepithelial myofibroblasts, and fibrocytes a role in airflow obstruction (26,46,47). All these structural and cellular alterations can lead to airflow limitation, which may increase the resistance within the airway (48).

1.4 Diagnosis and monitoring of asthma

1.4.1 Asthma diagnosis in children

The signs and symptoms of asthma include cough, chest tightness, shortness of breath and wheezing. The asthma characteristics vary according to the pattern and the nature of the

symptoms, timing of the triggers, and the response to treatment (26). The signs of asthma are not specific (26); it is therefore insufficient to base a diagnosis on symptoms alone (2). Children should have objective lung function testing to support the diagnosis of asthma, namely spirometry, bronchodilator reversibility testing and FeNO (49).

National and international guidelines for asthma diagnosis in clinical practice have been developed. The Global Initiative for Asthma (GINA) recommends that specific criteria should be met for a diagnosis of asthma, including a history of respiratory symptoms and evidence of airflow limitation (25). The UK National Institute for Health and Care Excellence (NICE) guidelines for asthma diagnosis suggest the use of a clinical history in addition to objective testing (50,51). Furthermore, clinical judgment and objective testing were also suggested by the British Guideline on the Management of Asthma (BTS/SIGN) to asthma diagnosis (51,52). The European Respiratory Society (ERS) has also developed a specific protocol to improve asthma diagnosis in children based on objective testing and proposed cut-offs for these objective tests (53).

There is no single gold standard test for asthma diagnosis (50). Asthma is a heterogeneous disease characterized by variable airflow obstruction; therefore, airflow obstruction may not always be present (26,49). Expiratory airflow limitation is defined as an abnormal value of the ratio of the forced expiratory volume in 1 second (FEV_1) to the forced vital capacity (FVC), outside of normal reference ranges for healthy people according to age, sex, height and race (26). Assessment of the variability in expiratory airflow can be examined in different ways (26). The most common is to evaluate the bronchodilator reversibility, which is defined by an increase in FEV_1 of more than 12% of the predicted value 10–15 minutes after the administration of a rapid-action bronchodilator (β2 agonist) (54,55). Variability in expiratory flow can also be investigated by measuring the average daily variability of peak expiratory flow (PEF) measurements, with an average variability of more than 12% considered to be indicative of asthma in children (53). Another technique that is used to confirm asthma diagnosis is the bronchial provocation test using a direct challenge drug (methacholine and histamine) or an indirect challenge (mannitol, hypertonic saline, or eucapnic hyperventilation). An asthma diagnosis is confirmed by a reduction in FEV_1 of at least 20% for the direct challenge or 15% for the indirect challenge. These tests are less frequently conducted in children (26). The GINA indicates that a positive exercise challenge test in children can confirm the presence of airflow limitation. Unfortunately, exercise challenges are difficult to perform properly in practice, and the criteria for a positive exercise challenge are controversial (23,26). The appropriate

performance of these tests is crucial to avoid false-positive results. Negative tests do not necessarily exclude a diagnosis of asthma (26). Fractional exhaled nitric oxide can serve as a further test to support an asthma diagnosis (52). Eosinophilic inflammation associated with asthma is suggested by FeNO levels of ≥25–35 ppb (50,52,53). In summary, diagnosis of asthma should not be made on the basis of symptoms alone and objective tests are required to confirm the diagnosis.

Correspondingly, several other variables support the assessment and identification of asthma. First, the presence of asthma symptoms and exacerbations (if the symptoms were consistently present within the past 4 weeks or if the number of exacerbations and hospitalization increased because of acute asthma within the last year) indicate probable asthma (56). Furthermore, other variables can affect asthma and can be easily identified from interviews, such as age, sex, time of the first onset of asthma symptoms, physician diagnosis, any type of allergies, family history of asthma, smoking exposure, and the presence of pets at home. In addition, other objective measurements upon examination, such as height, weight, and body mass index, along with serum eosinophil and total serum IgE measurements, may be beneficial in the diagnosis of asthma (56).

Although different techniques can be used to diagnose asthma, unfortunately, there is no gold standard tool (57). The different methods and techniques to assess and diagnose asthma are explored in chapter 3.

1.4.2 Physiology and function test

1.4.2.1 Standard tests

1.4.2.1.1 Spirometry

In children, spirometry is a recommended method for evaluating lung function because it is considered a method to assess acute and chronic lung disease. The use of spirometry is suggested to differentiate between respiratory obstructive and restrictive diseases (58). It also plays a role in evaluating the severity of the disease and the progression of the disease over time, ruling out other causes of wheezing, and assessing the effect of medication on the disease (59,60). Additionally, it is also used to reflect lung function objective measurements, the severity of the obstruction, and the response to treatment (58).

The most common values obtained of spirometry are the FEV_1, FVC, and FEV_1/FVC ratio. Many other measurements can be extracted from either the time–volume or the flow–volume loop. However, many studies have attempted to find a better indicator to represent small airway

disease, as described in a literature review (61). Some of these studies demonstrated that a maximal expiratory flow between 25% and 75% of FVC (FEF_{25-75}) could serve as a good measure in the detection of peripheral airway abnormalities because some deterioration in these parameters was noticed even with normal FEV_1 and FVC in patients with small airway abnormalities (62,63). Nevertheless, a study by Viegi et al. suggested that during the forced exhalation, abnormalities in mid-flow measurements are not specific to small airway disease (64). This was supported by the suggestion of Philip et al. that the mid-expiratory flow rate does not add any diagnostic importance in the detection of small airway abnormalities because it is highly dependent on the expiratory flow indices and is affected by the quality of the FVC performance. In addition, it may represent some biological and statical noise variability correlated with spirometry (65).

The interpretation of the spirometry results is crucial in assessing lung function, developing a proper diagnosis, and monitoring the disease (58). It is also essential to consider age, weight, gender, height, race, type of medication, and the time at which it was taken, as these could affect the lung function values and the interpretation of these results (58). The GINA guidelines suggest conducting this assessment early, at the diagnostic stage, followed by different intervals at which the patient may experience deterioration or improvement in his or her condition. Following the guidelines provides a relevant perception of the asthma diagnosis and management in clinical practice in addition to a better outcome for patients (66).

Although spirometry is a crucial tool in pulmonary function testing, it still has some limitations; for example, performing the manoeuvre requires effort and coordination by the patient to provide an accurate measurement. It is also challenging for young children to follow the instructions and coordinate to perform the spirometry (67). This makes it difficult for children to perform different respiratory manoeuvres to reach the end test requirements, although children aged 6 years and older are mostly capable of performing acceptable spirometry (68).

1.4.2.1.2 Bronchodilator reversibility

Diagnosis of asthma can be supported by the presence of a response to the administration of a bronchodilator. This is done by performing spirometry tests before and after the administration of short-acting β agonist. An increase of more than 12% in the FEV_1 is consistent with an asthma diagnosis in children (69). However, it has noted that there is no evidence supporting the use of this cut-off in children and a cut-off of 8% may give better diagnostic sensitivity (49).

1.4.2.1.3 Test of variability of lung function

Variation of airway obstruction can be captured by monitoring lung function on a monthly, weekly or daily basis (69). Peak expiratory flow rate (PEF) is a physiological measurement used to assess the variation of airway obstruction. Measurements of the PEF are made at home and these measurements must be collected in the morning and evening for 1–2 weeks (53,69). The PEF results are then assessed by the clinician to determine the variability of the obstruction (53,69). A variable expiratory airway obstruction in children is indicated by a variability of more than 12% (53), but other cut-offs have been proposed (25,49,69).

1.4.2.1.4 Fractional exhaled nitric oxide

Airway obstruction can be identified using several diagnostic methods. However, further details about the disease are required in some of the conditions. For instance, an assessment of airway inflammation cannot be achieved by measuring spirometry or another physiological parameter. Fraction of exhaled nitric oxide (FeNO) testing is the most widely used non-invasive test in paediatric clinical practice to monitor airway inflammation and is useful to assess the risk of exacerbation (70). Exhaled nitric oxide (NO) can serve as a useful method for asthma diagnosis and adherence to the use of inhaled corticosteroids in conjunction with other clinical diagnostic methods to reach optimal asthma management (70). This is feasible with the availability of both online and offline NO collection (71). This is accomplished by measuring a steady exhalation breath after maximal inhalation, with both inhalation and exhalation performed into the mouthpiece of the machine (72). The exhaled NO readings are issued as a reflective measure of inflammation, especially eosinophilic inflammation (73).

1.4.2.2 Other tests

1.4.2.2.1 Multiple breath washout

Ventilation heterogeneity is present in asthma; it is aggravated by increased inflammation, airway closure, and bronchospasm (74). Ventilation distribution efficiency is assessed by both multiple breath inert gas washout (MBW) and single breath inert gas washout (SBW). MBW reflects the efficacy of the inert gas clearance from the lungs; on the other hand, gas mixing within a certain time frame is represented by SBW. Inert gases should be ideal and safe to use at different concentrations, should not be involved in gas exchange, and should not dissolve in the blood or other tissues. Both endogenous gases (nitrogen [N_2] and argon [Ar]), and exogenous gases (sulphur hexafluoride [SF_6], helium [He], and methane) are ideal for use in MBW. In patients with obstructive lung diseases, ventilation distribution abnormalities appear even

with normal ventilatory capacity as measured by spirometry. Washout tests could provide a better perception of the mechanism of abnormal ventilation distribution and the pathology location (75).

In asthma, both the conducting and the acinar (the peripheral area in the lung of the small airways) regions are affected by the inflammation and remodelling characteristics of the disease (48,76). Assessing the ventilation heterogeneity is accomplished by the N_2 SBW or MBW techniques. These techniques are used to reflect heterogeneity by representing the dependent indices of the phase III slope, the diffusion (S_{acin}), and the convection (S_{cond}). S_{cond} represents the ventilation heterogeneity in the conducting airways in which the pressures gradient difference influences the gas transport, whereas ventilation heterogeneity in the acinar region of the lungs is reflected by the S_{acin} (76,77). However, both S_{cond} and S_{acin} values are crucial and sensitive in detecting any changes in the heterogeneity of ventilation; in the paediatric literature, the lung clearance index (LCI) is the most commonly reported index of the MBW. The LCI is the volume ratio of the cumulative expired lung volumes over the functional lung residual capacity, lung turnover (TO, calculated as CEV/FRC), and represents the central and peripheral airways. Functional residual capacity (FRC) is the ratio of the volume of the exhaled nitrogen to the difference between initial and final end-tidal nitrogen concentration. The net cumulative volume required to wash out the nitrogen to the level of $1/40^{th}$ of the initial concentration is known as the cumulative expired volume; all these indices are used together to support the assessment of the ventilation distribution (75-78).

1.4.3 Rationale to improve asthma diagnosis

Asthma is a heterogeneous disease. Although recent years have seen an improvement in the understanding of asthma mechanisms and phenotypes, the definition and diagnosis of asthma is still a challenge (79). Although various studies and guidelines have suggested methods to support the diagnosis of asthma beyond taking a history and performing a physical examination (23,80), there is still no single gold standard test to diagnose asthma, and all of the objective tests described above are considered supportive evidence for an asthma diagnosis (49,50,79). Misdiagnosis of asthma resulting in over- or undertreatment remains a problem (81).

With the absence of a gold standard test, and the variability in asthma phenotypes and manifestation (25,49) , the diagnosis of asthma is based on symptoms and tests to classify the pathophysiological traits of asthma (49). Objective testing, such as spirometry, reversibility testing, PEF, challenge testing and FeNO, is used to diagnose asthma alongside observation of clinical

manifestations of disease, such as airflow obstruction, variation of the airflow, airway responsiveness and eosinophilic inflammation (52). However, there is a lack of adequate objective tests for phenotypes and endotypes of the disease that present with airflow limitation with no obstruction or with no eosinophilic inflammation (49).

Many children report uncontrolled asthma during routine follow-up, but this correlates poorly with objective measures of lung function and lung inflammation (82). In some cases, spirometry reveals normal results in asthmatic children when they are tested between exacerbations (83). This makes management decisions difficult, especially when the diagnosis of asthma cannot be confirmed in health care settings in which spirometry and FeNO measurements are not available, such as in primary care settings, or in children for whom spirometry and FeNO cannot be easily obtained (82,84). A further issue is that, while spirometry provides useful information on large airway function, it is relatively insensitive to peripheral airway disease (82).

Assessment of lung function is crucial to aid the diagnosis and evaluation of asthma. It is also vital for monitoring the response to treatment. As small airway disease is common in children with asthma, FOT has been suggested as an objective test as it can detect small airway abnormalities (85,86). No categorisation of asthma phenotypes using FOT has been described, although it has been speculated that FOT could be useful to the phenotyping of asthma according to the detection of small airway obstruction.

FOT is a promising method in the field of asthma diagnosis and monitoring, especially for young children upon whom other objective lung function tests, such as spirometry, cannot be performed. FOT can also detect disorders of the small airways, which could lead to better control of asthma.

1.5 Forced oscillation technique

FOT is a non-invasive method that is being assessed in different studies to determine whether it can be used to diagnose and evaluate asthma, measure lung dynamics, and assess lung impairment (87). FOT provides information on the resistance (Rrs) and reactance (Xrs) of the airways. FOT uses external pressure signals and the resulting flows to measure lung mechanics. These pressure flow relationships are distinct from the normal pattern of breathing. It is therefore a non-invasive method for assessing the mechanical characteristics of the airways. The test is quick, painless and requires little active participation by the patient (2,67). The ease of use of FOT makes it attractive as a diagnostic and monitoring tool, especially for children as young as 3 years old, for whom the administration of other lung function tests is difficult (7,88).

1.5.1 Principle of the test

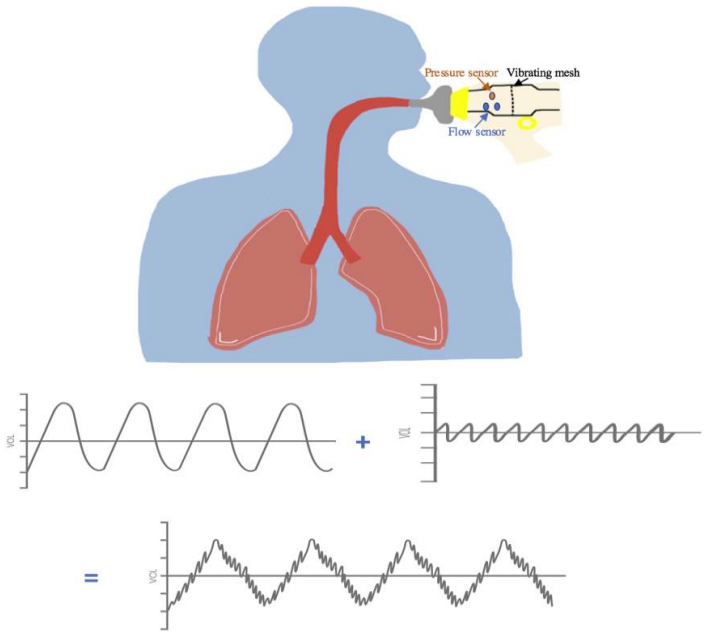
The concept of the FOT was introduced by Dubois et al. several years ago (89). FOT measurements are represented widely by impulse oscillometry (IOS) using a commercial clinical device (90). However, the FOT and IOS differ in several ways. During the performance of the FOT, the patient breathes normally (tidal breathing) through a mouthpiece for approximately 30 seconds (87,91,92). The machine generates waves, which are superimposed to the lungs while the participants perform normal tidal breathing (93) (Figure 1.3). The pressure waves of the FOT are generated by the vibrating mesh (94). However, the principle of generating the wave in some machines depends on a computer-driven loudspeaker that forms either mono- or multifrequency pressure waves in the form of pseudorandom noise waveforms (93). To differentiate between the regular breathing component of the respiratory system and the other oscillatory component (pressure and flow components) created by the forced oscillation, the software of the machine analyses the waves on the basis of the superimposition principle, which has the ability to separate the unique frequency from the other components (93). The ratio of the pressure to flow (i.e., impedance) is measured at each frequency (Equation 1) (2).

Equation 1: $\frac{p}{\dot{v}} = Zrs(f) = Rrs(f) + Xrs(f)$

The final numbers generated reflect the measurements, which include the ratio for both pressure and flow magnitude in addition to the phase shift between these signals (95). All the signals generated by the machine are separated and then analysed. They are also converted to digital form using an analogue to ensure the reliability of the measurement by processing it using a specific sorting and standardisation process (93).

Mono-frequency waves apply oscillations near the Fres (the point at which the reactance is near zero). This method has been commonly used to assess airway resistance in different sleep breathing disorders and measure the impedance of the respiratory system during the respiratory cycle. This method typically reflects the resistance only. In contrast, multi-frequency waves measure the resistance and reactance at different frequencies, which is achieved through applying the frequencies both below and above the Fres. This method is mostly used in clinics to assess the manifestation and the severity in the airways (93,96).

Figure 1.3: Forced oscillation technique setup and measurements



Legend: A representation of the forced oscillation technique's arrangements for the impedance measurements

The IOS machine applies intermittent direct pressure, known as an impulse, of 30–40 milliseconds. The impulse is a result of the reversible motion of the generator loudspeaker membrane that creates positive and negative pressure changes; during quiet breathing, signals are forced into the respiratory system, and these signals alter all anatomic structures within the respiratory system into oscillometry motion (7,93). A change in flow and pressure follows the forced oscillation. Analysis of both input and physiological impedance is achieved by calculating the pressure and flow characteristics that reflect all the mechanical properties of the respiratory system (93).

The FOT applies the sinusoidal waveform; within the FOT, the spectral analysis of the pressure and flow is discontinuous (93). The FOT has the advantage of providing a measurement of the respiratory resistance with very good time resolution and a good signal-to-noise ratio (93,97).

The impulses in IOS are in triangular waveforms, the analysis of the pressure and flow is continuous. In theory, the use of IOS is beneficial in reflecting underlying conditions of the respiratory system, such as pathologies presenting non-homogeneity of the impedance characteristics (93). However, the resolution of IOS is slightly low, and the pulses sent to the lungs by IOS may be uncomfortable (97).

Comparing and contrasting FOT and IOS demonstrated that the main crucial elements in the evaluation of the respiratory system, such as the resistance frequency (Rrs) and reactance frequency (Xrs) curve morphology, are the same in both methods (98). However, values provided by the IOS and FOT devices are not necessarily similar, even though both use multiple frequencies in the measurements of the resistance and reactance (97). The values for resistance measured at high frequencies by the IOS and the FOT have a fair agreement. However, they differ at low frequencies. Indeed, measuring high impedance values at a very low frequency is not recommended for the signal-to-noise ratio. Moreover, IOS applies impulses, unlike FOT, which uses pseudorandom noise. The former signals have a limited number of frequencies, providing an advantage to the signal-to-noise ratio for the FOT compared with IOS (95).

1.5.2 Impedance

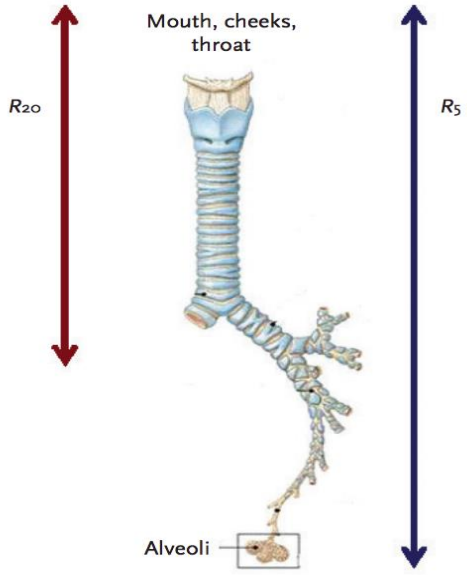
At the airway opening, the sinusoidal pressure waves are applied, and the flow is recorded. The pressure difference (between the airway opening and the alveoli) that is generated is known as the transrespiratory pressure (99). Impedance is calculated as the ratio of the transrespiratory pressure to the flow. It is reflected as the input impedance because the flow and pressure measurements are both recorded at the airway opening (93).

Impedance (Zrs) is composed of resistance, the value expressed as a relation of the pressure and the flow amplitude, and the reactance, which is the mathematical calculation of the time required for the pressure change to originate a flow change. Impedance measured in $cmH_2O \cdot L^{-1} \cdot sec^{-1}$ or $kPa \cdot L^{-1} \cdot sec^{-1}$ (93,97).

The **resistance (Rrs)** measurement is the real part of the impedance "in phase" portion of the pressure oscillation, and it is defined as the pressure–flow relationship. Resistance is considered the most familiar parameter in the measurement of the FOT (87,98). It is composed of airway resistance (Raw), the resistant of the lung tissue and the parenchymal component (Rtis), and the resistance of the chest wall and the diaphragm (Rcw) (98). Resistance is measured in $cmH_2O \cdot L^{-1} \cdot sec^{-1}$ or $kPa \cdot L^{-1} \cdot sec^{-1}$. Oscillometry evaluates the resistance of the respiratory system components with high sensitivity. However, the specificities of each of these components are not equal, excluding how resistance would differentiate between the central and peripheral resistance. Resistance at higher frequencies, such as 20 Hz, is mainly a reflection of the central airways, and the total airway resistance is represented by the resistance at 5 Hz. By contrast, the peripheral airway resistance is reflected at lower frequencies and can be calculated by subtracting Rrs20 from Rrs5 (93,97) (Figure 1.4).

The **reactance (Xrs)** is the imaginary part of the impedance "out phase"; it is a representation of two opposing forces of the respiratory system. The first is the inertial component of the Xrs, which represents the energy influence of the inertial forces. Inertial forces consist of the central airway air column motion and the respiratory system total tissue mass motion (parenchymal or non-parenchymal). The inertia component is a pressure acceleration relationship, and the importance of this component in the clinical field is still not clear (87,93,97). The other force is the capacitive component of the respiratory system; this reflects the pressure–volume relationship of the total respiratory system compliance, Crs, which represents both lung and bronchial wall compliance, in addition to the compliance of the thoracic gas compression and the upper airway compliance and the compliance of the abdominal and chest wall compartments (89,93,100). Reactance values are measured in $cmH_2O \cdot L^{-1} \cdot sec^{-1}$ or $kPa \cdot L^{-1} \cdot sec^{-1}$ (97).

Figure 1.4: Forced oscillation waves through the airways



Legend: A representation of the forced oscillation sound waves travelling different distances through the airways according to the frequencies (Figure adopted form [Brashier, 2015]) with permission

Elastic work is negative during normal inspiration, and it is a reflection of elastic energy storage. However, during passive normal expiration, when there is no impact of any additional energy, the elastic work is positive. This tends to bring the respiratory system elastic energy back to its former state of equilibrium (FRC) to overcome the resistance and the inertial forces (93). The effect of the flow changes that result in a pressure change is mainly in the form of

elastic recoil. Therefore, this results in a negative phase difference because the pressure change follows the flow change. However, pressure changes causing a flow change are essential to overcome the inertial forces. Therefore, when pressure changes are followed by flow changes, the phase difference is positive (93,96). Normally in low-frequency oscillation, the forced oscillation response is mainly due to the elastic element. The pressure changes following the flow changes result in negative Xrs values and phase differences (93). At a lower frequency, the capacitive properties are dominant within the peripheral airways; this is because the amount of loss of the oscillometry capacitive pressure is relatively high compared with the inertive pressure loss (97). The opposite occurs when the inertial forces are dominant in high-frequency oscillation because of the high value of acceleration; to create the flow, adequate pressure is needed. Additionally, as the pressure changes create flow changes, the phase difference and the Xrs value are positive (93). The inertive pressure increases while the oscillation frequency increases with a parallel decrease in the capacitive pressure (97). In an ideal respiratory system, the resistance is not influenced by the frequency of oscillation. By contrast, the reactance is affected by the frequency of the forced oscillation (93) (Figure 1.5).

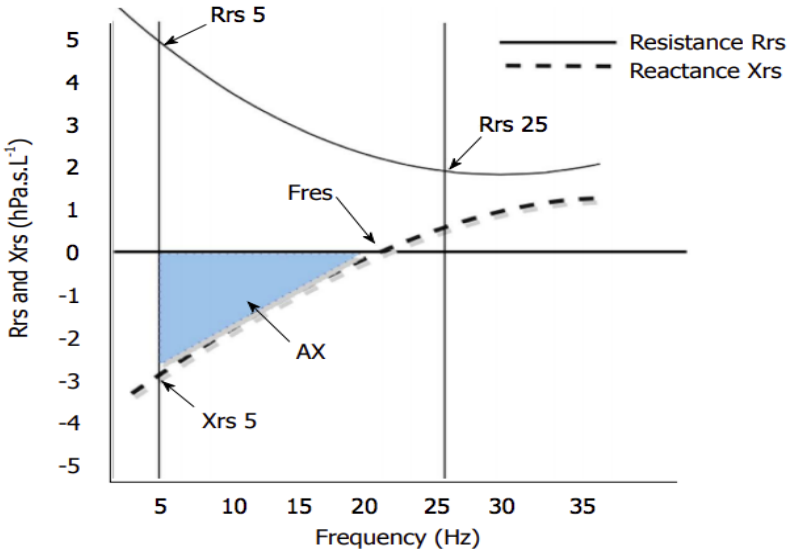
Although the influence of the elastance at the lower frequency of 5 Hz would dominate, the reactance at 5 Hz (Xrs5) still represents both the effects of the inertance and the tissue elastance. Xrs5 also represent the elastic recoil of the lung periphery, and it reflects significant information of the small distal airway. This is because the lungs are capable of maintaining and storing capacitive energy, which is mainly represented in the small airways. In some conditions, when the lung elasticity decreases, the capacitance increases negatively, which results in more negative values of Xrs5 (97).

Resonant frequency (Fres) is the frequency at which the inertial component forces and the capacitive forces are equal, and the value of the reactance and the phase difference between the pressure and the flow is equal to zero. This typically occurs at an intermediate frequency. Fres is the point of transition between the capacitive forces at the lower frequency and the inertive forces at the higher frequency. Within this point, the total impedance to the airflow is mainly due to the resistive flow (93,97).

The **area under the curve (AX),** also called the Goldman Triangle, is a representation of two axis curves: the point of the intersection of the y-axis to the curve at the minimum point of the Xrs and the point of the intersection of the x-axis to the curve at the resonant frequency point. This is a representation of the respiratory reactance at all the frequencies between the resonant

frequency and the frequency at 5 Hz (93,97). It is measured in $cmH_2O \cdot L^{-1}$ or $kPa \cdot L^{-1}$. AX is crucial in the evaluation of the total reactance of the respiratory system at frequencies lower than the Fres, the resonant frequency, and the curvature function of the Xrs. AX expresses the airway closure at the point of the closure at which the pressure wave diffusion travels to the bronchial tree periphery, which results in an increase in the AX values that elevates the effective elastance of the respiratory system (93,97). AX also represents the compliance of the respiratory system, mainly of the small airways; it is useful in the assessment of the degree of obstruction and the change in the peripheral airways. AX is somewhat related to the Rrs5-20 (97).

Figure 1.5: Resistance and reactance change as the frequency changes



Legend: This figure represents the resistance (Rrs) and reactance (Xrs) changes according to different frequencies of the forced oscillation. It also represents the resonant frequency (Fres) and the area under the curve (AX) (Figure adopted from [Alblooshi, 2017]) with permission

In Conclusion, the components of the respiratory system that can be evaluated using forced oscillation are the resistance of the respiratory system consisting of the central and the peripheral airways, chest wall, tissue mass, diaphragm, and the lung resistance as well as the bronchial tree, extrathoracic airway, pulmonary, chest wall, and diaphragm compliance. FOT also reflects the air column inertia and tissue mass compliance of the respiratory system (parenchymal or non-parenchymal). The resistance of the central and peripheral airways is the main indicator

of the resistance, Rrs. However, other factors, such as the chest wall, diaphragm, lung, bronchial, extrathoracic, and inertial force compliance, reflect the reactance (Xrs) (93).

1.5.3 Practical considerations

The FOT measurements must be taken in a seated position with a nose clip applied to the nose. The machine measuring head must be aligned with the body to keep the head and neck in a relaxed posture and avoid any other motion that may affect the impedance values. To minimize the artefacts from the upper airway, the cheeks must be supported by the patient or the technician (7,87,93). The lips and teeth must be sealed and adapted around the mouthpiece, keeping the tongue below the mouthpiece to prevent occlusion. The patient is instructed to breathe normally and quietly at the FRC level to achieve normal tidal breathing, and no further instructions regarding the depth and frequency of the breathing are needed. Any deviation from normal breathing could lead to a rejection of the attempt; for this reason, the technician should continuously monitor the breathing flow and volume for the 30 second interval (93,101). Three minutes is required between any forced maneuverer performance and the next test. It is recommended to perform the oscillometry before any other test that requires a forced maneuverer to prevent the effect of the changes to the bronchomotor tone caused by these tests. Three to five measurements are taken with a rest between the measurements, and the patient then moves his or her mouth away from the mouthpiece (93).

1.5.4 Limitations and artefacts

Different artefacts could develop while performing the test that may affect the measurements. This is typically because of improper technique during the examination, such as the **use of bacterial filters.** Adding a bacterial filter adds approximately 60 mL of dead space, and this leads to an increase in the resistance while performing the FOT. For this reason, the resistance values are higher when measurements are taken using a bacterial filter compared with those when the test is performed without the filter (96,97). In addition, improper **tongue position** could affect the measurements. Positioning the tongue into the mouthpiece restricts the airflow and results in a similar increase in the resistance at all frequencies, with a minimal effect on the reactance (93,96). Similarly, **poor cheek support** can influence the measurements. If the cheeks are not supported firmly throughout the test, the impedance will be affected by the extrathoracic airways, such as the upper airway, and the cheeks, mouthpiece, and the tongue, which affects the measurements. This could result in the underestimation of the results due to the decrease in the Rrs20 values. In addition, in patients with obstructive lung disease, the lack

of cheek support could significantly impact the values of Rrs5 and Xrs5, with less impact on healthy participants (97,102). The peripheral reactance could increase because of a **mechanical load** that is imposed on the respiratory system, such as tight clothes or belts. For this reason, these items must be removed before performing the test. Impedance parameters could also vary in participants with severe obstructions while performing the cheek support because of a worsening of the normal kinetics of the quiet breathing due to the hand elevation, which increases the mechanical load on the chest wall. In these conditions, it is recommended that the operator supports the cheeks. **Other common artefacts**, such as holding the breath, swallowing, vocalization, and air leak, must be avoided (97).

There are several other technical issues that the technician must be aware of to optimise the measurements, such as the apparatus and equipment quality control, excitation frequencies, signal and analysis, acquisition and reporting of results, and the report and interpretation (103).

1.5.5 Quality control

1.5.5.1 Coherence

Coherence is a statistical representation of reproducibility that reflects trial-to-trial variability (104). It is an important factor in interpreting the acceptability, measuring the linearity, and assessing the validity of the FOT measurements (7,104,105). Coherence is measured by comparing the back pressure wave of the respiratory system with the airflow of the lungs (91). Improper technique when performing the test, irregular breathing, swallowing, and glottis closure during the test could lower the coherence values (104). A coherence of more than 80–90 is considered acceptable for the FOT data (106). Coherence is usually calculated by the device software.

1.5.5.2 Coefficient of variation (CV)

The coefficient of variation is the measure of the trial-to-trial variability of the oscillometric parameters (7,87). It also reflects the quality of the impedance measurements by comparing the input and the measurements signals during the test (104). In children, the coefficient of variation is suggested to be less than or equal to 15% to accept the measurements (107).

1.5.6 The significance of FOT in asthma

To date, no method used to diagnose and monitor asthma has been established as a gold standard. Spirometry is commonly used in asthma. However, it requires an effort by the patient in addition to coordination, which may result in inaccurate measurements if it is not performed

accurately (108).Some research suggests that IOS could be used as a supplement to spirometry to support the diagnosis of asthma, especially when the spirometry expiratory curve is irregular (109).

IOS is a method that evaluates lung function through measurements of resistance and reactance; it is simple and requires minimal cooperation from the participants. Different pathophysiological features of asthma could be reflected by the resistance and reactance. The degree of obstruction is mainly reflected by the AX and the reactance at 5 Hz. However, the obstruction characteristics of the small and large airways could be reflected by the resistance at 5 Hz. Resistance at 20 Hz is mainly responsible for the resistance in the large airways. Rrs20 is subtracted from Rrs5 to measure the resistance of the small airways (91,108). Changes in the small airways at early stages could be used to diagnose asthma (86). Rrs5 and AX have the highest sensitivities for differentiation between patients with and without asthma. (110,111). One study suggested that Rrs5 is the proper parameter to assess the obstruction in the airways because it has a strong correlation of IOS with FEV_1, although this study only assessed a group of patients with asthma (112). Moreover, AX was suggested to be a sensitive measure of airflow obstruction (113).However, to rule out asthma, Xrs5 is used because it reveals any variation and the degree of obstruction in the peripheral airways (108).

IOS could be a beneficial assessment tool in children and preschool children (114). The IOS in children was shown to be superior in detecting peripheral airway impairments, rather than other pathologies of asthma in the central airways, compared with spirometry (115).

Several guidelines suggest the use of bronchodilator in the diagnosis of asthma because assessing the reversibility degree in lung function after the administration of a bronchodilator plays a major role in the diagnosis of obstructive lung diseases (23,50,116,117).

Measuring the response of the bronchodilator during spirometry is characterized by an increase in FEV_1 by more than 12%, with some significant changes in forced vital capacity (FVC) and forced expiratory flow at 25–75% (FEF_{25-75}) (108,118). However, the positive response of using the bronchodilator during the FOT is mainly described to be the reduction of resistance. Some changes are noticed in the measurements of FOT, such as Rrs5, Rrs20, Xrs5 and AX, but the highest sensitivity was observed in Rrs5 and AX (66,87,108,110). Different studies suggested cut-off points to assess the reversibility in FOT measurements after the bronchodilator administration (110,111,119-122). However, the exact percentage of the resistant reduction that confirms the positive response of the bronchodilator relies on the patients' condition,

age, and the measured resistance to specific frequencies. All these factors must be taken into consideration (2,87).

Studies have demonstrated that assessing bronchodilator reversibility using the FOT was able to discriminate between healthy participants and patients with asthma (111,123). Some other studies demonstrated that the FOT has a higher sensitivity in detecting bronchodilator reversibility compared with other lung function testing in children with asthma (119). However, other data revealed a similar relationship between the FOT and other lung function tests, such as spirometry, in assessing the response of bronchodilator administration (110,124).

Research results support the use of IOS/FOT in the early detection of asthma and the assessment of airway obstruction in children as young as 3 years old and in some cases when other lung function tests are not applicable or when forced expiratory manoeuvre cannot be performed by children, especially preschool children (110,111,122,125). Studies have also supported the use of the FOT to monitor patients with asthma and to assess the severity and asthma control in children (86,111).

1.5.7 Feasibility of FOT in children

IOS is an easy method to assess the airways properties because it is passive and requires only normal tidal breathing, with no forced effort while performing the test (126). The feasibility of the forced oscillation measurements has been reported by different studies in the paediatric population. A study conducted by Malmberg et al. showed that preschool children were able to perform the test easily (127). Delacourt et al. found that 313 patients aged 4.3–15.7 years were also able to complete the test successfully (122). Moreover, in a younger group aged 2–4 years, the participants achieved the forced oscillation manoeuvre (128). Likewise, Hellincks et al. recruited participants in kindergarten, and they were able to perform the FOT measurements effectively (129).

1.5.8 Dependence and reference values of FOT

Different predictors and regression equations have been reported for both resistance and reactance in children in several studies (88,130-134). The main factors considered in providing reference data and the prediction equation of the FOT measurements were height, weight, age, gender, and the machine used (88,132,134). However, among these studies, height was the strongest predictor that affected the resistance and reactance values (88,130-134), with a negligible contribution of gender (130,134).

In children, the values of resistance and reactance could be affected by age and height. The number and size of the alveoli and the airway calibre increase as the lungs grow. For this reason, as the age and height increase, the respiratory resistance values decrease. Nevertheless, the value of Xrs5 becomes less negative as height and age increase, with a minimal change in the Xrs20 values. However, height is the main dependent factor; it has an impact of 56–60% variance for the impedance, including resistance, reactance, AX, and Fres values (97). In conclusion, an increase in height increases the reactance and decreases the resistance. This means that an increase in height affects the resistance and the reactance in opposite ways (93).

1.5.9 Multifrequency signals

Different studies recommended using the signal frequency range of 4–30 Hz to better reflect impedance, especially at lower frequencies (87). In healthy children and children with stable and acute asthma, the resistance was studied at different frequencies.

The resistance at different frequencies was studied for the best presentation of airway obstruction. Resistance at 0, 4, 5, 8 and 10 Hz were shown to be a reflective measure of children with asthma and either correlated to spirometry values, clinical asthma severity, or the response to the bronchodilator (122,135-138). However, FOT-specific index to reflect the airway obstruction in children is still needed (87). In this study, multifrequency waveform ranges of 5–37 Hz and 7–41 Hz were used to reflect the impedance in healthy children and children with asthma.

1.5.10 Clinical applications

The application of FOT in the clinical field could target different aspects. **First, it could reflect different clinical conditions of chronic respiratory disorders in the paediatric population** (103), as it was estimated that the FOT parameter could reflect some respiratory properties that differ from spirometry (139). It could also be used in longitudinal studies that provide a follow-up assessment from early childhood to adolescence (140). FOT also evaluates the effect of interventions on inflammation (141). **Second, FOT could be used as a diagnostic tool to identify patients with bronchial asthma and assess bronchial responsiveness**. In reversibility testing, the FOT can be used to assess the effect of bronchodilator on the airways in children with asthma. In addition, FOT is considered a diagnostic tool used in airway challenge testing to assess bronchoconstriction (87,103). **Third, FOT could be used to assess and study any physiological or pathological situation that may affect the respiratory system** (103).

The most essential information gathered by the FOT is resistance and reactance. Resistance mainly represents the airways; however, reactance reflects the respiratory elastic properties. In the past decade, paediatric applications of FOT have increased, especially with uncooperative children. Findings of FOT abnormalities in children with asthma were high when the FOT was studied in asthma clinics. In longitudinal studies conducted over weeks to months in children with asthma, Xrs was identified among the FOT parameter to be sensitive in the management of the inflammation, including allergen control and inhaled steroids (103,142). A decrease in Rrs after bronchodilator administration could suggest asthma because a decrease in Rrs is unusual in healthy children (143). A positive response to an indirect airway challenge, such as exercise, cold airway hyperventilation, or inhaled adenosine 5-monophosphate, is reflected by an increase in Rrs and decrease in Xrs, in line with the results of spirometry in response to the histamine and the methacholine challenge. In asthma and other obstructive lung diseases, the frequency response and respiratory impedance time course aid the understanding of the pathological mechanics of ventilation inhomogeneity, airway compliance, and bronchomotor tone (103,136,143).

1.5.11 Relevance of oscillometry in clinical practice

1.5.11.1 Sensitivity of FOT in detecting the peripheral airway impairment

Since FOT is a new approach in the field of asthma diagnosis, it has been studied and compared with other diagnostic procedures. The main distinguishing feature in the FOT is the sensitivity of detecting a small airway obstruction. Although spirometry provides reflective measurements and loops of airway obstruction, it is mainly focused on the large airways rather than the small airways. Additionally, spirometry readings could be affected by other factors, such as the patient's effort while performing the procedure, the strength of the respiratory muscles, lung volume, and elastic recoil. The following section provides a review of clinical studies, including a comparison of the FOT and spirometry and their sensitivities (7,73).

Several studies were conducted in both adults and children to compare the sensitivities of FOT and spirometry in detecting peripheral airway obstruction, evaluating the bronchodilator effect on the airways, and assessing the airway hyperactivity. For example, a study that compared adults with asthma with healthy controls showed that the sensitivity and specificity of detecting patients with asthma were highest in the resistant (R0), mean reactant (Rm), and the slope of the resistive component of the impedance (S), which represent the measurements of the FOT (144). Conversely, another study comparing the effect of bronchodilators on patients with asthma revealed similar sensitivities of the FOT and spirometry in identifying the

bronchodilator effect on the airways (145). However, the FOT was suggested as a solution to one of the drawbacks that affect the readings during the performance of spirometry. This is because the performance of deep inspiration during the manoeuvre of spirometry affects the bronchomotor tone of the lung momentary, which may affect the reading (145). By contrast, a study conducted in children that assessed the sensitivity of FOT in identifying airway hyperreactivity revealed that the sensitivities of FOT and spirometry were similar. However, this study suggested the use of the FOT because it is considered to require less effort and cause less stress in children (146).

1.5.11.2 Assessment of peripheral airways and reversibility

The FOT is not used only as a diagnostic method; it is also used to assess and monitor the response of the treatment. Monitoring the therapy is crucial in assessing the disease and the improvement of airway functions (7).

To assess the FOT in detecting peripheral airway obstruction and monitor the response to the bronchodilator in asthmatic patients, various studies conducted in children and adults used the FOT as one measure compared with spirometry as another measure. These studies were conducted in patients with asthma as well as control groups of healthy volunteers. Different spirometry measurements, such as FEV_1, FVC, the ratio of FEV_1 to FVC (FEV_1/FVC), and the forced expiratory flow between 25% and 75% were collected in these studies. However, the values of Rrs and Xrs at different frequencies, in addition to AX and Fres, were gathered to represent FOT measurements. Two studies that compared the use of the FOT to spirometry in adults and children demonstrated that the FOT was superior in detecting peripheral airway obstruction compared with spirometry (122,147). In the study by Delacourt et al., the FOT and spirometry were similar in providing data about asthma, although the FOT reflected the peripheral airways, which makes the FOT an additive informative method to diagnose and control asthma (122). Further studies were conducted to compare the use of the FOT and spirometry in detecting the response of the bronchodilator effect and the values of spirometry and the FOT were evaluated before and after the administration of salbutamol. One study revealed that the resistance at 5 Hz had a higher sensitivity in detecting the bronchodilator effect, and the resistance at 5 and 10 Hz was more sensitive in distinguishing the asthmatic and non-asthmatic groups when comparing FOT measurements to spirometry (111,148). The FOT also demonstrated a higher capability of detecting the reversibility of bronchodilators in children with mild asthma compared with spirometry, as it showed that 71% of the children with asthma had an

improvement in the FOT parameters after bronchodilator administration; by contrast, spirometry determined that 39% of patients showed improvements in FEV_1 (119). However, another study that was conducted for the same purpose demonstrated that the IOS and spirometry measurements after bronchodilator administration correlated with each other, which led the authors to suggest the use of IOS as an alternative method to spirometry in the clinical setting (110).

Some studies have explored the effect of bronchodilators on FOT measurements. One study showed that the resistance decreases after bronchodilator administration, and the reactance becomes less negative (143). Another study specifically identified the effect of bronchodilator on inspiratory and expiratory resistance and reactance. After the administration of the bronchodilator, the inspiratory and expiratory resistance improved. However, a significant change was noticed for the expiratory reactance but not the inspiratory reactance. To identify asthma, comparing the measurements of the FOT before and after bronchodilator administration is superior to solely using baseline measurements (123).

Cut-off points for significant changes in IOS/FOT measurements following bronchodilator administration have been suggested. In a study performed in children aged 2–5 years attending the outpatient asthma clinic, a 40% change in resistance at 5 Hz following bronchodilator administration was proposed as a positive bronchodilator response, with resistance measurements made by IOS (149). However, in 4-year-old children with asthma, a change of −26.9% in Rrs5 and 35.8% in Xrs5 was suggested as a positive bronchodilator response (105). In a study of children aged 3–18 years, an Rrs10 cut-off of −8.6% and an AX cut-off of −29.1% were proposed (111). In a study by Batamz et al. including a group of children with both acute and stable asthma, a percent change of −39.05% response change in AX was suggested to detect airway reversibility following bronchodilator administration (110).

1.5.12 Variability and repeatability

The measurement of the FOT requires some cooperation of the patient, which allows the measurements to be easily obtained during normal tidal breathing while performing good support of the cheeks. A specific standard for both the data collection and the machine specification is available. Within-session variability, between-session variability, and repeatability are essential and must be documented to assess the bronchomotor response (103). Regarding **variability,** after the measurements by the FOT, variability should be reported in addition to the mean resistance and reactance. Variability was considered an index for quality control of lung function (103). However, an increase in airway variability is noticed in patients with asthma; this

could be explained by the increase in the variability in the airway calibre (150). Some studies showed an increase in the Rrs variability in children with asthma compared with the control group (151). Regarding **repeatability**, while performing the FOT, repeatability should be assessed by repeating the measurements after 10–20 minutes; this technique could be used as a reference when evaluating the response to bronchodilation or bronchoconstriction agents (93,103).

The repeatability and variability of the FOT in school-aged children were explored using different methods in several studies. This was accomplished by evaluating the within-test, daily, and weekly variability. Specific consideration was given to measuring the variability; within the test variability, a specific time was maintained between the measurements. Furthermore, for the daily and weekly variability, measurements were collected at the same time of day. In one study, the variation in the FOT was larger than that in spirometry within participants between the days and within participants between immediately repeated measurements; by contrast, the other study found that the resistance and reactance did not change significantly in terms of the within-test variation. In addition, the day-to-day variability of FOT increased in children with asthma, and it was affected by the asthma severity and control (152-154).

1.5.13 Devices

Various devices have been developed based on the concept of forced oscillometry to assess lung mechanics. Examples of these are the PulmoScan by Cognita Labs (Santa Ana, United States), the Resmon PRO by MGC Diagnostics Corporation (Milan, Italy) and the Tremo-Flo®C100 by Thorasys (Copenhagen, Denmark). Although these devices are all based on the same principle of measuring lung mechanics, they differ in some important features, such as the multifrequency waveforms used, test times and the analysis of the breathing pattern. The TremoFlo was chosen for our study due to the availability of the device, the ease of installation and calibration, the portability of the device and the short testing period. The device has an intra-breath analysis and an automated workflow for before and after administration of the bronchodilator test.

To summarize, the FOT allows testing to be performed without any active effort or forced manoeuvre, and it could be used in children and participants who cannot perform the forced expiratory manoeuvre. It also reflects the mechanical properties of the respiratory system and aids in the evaluation of the small airways. In the clinical field, FOT could be used as an

alternative or an additional method to support other lung function testing. However, further studies are needed to assess the use of the FOT in the field.

CHAPTER 2 THESIS AIMS AND HYPOTHESES

2.1 Where are we?

Asthma mainly affects the central airways. However, in recent years, various pathological and physiological evidence has suggested that the inflammatory effect of asthma extends to the small airways (155). The pathological changes within the small airways usually appear in the early stage of the disease, even before the appearance of symptoms or changes in the spirometry measures (73). Therefore, a new method to assess the peripheral airways was introduced to the field. The forced oscillation technique (FOT) is a non-invasive, effort-independent method that showed the ability to detect early changes in the peripheral airways and to effectively monitor asthma (73,156). In children, FOT measurements have been shown to be more sensitive than spirometry in detecting peripheral airway obstruction and in distinguishing uncontrolled asthma (157). In addition, FOT has been shown to be feasible in children and suitable for patients who cannot perform forced manoeuvres (73,141).

2.2 Where is the gap in knowledge?

Even though the FOT is an easier and faster way to measure lung functions compared to spirometry, the relative lack of data comparing the repeatability and performance of spirometry to FOT in children must be considered (2). In addition, in some cases, FOT was not considered a satisfactory analysis tool to discriminate between obstructive and restrictive diseases (141). Further studies are suggested to measure the repeatability and sensitivity to detect an effect of a bronchodilator in obstruction cases. Specific interpretation and assessment of the resistance and reactance in different lung conditions is also crucial (2). Studies are also needed to evaluate the ability of the FOT/IOS and single-breath or multiple-breath nitrogen washout combined with spirometry to assess the peripheral airways in children with asthma (106,158,159). Moreover, future work is required to determine the role of FOT in the diagnosis and monitoring of asthma in the clinical field and the relevance of FOT in clinical practice (108,160).

All these points must be acknowledged in further studies to fill the gaps in knowledge about the FOT and to determine whether it should be considered an alternative to spirometry or an additional tool that may aid the clinical diagnosis and management of asthma.

2.3 Thesis aims

1- To investigate whether measurements of FOT in healthy children tested in a local population would match the reference data set of healthy children based on the pre-programmed predicted values in TremoFlo.

2- To study the correlation of the height, weight, and age to the measurements of the FOT at 5–37 Hz and 7–41 Hz using TremoFlo in healthy children.

3- To assess the accuracy (sensitivity and specificity) of the FOT using TremoFlo in detecting asthma in children attending the asthma clinic.

4- To investigate the association of the FOT indices using TremoFlo to other traditional measures of lung function (e.g., spirometry) in children attending the asthma clinic.

5- To investigate the association of the FOT indices using TremoFlo with the measures of airway inflammation (FeNO) in children attending the asthma clinic.

6- To assess FOT indices using TremoFlo in children with acute asthma attending the emergency department or following admission to the children's ward.

7- To evaluate FOT parameters before and after bronchodilator administration in children with acute asthma.

8- To explore the differences between the FOT measurements at 5–37 Hz and 7–41 Hz waveform frequencies in children with acute asthma.

9- To investigate the association between FOT indices at the frequency waveforms 5–37 Hz and 7–41 Hz using TremoFlo and spirometry parameters (forced expiratory volume in 1 second [FEV_1] and FEV_1/forced vital capacity [FEV_1/FVC]), the lung clearance index (LCI) from multiple breath nitrogen washout (MBNW) and airway inflammation (FeNO) in children with uncontrolled asthma.

10- To monitor changes in asthma control and clinical outcomes between two visits over a period of 2 to 4 months using the ACT or cACT and measurements of FOT at the frequency waveforms 5–37 Hz and 7–41 Hz in relation to the adherence to inhaled corticosteroids by remote monitoring using electronic smart inhalers monitoring devices in children with uncontrolled asthma.

11- To evaluate the BDR on FOT indices at the frequency waveforms 5–37 Hz and 7–41 Hz in children with uncontrolled asthma.

2.4 Thesis hypotheses

1- In healthy children, the FOT measurements of resistance and reactance by TremoFlo using frequency waveforms at 5–37 Hz and 7–41 Hz (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20 and Xrs7) fall within the reference ranges of the pre-programmed predicted values dataset.

2- The FOT measurements of resistance and reactance using frequency waveforms at 5–37 Hz and 7–41 Hz (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz) correlate to the height, weight, and age in healthy children, with the highest correlation to the height.

3- The FOT measurements of resistance and reactance by TremoFlo using 5–37 Hz oscillation waveforms (Rrs5-Rrs5-20 and AX) are sensitive measurements in reflecting airway obstruction and the subsequent diagnosis of asthma in school-age children attending the asthma clinic.

4- The FOT measurements of resistance and reactance using 5–37 Hz oscillation waveforms (Rrs5, Rrs5-20 and AX) correlate with the spirometry parameters (FEV_1, FVC, FEV_1/FVC) of school-age children with asthma attending the asthma clinic.

5- FOT measurements of resistance using 5–37 Hz oscillation waveforms (Rrs5) correlates to the FeNO in school-age children attending the asthma clinic.

6- The FOT measurements of resistance and reactance by TremoFlo using frequency waveforms at 5–37 Hz and 7–41 Hz (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20 and Xrs7) reflect airway obstruction in school-age children with acute asthma.

7- Most of the abnormal FOT measurements of resistance and reactance using frequency waveforms at 5–37 Hz and 7–41 Hz (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz) exhibit change after bronchodilator administration in school-age children with acute asthma.

8- The measurements of FOT using waveforms at 7–41 Hz will be more useful reflection of abnormalities than measurements at 5–37 Hz in school-age children with acute asthma.

9- FOT measurements of resistance and reactance using TremoFlo at the 5–37 Hz and 7–41 Hz oscillation waveforms (Rrs5, Xrs7, Rrs7 and Xrs7) correlate with spirometry parameters (FEV_1 and FEV_1/FVC), the LCI and the FeNO in school-age children with uncontrolled asthma.

10- FOT measurements of resistance and reactance (Rrs5, Rsr5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz) and ACT scores improve with good adherence to inhaled corticosteroids in school-age children with uncontrolled asthma.

11- FOT measurements of resistance and reactance at the frequency waveforms 5–37 Hz and 7–41 Hz (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz) exhibit a change after bronchodilator administration in school-age children with uncontrolled asthma.

2.5 Structure of the thesis

This thesis contains nine chapters. The introduction and literature review are presented in Chapter 1, followed by the aims and the hypotheses in Chapter 2. The other chapters will include:

- Materials and methods, including data collection, reporting, and processing
- Diagnosis of asthma in children aged 5–18 years using the forced oscillation technique: A systematic review
- Assessing the forced oscillation technique in healthy children
- Assessing the forced oscillation technique in children with asthma
- Comparison of the forced oscillation technique to other lung function tests
- Assessing the adherence to treatment using the smart inhaler in children with asthma
- Conclusion chapter including a summary of the most important results and their clinical implications for future research

Each chapter includes the results of the study, as well as a description of the aims, hypotheses, populations, statistical methods and analysis and an interpretation of the results. Descriptions of the equipment and data processing will be summarised in the methods chapter.

CHAPTER 3 METHODS

3.1 Summary of the study design

This chapter includes a description of the equipment, the method of the procedures, and the data processing employed throughout the research study. The study aimed to:

1- Collect longitudinal lung function data, including the FOT, spirometry, and MBNW and measures of airway inflammation (FeNO) from school-aged children with wheezing/asthma.
2- Conduct a cross-sectional study with lung function data from age-matched healthy control children.
3- Conduct a cross-sectional study to measure adherence using the smart inhaler in school-aged children with asthma.

3.2 Participants

3.2.1 Children with asthma

Children aged 5–16 years who attended the asthma clinic at Leicester Royal Infirmary with stable asthma were recruited. Asthma was defined as stable based on physician diagnosis of non-frequent use of SABA and no asthma attacks for an extended period. All diagnoses were supported by objective testing as recommended by the NICE and ERS guidelines (50,53).

Children aged 5–15 years who attended the asthma clinic at Leicester Royal Infirmary with uncontrolled asthma were recruited. Uncontrolled asthma was defined as a childhood asthma control test (cACT) score of <20 in children aged 4–11 (seven questions) and an asthma control test (ACT) score of <20 (five questions) in children aged 12 and older (161).

Children aged 5–15 years who attended the emergency departments or wards at Leicester Royal Infirmary with acute asthma were recruited following a physician diagnosis of acute wheeze or asthma.

The age ranges differed between groups: in children with stable asthma, the age range of inclusion was up to and including 16 years, however, in children with acute and uncontrolled asthma included in the longitudinal study, the maximum age at recruitment was 14 years as we intended that each child would participate for up to 12 months and not remain in the study beyond their 16th birthday, in accordance with our ethical approval.

Participants were invited to perform lung function tests in the emergency department (ED), wards, asthma clinic, or the lung function laboratory. Children with acute and stable asthma

were studied upon their arrival to the ED, ward, or asthma clinic. However, children with uncontrolled asthma were studied in the lung function laboratory and were invited to a follow-up visit to the respiratory laboratory.

3.2.2 Healthy controls

Healthy children with no history of wheezing or chronic respiratory conditions aged 5–15 years were recruited from Leicester Royal Infirmary using posters in different departments within the hospital, such as the medical, surgical, dermatology, and diabetes clinics; other general or specialist non-respiratory clinics; and paediatric wards. The researcher approached the consultant in charge of each clinic and gave him or her the information about the study. When possible, one of the research team members approached the control children by approaching the parents and the children attending the hospital for non-respiratory problems in the waiting area when they attended outpatient clinics or in the wards; the study was discussed with the family, and they were left with an information sheet and an age-appropriate child information leaflet. Contact details were taken from the family, and the researcher approached the family after 24 hours to ask if they were willing to join the study. If the family agreed to join, they were invited to one lab visit to perform lung function tests. On some occasions, tests were performed in the wards within the period of admission.

Participants could not enter the study if any of the following applied:

- Children and young people less than 5 years old or older than 16 years old
- Any child or young person without informed consent from the parent or guardian
- Any child or young person who is unable or unwilling to give informed consent or who, in the opinion of the researcher working with the child, appeared unwilling to give assent
- Major co-morbidities that, in the opinion of the Chief Investigator, could influence the results, such as other chronic respiratory conditions or significant known musculoskeletal abnormalities (e.g., severe scoliosis)
- Unable to understand spoken or written English

3.3 Ethical approval

Ethical approval was obtained by Cambridge South Research Ethics Committee for all the procedures within this thesis. Information sheets for both parents and children were provided to the participants and parents before their involvement in the study. Consent and assent from the parent and the participants were obtained before enrolment in the study. (Appendices B-E)

Assent and informed consent were obtained from children with acute asthma and their parents during the emergency department visit or upon admission. However, informed consent and assent of the uncontrolled asthma and control group were obtained at the laboratory visit or on the wards within the period of hospital admission. Eligibility criteria were confirmed through phone calls before the visits.

3.4 Test procedure

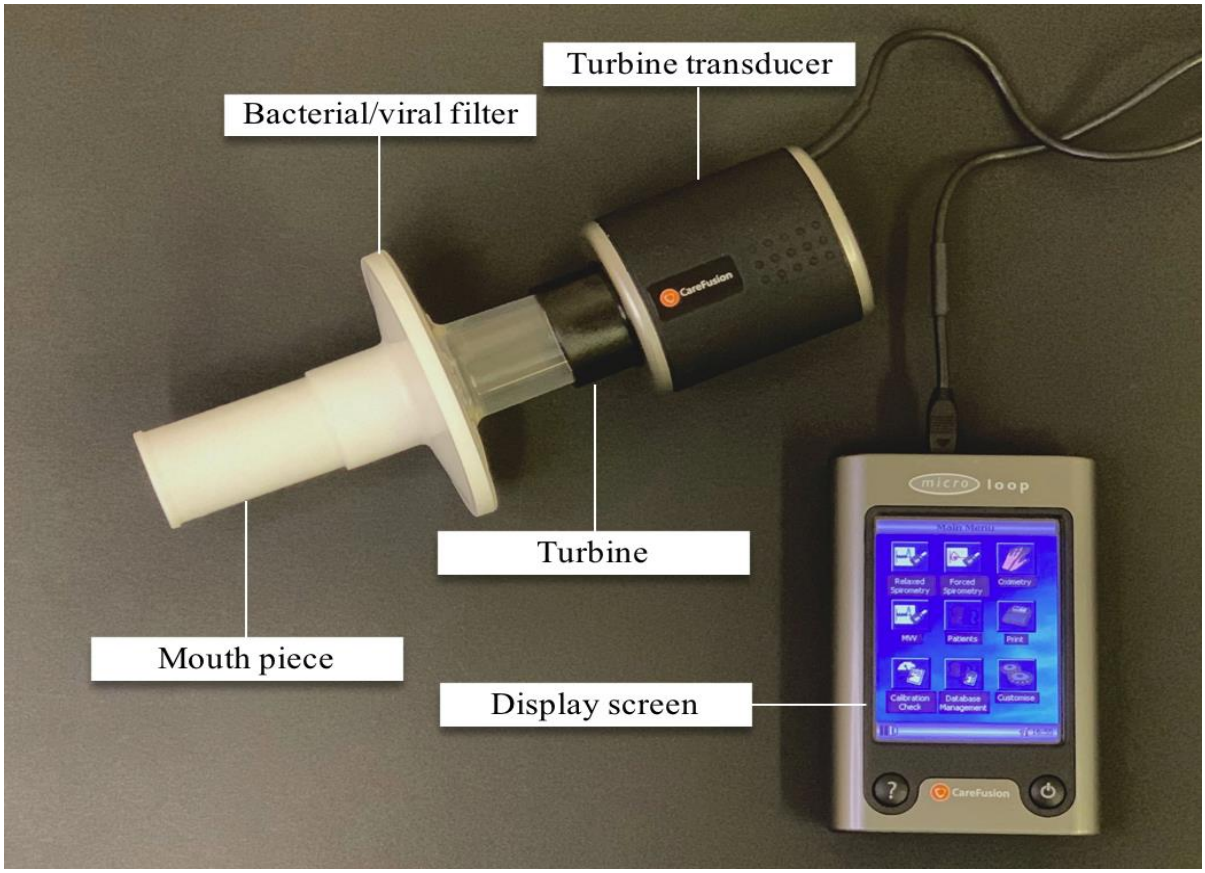
Within the emergency department, ward, and the laboratory visits, the procedures were explained to the patient and their parent. Demonstration of lung function tests through videos were also shown to the patients when possible. At each visit and for each participant, baseline characteristics were obtained. Each participant's standing height was measured without shoes, and weight was measured using a calibrated scale. Questionnaires were completed by the parent either by phone, at the emergency department, in the ward, or during the lab visits. The participant then performed the FOT, FeNO, MBNW, and spirometry. Education about the electronic monitoring fitting for the smart inhaler was also provided. Adherence was discussed by the researcher with both the parent and the participants within their first and follow-up lab visit after the smart inhaler fitting. All the procedures were performed following specific study protocols. Details about the procedures are provided below.

3.4.1 Spirometry

3.4.1.1 Equipment and calibration

Portable spirometry devices CareFusion MicroLoop or CareFusion MicroLab (Micro Medical, Quayside, U.K) were used for participant testing. The turbine (Vyaire Medical GmbH, Berlin, Germany) was fitted to the turbine transducer, which was connected and plugged into the machine through a socket at the side of the instrument (Figure 3.1).

Figure 3.1: Components of the spirometry setup



All the participants' data were entered into the machine prior to the testing, including their name, ethnicity, sex, height, weight, and date of birth. If a participant's ethnic group had no prediction value set in the device, a factor was added manually. The factor allowed for a change in the predicted values of volumes by applying a percentage to it. A suggested factor was provided by the spirometry manual for specific ethnic groups, such as Hong Kong Chinese (100%), Japanese American (89%), Polynesians (90%), North Indians and Pakistanis (90%), and South Indians and those of African descent (87%) (162).

Calibration was performed using a 3 L syringe that was connected to a transducer using an adaptor. Calibration started by emptying the syringe by pushing the handle fully, followed by filling the syringe through pulling the handle, which was performed slowly and at a constant rate to maintain the flow rate and keep the trace within the grey area (Figure 3.2). If this was not achieved, the trial was rejected, and a repetition of the calibration was performed. Another calibration was also performed at low and high flow rates following the first calibration, starting with the calibration at a low flow rate, and the calibration was performed again at a higher flow rate (Figure 3.3). After the three calibrations were completed at the three flow rates, the

calibration result was checked, and spirometry was ready to be used (Figure 3.4) To pass the calibration check, an error of less than 3% needed to be achieved; if this was not achieved and the error was higher than 3%, the calibration was repeated to reach the acceptance criteria for calibration with special consideration to emptying the syringe in a smooth manner and inspecting the turbine transducer to check if any cleaning was needed.

Figure 3.2: First spirometry calibration

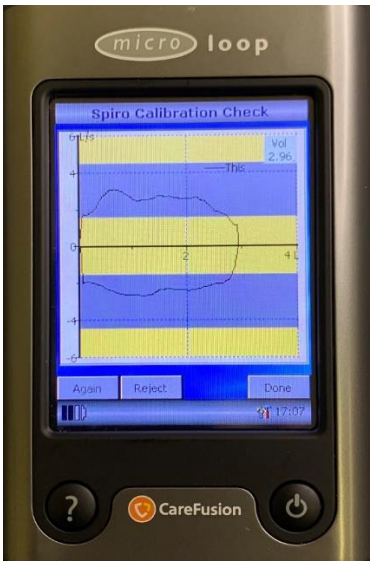


Figure 3.3: Calibration at low and high flow rates

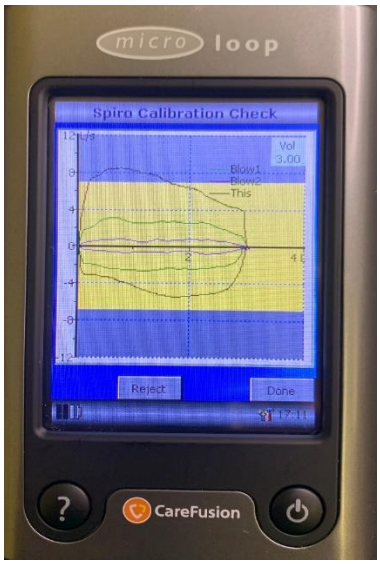
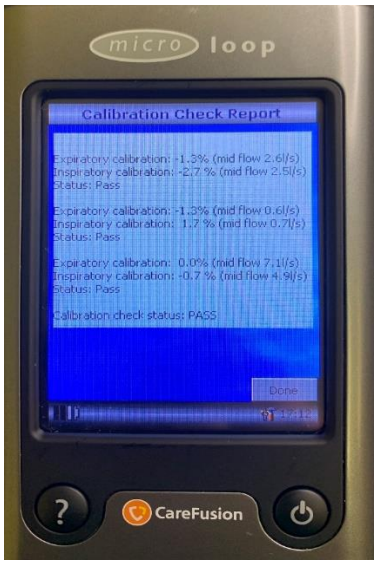


Figure 3.4: Calibration check report



3.4.1.2 Data collection and reporting

All participants performed the measurements in an upright standing position with a nose clip on their nose. A disposable bacterial/viral filter (MicroGrad ®CareFusion GmbH, Berlin, Germany) was attached to the turbine part of the transducers.

Participants were asked to take a deep maximal inspiration away from the device; they were then instructed to put their mouth around the mouthpiece, maintain a good mouth seal, and exhale forcefully (Figure 3.5). During the test, the participants were encouraged to perform their best and to maintain their exhalation. An incentive screen by CareFusion MicroLoop and MicroLab software was used for some of the participants to encourage them to blow as fast and hard as possible, and to continue the exhalation. To maintain acceptable measurements, the patient's effort, flow volume loop, volume time curve, and the obtained measurements on the screen within and between the tests were continuously monitored. The test was repeated up to eight times to obtain three acceptable performances with two repeatable tests; the two largest

values of FVC were required to be within 150 mL of each other or within 5% FVC or <100 mL if FVC was <1000 mL, and the two largest values of FEV_1 needed to be within 5% FVC or <100 mL if FVC was < 1000 mL for repeatability. An acceptable manoeuvre was defined to be free of artefacts of cough, leak, glottis closure, early termination of the test, poor effort, and mouthpiece obstruction. A maximal forced exhalation without any hesitation or cough within the first second of the exhalation represented a good start of the test. A satisfactory end test criterion in children was maintaining the exhalation to 3 seconds (60,163). A review of the results was available on the screen. Measurements were taken before and after the administration of the bronchodilator in children with asthma, and only a baseline measurement was taken in the healthy control group.

Figure 3.5: Child performing spirometry (with permission)

Legend: The transducer is attached to a bacteria/viral filter and mouthpiece. The child is in a standing position and instructed to take a deep breath and blow as fast and as strong as possible while wearing a nose clip

Unacceptable measurements were excluded but not deleted. The highest value of the FEV_1 and the highest value of the FVC were reported, along with the ratio of these highest values (FEV_1/FVC). The data measured were compared to the predicted values, which were the

reference values that were based on healthy individuals with the same characteristics of age, sex, height, and ethnic group (64,164).

Predicted values in percentages and the actual values in litres of the FEV_1 and the FVC were reported, in addition to the actual value of the FEV_1/FVC. Z-scores were also reported; this was recommended because they are applied to different ages, sexes, and ethnic groups among the spirometry indices (165).

3.4.2 Multiple breath nitrogen washout

3.4.2.1 Equipment and calibration

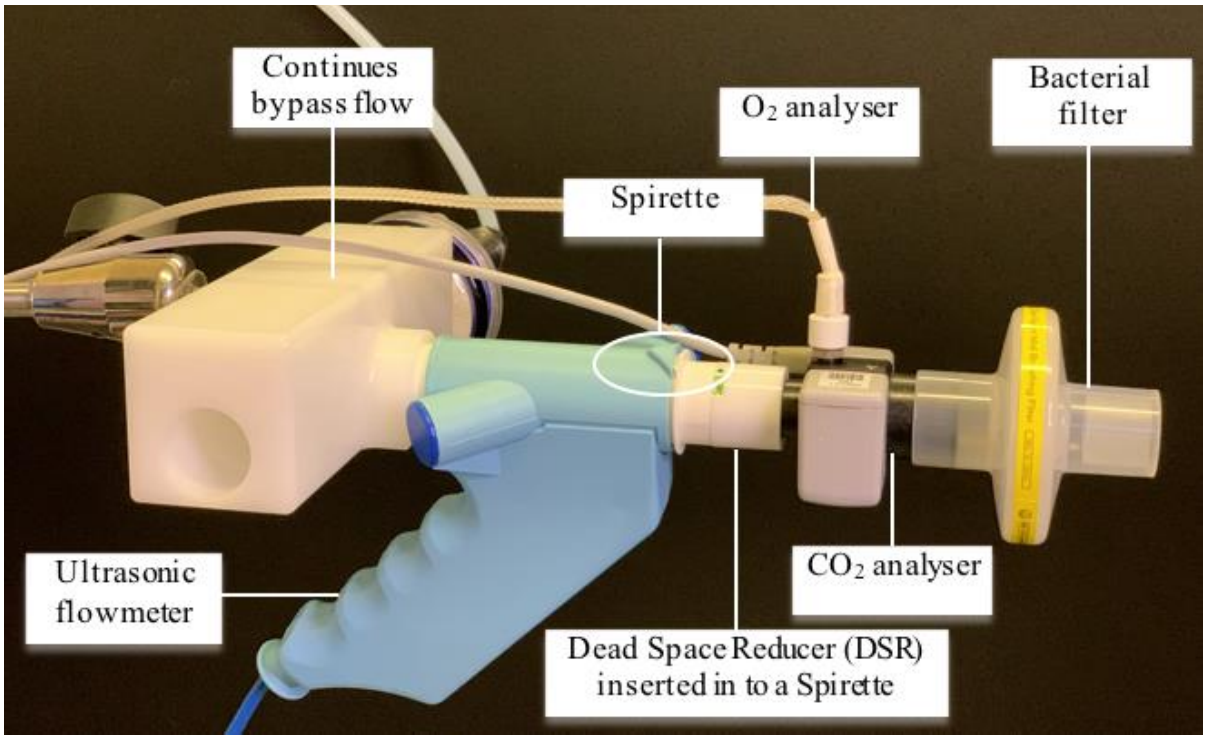
An open circuit MBNW was measured using the indirect technique operated by the EXHALYZER® D and Spiroware 3.2.1 (Eco Medics, Dürnten, Switzerland) (Figure 3.6) to determine the N_2 concentration; this was achieved through the measurement of carbon dioxide (CO_2) with a mainstream infrared analyser and side stream sampling for the oxygen (O_2) measurements with a flow of 200 mL/min to the O_2 analyser (166).

Figure 3.6: Setup of the device

The bacterial filter was connected to the mainstream CO_2 sensor with the side stream O_2 sensor, which was followed by a Dead Space Reducer (DSR) inserted into a Spirette, with DSR Set 2

for participants weighing 15–35 kg and DSR Set 3 for participants weight >35 kg, followed by an ultrasonic flowmeter connected to a continuous bypass flow system (Figure 3.7).

Figure 3.7: Components of the apparatus



The device was calibrated on a daily basis, starting with the flow calibration followed by channel calibration. The calibration was performed a few minutes after switching the machine on to reach the maximal performance after a warm-up period. Flow calibration was performed by applying 10 strokes using a certified syringe for calibration, starting with the plunger of the syringe all the way in, then connecting the syringe to the bacterial filter and applying 10 strokes steadily to maintain the flow between the green lines on the screen. Successful flow calibration was indicated when the peak flow was maintained within the shaded area on the screen, the volumes recorded were similar to what was expected with a mean volume of 1000 mL ± 30 mL, and deviation both inspiratory and expiratory were less than ±2%. Recording the flow and volume of the new calibration was performed by comparing it with the previously stored calibration and updating if necessary. Channel calibration was performed at two points: a high point of 100% O_2 and a low point of 20.94% O_2 (medical air) following the flow calibration. The system typically started the calibration at the low point of the medical air, and after a few moments, it switched automatically to the level of 100% O_2, resulting in a stepwise change. Flow during the channel calibration was observed to be 950 mL/s throughout the calibration. The calibration typically stopped automatically once it was complete (Figure 3.8, Figure 3.9).

Figure 3.8: Flow calibration

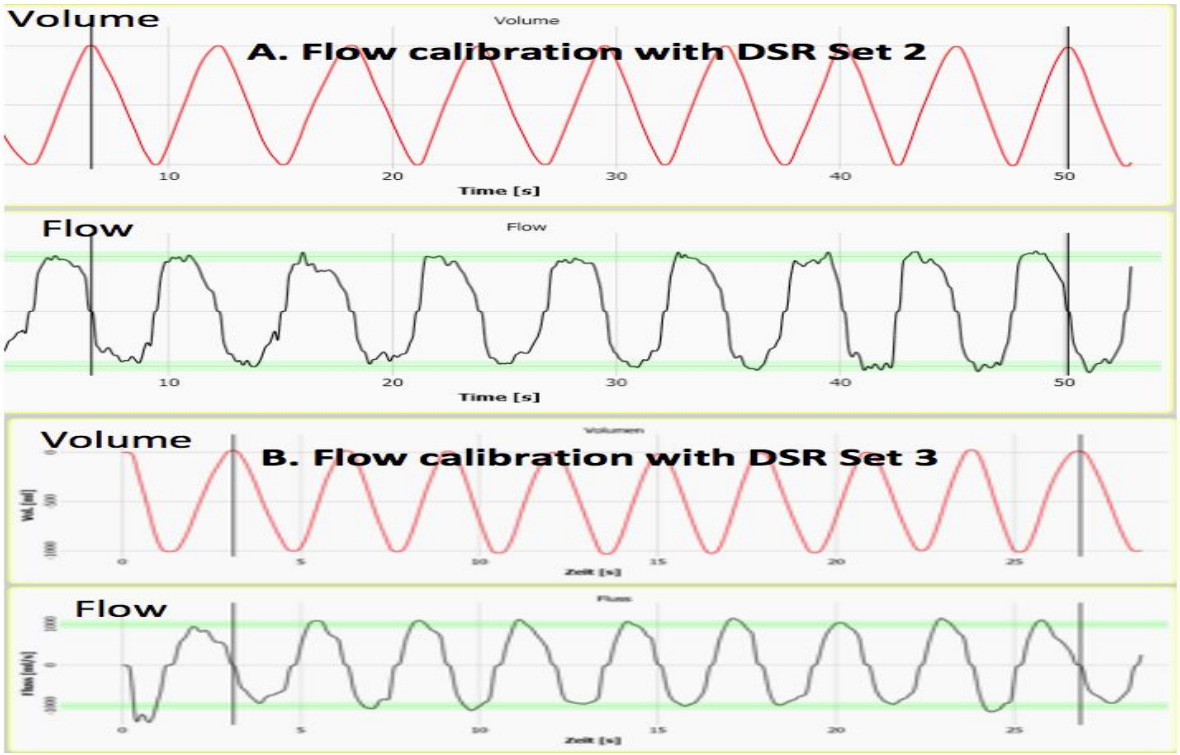
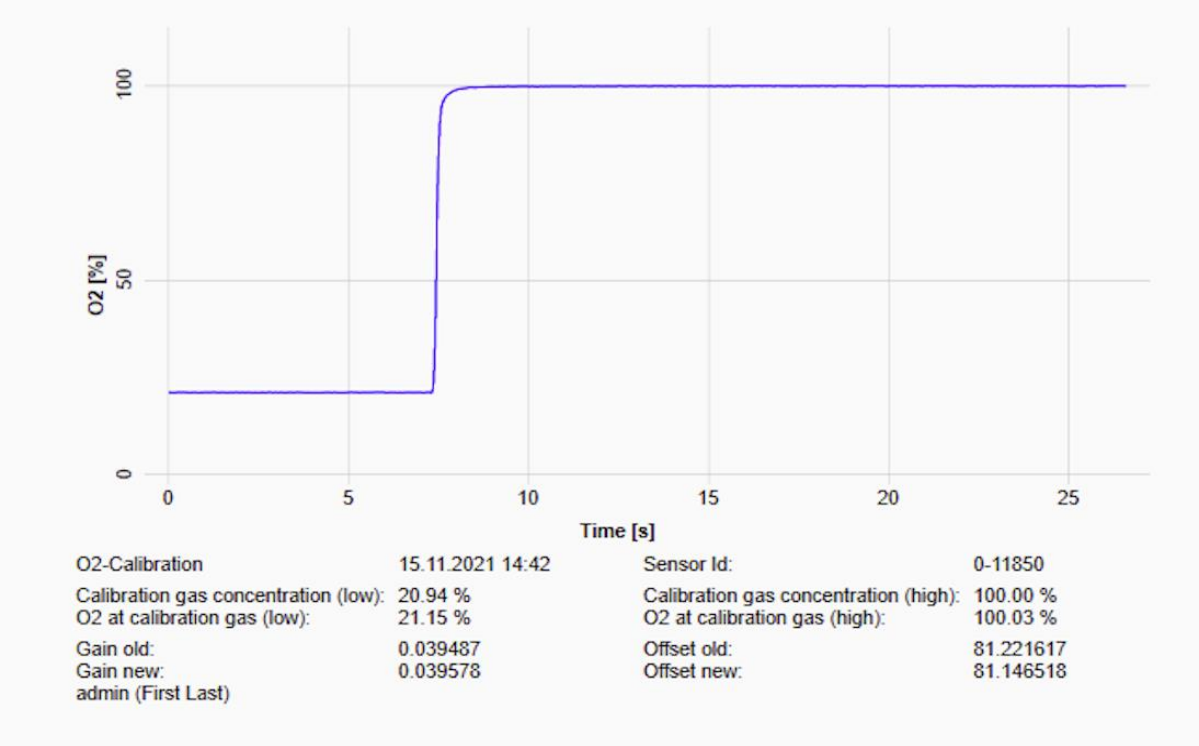


Figure 3.9: Channel Calibration



3.4.2.2 Data collection and reporting

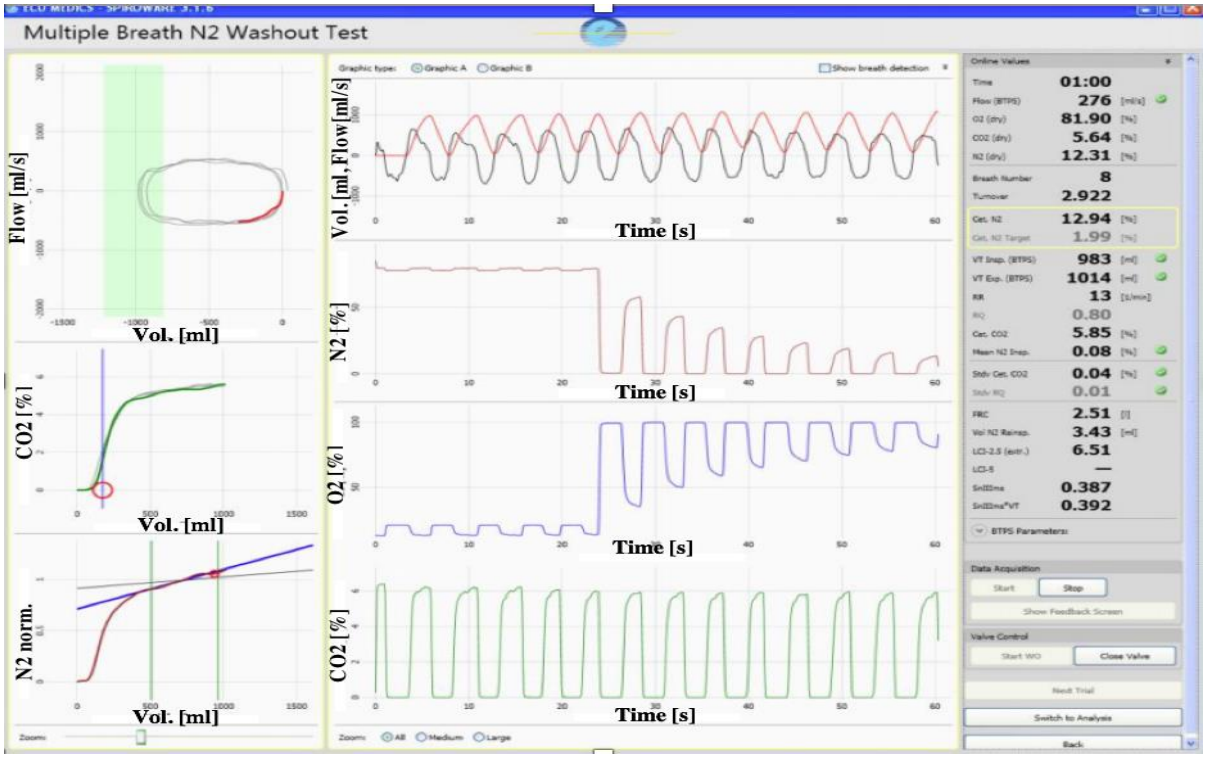
The test was performed while the participants were in a seated position using a nose clip, and the participants were instructed to maintain a good mouth seal around the filter mouthpiece and breathe normally (Figure 3.10). The EXHALYZER® D provides a continuous flow while the participant is breathing through the circuit. Once a stable breathing pattern was achieved, the process of the washout started by providing 100% O_2 to the participants using a continuous bypass flow. The participants were instructed and encouraged during the performance of the test to breathe normally. An incentive graph from the software was displayed; breathing within the tidal volume limit was guided by a smiley face animation incentive displayed on the screen while the participant was breathing. The face becomes a smiley green face when the participant breathes within the pre-set tidal volume limit and turned into a red sad face if the participant breathes above or below the tidal volume limits. The washout trace, nitrogen concentration, breathing pattern, and appearance of the leak were monitored to maintain acceptable measurements (Figure 3.11). In case of the appearance of a leak, the test was stopped. The test was terminated automatically after achieving three consecutive breaths with a nitrogen concentration of less than 1/40 of the starting concentration. The test was repeated to obtain three acceptable measurements, maintaining the recommended wait time between the measurements of at least the washout time for the inert gas concentration to return to baseline.

The recordings obtained after the performance of the test were reviewed by the operator. Another review was conducted by another investigator (Dr Caroline Beardsmore). Any unacceptable measurements due to artefacts, leaks, or an inappropriate start of the test were excluded from the average of the recordings. Any unacceptable test was not deleted in case further inspection was needed. The lung clearance index (LCI) was reported as the mean of at least two acceptable measurements within a 10% difference of the FRC with a coefficient of variation of less than 10% (75,167).

Figure 3.10: Child performing multiple breath nitrogen washout (MBNW) (with permission)

Legend: The child is in seated position and instructed to breathe normally, maintaining good mouth seal around the filter, while wearing a nose clip

Figure 3.11: Test screen

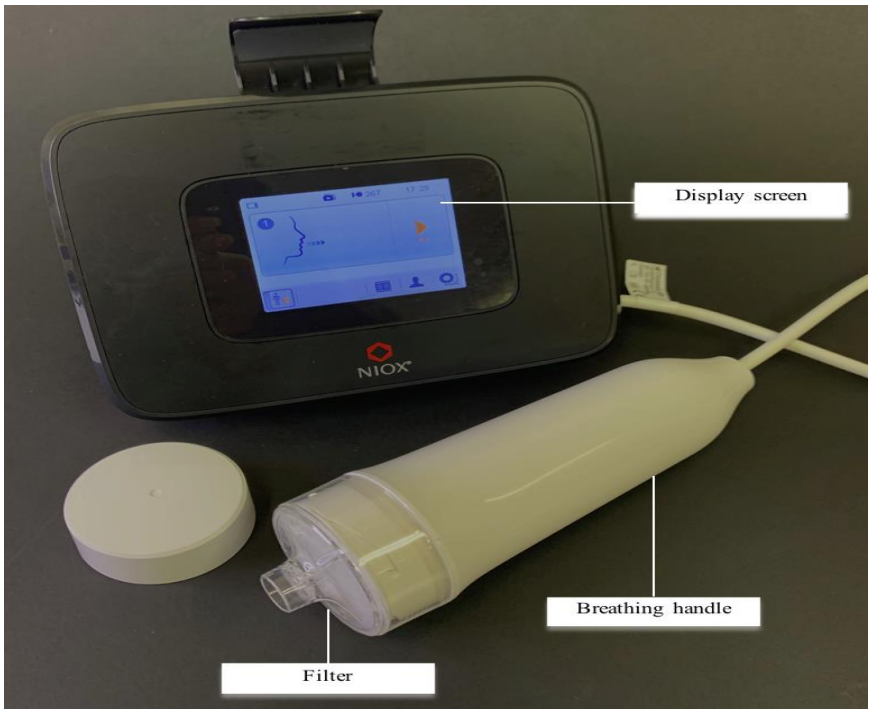


3.4.3 Fractional exhaled nitric oxide

3.4.3.1 Equipment and calibration

A NIOX VERO® machine was used for the FeNO measurements. The device was connected to the breathing handle, to which the filter was attached (Figure 3.12). The machine requires no calibration prior to use; it is already calibrated when it is manufactured.

Figure 3.12: Components of the apparatus



3.4.3.2 Data collection and reporting

Participants were given the breathing handle and were instructed to breathe out until their lungs were empty. This was followed by the insertion of the mouthpiece into the mouth and maintaining a good seal to prevent any air leakage around the mouth; the participants were then instructed to inhale deeply to the maximal lung capacity, followed by an exhalation while maintaining appropriate exhalation pressure. This was achieved by instructing the participants to breathe out at a steady rate, resulting in a consistent beeping sound from the machine. If the pitch of the noise changed, reflecting exhalation pressure that was too high or too low, the participants were instructed to breathe more slowly or slightly harder if needed. Also, inhalation and exhalation were guided by the animation incentives that appeared on the screen (Figure 3.13). At the end of a successful manoeuvre, measurements of FeNO appeared in numerical format measured in parts per billion (ppb) (Figure 3.14).

Figure 3.13: Child performing fractional exhaled nitric oxide (FeNO) (with permission)

Legend: The child is instructed to take a deep breath and then exhale at a steady rate

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Figure 3.14: Display screen of FeNO

3.4.4 Electronic monitoring

3.4.4.1 Equipment and calibration

An electronic monitoring device (smart inhaler), the Hailie sensor® for Seretide HFA, for Ventolin HFA and for Symbicort Turbuhaler, (Adherium, Auckland, New Zealand) was used to monitor the adherence to the treatment. The prescribed medications were fitted into the sensor. No calibration was required prior to use.

3.4.4.2 Data collection and reporting

Participants with uncontrolled asthma who had been prescribed preventer or reliever medication and arrived for treatment at the asthma clinic were eligible to be fitted for the smart inhaler monitor. The first step was creating an account for the participant on the Hailie web portal. Families were asked to download the Hailie app onto their smartphones. The prescribed medication was then fitted to the sensor, followed by pairing the sensor to the smartphone, ensuring that Bluetooth was turned on. Once the Hailie sensor was paired, it appeared in the paired section in the application. All medical data needed, including the participants' basic information, prescribed medication, and usage of the medication, appeared on both the Hailie app and the web portal.

Participants were instructed to maintain the regular usage of their medication as prescribed, ensuring that they established a good press of the medication by holding the canister with one hand and keeping the thumb under the bottom of the Hailie sensor and the index or the other fingers on the top of the canister. The Hailie LED in the sensor flashes after three seconds, which reflects successful detection of the administered medication. The sensor tracked each time the inhaler was used by the participants, reminded the participants through the Hailie app if any of the prescribed doses were missed and displayed the usage over time. Parents were provided with contact information for the investigator in case any technical problems appeared.

3.4.5 Forced oscillation technique

3.4.5.1 Equipment and calibration

The FOT reflects lung functions by measuring the resistance and reactance of the lung. Multi-frequency airwaves of pressure and flow are superimposed over the spontaneous breathing of the patient (flow nominal range ± 2.5 L/s with the mouth pressure nominal range of ±10 cmH_20) (87). Measurements of impedance were taken using a portable TremoFlo®C100-Thorasys machine (Nowus Healthcare, Copenhagen, Denmark), which consists of a handheld unit connected to the software through an Ethernet connection (Figure 3.15).

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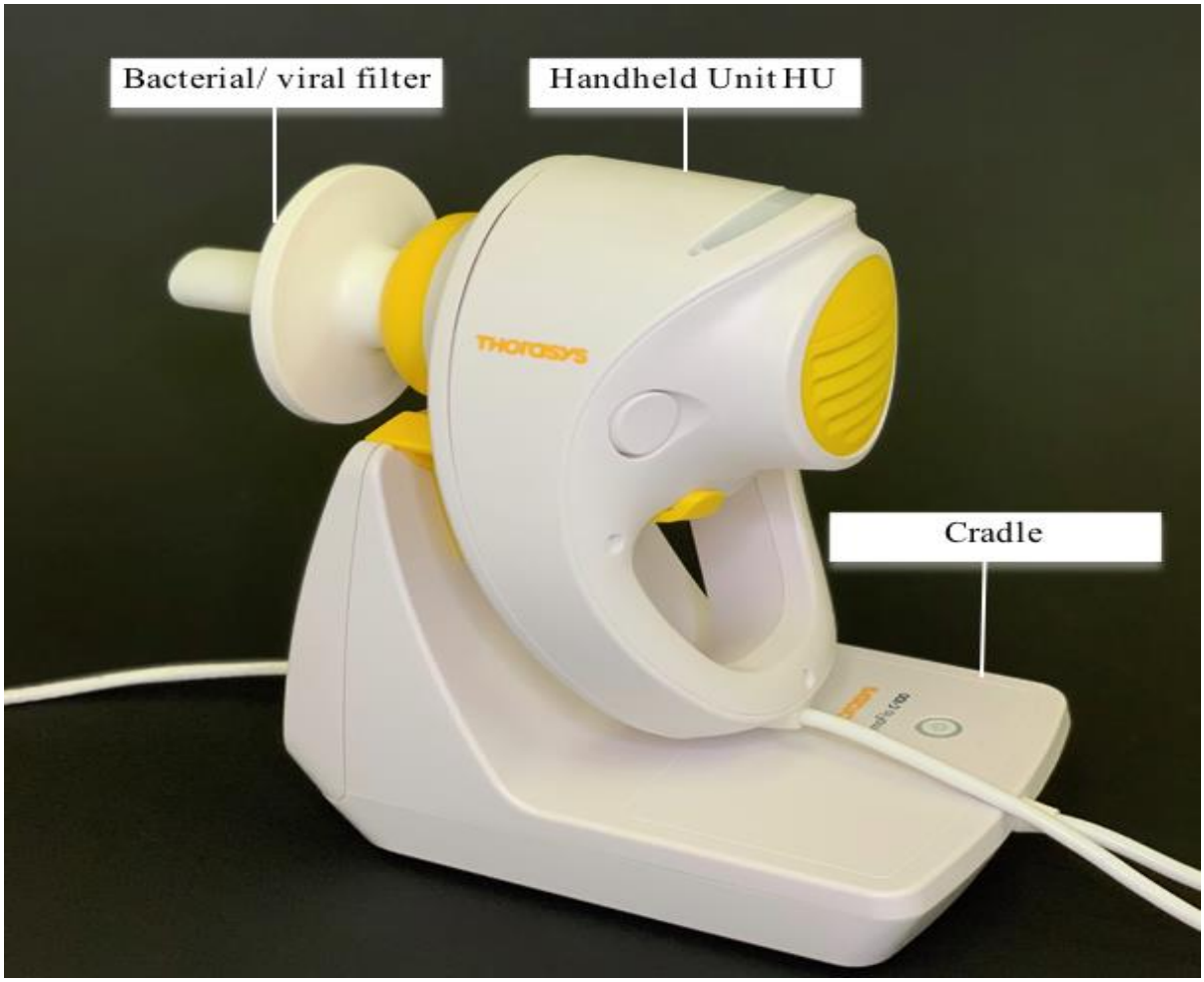
Figure 3.15: Components of the apparatus



A field calibration was conducted daily, as recommended by the TremoFlo manual, to detect any changes or damage to the machine and ensure the accuracy of the measurements. The field calibration took less than 1 minute. It was achieved by connecting the test load calibration and entering the ID assigned to the calibrator (Figure 3.16). This ID was needed because the calibration test load was changed annually per the expiration date. By starting the calibration, a waveform was generated; each waveform during the test took approximately 8–16 seconds (Figure 3.17). Once the calibration was complete, the software proceeded directly to the results screen. If the results screen displayed a green checkmark, it indicated that the calibration had reached the acceptance criteria that were predefined to the test calibration load, and the calibration was complete (Figure 3.18).

Figure 3.16: Calibration test load adaptor

Figure 3.17: Field calibration

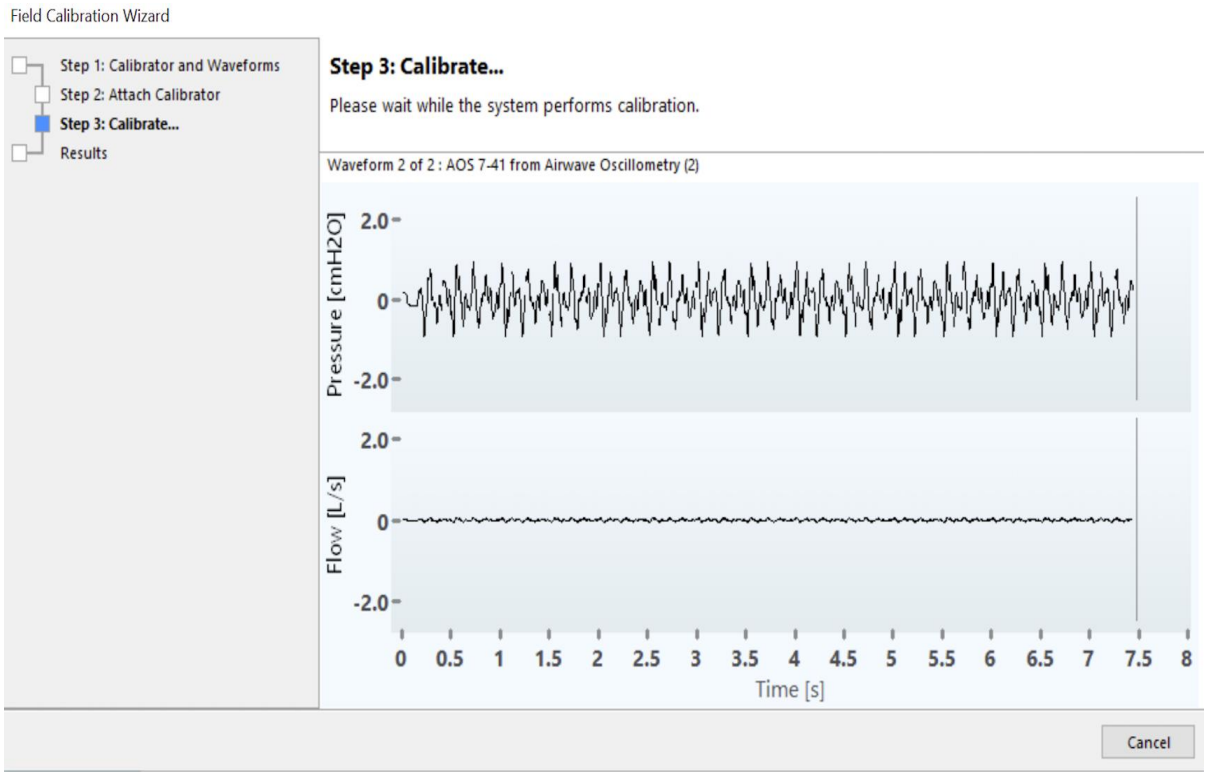
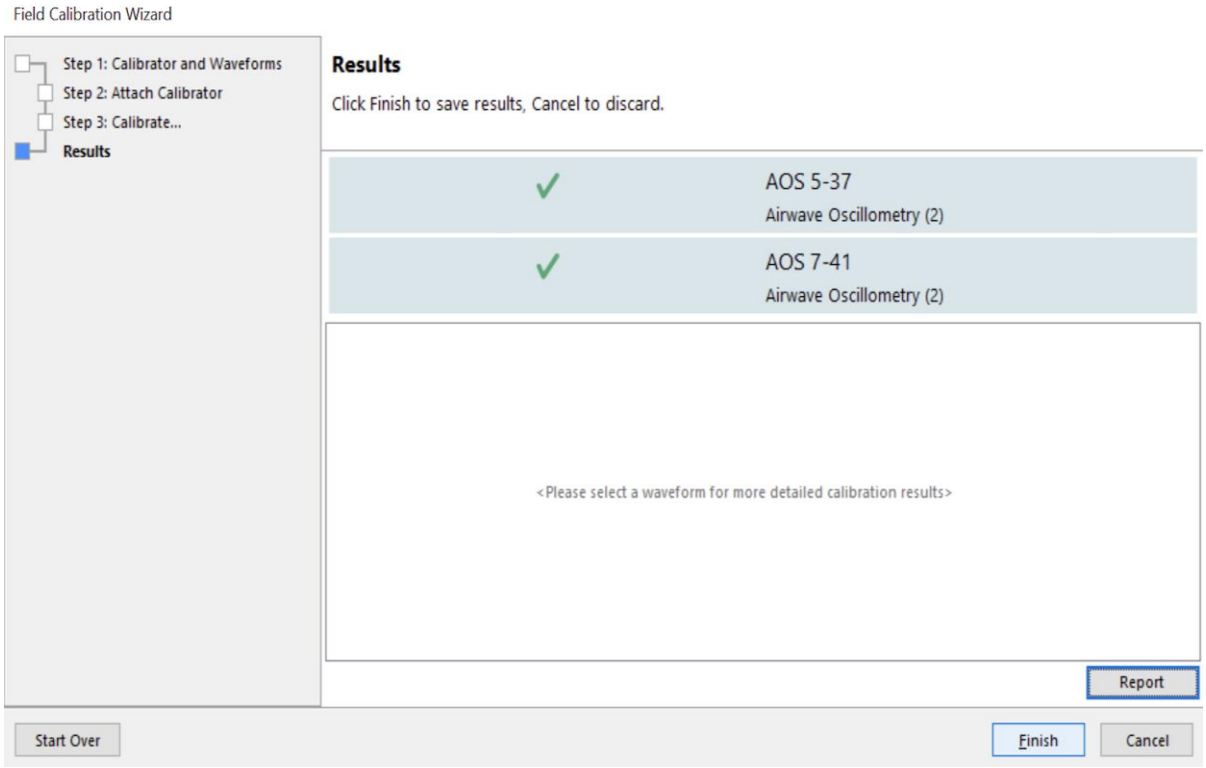


Figure 3.18: Calibration results screen



3.4.5.2 Data collection and reporting

The participant was instructed to breathe normally through a mouthpiece into the TremoFlo machine for a period of 16–20 seconds in a seated position. The nasal airflow was blocked by a nose clip, and the participants were instructed to hold their cheeks while performing the test. In some cases, the cheeks were supported by the parent or the operator if assistance was needed (Figure 3.19). By the end of the test, the results were displayed by the software. Special consideration was given to the insertion of the mouthpiece into the mouth, maintaining a good seal around the mouthpiece, and assuring that the participants were instructed to place their tongues under the mouthpiece to prevent obstructing the airflow pathway. Moreover, to prevent any resistance due to the compression as a result of the position, the participants were instructed to look forward and upward slightly and were encouraged to maintain quiet and steady breathing for the whole period of the test. The operator observed the breathing pattern of the participants to eliminate any heavy or shallow breathing while performing the test. Between the tests, the mouthpiece was removed from the mouth to allow relaxation.

Figure 3.19: Child performing the forced oscillation technique (FOT) (with permission)

Legend: Participant maintained an upright head posture supporting the cheeks and the mouth with the hands and maintained good seal around the mouth while wearing a nose clip

In preparation for measurements, the participants were instructed to perform quiet breathing for a few seconds before the operator applied the vibration to start the test (Figure 3.20 and 3.21). During the performance of the test, multi-frequency airway oscillometry waveforms (AOS 5 to 37 Hz and AOS 7 to 41 Hz) were used for the FOT measurements. The software analysed the resistance and reactance at each frequency with an intra-breath and whole-breath analysis. The measurements were recorded for 16–20 seconds, with pressure, flow, and volume time course shown on the left side of the screen and the numerical reading displayed on the right side of the screen by the end of the test after 20 seconds of measurement (Figure 3.21).

Figure 3.20: Forced oscillation measurement (Breath preparation by quiet breathing)

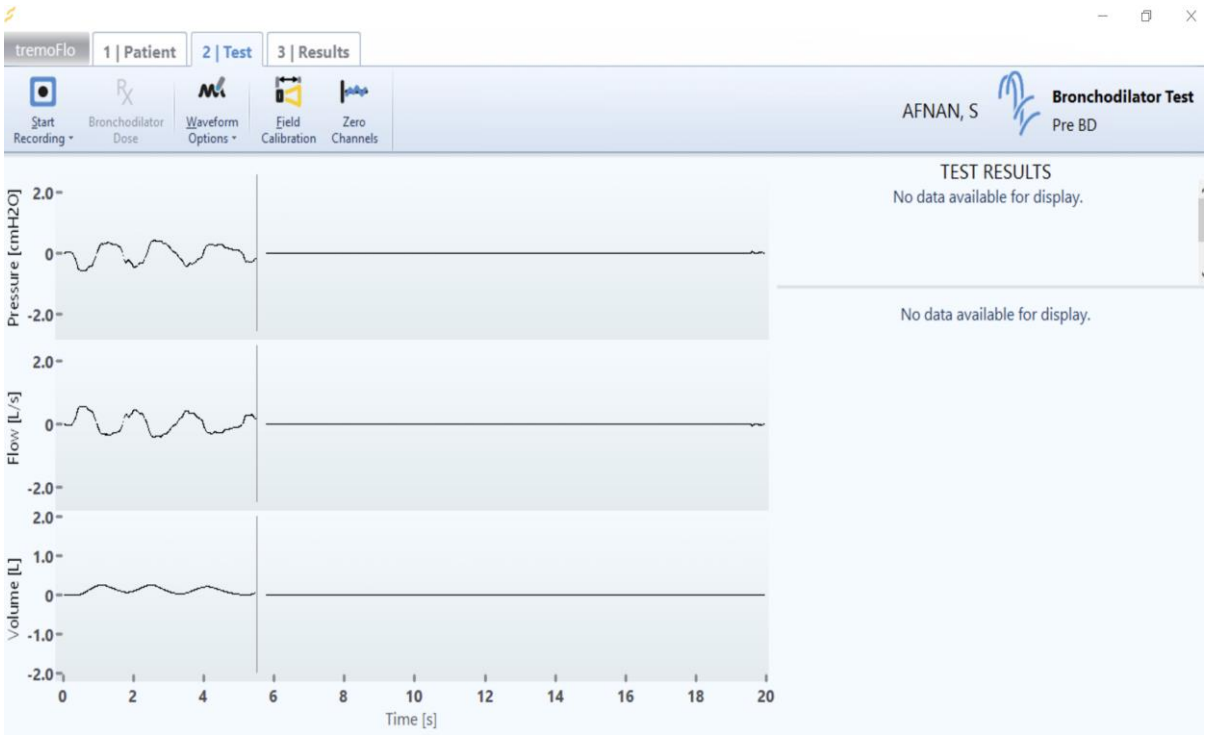
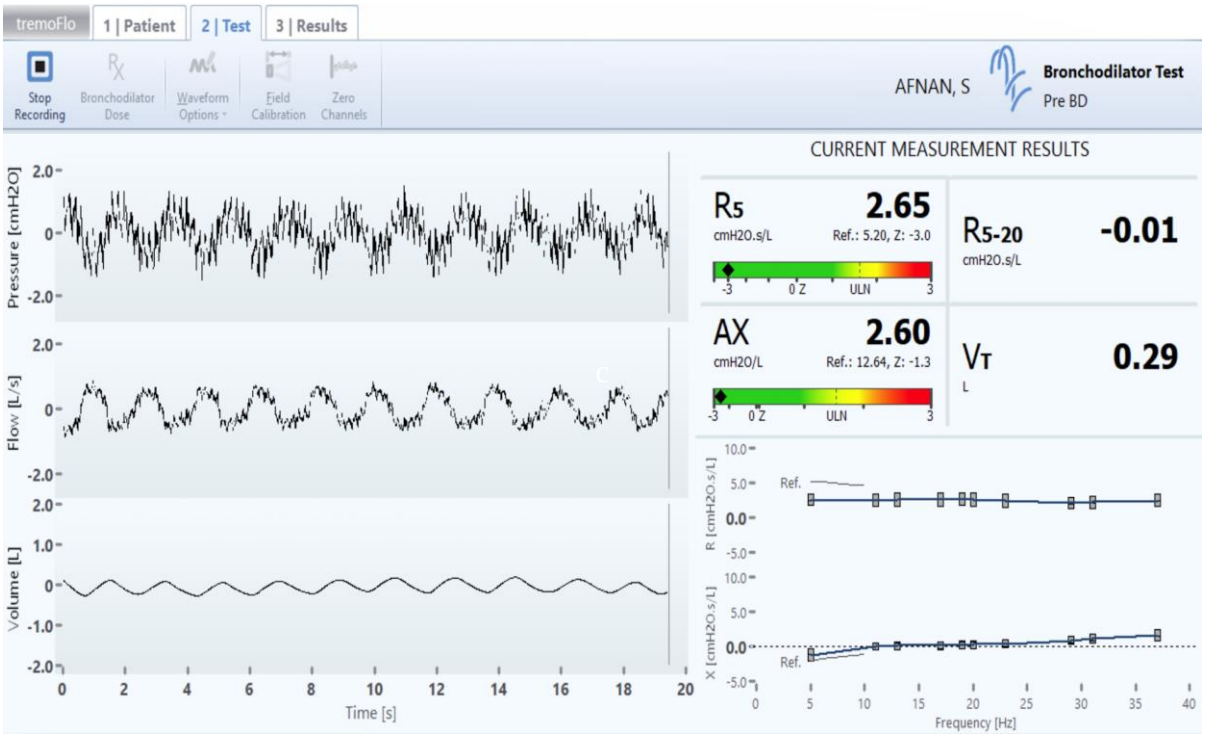
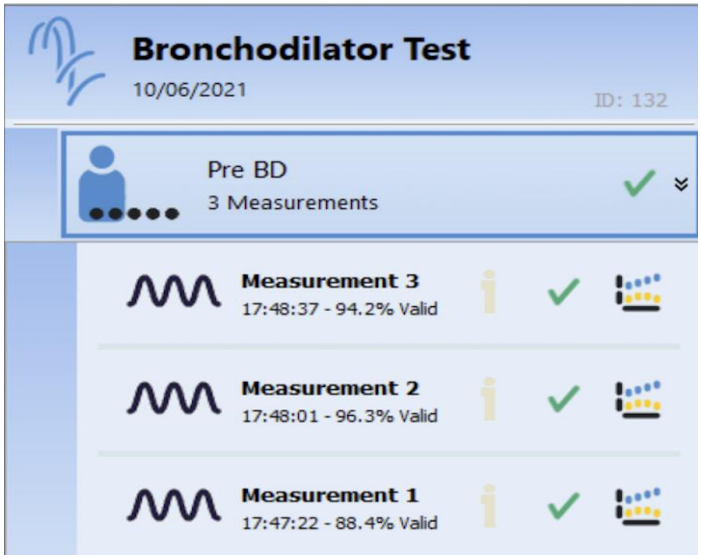


Figure 3.21: Forced oscillation measurement (Starting the test by applying the vibration)



A baseline test was performed with at least three acceptable measurements; measurements were repeated up to five times if needed (Figure 3.22). Each measurement was reviewed to meet the acceptable criteria. At the end of the measurements, all numerical and graphical results and quality control were reviewed and reported.

Figure 3.22: Acceptable measurements

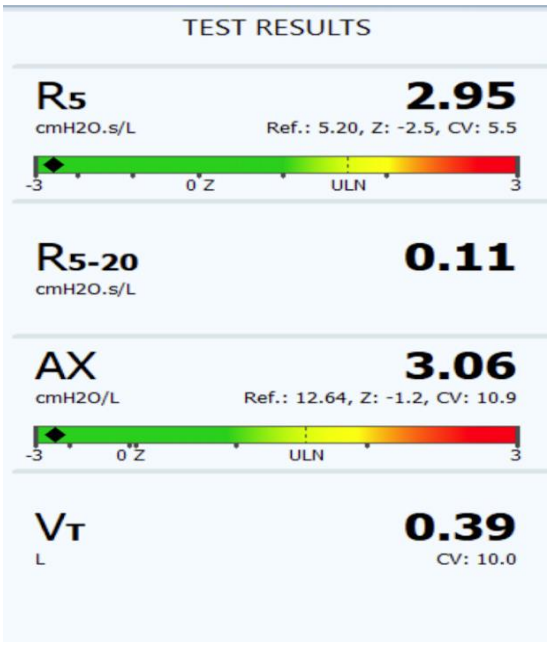


During the tests, the artefacts were minimized as much as possible. In cases in which this was not possible, the software was able to exclude brief artefacts, such as swallowing, coughing, air leaks around the mouthpiece, speaking, or laughing. However, if many of these artefacts appeared within a measurement, the measurement was excluded; typically, the machine excluded it automatically. If a strong cough occurred during the test, the device was reset before taking any other measurements to prevent errors in the further attempt. If at any time the operator noticed unacceptable measurements, the test was stopped, and the machine automatically assessed the measurement to store part of the measurements or to discard it.

The results were reviewed on the right side of the screen, and the value of each single parameter appeared as a number in addition to the reference value, Z-scores, coefficient variation of the parameter, and a visual gauge scale. A black diamond indicator within each gauge ranged between green, yellow, or red to indicate the outcome of the patient measurement relative to the normal reference value. Each colour represented the significance of the measurement's reading. Green indicated that the outcome readings were within the 95% confidence interval of the predicted value. Yellow indicated that the readings were around the upper and lower normal limits of the 95% confidence interval of the normal values. Red indicated that the readings

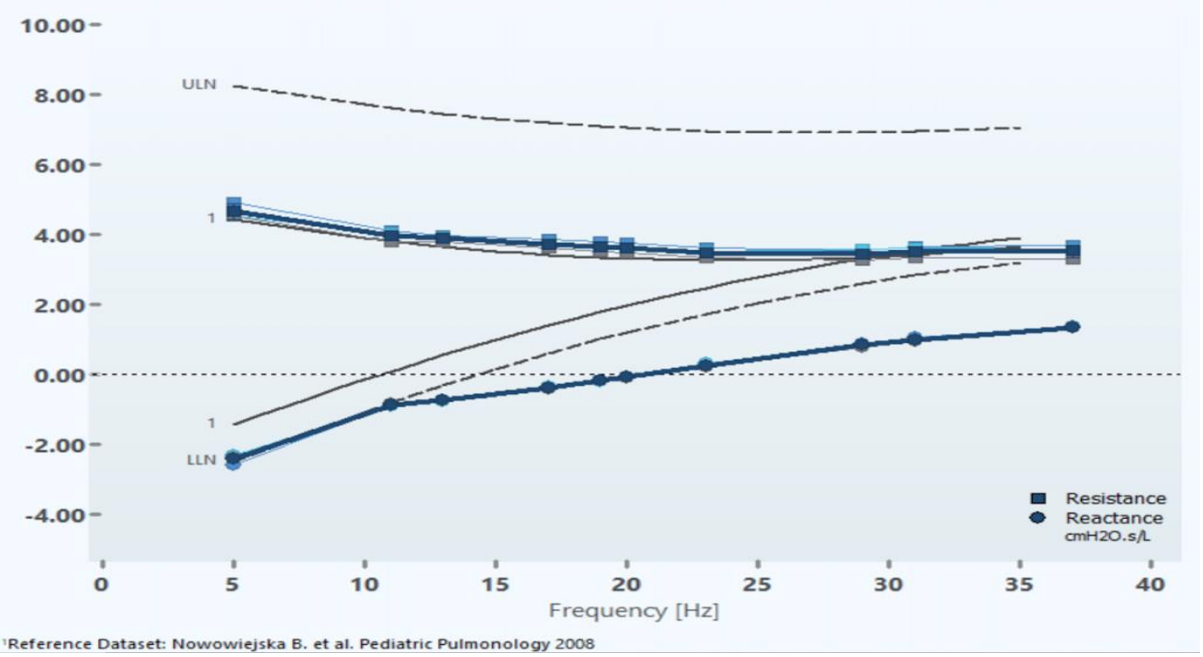
were either above or below the limit of the normal values, outside the 95% confidence interval of approximately the normal value (Figure 3.23).

Figure 3.23: Test results represented at the side of the screen



Further interpretation was also carried out for the impedance using the impedance chart. The impedance chart was represented by a graph visualizing both the resistance and reactance. Each measurement was displayed by thin lines in different colours. A test average was represented by a thick, dark blue line; normal reference values for the same age, sex, height, and weight of the studied participants appeared in a black line, with the sources of the reference values at the bottom left of the chart. The upper and lower normal limits were represented by a black dashed line (Figure 3.24).

Figure 3.24: Impedance chart



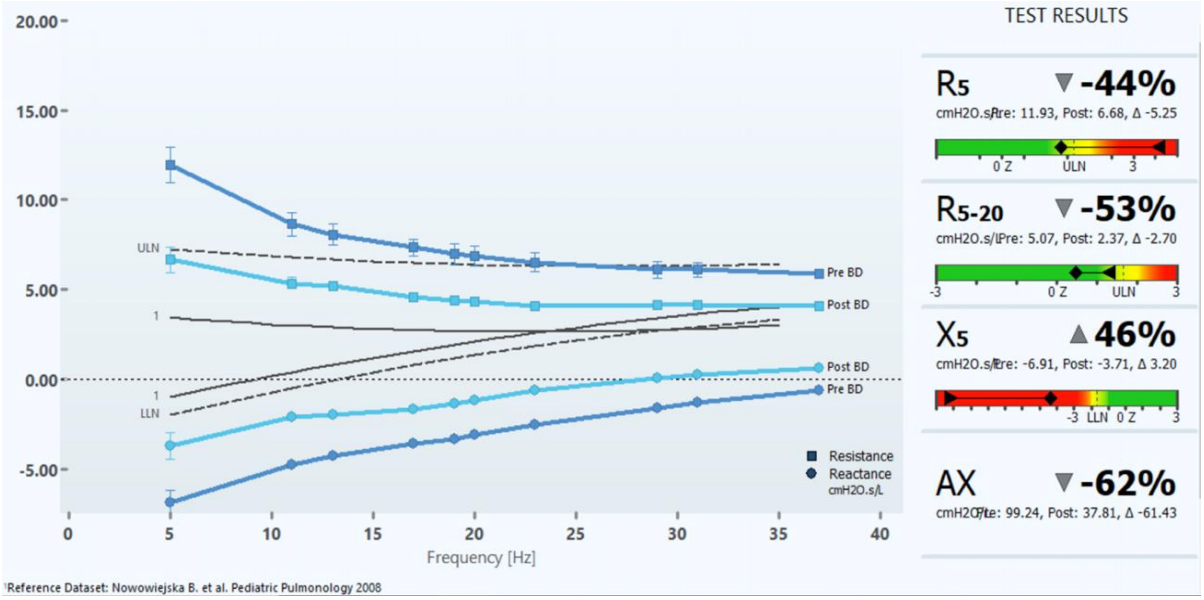
An additional detailed evaluation of the results was completed by reviewing all the results in the form of a table. The table view presented the reference value, unit of measurement, test average, coefficient variation, standard deviation, % predicted, and the Z-score. In addition, the individual readings for each were measured separately. In some cases, when the outcome of the reactance value was a normal value close to zero, neither of the % predicted nor the coefficient variation were evaluated for these parameters because of the risk of divisions by zero and because the parameters are not meaningful. Furthermore, the % predicted and the Z-score were evaluated only for parameters that had reference values (Figure 3.25).

Figure 3.25: Results in table view

	Reference	Test Average	SD	CV %	Z Score	Abs. Diff.	% Pred.	M1	M2	M3
R5 cmH2O.s/L	4.766	3.367	0.2784	8.27	-1.559	-1.4	70.63	3.462	3.585	3.053
R5-20 cmH2O.s/L		0.137						0.104	0.217	0.089
AX cmH2O/L	9.672	4.606	0.3723	8.083	-0.6665	-5.066	47.62	4.444	5.032	4.342
VT L		0.892	0.07189	8.058				0.902	0.959	0.816
COH5		0.920						0.913	0.930	0.916

Readings and traces of the resistance and reactance before and after the administration of the bronchodilator were available for viewing after the bronchodilator administration in addition to the percent change for each of the displayed measures of the FOT (Figure 3.26).

Figure 3.26: Before and after bronchodilator administration test results comparison



The results were reviewed for the quality control before the final reports, which were performed by the smart processing of the TremoFlo and by reviewing the result navigation panel and toolbar (Table 3.1).

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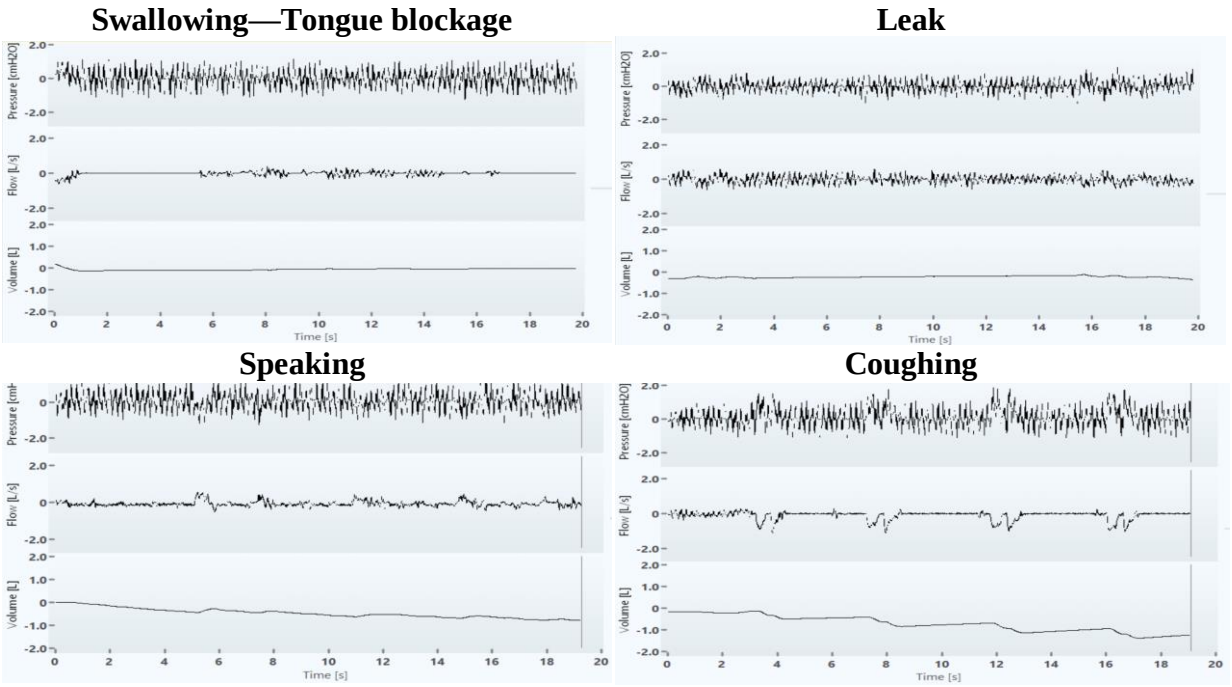
Table 3.1: Quality control

Raw data validation	TremoFlo software at the stage of data analysis typically assesses raw data collection; if any problem exists within the data, the software automatically excludes the data.
Artefacts detection	The software identifies any artefacts in the resistance and reactance and scans for any irregularities, such as a negative or excessive outlier. This is achieved through a default set to anything more than three standard deviations of the resistance. These irregularities could appear because of artefacts, and they could also visually appear within the display in the time course view. Flattening of the flow and volume curve, in addition to the suppression of the oscillation amplitude and a large fluctuation in the resonance and reactance, could represent **swallowing** or **tongue blockage** artefacts. However, a **leak** is represented by a flattened volume curve, and resistance and reactance are near zero. **Speaking** is displayed as irregular breathing pattern, with negative resistance values and random excursion in the resistance and reactance with noisy expiration. A large change in the resistance, reactance, volume, and flow readings is probably a reflection of a **coughing** artefact (Figure 3.27)
Measurements validation	The software either issues a warning or excludes the measurements directly. The measurement will typically be automatically excluded if the minimum duration of less than 6 seconds is not met. However, the measurements are not excluded automatically in case of invalid percentages, valid percentages of ≥70% of the portion of valid data among all the frequencies, and with poor coherence of less than 0.6. Coherence was calculated to assure the stability between the different data and the waveform.
Test validation	The test was validated by three valid measurements and a coefficient of variation of ≤15%, as per the ERS guidelines measured after the exclusion of the outlier's measurements (117).

Figure 3.27: Artefacts



3.4.5.3 Acceptable and replicate measures

It is crucial to develop acceptability criteria for the test. Testing acceptability could be confirmed by visual inspection of the traces during the test; this is essential to capture replicates of three artefact-free breaths (107).

In children, it is recommended by King et al. to take the mean of three acceptable measures with no artefacts. All measurements with artefacts must be removed before the calculation of the mean. A coefficient of variation of 15% is recommended for the replicated measurements; any outliers must be excluded from the calculation of the mean (107).

Any negative resistance values must be excluded because this physiologically impossible and is likely the result of an artefact, such as cough. Impedance values could be affected by the presence of a leak. Special consideration was given to the flow time and volume time traces that would provide an identification of common artefacts while performing the test (107). According to Alblooshi et al., the reactance is negative at low frequencies and becomes positive at higher frequencies, and the resistance decreases as the frequency increases (168).

Acceptability and exclusion criteria developed for the study:

All tests and traces were reviewed individually. They were visually inspected and assessed for acceptability as follows:

1- Test duration of 20 seconds for each trial
2- If any inconsistent breathing or artefacts were noticed during the performance of the test or upon observation of the traces, the trial was rejected
3- Three acceptable replicates were required to calculate the mean
4- Coherence (calculated by the machine) of more than 90%
5- Coefficient of variation of less than or equal to 15%
6- Positive resistance values, with resistance decreasing as frequency increased
7- Reactance negative at low frequencies and becoming positive at higher frequencies

(Figure 3.28 and Figure 3.29 depict examples of acceptable and unacceptable traces, respectively)

If any of the criteria above were not met, the test was rejected. This was applied for all measurements collected at both 5–37 Hz and 7–41 Hz for all participants. For healthy children, baseline measurements were reviewed. In children with asthma, measurements both before and after the bronchodilator administration were assessed. Traces about which the author was uncertain were reviewed in collaboration with the clinical science director of Thorasys.

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Figure 3.28: Acceptable measurements and traces of forced oscillation technique

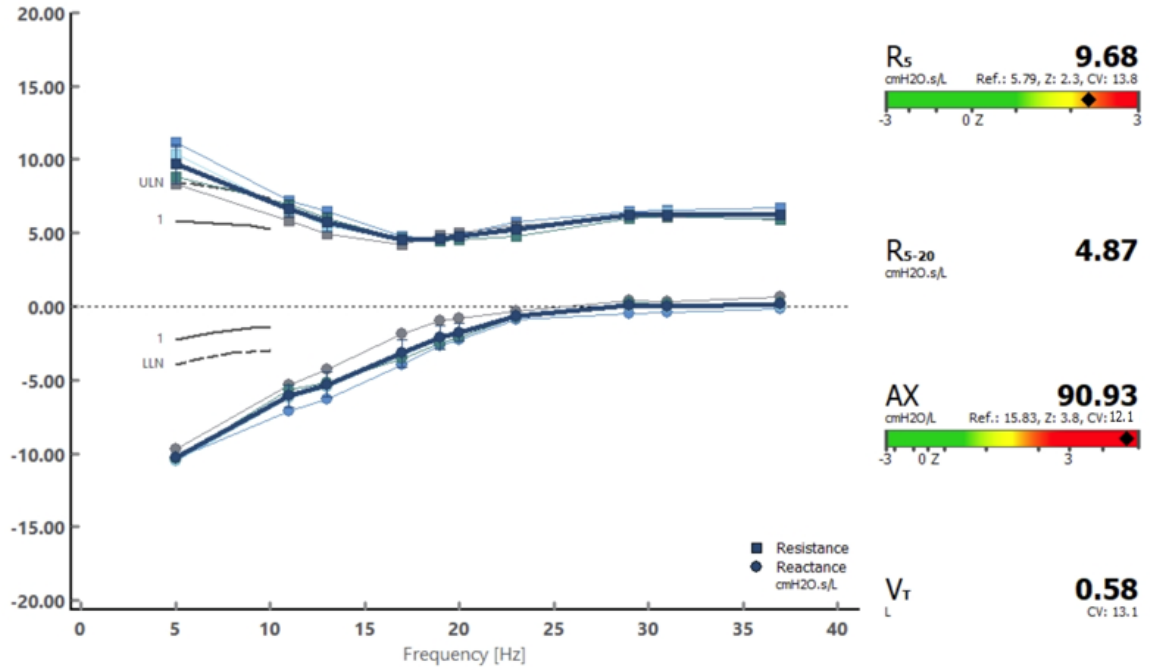
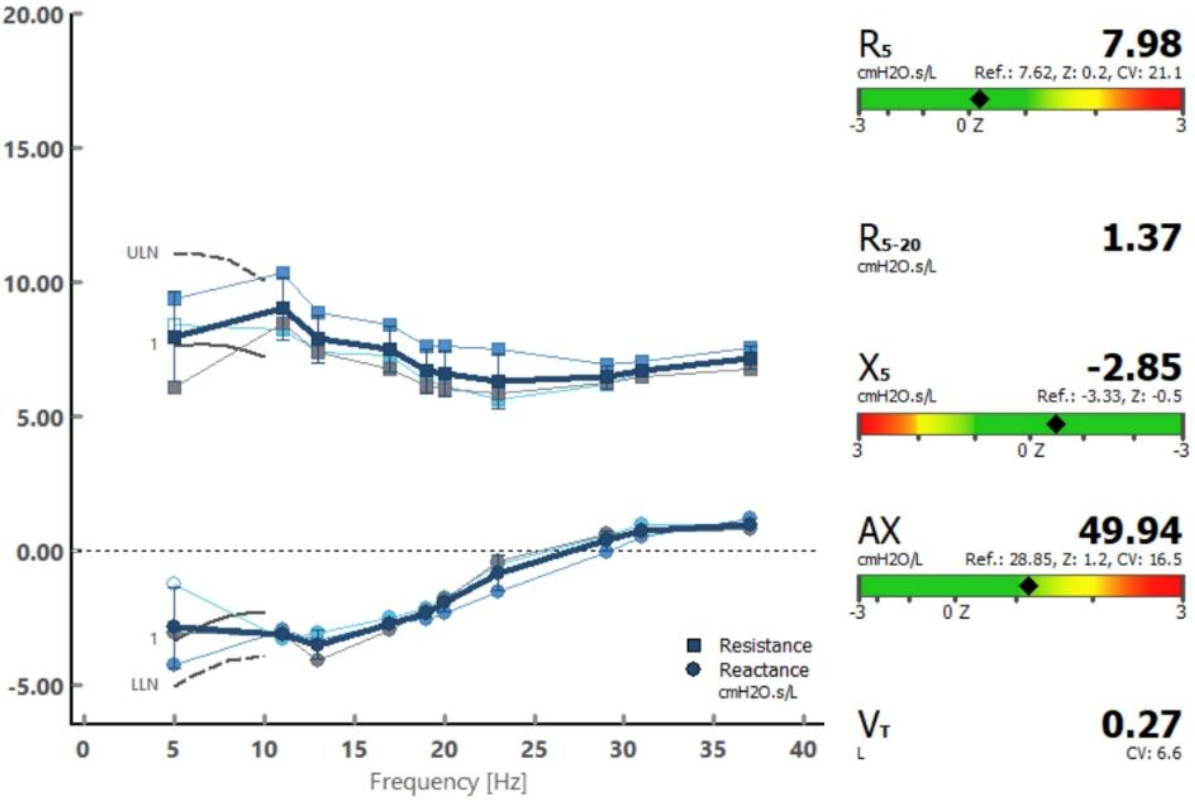


Figure 3.29: Unacceptable measurements and traces of forced oscillation technique



3.5 General testing consideration

3.5.1 Guidelines

To maintain standardisation, all the measurements were performed according to the European Respiratory Society and the American Thoracic Society (ERS/ATS) guidelines and specific task forces (117). Calibration was performed daily to maintain the accuracy of the measurements in consideration of the ambient and pressure adjustments. The operator maintained close supervision of the participants while performing the test, and the opinion of a second reviewer was sought when necessary.

3.6 Statistical methods

3.6.1 Samples sizes

Power calculations were initially conducted to identify the appropriate sample size needed to determine whether FOT is appropriate for the diagnosis and monitoring of children with asthma.

A total of 146 children needed be recruited into the study, comprising:

- 86 children with stable asthma, acute asthma and uncontrolled asthma, recruited from University Hospitals of Leicester (UHL) paediatric asthma clinics, UHL children's wards or children's Emergency Department
- 60 control children

Kreetapirom et al. reported a 32% difference in mean Rrs5 between cohorts of children with controlled and uncontrolled asthma (169). Based on published data, we expect about half the uncontrolled children to become controlled after asthma education and using electronic monitoring with appropriate feed-back (170).

Based on these data, a sample size of 86 participants aged 5–16 years (72 + 20% inflation for loss to follow-up, unusable FOT data, etc.) was calculated to be sufficient to detect a clinically meaningful 20% difference between the Rrs5 of children who become controlled from baseline and the Rrs5 of children who remained uncontrolled, with power of 80% and two sided significance level of 5%.

We will compare FOT data from healthy controls with that obtained from asthma patients. There is little data available from the Tremoflo device in healthy children. Children with stable asthma often have spirometry results that are similar to those of healthy controls. This

comparison will establish whether children with stable asthma have similar airway resistance and reactance to healthy controls.

3.6.2 Statistical analysis

The statistical analyses within this thesis were performed using Statistical Package for the Social Sciences (SPSS, IBM SPSS Statistics 26) and (GraphPad Prism, GraphPad Prism 9). Further detailed statistical analysis description and the study population will be provided in the coming chapters.

CHAPTER 4 DIAGNOSIS OF ASTHMA IN CHILDREN AGED 5 TO 18 YEARS USING THE FORCED OSCILLATION TECHNIQUE: A SYSTEMATIC REVIEW

4.1 Abstract

Background: The diagnosis of asthma in children is often difficult. Studies have evaluated the use of impulse oscillometry (IOS)/forced oscillation technique (FOT) for the diagnosis of asthma in children. We aimed to determine the diagnostic accuracy of FOT in children with asthma using spirometry with bronchodilator reversibility as a comparator.

Method: A systematic review of the literature on the diagnostic accuracy of FOT in children with asthma aged 5–18 years was performed. The Ovid MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO, Elsevier's Scopus, Web of Science and Cochrane Library databases were searched. Quality assessment was performed by two independent reviewers using the QUADAS-2 tool. The sensitivity and specificity of FOT resistance and reactance was reported from the studies.

Results: Three case-control studies of children with asthma and healthy controls were eligible to be included, for a total of 447 participants with and without asthma. The systematic review showed that IOS/FOT measurements can discriminate between children with asthma and healthy children. A meta-analysis was not feasible with the available data.

Discussion: The results of the included studies suggested that IOS/FOT may be useful to distinguish between children with asthma and healthy children. However, this systematic review was limited by the small number of studies and study participants. In addition, there were inconsistencies in some reported measures at different frequencies. Further, there were different ages, ethnicities and asthma severities in each group within these studies, which could lead to bias in the data interpretation. Further work is required to assess the usefulness of the FOT in the monitoring and diagnosing of asthma in children in the clinical setting.

PROSPERO registration number: CRD42021231843

4.2 Introduction

Asthma is one of the most common diseases affecting children (171). It is a heterogeneous disease that varies from patient to patient and within the same patient over time (172,173). Though the diagnosis of asthma depends on the clinical findings, it is crucial to also have objective evidence, including bronchodilator reversibility (BDR) testing, to support the diagnosis (172). However, due to the variable nature of asthma and the difficulty of performing some of the recommended objective tests in children, diagnosing asthma in children is challenging (174,175).

Spirometry and BDR are used as objective tests to confirm the diagnosis of asthma (23). Performing spirometry, especially in young children, can be difficult because the tests require cooperation from the child performing the expiratory manoeuvres (157). Impulse oscillometry (IOS) and the forced oscillation technique (FOT) are lung function tests that can be used in younger children because these tests are effort-independent and only require passive breathing (91,114). FOT measures the resistance and reactance of the airways (96), and measurements of the resistance and reactance at different frequencies are used to reflect the airway mechanics. For instance, the resistance at 5 Hz (Rrs5) reflects the total airway resistance, the resistance at 20 Hz (Rrs20) indicates the resistance of the large airway, and the difference between these two resistances (Rrs5-20) reflects the resistance of the small airways. In addition, the reactance (Xrs) provides information about the peripheral airways, as it reflects the capacitive properties of the small airways (91,176). The area under the curve (AX) represents the reactance at all the frequencies in which the elastic properties are mainly reflected by the capacitance. Both Xrs and AX are considered informative measures reflecting the properties of the peripheral airways (91).

Several studies have shown that IOS/FOT may be more sensitive than spirometry for the diagnosis of asthma or could serve as an additional tool to confirm the diagnosis of asthma in children attending the pulmonary clinic (122,148).In this systematic review, we aimed to study the role of the FOT in the diagnosis of asthma in children and to assess the sensitivity and specificity of FOT resistance and reactance measures (Rrs, Xrs, AX and the resonant frequency [Fres]) in identifying children with asthma. We also compared these FOT parameters to spirometry and BDR in school-aged children with asthma.

4.3 Methods

4.3.1 Eligibility criteria

Inclusion criteria: Studies that were relevant to the main objective of the systematic review were included. These studies included randomised controlled trials, observational studies and case-control studies that compared FOT with spirometry and BDR tests to detect asthma in school-aged children. Only studies published in the English language or translated into English were included. Studies of children aged 5–18 years with wheeze or asthma were included if they contained a clear definition of the disease that was based on clinical diagnosis or guidelines and used the objective reference tests spirometry and BDR testing. Studies included FOT measurements of resistance and reactance that were compared to spirometry and BDR.

Exclusion criteria: Studies of populations with another respiratory disease; non-original research studies such as reviews, editorials, or case reports; studies with no control group; and studies with populations predominantly aged less than 5 years or more than 18 years were excluded. Finally, studies with insufficient data to calculate the sensitivity and specificity of relevant FOT parameters were also excluded.

4.3.2 Technique used

Impulse oscillometry (IOS) and forced oscillation techniques (FOT) were used in the included studies to assess airway mechanics (110,111,177). IOS measures both resistance and reactance of the airways by applying small pressure oscillations at the mouth that are transmitted to the airways throughout passive breathing and allow the evaluation of airflow limitation (110,111). In one study, FOT was used to measure respiratory function by two techniques referred to as standard generator (SG) and head generator (HG) (177). In the SG technique, the oscillation was applied around the mouth using a loudspeaker to generate excitation signals; such signals commonly consist of pseudorandom noise (177,178). When using this technique, the upper airway shunt could affect impedance values, especially at high frequency, which may result in underestimation of the airway obstruction (87,177). In the HG technique the oscillation is applied around the head. This helps to minimise artefacts as it cancels the transmural pressure across the upper airways to minimise the upper airway shunts (87,177).

4.3.3 Outcomes

The main objective of the review was to study the accuracy (sensitivity and specificity) of the FOT parameters of resistance and reactance (Rrs, Xrs, Fres and AX) in the diagnosis of asthma

in children aged 5 to 18 years. The secondary objective was to compare the diagnostic accuracy of FOT parameters to that of spirometry and BDR.

4.3.4 Search strategy

A literature search was carried out in the following databases: Ovid MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO, Elsevier's Scopus, the Web of Science database and the Cochrane Library database. Searches were restricted to the English language. The search terms included: "forced oscillation*", "impulse oscillometry*", FOT, IOS, "respiratory resistance", "airway resistance", "respiratory impedance", "respiratory reactance", "airway impedance", "airway reactance", "peripheral airway*", "peripheral lung*", "small airway*", "distal airway*", "distal lung*", asthma*, wheez*, bronchoconstriction, "bronchial spasm", bronchospasm, "pulmonary function", "respiratory function", "lung function", spirometry, spiromet*, BDR, bronchodilation*, "bronchodilator*, "bronchodilator response*", "airway reversibility" and "reversibility test".

The following search strategy was used: 1- "forced oscillation*"OR "impulse oscillometry*" OR FOT OR IOS OR "respiratory resistance" OR "airway resistance" OR "respiratory impedance" OR "respiratory reactance", "airway impedance" OR "Airway reactance"; 2- "peripheral airway*" OR "peripheral lung*" OR "small airway*" OR "distal airway*" OR "distal lung*" OR asthma* OR wheez* OR bronchoconstriction OR "bronchial spasm" OR bronchospasm; 3- "pulmonary function" OR "respiratory function" OR "lung function" OR spirometry OR spiromet*; 4- BDR OR bronchodilation* OR bronchodilator* OR "bronchodilator response*" OR "airway reversibility" OR "reversibility test"; 5- 1 AND 2 AND 3 AND 4. A limit to studies of children and adolescents or all children (0–18 years) was applied via check box options in Ovid, EBSCO and Scopus. Since this was not applicable in Web of Science and Cochrane, additional keywords were used to apply this limit: child*, children, "school age" and "adolescent*".
A detailed search strategy for each database is included in Appendix H.

4.3.5 Study selection and data extraction

Titles and abstracts were screened and reviewed by the two reviewers (including myself) to assess the eligibility of the study according to the inclusion and exclusion criteria listed above. Ten percent of the titles and abstracts were reviewed by the two supervisors to check for consistency. All data were recorded in an Excel spreadsheet that was used during the review

process and to de-duplicate references both via RefWorks and manually. The two main reviewers (my colleague and I) checked all the relevant studies independently to assess the quality of the studies.

Data were extracted from the three studies included in the review. Information extracted included study design and methodology, patients' demographics, baseline characteristics, diagnostic details, and all reported patient-important outcomes, all of which were collected using a customised electronic data extraction form through the Covidence website. The data extraction form was assessed by the reviewers. If there was missing data or additional detail was required, authors were contacted through email. An Excel spreadsheet was used to record data and decisions.

4.3.6 Risk of bias assessment

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was used to evaluate the methodological quality of the selected research articles (Table 4.1) (179). Three studies received the quality assessment. This was undertaken by two separate reviewers (my colleague and I). Where there was disagreement, a third reviewer served as an arbitrator.

4.3.7 Statistical analysis

This is a systematic review without a meta-analysis due to the heterogeneity of the data. The methodological characteristics, population and intervention were extracted from each study. In addition, the statistical data were reported from each study separately. The results from each study were summarised, followed by a cross-evaluation of the results across the studies with consideration to the populations, interventions and reported outcomes.

Table 4.1: Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Description	Describe methods of patient selection Describe included patients (previous testing, presentation, intended use of index test, and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 × 2 table (refer to flow diagram) Describe the interval and any interventions between index tests and the reference standard
Signaling questions (yes, no, or unclear)	Was a consecutive or random sample of patients enrolled? Was a case–control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it prespecified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?
Risk of bias (high, low, or unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns about applicability (high, low, or unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or its interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM, QUADAS-2 Group*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine. 2011 Oct 18;155(8):529-36.

4.4 Results

4.4.1 Study selection

A total of 421 abstracts and titles were screened, as presented in the PRISMA flow diagram (Figure 4.1). Of the 421 articles, 315 remained after removing the duplicated articles. Thirty-three articles were included in the full text review based on the inclusion criteria for the abstracts. Of these, three case-control studies were selected for this systematic review (110,111,177). The other 30 articles were excluded for the reasons shown in Figure 4.1. Eleven studies included insufficient or no data to allow the calculation of the sensitivity and specificity of FOT. Four studies focused on an adult population and two studies included predominantly preschool-aged children. For three studies, participants under 5 years or more than 18 years of age were included, and the results for the intended age group of 5–18 years were not separately presented in the study. We were unable to obtain the full text articles for three studies either because the abstract was available, but not the published article, or the abstract was in the English language, but the full text was in another languages. Two studies had a different study aim than asthma diagnosis. Two studies included no clear definition of asthma, or the

investigators studied different diseases. Two studies did not use FOT or IOS techniques. One study did not include a control group.(86,114,119-122,124,125,135,140,147,148,151,159,180-195).

4.4.2 Study characteristics

The selected studies included a total of 447 participants aged 3 to 18 years. Study summaries are shown in Tables 4.2, 4.3 and 4.4.

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Figure 4.1: PRISMA flow diagram of search results and study selection

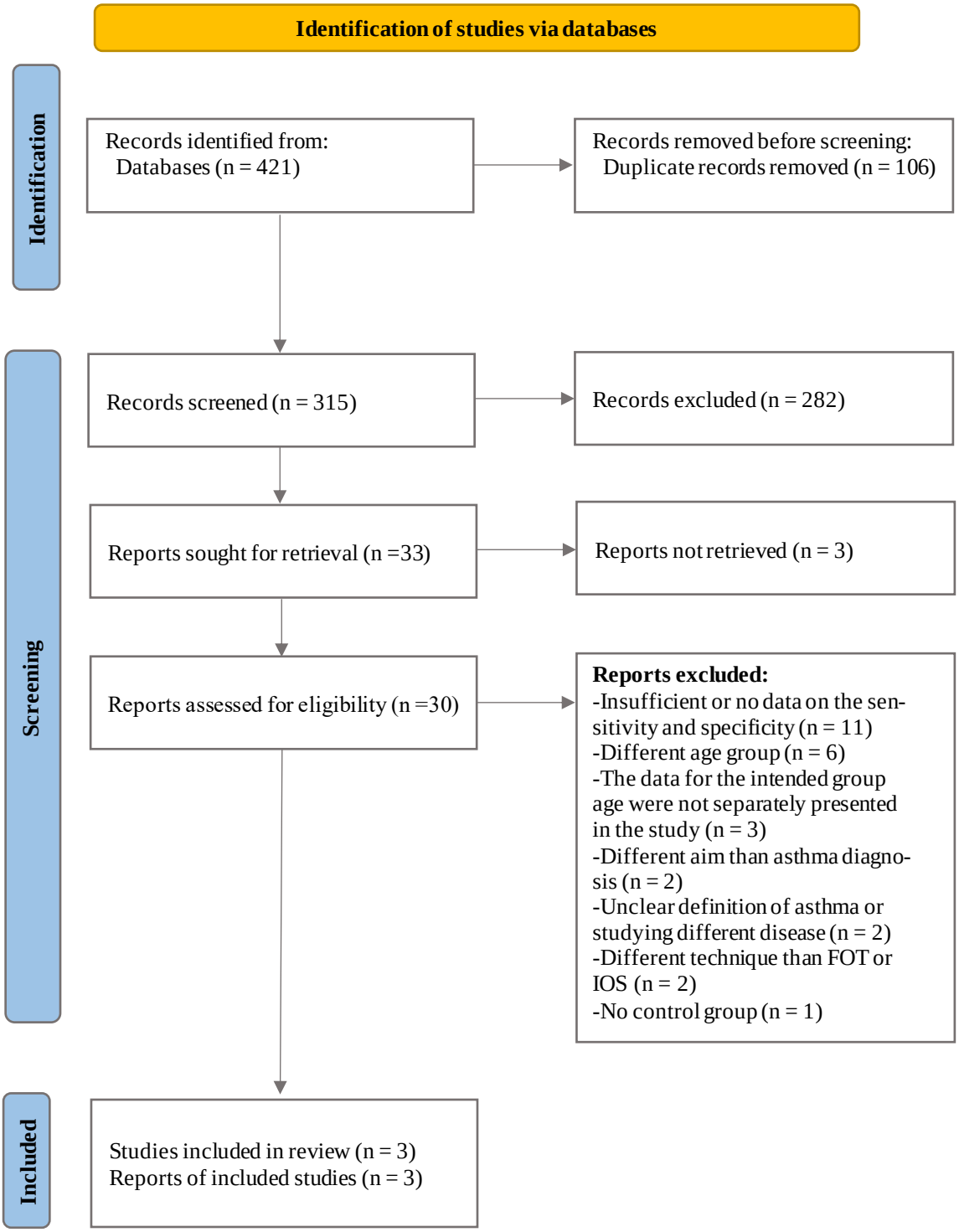

Table 4.2:Participant characteristics of the included studies on the accuracy of impulse oscillometry and the forced oscillation in the diagnosis of asthma

	Sample number		Age (years) Mean (SD)		Height (cm) Mean (SD)		Weight (Kg) Mean (SD)	
	Asthma group	**Control group**	**Asthma group**	**Control group**	**Asthma group**	**Control group**	**Asthma group**	**Control group**
Komarow 2012	88* (50 male)	29** (16 male)	3–18 7.7 (±3.6)	3–17 7.3 (±4.2)	126.4 (±19.9)	126.8 (±25.5)	33.9 (±27.2)	30.4 (±16.9)
Batmaz 2015	35 acute asthma exacer-bation (17 male) 107 stable asthma (58 male)	103 (55 male)	Acute Asthma 10.28 (±2.53) 6–16 Stable asthma 10.57 (±2.5) 7–17	11.35 (±2.54) 7–17	Acute Asthma 144.68 (±13.88) Stable asthma 143.94 (±14.04)	146.78 (±14.63)	Acute Asthma 40.37 (±12.65) Stable asthma 40.64 (±16.11)	21-77
Ioan 2015	58 ‡ (36 male)	27‡‡ (12 male)	8.1 (±1.5)	7.9 (±1.7)	129 (±10)	131 (±13)	27 (±5)	28 (±8)

**66 performed spirometry; **16 performed spirometry; ‡ 57 and 55 had successful measurements for SG FOT and HG FOT, respectively; ‡‡ 22 and 23 had successful measurements for SG FOT and HG FOT, respectively*

Table 4.3: Study characteristics of the included studies on the accuracy of impulse oscillometry and the forced oscillation in the diagnosis of asthma

	Country	Population description	Setting	Asthma diagnosis	Treatments in group of children with asthma	Healthy control population
Komarow 2012	USA	All children who were referred to the paediatric allergy clinic	Paediatric allergy clinic	Children were included based on confirmation of the asthma diagnosis through history, physical examination, clinical manifestation, and physician diagnosis. The physician diagnosis was based on the NHBLI guidelines, only subset of the group had their diagnosis confirmed on lung functions of abnormal spirometry suggesting an airway obstruction and improvement of ≥12% following the bronchodilator administration	Of the 88 children with asthma: 32 (36.4%) use of inhaled corticosteroids 18 (20.5%) use of the leukotriene inhibitor 56 (64.1%) use short or long-acting beta 2 agonist	There was no difference in the mean of the height, age, gender and weight between the group of the healthy control and the group of asthma

Table 4.3 (Continued)

	Country	Population description	Setting	Asthma diagnosis	Treatments in group of children with asthma	Healthy control population
Batmaz 2015	Turkey	All children diagnosed with asthma and who came to the paediatric department	Department of paediatric	-Asthma diagnosis according to the National Heart, Lung and Blood Institute (NHLBI) guidelines -Asthma exacerbations were defined as an acute or subacute episode of progressively worsening of cough, shortness of breath, tachypnea, chest tightness, and wheezing, or some of these symptoms and findings on physical examination. -Well-controlled asthma according to the NHLBI was assigned for the stable asthma for at least three months	-Short acting beta 2 agonist was stopped 12 hours prior the test -None of children with asthma were on any medication at their presentation -If any of the children had taken any medication prior to the test, they were excluded -Nothing was reported regarding the use of the inhaled corticosteroids	There was no difference in the mean of the height, age, gender and weight between the group of the healthy control and the group of asthma

Table 4.3 (Continued)

	Country	Population description	Setting	Asthma diagnosis	Treatments in group of children with asthma	Healthy control population
Ioan 2015	France	Children attending paediatric pulmonary clinic	Paediatric pulmonary clinic	Asthma was confirmed in children with past medical history, positive skin prick test, the presentation of the one or more of the following: wheeze, cough, dyspnoea, and beneficial use of anti-asthma medication for the past year.	-The antileukotriene and the inhaled steroids were documented -Bronchodilations were stopped for 12 hours prior to the test -Nothing was reported regarding the use of the inhaled corticosteroids	There was no difference in the mean of the height, age and weight between the group of the healthy control and the group of asthma (62% male of the group of asthma and 44% male in the group of healthy control)

Table 4.4: Study description of the included studies on the accuracy of impulse oscillometry and the forced oscillation in the diagnosis of asthma

Study	Index and reference test	Type of the bron-chodilator used	Type of the device used for index test	Type of devise used for reference test	Values reported
Komarow 2012	Index test: IOS Reference test: Spirometry and BDR *Tests were done before and after bronchodilator administration*	Salbutamol (180 µg)	IOS system Master-Screen Impulse Oscil-lometry by CareFusion, Yorba Linda, CA, USA	Care Fusion, Yorba Linda, CA, USA	Absolute values
Batmaz 2015	Index test: IOS Reference test: Spirometry and BDR *Tests were done before and after bronchodilator administration*	Salbutamol (200 µg)	MasterScreen Impulse Oscillometry System, Jaeger Co., Würzburg, Germany	Master Screen Spirometry System, Jaeger Co., Würzburg, Germany	Absolute values

Table 4.4 (Continued)

Study	Index and reference test	Type of the bron-chodilator used	Type of the device used for index test	Type of devise used for reference test	Values reported
Ioan 2015	Index test: Standard generator FOT (SG) Head generator FOT (HG) Reference test: Spirometry and BDR *Tests were done before and after bronchodilator administration*	Salbutamol (200 µg)	Pulmosfor, SEFAM, France	Masterscope Erich Jaeger GmbH, Würzburg, Germany	Absolute values

4.4.3 Population selection and recruitment setting

The children in these studies were recruited from paediatric allergy clinics and paediatric respiratory departments. However, there was no clear information about how participants were invited to join the studies. All participants were included according to the inclusion criteria of children with the confirmation of asthma diagnosis through history, physical examination, clinical manifestation, physician diagnosis or asthma diagnosis according to the National Heart, Lung, and Blood Institute (NHLBI) guidelines (173). In addition to the group of children with asthma, a group of healthy children were included in each study, which allowed a comparison of the spirometry and FOT/IOS data between the two groups and calculation of both sensitivity and specificity of the FOT/IOS measurements of the resistance and reactance, as well as the spirometry flow and volume measures.

4.4.4 Index and reference tests

The index test was the IOS or FOT test, with a reference to spirometry with the use of bronchodilator. Both the IOS and spirometry tests were performed at baseline and after the administration of a bronchodilator. A clear, detailed description of the instructions to perform both tests following specific guidelines was provided in the three studies (87,117), which allowed high standards for the test procedure to be maintained.

4.4.5 Reference standard

In the included studies, spirometry with bronchodilator reversibility was the reference standard. In one study, it was clearly stated that the spirometry was performed by one trained research nurse. However, no description of who performed the test was found in the other two studies.

4.4.6 Comparison of test accuracy

Asthma diagnosis in the children included in these studies was based on the International Study of Asthma and Allergies in Childhood, ISAAC-based questionnaire data, clinical history and allergy testing using either skin prick testing or RAST testing according to the National Heart, Lung, and Blood Institute NHBLI guidelines (173,196). A history of positive episodes of cough, wheeze and the use of asthma controller medication was considered to aid the diagnosis of asthma. The comparator groups included age-matched healthy children with no history of respiratory problems.

4.4.7 Risk of bias

The risk of bias in the three studies was assessed using the QUADAS-2 evaluation tool (179). The QUADAS-2 tool contains four main domains composed several questions to assess the quality of the study. Figure 4.2 and Table 4.5 present the quality assessment for the three studies that were included in this systematic review.

Figure 4.2: QUADAS-2 tool for assessing methodological quality and risk of bias of the included studies

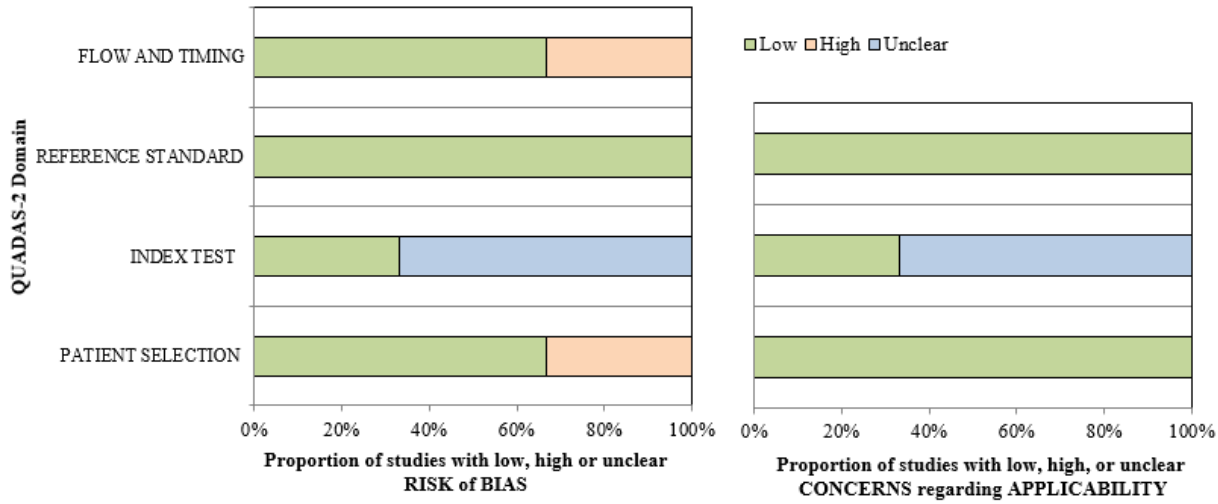

Table 4.5:Risk of bias and applicability concerns assessed by the reviewers for the included studies

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Komarow 2012	☹	☺	☺	☹	☺	☺	☺
Batmaz 2015	☺	?	☺	☺	☺	?	☺
Ioan 2015	☺	?	☺	☺	☺	?	☺

☺Low Risk ☹High Risk ? Unclear Risk

4.4.8 Quantitative data assessment

The studies were mainly assessed for the reported sensitivity and specificity of FOT resistance and reactance. In addition to determining the area under the curve (AUC) of the receiver operating characteristic (ROC) curve, cut-off points were adopted for the definition of asthma and the area under the ROC curves of spirometry and IOS/FOT measurements, while cut-off points

for BDR test were based on the percentage of change after bronchodilator administration and the area under the ROC curves of spirometry and IOS/FOT measurements, with the Youden index when applicable. The positive and negative likelihood ratios were calculated manually as required for the IOS/FOT and spirometry measurements in each study.

4.4.9 Methodological quality

Most of the studies had a clear description of the number of participants and the category of asthma. Nothing was mentioned about the number of or reasons for withdrawals in any of the studies. A customised quality of reporting assessment was performed in addition to the risk of bias assessment (Table 4.6). These studies were designed to make clinical recommendations; it is therefore important to assess the quality of these studies in order to establish the strength of the recommendations. The quality of data reporting and the effect of performing the FOT/IOS before or after the spirometry in the included studies in respect to both reference and index tests was considered in addition to other criteria that were not clearly seen in the QUADAS-2 tool.

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Table 4.6: Quality reporting of the included studies

Criteria	Komarow 2012	Batmaz 2015	Ioan 2015
Clear description of the recruitment	Y	Y	Y
Clear description of the participants	Y	Y	Y
Clear description of withdrawals	N	N	N
Participant flow diagram	N	N	N
Standard diagnostic criteria	Y	Y	Y
Index test performance following guidelines	Y	Y	Y
Reference test performance following guidelines	Y	Y	Y
The order effect was considered*	Y	Y	Y
All participants performed spirometry	N	Y	N
Clinical data available representative of routine practice	Y	Y	U

**FOT/IOS was performed before the spirometry*
Y=yes, N=No, U=Unclear

4.4.10 Assessing measurements of impulse oscillometry and spirometry before and after the administration of bronchodilator

Baseline measurements and bronchodilator response for spirometry and IOS/FOT shown in Table 4.7. Sensitivity, specificity and positive and negative likelihood ratios are presented in Table 4.8. A summary of the cut-off values of the percent change following the bronchodilator administration is shown in Table 4.9. In addition, the AUC of the ROC curve/Youden index for the IOS/FOT and spirometry measurements are presented in Table 4.9. (Likelihood ratios were calculated manually)

In the study by Komarow, there was no significant difference observed between the baseline measurement for either spirometry or IOS between the groups with and without asthma. However, there were significant changes in the R5, R10, X5 and AX following the bronchodilator administration in the in children with asthma compared to children without asthma, whereas none of the spirometry indices showed a significant change after the administration of

bronchodilator. According to the ROC curve, the R10 cut-off point of −8.6% presented the best profile of sensitivity (77%) and specificity (76%) to discriminate between children with asthma and healthy children. This was followed by the AX, which had a sensitivity and specificity of 67% and 69%, respectively, for the cut-off point of −29.1% to correctly diagnose children with asthma. However, comparing the percent change between the spirometry and IOS measurements between children with and without asthma revealed that changes in the response to the bronchodilator administration was significant for the AX ($p = 0.0092$), but not for any of the spirometry measurements. Based on the ROC cut-off points, sensitivity and specificity in the study by Komarow et al., IOS was a better tool than spirometry to identify children with asthma and healthy children (111).

In the study by Batmaz et al., all the baseline measurements for spirometry, as well as the R5, R5-20, X5, X10, X5, Fres and AX of the IOS, were able to discriminate between the studied groups of children with acute asthma, children with stable asthma and healthy children. Notably, the highest AUC was seen with the AX. The sensitivity and specificity of the AX cut-off point to discriminate between the children with acute asthma and stable asthma were 85% and 79.2%, respectively. In addition, a 79.3% sensitivity with 83.1% specificity to differentiate between children with stable asthma and healthy children was observed. However, the mean values of the forced expiratory volume in 1 second (FEV_1), R5, R10, Fres and AX following bronchodilator administration were able to differentiate between the studied groups. The highest AUC cut-off values (≤−39.05% change in the BDR test) were seen for ΔAX, which had a sensitivity of 72.3% and a specificity of 56.7%. Thus, the AX parameter of the IOS was found to be useful to differentiate between children with acute asthma, children with stable asthma and healthy children (110).

In the third study by Ioan, spirometry, FOT using the standard generator (SG) and FOT using the head generator (HG) were studied for their diagnostic values in asthma. The Rrs at baseline using the HG was the most discriminative measure to differentiate between children with asthma and healthy children. An indicator of the response to the bronchodilator administration, ΔRrs, was significantly different between children with asthma and the healthy control with HG, with no significant difference noticed using the SG. However, the Xrs had a very minimal difference between the children with asthma and healthy children at baseline; similarly, this was noticed with the Xrs response to bronchodilator. Nonetheless, the diagnostic values of the Xrs at baseline and following the bronchodilator administrator were greater with the SG than the HG. In the separation of children with asthma and healthy children, the highest Youden

index values for the bronchodilator response were seen for both the forced expiratory volume in 0.5 second ($FEV_{0.5}$) from spirometry and the Rrs of the FOT using the HG (177).

In all three studies, there was correlation between the spirometry and IOS measurements. However, the IOS/FOT measurements more clearly differentiated between children with asthma and healthy children.

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Table 4.7: Baseline measurements and bronchodilator response for spirometry and impulse oscillometry/forced oscillation technique

	Study groups				Study groups		
Komarow 2012	**Asthma**		**Healthy**		**Asthma**		**Healthy**
Baseline measurements				**Bronchodilator response**			
n (Spirometry)	**66**		**16**	**n (Spirometry)**	**66**		**16**
FEV_1 (%)	91.3 (23.9)		88.9 (15.2)	**Δ FEV_1 (%)**	6.1 (10.2)		4.2 (6.9)
FVC	2.3 (0.9)		2.3 (1.0)	**Δ FVC (%)**	2.7 (7.3)		3.2 (5.8)
FEV_1/FVC	80.6 (9.9)		87.4 (8.1)	**Δ FEV_1/FVC (%)**	4.9 (8.0)		1.7 (8.2)
n (IOS)	**66**		**16**	**n (IOS)**	**66**		**16**
R5 (cmH_2O/L/sec)	104.1 (26.0)		100.3 (18.6)	**Δ R5 (%)**	− 15.6 (12.1)		−10.6 (11.1)
R10 (cmH_2O/L/sec)	96.0 (23.8)		95.5 (15.1)	**Δ R10 (%)**	− 15.4 (10.4)		−10.7 (11.2)
R20 (cmH_2O/L/sec)	94.7 (23.5)		90.0 (18.0)	**Δ R20 (%)**	− 9.6 (12.5)		−10.0 (14.0)
X5 (cmH_2O/L/sec)	117.6 (53.0)		123.6 (41.1)	**Δ X5 (%)**	− 16.5 (24.6)		− 7.4 (20.5)
AX (cmH_2O/L)	126.8 (80.0)		131.7 (44.2)	**Δ AX (%)**	− 37.0 (20.9)		−18.5 (23.5)
Batmaz 2015	**Acute asthma**	**Stable asthma**	**Healthy**		**Acute asthma**	**Stable asthma**	**Healthy**
Baseline measurements				**Bronchodilator response**			
n (Spirometry)	**35**	**107**	**103**	**n (Spirometry)**	**35**	**107**	**103**
FEV_1 (%)	83.5 (19.5)	95.7 (13.2)	105.9 (13.9)	**Δ FEV_1 (%)**	13.20 (7.96)	7.15 (7.17)	5.21 (6.04)
FEV_1/FVC	72.51 (10.45)	80.53 (7.99)	87.58 (8.75)	**Δ FEV_1/FVC**	8.38 (9.9)	5.79 (5.55)	4.53 (8.51)
MMEF (%)	52.3 (28.4)	70.6 (24.5)	100.7 (27.9)	**Δ MMEF (%)**	33.49 (24.36)	27.49 (26.89)	24.69 (31.35)
n (IOS)	**35**	**107**	**103**	**n (IOS)**	**35**	**107**	**103**
R5 ($kPaL^{-1}s$)	0.86 (0.24)	0.74 (0.22)	0.67 (0.19)	**Δ R5 (%)**	−19.66 (14.31)	−17.45 (10.77)	−15.40 (12.28)
R10 ($kPaL^{-1}s$)	0.68 (0.27)	0.61 (0.17)	0.55 (0.16)	**Δ R10 (%)**	−16.55 (17.94)	−13.68 (11.67)	−9.12 (19.55)
R15 ($kPaL^{-1}s$)	0.56 (0.15)	0.57 (0.15)	0.49 (0.14)	**Δ R15 (%)**	−11.92 (17.84)	−8.02 (36.25)	−11.6 (12.93)
R20 ($kPaL^{-1}s$)	0.51 (0.15)	0.56 (0.15)	0.46 (0.12)	**Δ R20 (%)**	−14.55 (28.82)	−11.16 (10.7)	−9.07 (13.16)

Table 4.7 (Continued)

Batmaz 2015	**Acute asthma**	**Stable asthma**	**Healthy**		**Acute asthma**	**Stable asthma**	**Healthy**
Baseline measurements				**Bronchodilator response**			
R5-20 (kPaL^{-1}s)	0.35 (0.18)	0.24 (0.10)	0.18 (0.11)	**Δ R5-20 (%)**	−31.00 (25.54)	−35.86 (52.13)	−29.12 (56.7)
X5 (kPaL^{-1}s)	− 0.29 (0.15)	−0.22 (0.09)	−0.19 (0.1)	**Δ X5 (%)**	−20.66 (30.65)	−18.05 (36.45)	−25.86 (47.88)
X10 (kPaL^{-1}s)	−0.2 (0.12)	−0.11 (0.07)	−0.08 (0.18)	**Δ X10 (%)**	−23.39 (57.55)	−43.67 (55.38)	−34.97 (70.47)
X15 (kPaL^{-1}s)	−0.15 (0.09)	−0.09 (0.07)	−0.06 (0.07)	**Δ X15 (%)**	−46.3 (47.68)	−32.2 (24.87)	−18.85 (134.2)
X20 (kPaL^{-1}s)	0.01 (0.07)	−0.01 (0.6)	−0.2 (0.6)	**Δ X20 (%)**	−46.91 (31.65)	−77.06 (44.9)	25.68 (43.61)
Fres (Hz)	23.94 (6.14)	18.87 (5.88)	15.13 (5.72)	**Δ Fres (%)**	−18.91 (21.49)	−13.10 (31.64)	−11.64 (15.64)
AX (kPa/L)	2.16 (2.02)	1.79 (1.25)	1.23 (1.02)	**Δ AX (%)**	− 47.32 (26.01)	−42.82 (24.81)	−37.87 (45.81)
	Study groups					**Study groups**	
Ioan 2015	**Asthma**		**Healthy**		**Asthma**		**Healthy**
Baseline measurements				**Bronchodilator response**			
n (Spirometry)	**58**		**27**	**n (Spirometry)**	**57**		**26**
FVC (L)	2.0 (0.5)		2.0 (0.5)	-	-		-
FEV_1 (L)	1.7 (0.4)		1.8 (0.5)	**FEV_1(%)**	6.1 (8.5)		2.8 (5.3)
$FEV_{0.5}$ (L)	1.2 (0.3)		1.4 (0.4)	**$FEV_{0.5}$ (%)**	11.8 (10)		4.6 (6.0)
MMEF (L/S)	1.5 (0.5)		2.1 (0.7)	**MMEF (%)**	26 (26)		14 (15)
n (FOT-SG)	**57**		**22**	**n (FOT-SG)**	**53**		**21**
Rrs (hPa.s/L)	5.9 (1.4)		5.4 (1.3)	**Rrs (%)**	−13 (19)		− 11 (12)
Xrs (hPa.s/L)	− 1.0 (0.6)		−1.3 (0.6)	**Xrs (%)**	7 (10)		5 (5)
n (FOT-HG)	**55**		**23**	**n (FOT-HG)**	**53**		**21**
Rrs (hPa.s/L)	9.4 (3.4)		6.6 (1.8)	**Rrs (%)**	−25 (14)		−14 (12)
Xrs (hPa.s/L)	−0.02 (0.5)		0.1 (0.4)	**Xrs (%)**	2 (4)		1 (5)

Data presented as mean (SD) unless otherwise stated

Table 4.8: Diagnosis parameters of asthma for spirometry and impulse oscillometry/forced oscillation technique

		Spirometry					IOS/FOT			
		Sensitivity (%)	**Specificity (%)**	**Positive likelihood**	**Negative likelihood**		**Sensitivity (%)**	**Specificity (%)**	**Positive likelihood**	**Negative likelihood**
Komarow 2012	**FEV_1**	54	60	1.35	0.76	**R5**	73	66	2.15	0.41
	FVC	-	-	-	-	**R10**	77	76	3.20	0.30
	FEV_1/FVC	-	-	-	-	**R20**	62	65	1.77	0.58
						X5	59	69	1.90	0.59
						AX	67	69	2.16	0.47
Batmaz 2015	**FEV_1**	-	-	-	-	**R5**	47.7	75.6	1.95	0.69
	FEV_1/FVC	-	-	-	-	**R10**	47.7	73.9	1.83	0.71
	MMEF	-	-	-	-	**R15**	73.8	13.9	0.86	1.88
						R20	35.4	72.8	1.3	0.89
						R5-20	56.7	66.6	1.7	0.65
						X5	50	79.1	2.39	0.63
						X10	65.8	84.2	4.16	0.41
						X15	77.1	70.7	2.63	0.32
						X20	84.0	45.6	1.43	0.48
						Fres	52.3	68.9	1.68	0.69
						AX	72.3	56.7	1.67	0.49
Ioan 2015	**FEV_1**	44	85	2.93	0.66	**FOT–SG Rrs**	49	86	3.5	0.59
	$FEV_{0.5}$	50	96	12.5	0.52	**FOT-SG Xrs**	57	71	1.97	0.61
	MMEF	56	73	2.07	0.6	**FOT–HG Rrs**	79	65	2.26	0.32
						FOT-HG Xrs	62	50	1.24	0.76

Table 4.9: Cut-off points following bronchodilator administration (according to change as percentage) and area under the receiver operating characteristic curve of parameters of spirometry and impulse oscillometry/forced oscillation technique

	Spirometry			IOS/FOT		
		Cut -off	Area under ROC curve		Cut -off	Area under ROC curve
Komarow 2012	**FEV_1**	6.23	0.576	**R5**	− 11.24	0.650
	FVC	-	-	**R10**	− 8.58	0.662
	FEV_1/FVC	-	-	**R20**	− 5.91	-
				X5	− 18.15	0.658
				AX	− 29.11	0.641
Batmaz 2015	**FEV_1**	12	-	**R5**	≤− 22.34	0.599
	FEV_1/FVC	-	-	**R10**	≤− 22.81	0.564
	MMEF	-	-	**R15**	≤6.38	0.517
				R20	>− 2.7	0.507
				R5-20	≤16.9	0.509
				X5	≤− 33.85	0.658
				X10	≤18.7	0.567
				X15	≤− 23.1	0.502
				X20	≤11.81	0.578
				Fres	≤− 21.77	0.599
				AX	≤− 39.05	0.649
Ioan 2015	**FEV_1**	6	0.28*	**FOT –SG Rrs**	− 20	0.35*
	$FEV_{0.5}$	12	0.46*	**FOT- SG Xrs**	6	0.28*
	MMEF	20	0.29*	**FOT -HG Rrs**	− 13	0.44*
				FOT- HG Xrs	1	0.13*

**Maximal Youden index*

4.5 Discussion

4.5.1 General interpretation of the results based on previous studies

Using the sensitivity and specificity in addition to the AUC of the ROC in these studies was effective for describing the diagnostic accuracy of the clinical test (197). In this systematic review, the results provided evidence supporting the use of IOS/FOT to distinguish between children with asthma and healthy children. However, in one study, the values of the AUC were not described; thus, the interpretation was made based on the sensitivity, specificity and Youden index (110,111,177).

Correlations were observed between the spirometry and IOS/FOT measurements in children with asthma (110,177), which are supported by other studies that reported correlations between FOT and spirometry measurements in children (157,187,191). A study demonstrated a significant correlation between the resistance measurement at 8 Hz and the spirometry measures (FEV_1, FEV_1/FVC and $FEF_{25–75}$) in groups of children having a mean age of 11.6 years with moderate to severe asthma who attended the clinic (157). Others have shown a correlation between the FEV_1 and the impedance measurements at different frequencies of 5, 10, 20 and 35 Hz in groups of children with asthma aged 7–15 years (187). Though there was a satisfactory AUC value for the spirometry measures to discriminate between the children with asthma and healthy children following bronchodilator administration, as seen with the FEV_1 percent change (110), the IOS/FOT measures were even more discriminative in detecting asthma than the spirometry measures (110,111,177). In studies performed in preschool-aged children, studying the bronchodilator response for both spirometry and IOS at different frequencies ranges from 5 to 35 Hz, showed that IOS could statistically significantly discriminate between children with asthma and healthy children (105,114). However, no statistically significant finding was observed for the spirometry measurements (105,114), which suggests the superiority of IOS in differentiating between children with and without asthma based on the bronchodilator response (105,114). This was also proposed by Galant et al., who stated that IOS was superior to spirometry in determining asthma in children and predicting exacerbations and control loss (115). Thus, in children and adults with asthma, IOS could be used as an alternative or complement to spirometry (198).

In two of the studies, overall diagnostic accuracy was determined using the area under the ROC curve, and in the third, Youden's index was used. Reported areas under the curves (AUC) for FOT/IOS parameters ranged from 0.502 to 0.661 and Youden's index from 0.13 to 0.44. Most of the AUCs and Youden's indices were considered to be imperfectly discriminative diagnostic

measures, although higher AUC values and Youden's indices were reported for some of the FOT/IOS measures of the resistance and the area under the curve, which were found to effectively discriminate between children with asthma and healthy children. This was also supported by the higher sensitivities of these measures.

The most informative IOS/FOT measures were the resistance, the reactance at different frequencies and the area under the reactance curve (110,111,177). In particular, there was statistical significance value of the resistances at 5, 8, and 10 Hz and AX in discriminating between children with asthma and healthy children (110,111,177). This was compatible with previous studies showing the value of the resistance and the reactance at 5 and 10 Hz in differentiating between children with and without asthma (105,114). Though R5-15 and R5-20 have been reported to statistically significantly detect airway obstruction and assess asthma, this was not revealed in this systematic review as these measures were not addressed within two of the included studies (86,113,194). However, AX had great value in evaluating airways and differentiating between healthy children and adolescents and with asthma, a finding also supported by this review (86,113,194). A similar pattern of results was obtained in children aged 6–17 years, with AX being superior in differentiating asthma to all other IOS measures of resistance and reactance that were studied at frequencies of 5–20 Hz (86). Results directly aligning with the conclusion of AX superiority among IOS measurements using frequency wave forms of 5–35 Hz were also observed in children with small airway impairment (194). Moreover, AX was suggested to be a sensitive measure for reflecting airflow obstruction in adolescents with asthma (113).

4.5.2 Limitations of the review and the evidence included

The studies included in this systematic review differed in terms of the age groups, ethnicities, and asthma severities, which could lead to interpretation bias and influence the comparison of the studies. There were also differences in the methodologies, IOS/FOT and spirometry equipment, and frequency ranges of the oscillations. There could also be some limitations due to the methodological limitations in the included studies. For example, in one study, the performance of the spirometry was found to be more difficult in younger children, which may affect the accuracy of the testing. In addition, it was noticed in one of the studies that the number of the participants in some groups was lower than in the other group, which may influence some the statistical comparisons. Moreover, in one study, the measurements of IOS were performed at only a single frequency. In the same study, two different FOT methods were used, with

substantial division in the sample: the sample was divided for each FOT method used and for spirometry, and there was another subdivision of the sample for the bronchodilator reversibility testing (110,111,177).

4.5.3 Implication of the systematic review for practice, policy and future research

Findings from this systematic review suggest that IOS/FOT can be used to diagnose and assess the response to bronchodilator in children with asthma. Further studies with well-defined methodology, groups and number of participants are recommended to study the role of the FOT in the diagnosis of asthma in children aged 5–18 years. In future studies, special consideration should be given to including the recruitment criteria, exclusion criteria and information about the withdrawal of participants.

4.6 Other information

4.6.1 Registration

This systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021231843) and was conducted under the recommendations of PRISMA Transparent Reporting of Systematic Review and Meta-Analysis and reported following the PRISMA 2020 checklist.

CHAPTER 5 FORCED OSCILLATION TECHNIQUE IN HEALTHY CHILDREN

5.1 Introduction and rationale

Lung function testing is crucial in the diagnosis and evaluation of lung problems in children (199). These measurements of lung functions are vital in the assessment of disease prognosis, the effect of therapy and the severity of the abnormality.

In asthma, spirometry is a major component of diagnostic testing. However, it is difficult to perform the forced expiratory manoeuvre in younger children, which may limit the role of the spirometry (168). The forced oscillation technique (FOT) could be used to measure the respiratory properties and lung mechanics with minimal cooperation required of the participants (200).

Reference values from healthy children are crucial for the assessment of children with respiratory disease (199,201). Having a healthy control group from the same population as the studied group can improve the accuracy of the results (202). This was also recommended by the American Thoracic Society/ European Respiratory Society (ATS/ERS), which suggested using normal populations to generate reference values for respiratory measurements (117). Various studies in the field have reported reference values for the resistance and reactance of IOS/FOT at different frequency ranges with consideration of height, weight, age, gender, and ethnicity (88,123,131,133,143,199,200,203-206), since the interpretation of the lung function in clinical practice usually depends on the most important anthropometric factors, such as the height, age, weight, and gender (207). It is also important to report the race or ethnicity, as these characteristics may also affect the interpretation of the lung function (118). Reference equations in these studies varied according to the population included in the study and their characteristics, the protocol, the methodological approach, and the equipment used. Thus, all these factors should be considered during the interpretation of FOT measurements based on other reference prediction equations.

5.2 Aims

1- To investigate whether measurements of FOT in healthy children tested in a local population would match the reference data set of healthy children based on the pre-programmed predicted values in TremoFlo.

2- To study the correlation of the height, weight, age, and gender to the measurements of the FOT at 5–37 Hz and 7–41 Hz using TremoFlo in healthy children.

5.3 Hypotheses

1- In healthy children, the FOT measurements of resistance and reactance by TremoFlo using frequency waveforms at 5–37 Hz and 7–41 Hz (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20 and Xrs7) fall within the reference ranges of the pre-programmed predicted values dataset.

2- The FOT measurements of resistance and reactance using frequency waveforms at 5–37 Hz and 7–41 Hz (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz) correlate to the height, weight, and age in healthy children, with the highest correlation to the height.

5.4 Materials, Methods and Participants

5.4.1 Participants and study design

The participants in this study were children aged 5 to 15 years with no history of wheeze or respiratory problems who were recruited from the paediatric wards and non-respiratory outpatient clinics (such as surgical, dermatology, diabetes and other general or specialist non-respiratory clinics) at the Leicester Royal Infirmary. Information about the health condition of the participants was obtained through a questionnaire (Questionnaire on Breathing Problems in Children, Appendix F) that was provided to the parents of the participants to report the child's health condition, smoking history of the family and any previous respiratory problem to exclude the diagnosis of asthma. Informed consent from the parents and participants was also collected as part of the protocol.

5.4.2 Data collection and analysis

The FOT was performed until three tests had acceptable results (please refer to section 3.4.5.3 in chapter 3). Each test was performed at frequency ranges of 5–37 Hz and 7–41 Hz for 20 seconds each. Spirometry was not performed on all participants, as some declined to take this

test. All participants attempted FeNO testing, however, it was not successful for all participants. Impedance measurements of the forced oscillation were reflected as resistance at 5 Hz (Rrs5), resistance difference of 5–20 Hz (Rrs5-20), reactance at 5 Hz (Xrs5), reactance area using 5–37 Hz (AX using 5–37 Hz), resistance at 7 Hz (Rrs7), resistance difference of 7–20 Hz (Rrs7-20), reactance at 7 Hz (Xrs7) and reactance area using 7–41 Hz (AX using 7–41 Hz). Absolute values and Z-scores were recorded based on two references dataset by TremoFlo for the intended studied group (88,133) (Table 5.1). The best reference data set was retrieved automatically by the TremoFlo depending on the age, height, and weight of the participant. Spirometry measurements were taken, with indices of flow limitation and lung volumes reflected as the forced expiratory volume in 1 second ($FEV_{1)}$, forced vital capacity (FVC) and FEV_1/FVC absolute values, the predicted percentages and Z-scores published by Quanjer et al. in 2012 were obtained (164). FeNO is reported as a number in parts per billion (ppb). A detailed description of the procedures and the acceptance criteria is provided in Chapter 3.

Table 5.1:Summary of references dataset by TremoFlo

Reference	**Nowoweiejska et al.**	**Calogero et al.**
Year of publication	2008	2013
Subject number	626	760
Age (years), range	3.1-18.9	2.7-12.9
Height (cm), range	95-193	92.3-159
Weight (kg), range	14-93	13-68
Ethnic group	Caucasian - Polish	Caucasian- Italian and Australian
Reported prediction equation variables	R at 5-35 Hz X at 5-35 Hz /Fres	Rrs at 6, 8 and 10 Hz /Xrs at 6, 8 and 10 Hz /Fres/AX

5.4.3 Statistical analysis

All the participants' characteristics (age, height, weight, and sex) were reported. Per the recommendation of ATS/ERS, we used the Z-score as an interpretive method since it is independent of age, height, and sex (64,117). The Z-scores were calculated as (measured – predicted mean)/ (standard deviation of the residuals) (208,209), with Z-scores of less than −1.64 or more

than +1.64 classified as an abnormal result (165,208). The normality of the data was tested using histograms and the Shapiro–Wilk test of normality, for which a normal distribution is indicated by a p-value > 0.05. Relationships between the anthropometric measurements and the FOT indices were determined using the Pearson correlation coefficient (r). Linear regression analysis was performed if any correlation was observed, and the square of the correlation coefficient (r^2) was reported, with p-values of less than 0.05 indicating statistical significance.

5.4.4 Approach to analysis

To determine whether the studied population fell within the reference ranges for the pre-programmed predicted values in healthy children, normal and abnormal Z-scores for all the FOT measurements in healthy children were determined, with the exception of the AX using 7–41 Hz, since there were no reference values or Z-scores available for this measure in the TremoFlo machine for the studied population. Z-scores of the spirometry and numerical FeNO data available were also reported.

5.5 Results

Of the 52 families approached, 22 participants agreed to join the study (Figure 5.1). Demographic characteristics of the population are shown in Table 5.2 and group mean data for FOT measurements are shown in Table 5.3.

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Figure 5.1: Flow chart of the entire cohort of healthy school-aged children who were approached

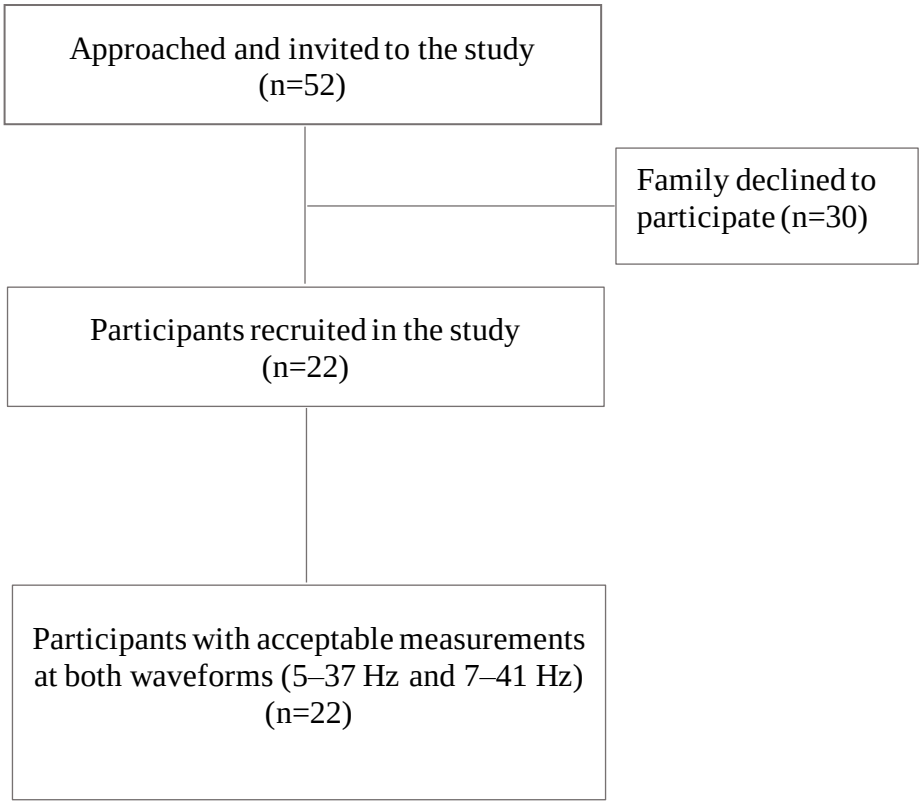


Table 5.2: Demographic characteristics of enrolled healthy children

	Mean (SD)
Sex (male: female)	8:14
Age (years)	9.39 (2.79)
Height (cm)	135.5 (17.95)
Weight (kg)	36.14 (15.58)

Data presented as mean (SD) unless otherwise stated

Table 5.3: Forced oscillation technique measurements at 5–37 Hz and 7–41 Hz in healthy children

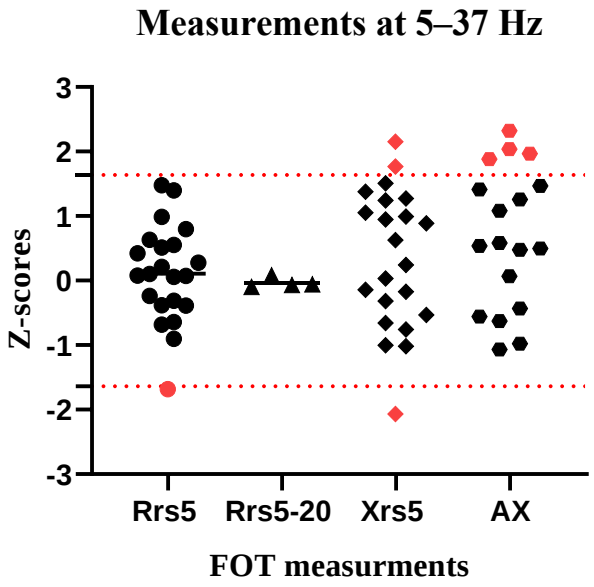
Measurements at 5–37 Hz	Actual values		Z-scores		Measurements at 7–41 Hz	Actual values		Z-scores	
	n	Mean (SD)	n	Mean (SD)		n	Mean (SD)	n	Mean (SD)
Rrs5 ($cmH_2O \cdot sec/L$)	22	6.48 (1.98)	22	0.106 (0.75)	**Rrs7 ($cmH_2O \cdot sec/L$)**	22	6.27 (1.83)	22	0.044 (0.99)
Rrs5-20 ($cmH_2O \cdot sec/L$)	22	1.58 (1.13)	4	−0.035 (0.08)	**Rrs7-20 ($cmH_2O \cdot sec/L$)**	22	1.38 (1.15)	4	−0.073 (0.06)
Xrs5 ($cmH_2O \cdot sec/L$)	22	−3.21 (1.19)	22	0.338 (1.08)	**Xrs7 ($cmH_2O \cdot sec/L$)**	22	−2.53 (1.31)	22	0.425 (1.11)
AX using 5–37 Hz (cmH_2O/L)	22	31.11 (21.16)	18	0.662 (1.09)	**AX using 7–41 Hz (cmH_2O/L)**	22	24.69 (18.66)	-	-

Data presented as mean (SD), n= number of the participants with available data, no reference values, or Z-scores available for AX using 7–41 by the TremoFlo

5.5.1 Measurements of FOT in healthy children tested in a local population

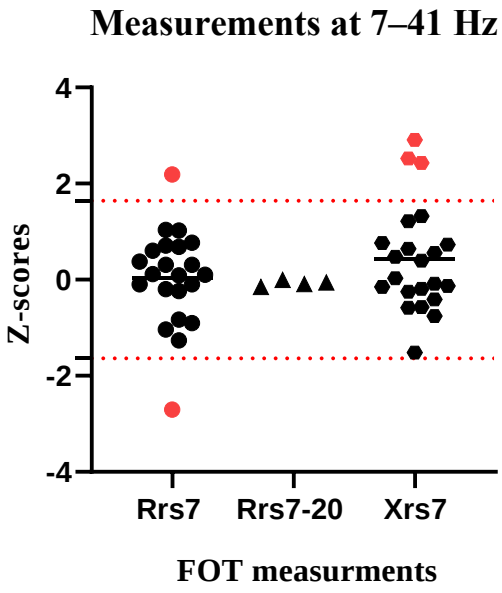
Among the 22 healthy participants tested with the FOT measurements at 5–37 Hz and 7–41 Hz, 11 were able to perform spirometry, and data from 10 of these participants were acceptable and reportable. In addition, 15 participants performed FeNO successfully. Of the 22 participants, an abnormal Z-score for Rrs5 was seen in 1 participant, 3 participants had abnormal Z-scores for Xrs5, and 4 participants had abnormal AX using 5–37 Hz Z-scores. Abnormal Z-scores for Rrs7 were observed in two participants, and three participants were found to have abnormal Z-scores for Xrs7. However, among those who had Z-scores for Rrs5-20 and Rrs7-20, all were normal (Figure 5.2 and Figure 5.3). Spirometry Z-scores for FEV_1, FVC and FEV_1/FVC were found to be normal in all participants except two: one had an abnormal Z-score for FEV_1 and the other had an abnormal Z-score for FEV_1/FVC. None of these participants had abnormal Z-scores for the FOT measurements at 5–37 Hz or 7–41 Hz. All participants with FeNO readings had normal readings of less than 35 ppb. None of the participants presented with known allergies.

Figure 5.2:Z-scores for the measurements at 5–37 Hz in the healthy group



……. Represents cut-off for abnormal Z-score of ≥1.64 or ≤−1.64
(Black) Normal Z-scores **(Red)** Abnormal Z-scores

Figure 5.3:Z-scores for the measurements at 7–41 Hz in the healthy group



……. Represents cut-off for abnormal Z-score of ≥1.64 or ≤−1.64
(Black) Normal Z-scores **(Red)** Abnormal Z-scores

5.5.2 Correlation of the forced oscillation technique measurements at 5–37 Hz and 7–41 Hz to the anthropometric data

A significant correlation was observed between the height, weight, and age and all the FOT measurements at 5–37 Hz. The standing height had the strongest correlation to the resistance measurement (Rrs5), followed by the age ($r = -0.791$ and $r = -0.784$, respectively). This was also seen for the Rrs5-20. However, age had a higher correlation to the reactance measure of Xrs5 than did height ($r = 0.725$ and $r = 0.712$, respectively), which was similar to what it was seen for the correlation between the AX using 5–37 Hz and these participant characteristics. The lowest correlation was observed between the FOT parameters at 5–37 Hz and weight (figures in Table 5.4 and Table 5.5).

For the measurements at 7–41 Hz, there was a significant correlation between the age and height and all the resistance and reactance FOT measurements. The Rrs7-20 and the AX using 7–41 Hz had no significant correlation to the weight. The strongest correlation between the FOT measurements at 7-41 Hz was seen for age to the Rrs7 ($r = -0.703$). The lowest correlation for age was observed for the Rrs7-20 ($r = -0.480$; Tables 5.4 and 5.6).

In comparing the FOT measurements at 5–37 Hz and 7–41 Hz and their relationship to the gender, no significant differences were observed between female and male participants for any of the FOT measurements (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz) in the studied healthy group.

For both FOT measurements at 5–37 Hz and 7–41 Hz, the height, weight, and age were negatively correlated to the Rrs5, Rrs7, Rrs5-20, Rrs7-20 and AX using 5–37 Hz and 7–41 Hz. In addition, positive correlations were observed between these anthropometric variables and the Xrs5 and Xrs7. Correlations of the height, weight and age were higher to FOT measurements at 5–37 Hz than to the measurements at 7–41 Hz.

Table 5.4: Correlation of the forced oscillation technique measurements to height and age

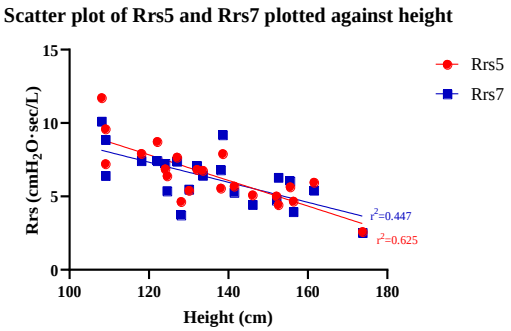
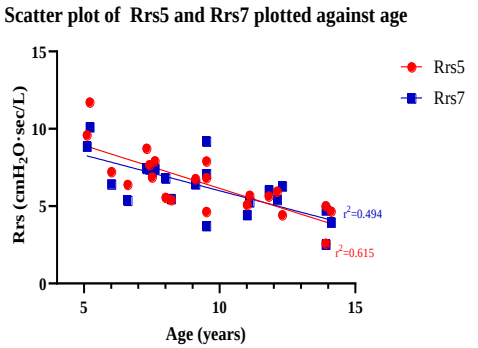
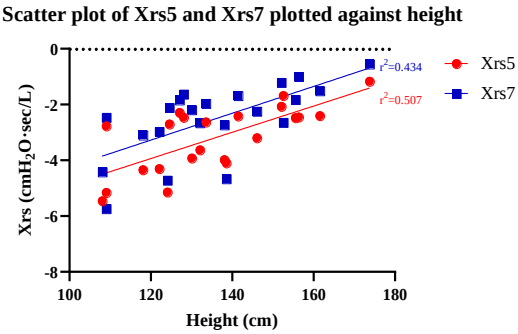
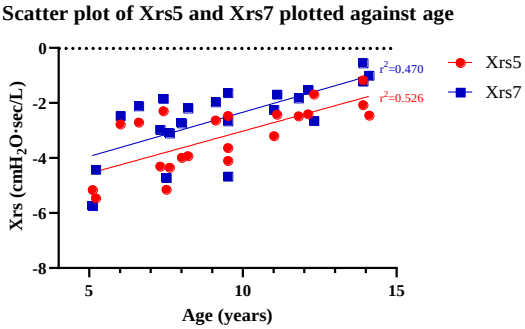
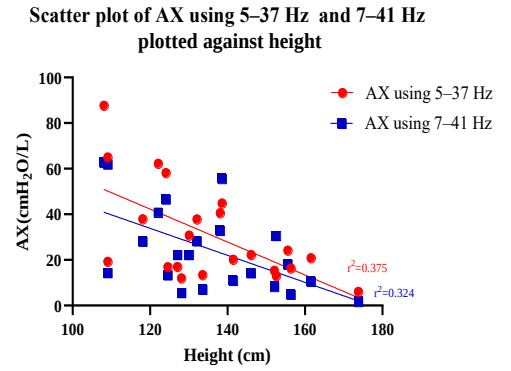
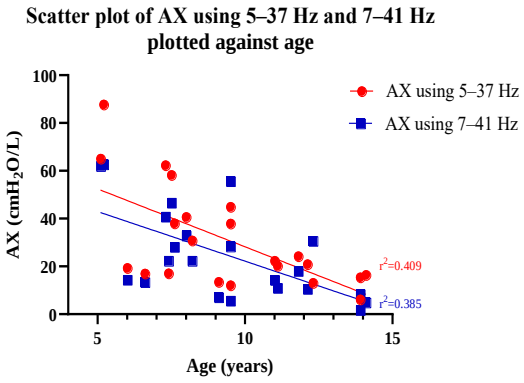
Correlation of the resistance at 5 and 7 Hz to the height	Correlation of the resistance at 5 and 7 Hz to the age
	
The line represents the line of best fit	The line represents the line of best fit
Correlation of the reactance at 5 and 7 Hz to the height	**Correlation of the reactance at 5 and 7 Hz to the age**
	
The line represents the line of best fit	The line represents the line of best fit
Correlation of the area under the curve using 5–37 Hz and 7–41 Hz to the height	**Correlation of the area under the curve using 5–37 Hz and 7–41 Hz to the age**
	
The line represents the line of best fit	The line represents the line of best fit

Table 5.5: Correlation of the actual values of the forced oscillation technique measurements at 5–37 Hz to the height, weight and age

	Height (cm)		Weight (kg)		Age (years)	
	r	**p-value**	***r***	**p-value**	***r***	**p-value**
Rrs5 ($cmH_2O \cdot sec/L$)	−0.791	0.000*	−0.615	0.002*	−0.784	0.000*
Rrs5-20 ($cmH_2O \cdot sec/L$)	−0.584	0.004*	−0.426	0.048*	−0.550	0.008*
Xrs5 ($cmH_2O \cdot sec/L$)	0.712	0.000*	0.678	0.001*	0.725	0.000*
AX using 5–37 Hz (cmH_2O/L)	−0.612	0.002*	−0.539	0.010*	−0.640	0.001*

*r = correlation coefficient; *statistically significant*

Table 5.6: Correlation of the actual values of the forced oscillation technique measurements at 7–41 Hz to the height, weight and age

	Height (cm)		Weight (kg)		Age (years)	
	r	**p-value**	***r***	**p-value**	***r***	**p-value**
Rrs7 ($cmH_2O \cdot sec/L$)	−0.668	0.001*	−0.464	0.030*	−0.703	0.000*
Rrs7-20 ($cmH_2O \cdot sec/L$)	−0.443	0.038*	−0.270	0.225	−0.480	0.023*
Xrs7 ($cmH_2O \cdot sec/L$)	0.659	0.001*	0.513	0.015*	0.685	0.000*
AX using 7–41 Hz (cmH_2O/L)	−0.569	0.006*	−0.417	0.054	−0.621	0.002*

*r = correlation coefficient; *statistically significant*

5.6 Discussion

The choice of reference values is critical, as it impacts the interpretation of lung function data in children and thus has a substantial influence on research and patient care (117). The data in our study of healthy children are mostly in line with the reference prediction equation used by the TremoFlo (88,133).Recently, larger data set of reference values for respiratory measurements for TremoFlo has been by published (210). In our study, there were a few abnormal Z-scores. Notably, the lung function variables between healthy children and children with the disease could overlap to some extent, and abnormal values of lung function will not necessarily be associated with disease (117).

In this study, the participants' characteristics were correlated to the FOT measurements; in addition, the raw FOT data was plotted against height and age to generate a linear regression. In agreement with most previous studies, height was the variable with the greatest influence on resistance measurements (129,131,200,211-215). Overall, these findings are in accordance with those of a previous study in healthy children aged 2–18 years in which height was the only predictor for the impedance measurements at 2, 4 and 12 Hz (211). They are also consistent with the findings based on a group of 360 healthy children aged 2–11 years, in whom the respiratory resistance and reactance at 5, 10, 15 and 20 Hz showed the highest correlation to height and a weak relationship to weight (200). Previous findings also demonstrated that height was one of the main determinants of the oscillometric variables at 5 Hz and 25 Hz in children and adolescents (131,212). Even though this study was done in school-aged children, other studies in preschool-aged children reported similar results, demonstrating that height was the main factor affecting resistance and reactance measurements since growth affects lung volumes and airway dimensions (213-215). In our study, the strongest correlation to height was observed for the resistance at 5 Hz. However, there were significant correlations between the height, age, and weight for most of the FOT variables at different frequencies. This agrees with some previous studies done in children belonging to different ethnic groups (143,213-215). Our results broadly align with those of a study showing that height was the predictor most strongly correlated to FOT measurements using frequency waveforms of 4–32 Hz in preschool-aged children (214). A similar pattern was also noticed in FOT measurements of the resistance and reactance at 8 Hz, which had a significant correlation to height in a population of healthy children aged 6–11 years (143). Additionally, in children aged 2–7 years, IOS measurements at a frequency range of 5–35 Hz correlated to height, age, and weight (213,215).

The results of other studies have shown that height is negatively correlated with resistance and positively correlated with reactance (199,204,215). These reports were in line with the conclusion reached by Fri et al., who showed that height correlated positively to the reactance and negatively to the resistance studied by IOS at a frequency range of 5–35 Hz in healthy children aged 3–10 years (204). Similar results have been noted in different groups of preschool-aged children (199,215).

No significant difference in FOT measurements was observed between the female and male participants in this study. These results are in accord with those of previous studies in the field in preschool and school-aged children (129,200,204).

Though this study followed the recommendation of testing healthy controls with similar characteristics to the population to be studied (117), the results of this study were in agreement with those of other studies. However, the results of this study could be biased due to the small sample size, making these results from healthy controls perhaps less useful as a reference values. Notably, special consideration must be taken in interpreting the data and the results, as the studied local population had a different ethnicity than individuals who were previously studied. In addition, consideration must be given to the different software, methods and equipment used.

This study's findings aligned with its hypotheses and aims. The majority of resistance and reactance of FOT measurements in the healthy control group fell within the predicted values and reference ranges provided by the TremoFlo. In addition, most of FOT resistance and reactance measurements at both frequency waveforms 5–37 Hz and 7–41 Hz were correlated with height, age, and weight, with the strongest correlation between height and FOT resistance at 5 Hz.

CHAPTER 6 FORCED OSCILLATION TECHNIQUE IN CHILDREN WITH STABLE ASTHMA

6.1 Introduction and rationale

Asthma is the most common chronic childhood respiratory disease (24). According to the GINA guidelines, an asthma diagnosis can depend on the patient's medical history as well as a physical examination and pulmonary function testing (25,216). Many children with asthma are misdiagnosed (217), which could be because asthma is frequently diagnosed in primary care, with the diagnosis based on clinical criteria and children are not usually assessed with objective tests in this setting (218). In addition, a patient is often asymptomatic unless they have had an exacerbation at the time of their clinical examination (218). New tests and biomarkers are urgently needed to improve asthma diagnosis, and this has been highlighted as a research priority by Asthma UK (219).

In children aged five years and above, spirometry is considered standard test to diagnose and monitor asthma (50,163,175). Both large and moderately sized airways can be investigated using spirometry (220,221) with the FEV_1, FVC and FEV_1/FVC values indicating abnormal airways in children with asthma (222), particularly if the FEV_1/FVC ratio is less than the lower limit of normal (LLN) (50,164). Bronchodilator reversibility testing can also be used to diagnose asthma, with a 12% improvement in FEV_1 after the administration of a bronchodilator confirming the diagnosis (50). However, even though spirometry is widely used in pulmonary function testing, it requires the patient to be fully cooperative and can be exhausting (223). This makes it particularly difficult to achieve good spirometry results in children (175).

One of the main symptoms of asthma is airway inflammation. This can be represented by the presence of eosinophilic airway inflammation and be reflected by the fractional exhaled nitric oxide (FeNO) test. FeNO testing adds a clinical benefit in supporting the diagnosis and the monitoring of asthma in children (50,224). In patients with asthma, FeNO levels will decrease with the use of inhaled steroids, oral steroids and other anti-inflammatory medications (225). Reducing FeNO levels in patients with asthma could lead to better clinical outcomes and a lower incidence of exacerbation. This represents a high clinical value of FeNO in the management of asthma (226,227). However, the utility of FeNO in guiding the treatment of children with asthma is still debatable as adding routine measures of FeNO in children with asthma did

not seem to add any value to the treatment guidance compared with basing treatment decisions on asthma symptoms only (228).

The forced oscillation technique (FOT) is a novel, non-invasive technique for measuring airway dynamics. The test does not require forced expiration making it suitable for young children (7,87,89). The FOT test provides information on the resistance (Rrs) and reactance (Xrs) of the airways by using external pressure signals and their resulting flows to measure lung mechanics. The test is quick, painless, and requires little active participation by the patient (2,67,107). In children with asthma, the FOT test was able to identify baseline airway obstruction (122) as it can reflect total airway resistance, including the peripheral and larger airways (122,135). The FOT could facilitate the diagnosis and the management of asthma as a reflective measure of lung dynamics in children who are unable to tolerate spirometry (168).

6.2 Aims

1- To assess the accuracy (sensitivity and specificity) of the FOT in detecting asthma in children attending the asthma clinic.
2- To investigate the association of the FOT indices using TremoFlo to other traditional measures of lung function (e.g., spirometry) in children attending the asthma clinic.
3- To investigate the association of the FOT indices using TremoFlo with the measures of airway inflammation (FeNO) in children attending the asthma clinic.

6.3 Hypotheses

1- The FOT measurements of resistance and reactance by TremoFlo using 5–37 Hz oscillation waveforms (Rrs5-Rrs5-20 and AX) are sensitive measurements in reflecting airway obstruction and the subsequent diagnosis of asthma in school-age children attending the asthma clinic.
2- The FOT measurements of resistance and reactance using 5–37 Hz oscillation waveforms (Rrs5, Rrs5-20 and AX) correlate with the spirometry parameters (FEV_1, FVC, FEV_1/FVC) of school-age children with asthma attending the asthma clinic.
3- FOT measurements of resistance using 5–37 Hz oscillation waveforms (Rrs5) correlates to the FeNO in school-age children attending the asthma clinic.

6.4 Materials, Methods and Participants

6.4.1 Study design and participants

An observational prospective cohort study (UHL Clinical Audit No. 9986) was conducted on school-age children aged 5–16 who attended the Leicester Royal Infirmary asthma clinic from September 2018 to November 2019 as part of their clinical review. A FOT was performed in addition to their regular care.

The parents of the participants were initially approached during their clinical visit. An explanation of the service improvement project and how the FOT test was performed was provided to both the children and their parents. They then were asked if the child would agree to participate in the service improvement project by performing the FOT test. They were informed that it was completely voluntary and that they could decline to participate. However, most of the participants approached agreed to perform the test. (Appendix A)

6.4.2 Eligibility criteria

Patients attended the asthma clinic and were not acutely unwell. The diagnosis of stable asthma during the clinical visit was based on a physician's assessment. Subsequently, objective evidence of lung function measures and evidence of airway inflammation were extracted from patient records to categorize the groups according to NICE and ERS criteria (50,53). All spirometry, FOT and FeNO data reported and used for the analysis within this chapter were collected during the clinic visit. Asthma severity for these participants was classified according to the GINA guidelines based on the daily dose of asthma controller medication (25).

6.4.3 Data collection and analysis

Children attending the asthma clinic performed the FOT test during their clinical visit. Spirometry and FeNO tests were also performed, when possible, by the respiratory physiologist as part of the participants' clinical review. The FOT was performed until three acceptable test results were achieved. Each test lasted approximately 20 seconds and was measured in the 5–37 Hz frequency range. Impedance measurements of the forced oscillation were reflected as resistance at 5 Hz (Rrs5), resistance difference of 5–20 Hz (Rrs5-20) and reactance area (AX). Absolute values with Z-scores were recorded based on two reference datasets provided by the TremoFlo for the intended studied group (88,133). The best reference dataset was retrieved automatically by the TremoFlo depending on the age, height, and weight of the participant. Spirometry measurements with indices of flow limitation and lung volumes reflected as FEV_1,

FVC and FEV_1/FVC absolute values, were collected in addition to predicted percentage and the Z-scores based on the GLI data published by Quanjer et al. (164). The FeNO values were reported in parts per billion (ppb). The spirometry and FOT data were performed according to the ATS/ERS guidelines (60,117). The guidelines used for FOT are for preschool-aged children. However, they can be applied to school-aged children even though they are intended for preschool-aged children as they were based on some studies of school-aged children. A detailed description of the procedures and the acceptance criteria is provided in Chapter 3.

6.4.4 Statistical analysis

The participants' demographics (age, height, weight, and sex) were collected, and the diagnostic accuracy when reporting sensitivity and specificity are reflected in a 2 x 2 classification table (197). The normality of the data was tested using histograms and the Shapiro–Wilk normality test. The relationship between the FOT indices, the spirometry indices and the FeNO values was studied for each group using either a Pearson or Spearman's correlation coefficient (r). Linear regression analysis was performed to test for correlations. The square of the correlation coefficient was reported (r^2) with a p-value of less than 0.05 denoting statistical significance. Any correlations between the FOT and the spirometry indices for each group were determined by comparing the Z-scores as per the recommendation of ATS/ERS to use the Z-score as an interpretive method since it is independent of age, height, and sex (64,117). The Z -scores were determined as (measured – predicted mean) / (standard deviation of the residuals) (208,209).With Z-scores of less than –1.64 or more than +1.64 classified as an abnormal result (165,208). Comparisons between the groups were made using the Kruskal–Wallis test, and comparisons of different groups were made using the unpaired t-test for the parametric data and the Mann–Whitney U test for the non-parametric data, with a p-value of less than 0.05 denoting statistical significance.

6.4.5 Approach to analysis

The participating patients were divided into three groups. A group of asthma patients with the diagnosis confirmed by objective tests according to NICE and or ERS guidelines (50,53). The second group consisted of asthma patients with incomplete objective evidence of asthma based on NICE and/or ERS guidelines, and third group consisted of patients with suspected asthma but no objective evidence.

In order to determine the ability of the FOT parameters (Rrs5, Rrs5-20 and AX) to correctly identify asthma in children attending the asthma clinic, the three groups were further subdivided according to the availability of the Z-scores of these measures. Each group was divided depending on whether they had Rrs5-20 or AX Z-scores. The availability of the Z-scores depended on the reference that was selected by TremoFlo. The best reference dataset was retrieved automatically by the TremoFlo depending on the age, height, and weight of the participant (88,133), the pre-set programmed references had either the Rrs5-20 or the AX reference values (Figures 6.1–6.3).

Figure 6.1:Population of children with asthma with complete evidence divided according to the availability of Z-scores of Rrs5, Rrs5-20 and AX

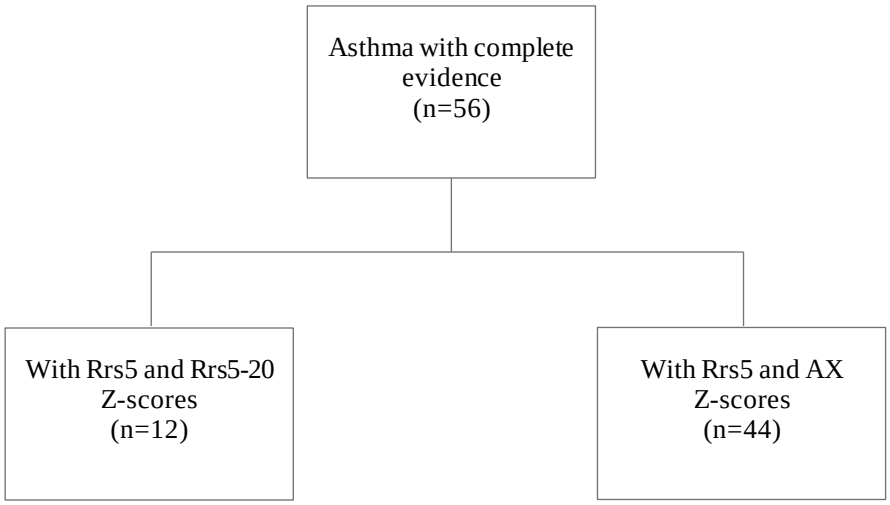


Figure 6.2: Population of children with asthma with incomplete evidence divided according to the availability of Z-scores of Rrs5, Rrs5-20 and AX

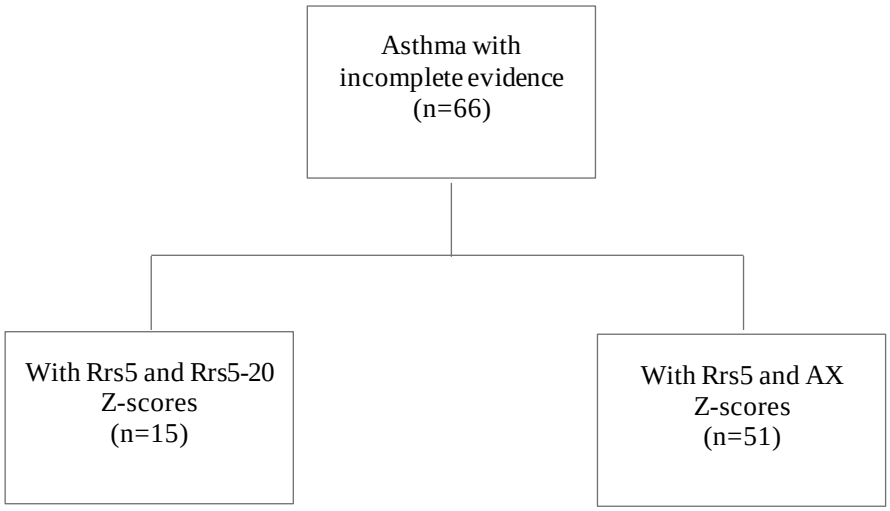
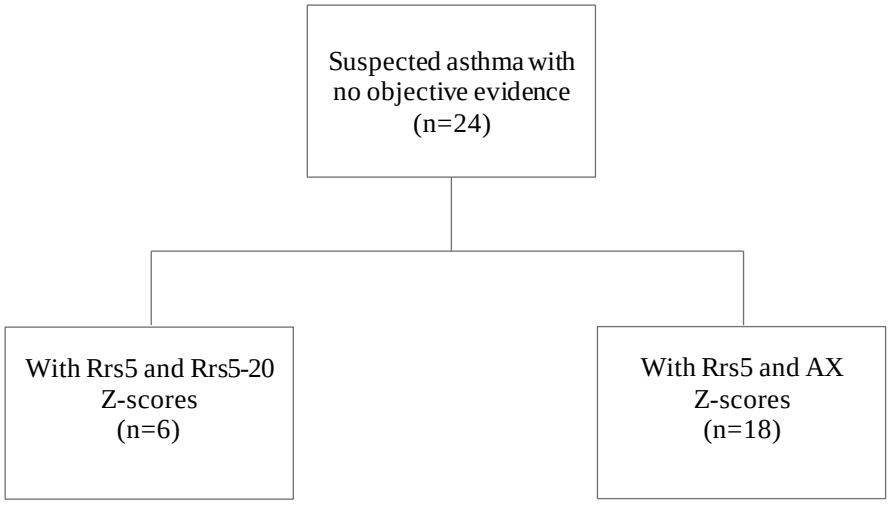


Figure 6.3: Population of children suspected asthma with no objective evidence divided according to the availability of Z-scores of Rrs5, Rrs5-20 and AX



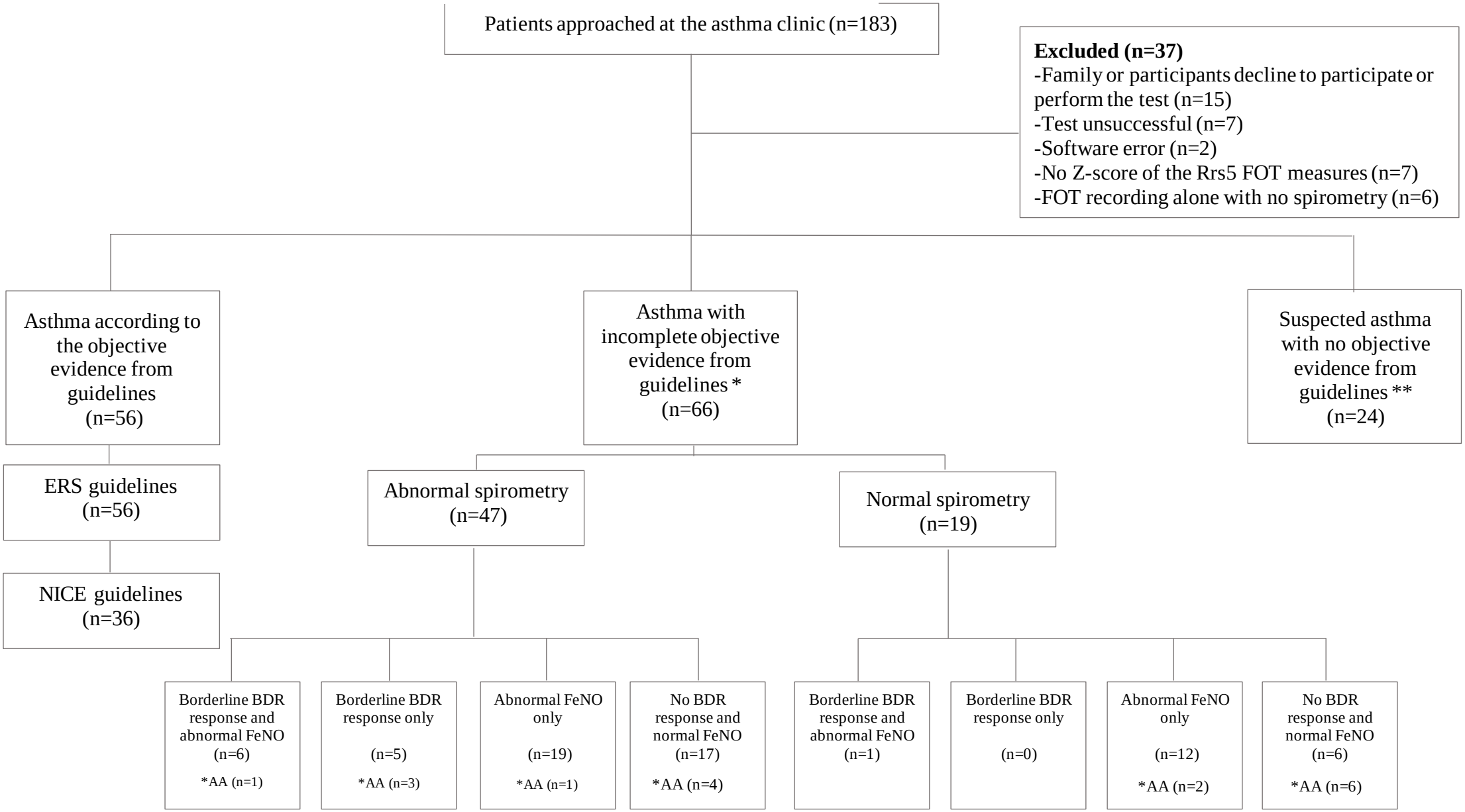
6.5 Results

A total of 183 school-aged children were approached in the asthma clinic. Of these, 37 were excluded from the study for reasons that included unsuccessful tests, software errors, no Z-score for the Rrs5 FOT measurement, or FOT without associated spirometry readings. Also, some of the children or their families declined to participate (Figure 6.4).

The group of children who were diagnosed with asthma with complete evidence followed the ERS and the NICE guidelines for asthma diagnosis in children aged 5–16 years and considered abnormal FeNO levels to be ≥25 ppb and ≥ 35 ppb (50,53). The group containing children who were diagnosed with asthma with incomplete evidence was defined as having one or more abnormal objective tests as suggested by the ERS and NICE guidelines. The borderline bronchodilator response cut-off point for the group of children with incomplete objective evidence was set at an 8% improvement in FEV_1 after administering of short-acting beta-2 agonists (SABA), as lower cut-off points than 12% have greater sensitivity but lower specificity when differentiating between children who have asthma and those who do not (229-231). However, for children who had a BDR falling between 8 and <12%, we considered this as supporting but not confirming an asthma diagnosis. The group of children who had suspected asthma, but no objective evidence had normal spirometry and FeNO levels and had never suffered an asthma attack according to their all-past medical records (Figure 6.4).

For the 146 children who attended the asthma clinic, controller medicine was as follows: leukotriene inhibitor (20.5%), inhaled corticosteroid (40.4%), and combination of long acting β2 agonist and inhaled corticosteroid (37.7%). Oral steroids had been taken by 4.8% of the participants according to family reports. Asthma attacks within the past two years were reported in 12.3% of these 146 children. Only 4.1% of participants or their families reported frequent use of SABA. (Table 6.1).

Figure 6.4: The entire cohort of school-aged children approached at the asthma clinic



Abnormal spirometry: FEV_1/FVC or FEV_1 Z-score above 1.64 or below –1.64
Abnormal FeNO: FeNO level ≥25 ppb
Borderline BDR response: ≥8%
*17 participants had asthma attack (n= 14 type-1 asthma attack with low FeNO levels, n=3 type-2 asthma attack with high FeNO levels).
** Participants had normal spirometry, FeNO and had never had an asthma attack.
*AA= Asthma attack (presented at the Emergency Department with worsening symptoms and who had either been treated with salbutamol or were hospitalised within the last two years)

Table 6.1: Clinical characteristics of children studied in the asthma clinic

	Asthma with complete evidence (n=56)	Asthma with incomplete evidence (n=66)	Suspected asthma with no objective evidence (n=24)
Asthma attack, n (%)	1 (1.8%)	17 (25.8%)	0 (0%)
Beclometasone dipropionate, n (%)	21 (37.5%)	31 (47%)	8 (33.3%)
Combination of long acting β2 agonist and inhaled corticosteroid, n (%)	31 (55.4%)	21 (31.8%)	3 (12.5%)
Leukotriene inhibitor, n (%)	19 (33.9%)	11 (16.7%)	0 (0%)
Oral steroids, n (%)	5 (8.9%)	2 (3%)	0 (0%)
Frequent use of SABA, n (%)	3 (5.4%)	3 (4.5%)	0 (0%)
Severity according to the GINA strategy document usage of the of the medication, n (%)	*None in any medication* 0 (0%) *Mild asthma* 43 (76.8%) *Moderate asthma* 12 (21.4%) *Severe asthma* 1 (1.8%)	*None in any medication* 12 (18.2%) *Mild asthma* 43 (65.2%) *Moderate asthma* 10 (15.1%) *Severe asthma* 1 (1.5%)	*None in any medication* 13 (54.2%) *Mild asthma* 10 (41.7%) *Moderate asthma* 1 (4.2%) *Severe asthma* 0 (0%)

6.5.1 Sensitivity and specificity of FOT parameters (Rrs5, Rrs5-20 and AX) in detecting asthma in children attending the asthma clinic

A group of children aged 5–15 years with acute asthma who were diagnosed after presenting with an asthma attack in the emergency department or on the children's ward (please refer to section 7.4.1 and 7.4.2 in chapter 7). And healthy children aged 5–15 years with no history of wheeze or respiratory problems who were recruited from the paediatric wards and non-respiratory outpatient clinics (please refer to section 5.4.1 and 5.4.2 in chapter 5) were used as a control group. The demographic characteristics of the study population are presented in Table 6.2. Forced oscillation technique, spirometry and fractional exhaled nitric oxide measurements for different study groups are shown in Table 6.3.

Table 6.2: Characteristics of children diagnosed with acute asthma, asthma with complete evidence, asthma with incomplete evidence, suspected asthma with no objective evidence and healthy control group

	Acute asthma (n=22)	**Asthma with complete evidence (n=56)**	**Asthma with incomplete evidence (n=66)**	**Suspected asthma with no objective evidence (n=24)**	**Healthy control group (n=22)**
Sex, Male n (%)	16 (72.7%)	39 (69.6%)	39 (59.1%)	14 (53.3%)	8 (36.4%)
Age (years)	8.41 (2.49)	10.28 (2.75)	10.15 (3.32)	10.42 (2.87)	9.40 (2.79)
Height (cm)	132.8 (14.77)	140.8 (17.96)	140.4 (19.51)	141.4 (20.96)	135.5 (17.95)
Weight (kg)	32.49 (15.58)	38.40 (15.34)	39.96 (16.65)	39.50 (19.07)	36.14 (15.58)

Data presented as mean (SD) unless otherwise stated

(There were no statistically significant differences in age, height, and weight between any of the groups studied)

Table 6.3:Forced oscillation technique, spirometry and fractional exhaled nitric oxide for different study groups

	Acute asthma (n=22)	Asthma with Complete evidence (n=56)	Asthma with incomplete evidence (n=66)	Suspected asthma with no objective evidence (n=24)	Healthy control group (n=22)
Number of participants with FOT readings	**(n=22)**	**(n=56)**	**(n=66)**	**(n=24)**	**(n=22)**
Rrs5 ($cmH_2O \cdot sec/L$)	8.64 **(**2.38)	7.68 **(**2.49**)**	6.43 **(**2.62**)**	5.90 (1.82)	6.48 (1.98)
Rrs5-20 ($cmH_2O \cdot sec/L$)	3.43 (1.37)	2.53 (1.53)	1.57 (1.33)	1.29 (1.30)	1.58 (1.13)
AX (cmH_2O/L)	62.07 (32.69)	41.32 (27.94)	25.98 (20.91)	20.38 (15.25)	31.11 (21.16)
Number of participants with Rrs5 Z-score	(n=22)	(n=56)	(n=66)	(n=24)	(n=22)
Rrs5 Z-scores	1.25 (1.28)	1.04 (0.97)	0.24 (1.02)	0.11 (0.79)	0.11 (0.75)
Number of participants with Rrs5-20 Z-score	(n=2)	(n=12)	(n=15)	(n=6)	(n=4)
Rrs5-20 Z-scores	0.59 (0.98)	0.08 (0.29)	−0.10 (0.20)	−0.08 (0.20)	0.85 (0.39)

Table 6.3 (Continued)

	Acute asthma **(n=22)**	**Asthma with Complete evidence** **(n=56)**	**Asthma with incomplete evidence** **(n=66)**	**Suspected asthma with no objective evidence** **(n=24)**	**Healthy control group** **(n=22)**
Number of participants with AX Z-score	(n=20)	(n=44)	(n=51)	(n=18)	(n=18)
AX Z-scores	2.18 (1.43)	1.50 (1.20)	0.60 (0.94)	0.18 (0.91)	0.66 (1.09)
Number of the participants with spirome-try readings	**(n=1)**	**(n=56)**	**(n=66)**	**(n=24)**	**(n=10)**
FEV_1 (% predicted)	115 *	80.27 (18.75)	94.02 (12.19)	100.5 (9.07)	95.6 (8.91)
FVC (% predicted)	123*	90.70 (18.97)	98.83 (12.44)	100.9 (9.94)	98.4 (8.36)
FEV_1/FVC %	82*	77.64 (9.34)	83.97 (7.25)	88 (5.19)	86.8 (4.78)
FEV_1 Z-scores	1.28*	−1.53 (1.71)	−0.43 (1.07)	0.04 (0.77)	−0.38 (0.74)
FVC Z-scores	1.94*	−0.77 (1.63)	−0.11 (1.03)	0.07 (0.85)	−0.14 (0.68)
FEV_1/FVC Z-scores	−1.16*	−1.72 (1.59)	−0.82 (1.21)	−0.14 (0.75)	−0.54 (0.76)

Table 6.3 (Continued)

	Acute asthma (n=22)	Asthma with Complete evidence (n=56)	Asthma with incomplete evidence (n=66)	Suspected asthma with no objective evidence (n=24)	Healthy control group (n=22)
Number of the participants with FeNO readings	**(n=4)**	**(n=33)**	**(n=40)**	**(n=16)**	**(n=15)**
FeNO (ppb)	40.5 (25.38)	57.45 (49)	42.5 (39.45)	14.69 (5.89)	10.60 (3.92)

Data presented as mean (SD) unless otherwise stated
** Represents the reading for one participant*

Resistances at 5 Hz (Rrs5) were compared between the different study groups. In children with acute asthma, Rrs5 had the highest percentage of abnormal Rrs5 Z-scores (41%) compared with the other groups. This was followed by the group that had asthma with complete evidence and the group with incomplete evidence, with 18% and 15% abnormal Rrs5 Z-scores, respectively. The lowest percentages of abnormal Rrs5 Z-scores were found in the group that had suspected asthma with no objective evidence and the healthy control group. Interestingly, no abnormal Rrs5-20 Z-scores were found in any of the groups. By contrast, AX had the highest percentages of abnormal Z-scores in the group of children with acute asthma (50%) and in the group of children with asthma with complete evidence (41%). The AX had a higher percentage of abnormal Z-scores compared with the Rrs5 in all of the groups except for the group of children with suspected asthma and no objective evidence, similar percentages have been noticed, where both Rrs5 and AX had one participant with abnormal Z-scores (Table 6.4).

Table 6.4: Forced oscillation Z-score of Rrs5, Rs5-20 and AX and Spirometry Z-scores of FEV_1 and FEV_1/FVC for the different study groups

	Acute Asthma	Asthma with complete evidence	Asthma with incomplete evidence	Suspected asthma and no objective evidence	Healthy control group
Number of participants with FOT readings	**(n=22)**	**(n=56)**	**(n=66)**	**(n=24)**	**(n=22)**
Abnormal Rrs5 Z-score, n (%)	9 (40.9%)	10 (17.9%)	10 (15.2%)	1 (4.2%)	1 (4.5%)
Number of participants with Rrs5-20 Z-score	(n=2)	(n=12)	(n=15)	(n=6)	(n=4)
Abnormal Rrs5-20 Z-score	No abnormal Z-scores of Rrs5-20				
Number of participants with AX Z-score	(n=20)	(n=44)	(n=51)	(n=18)	(n=18)
Abnormal AX Z-score, n (%)	10 (50%)	18 (40.9%)	7 (13.7%)	1 (5.6%)	4 (22.2%)

Table 6.4 (Continued)

	Acute Asthma	Asthma with complete evidence	Asthma with incomplete evidence	Suspected asthma and no objective evidence	Healthy control group
Number of the participants with spirome-try readings	**(n=1)**	**(n=56)**	**(n=66)**	**(n=24)**	**(n=10)**
Abnormal FEV_1 Z-score, n (%)	0 (%)	29 (51.8%)	9 (13.6%)	0 (%)	1 (10%)
Abnormal FVC Z-score, n (%)	1 (100%)	13 (23.2%)	7 (10.6%)	1 (4.2%)	0 (%)
Abnormal FEV_1/FVC Z-score, n (%)	0 (%)	25 (44.6%)	21 (%31.8)	0 (%)	1 (10%)

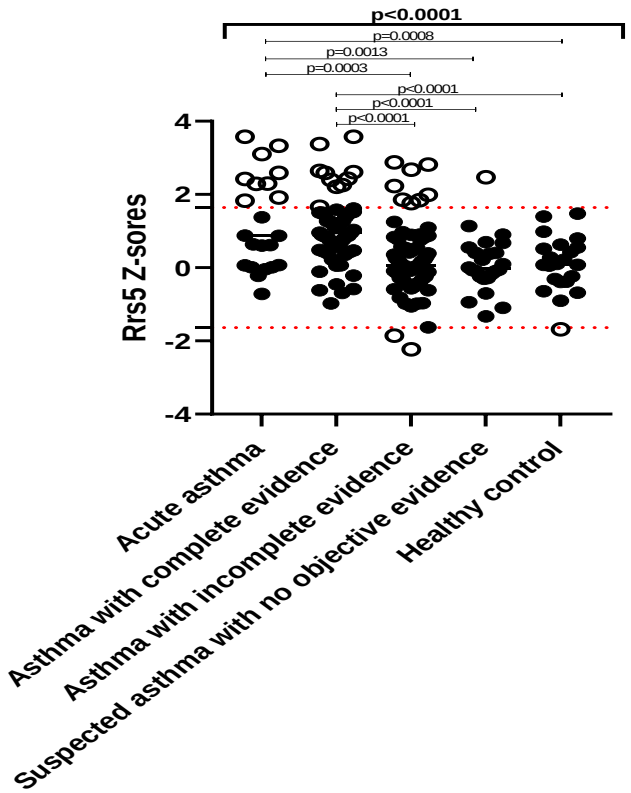
Abnormal Z-score: Z-score of ≥1.64 or ≤ −1.64

The sensitivity of the Rrs5 Z-scores in the group with stable asthma and complete evidence was 18% with a specificity of 95%, while the sensitivity and specificity of the Rrs5 Z-scores in the group with asthma and incomplete evidence were 15% and 95%, respectively. The AX had a higher sensitivity (41%) in the group with complete evidence compared with the Rrs5, and a lower specificity of 61%. In the group with incomplete evidence, the sensitivity and specificity for the AX Z-scores were 14% and 61%, respectively. Sensitivity and specificity were measured in the group with incomplete evidence as we assumed children had asthma based on at least one objective test.

The Rrs5 Z-scores were statistically different between the groups, $p < 0.0001$. The different groups that were studied are; group of acute asthma (n=22), group with complete evidence for asthma (n=56), group with incomplete evidence (n=66) group with suspected asthma with no objective evidence (n=24), healthy control (n=22).Specified by a statistically significant difference between the group with acute asthma compared with the group with incomplete

evidence, the group with suspected asthma and no objective evidence and the healthy control group, with p-values of 0.0003, 0.0013 and 0.0008, respectively, but not with the group that had asthma with complete evidence. However, there was a statistically significant difference between the group with asthma and complete evidence compared with the group with asthma and incomplete evidence, the group with suspected asthma with no objective evidence and the healthy control group, with p-values of <0.0001 for all. The group with asthma and incomplete evidence showed no significant differences with either the group with suspected asthma and no objective evidence or the healthy control group. There was also no significant difference between the group with suspected asthma and no objective evidence and the healthy control group (Figure 6.5).

Figure 6.5: Rrs5 Z-scores for the different study groups



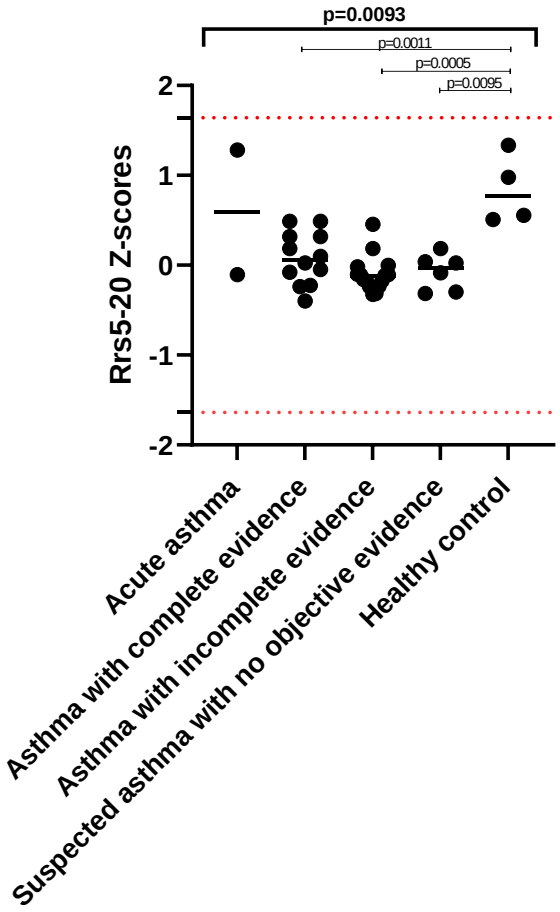
……. Represents cut-off for abnormal Z-score of ≥1.64 or ≤−1.64

●Normal Z-scores ○Abnormal Z-scores

The Kruskal–Wallis test showed statistically significant Rrs5-20 Z-scores between the different groups of acute asthma (n=2), complete evidence (n=12), incomplete evidence (n=15)

suspected asthma and no objective evidence (n=6) and the healthy control (n=4), p-value= 0.0093, though there were no abnormal Rrs5-20 Z-scores in any of the groups. A separate comparison between the groups showed that there were no statistically significant differences between the groups, except for between the healthy control group and the group with asthma and complete evidence, asthma with incomplete evidence, and suspected asthma with no objective evidence, with p-values of 0.0011, 0.0005 and 0.0095, respectively (Figure 6.6).

Figure 6.6: Rrs5-20 Z-scores for the different study groups



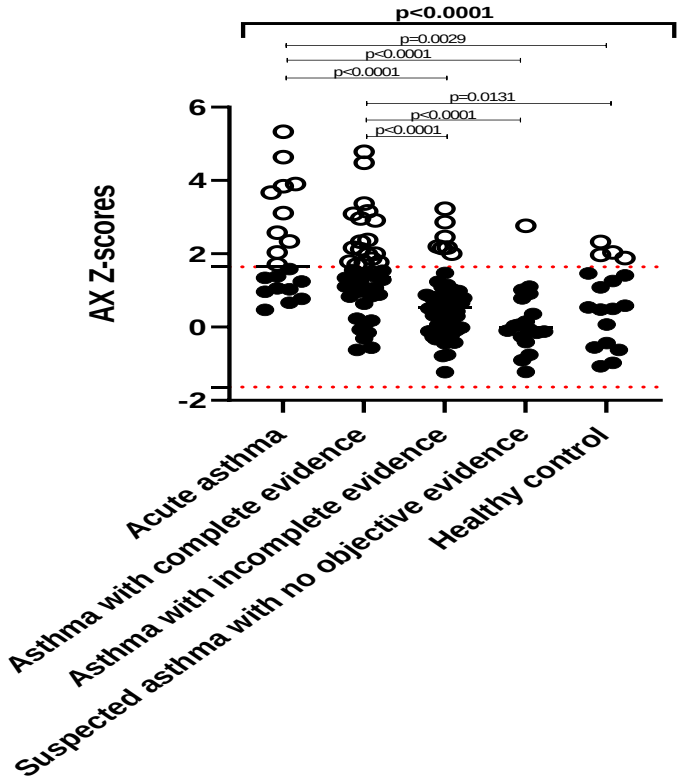
……. Represents cut-off for abnormal Z-score of ≥1.64 or ≤−1.64

●Normal Z-scores ○Abnormal Z-scores

The Z-scores of the AX between the different groups of acute asthma (n=20), complete evidence (n=44), incomplete evidence (n=51) suspected asthma and no objective evidence (n=18) and the healthy control (n=18) were statistically significant, p-value = <0.0001. This was described by statistically significant difference between the group with acute asthma and the

groups with incomplete evidence, suspected asthma with no objective evidence and the healthy control group, with p-values of <0.0001, <0.0001 and 0.0029, respectively, but not with the group with asthma and complete evidence. However, there was a statistically significant difference between the group with asthma and complete evidence and the group with incomplete evidence, suspected asthma with no objective evidence and the healthy control group, with p-values of <0.0001, <0.0001 and < 0.05, respectively. There was no statistically significant difference between the group with asthma and incomplete evidence and the group with suspected asthma and no objective evidence or the healthy control group. There was also no difference between the group with suspected asthma and no objective evidence and the healthy control group, when either the unpaired t-test or the Mann–Whitney U test were used for separate means comparison (Figure 6.7).

Figure 6.7: AX Z-scores for different study groups



……. Represents cut-off for abnormal Z-score of ≥1.64 or ≤−1.64

● Normal Z-scores ○ Abnormal Z-scores

6.5.2 Correlations between the FOT indices (Rrs5, Rrs5-20 and AX) Z-scores to the spirometry indices (FEV_1, FVC and FEV_1/FVC) Z-scores

The correlation of the Rrs5 Z-scores to the spirometry indices (FEV_1, FVC and FEV_1/FVC) Z-scores in children attending the asthma clinic is shown in Table 6.5. In the group that had asthma with complete evidence (n=56), a significant correlation was seen between the Rrs5 and both of the FEV_1 and the FEV_1/FVC Z-scores, with the highest correlation of Rrs5 to the FEV_1/FVC of $r = -0.497$ and $p < 0.001$ (Figure 6.8), followed by the correlation of the Rrs5 to the FEV_1 $r = -0.465$ and $p < 0.001$. However, no correlation was noted between the Rrs5 and the FVC Z-scores. Conversely, in the group with asthma and incomplete evidence (n=66) and in the group with suspected asthma and no objective evidence (n=24), no correlation was noted between the Rrs5 Z-scores and any of the spirometry indices Z-scores (Appendix I).

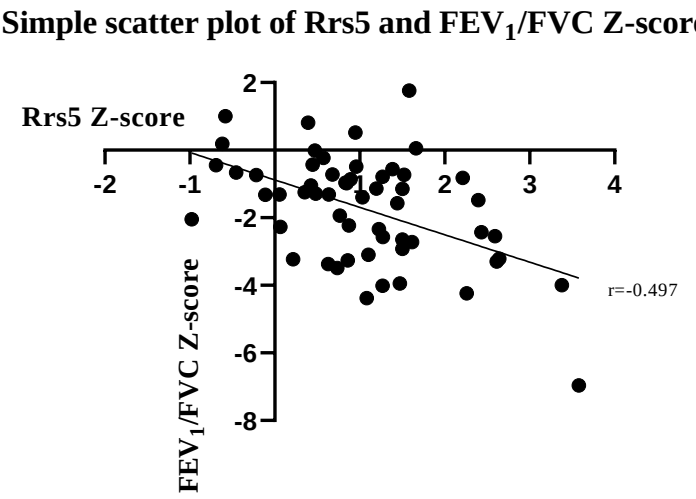
Table 6.5: Correlation between the Rrs5 Z-scores to spirometry indices Z-scores

Rrs5 Z-score	**Asthma with complete evidence (n=56)**		**Asthma with incomplete evidence (n=66)**		**Suspected asthma with no objective evidence (n=24)**	
	r	**p-value**	***r***	**p-value**	***r***	**p-value**
FEV_1 Z-score	−0.465	< 0.001*	−0.195	0.117	0.042	0.846
FVC Z-score	−0.221	0.101	0.072	0.565	0.076	0.723
FEV_1/FVC Z-score	−0.497	< 0.001*	−0.165	0.186	−0.146	0.495

*r = correlation coefficient * statistically significant*

Spirometry and FOT were done during the same lab visit

Figure 6.8: Correlation of the resistance at 5 Hz (Rrs5) with the forced expiratory volume in 1 second to the forced vital capacity (FEV_1/FVC) in the group with asthma and complete evidence



The line represents the line of best fit

Legend: Note the significant negative relationship between the Rrs5 Z-scores and the FEV_1/FVC Z-scores in children with asthma and complete evidence (r^2 = 0.247 and p = <0.001)

The correlations of the Rrs5 and Rrs5-20 Z-scores to the spirometry indices Z-scores in the group with asthma and complete evidence (n=12), asthma with incomplete evidence (n=15) and suspected asthma with no objective evidence (n=6) are shown in Table 6.6. The sample was customised in this approach because of the availability of the Rrs5-20 Z-scores, as shown in Figures 6.1–6.3. No significant associations were noticed between the FOT indices and the spirometry indices Z-scores in the group with asthma and incomplete evidence and the group with suspected asthma and no objective evidence. However, in the group with asthma and complete evidence, a significant correlation was observed between the Rrs5 Z-scores to the FEV_1 and FEV_1/FVC Z-scores, with values of r = −0.663 and r = −0.635 respectively, the highest correlation of Rrs5 to the FEV_1 Z-scores (Figure 6.9). Conversely, Rrs5-20 Z-scores only correlated significantly with the FEV_1/FVC Z-scores (r = −0.775 and p = 0.0031) (Figure 6.10).

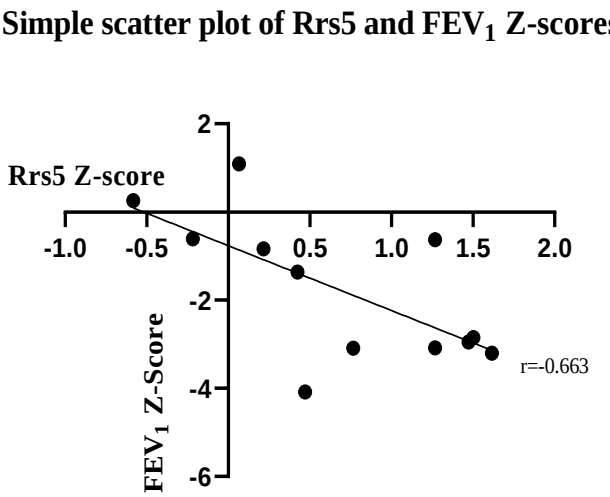
Table 6.6: Correlation between the Rrs5 Z-scores and Rrs5-20 Z-scores to the spirometry indices Z-scores

	Asthma with complete evidence (n=12)		Asthma with incomplete evidence (n=15)		Suspected asthma with no objective evidence (n=6)	
	r	**p-value**	***r***	**p-value**	***r***	**p-value**
Rrs5 Z-score and FEV_1 Z-score	−0.663	0.019*	0.000	> 0.999	0.086	0.919
Rrs5 Z-score and FVC Z-score	−0.351	0.263	0.175	0.529	−0.257	0.658
Rrs5 Z-score and FEV_1/FVC Z-score	−0.635	0.027*	−0.257	0.354	0.714	0.136
Rrs5-20 Z-score and FEV_1 Z-score	−0.377	0.227	−0.086	0.760	0.143	0.803
Rrs5-20 Z-score and FVC Z-score	0.064	0.843	0.306	0.266	0.086	0.919
Rrs5-20 Z-score and FEV_1/FVC Z-score	−0.775	0.003*	−0.164	0.558	0.200	0.714

*r = correlation coefficient * statistically significant*

Spirometry and FOT were done during the same lab visit

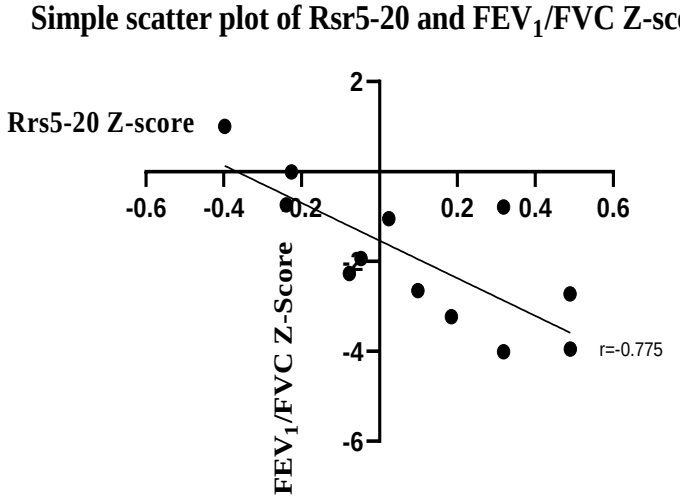
Figure 6.9: Correlation of the resistance at 5 Hz (Rrs5) to the forced expiratory volume in 1 second (FEV_1) in the group with asthma and complete evidence



The line represents the line of best fit

Legend: Note the significant negative relationship between Rrs5 Z-scores and the FEV_1 Z-scores in children with asthma and complete evidence ($r^2 = 0.440$ and $p = 0.019$)

Figure 6.10: Correlation of the resistance difference between 5–20 Hz (Rrs5-20) to the forced expiratory volume in 1 second to the forced vital capacity ratio (FEV_1/FVC) in the group with asthma and complete evidence



The line represents the line of best fit

Legend: Note the significant negative relationship between Rrs5-20 Z-scores and the FEV_1/FVC Z-scores in children with asthma and complete evidence ($r^2 = 0.600$ and $p = 0.003$)

The correlation of the Rrs5 and the AX Z-scores to the Z-scores of the spirometry indices was studied in the group with asthma and complete evidence (n=44), asthma with incomplete evidence (n=51) and suspected asthma with no objective evidence (n=18) as shown in Table 6.7. The sample was represented in this format due to the availability of the AX Z-scores (see Figures 6.1–6.3). The Rrs5 Z-scores correlated to the FEV_1 and the FEV_1/FVC Z-scores in the group of complete evidence, with values of r = −0.461 and r = −0.498, respectively (Figure 6.11). All spirometry indices Z-scores of FEV_1, FVC and the FEV_1/FVC correlated with the AX Z-scores, with the highest correlation being to the FEV_1 Z-scores (r = −0.604) (Figure 6.12). However, in the group with asthma and incomplete evidence and the group with suspected asthma and no objective evidence, none of the spirometry indices Z-scores correlated with the Rrs5 Z-scores or the AX Z-scores.

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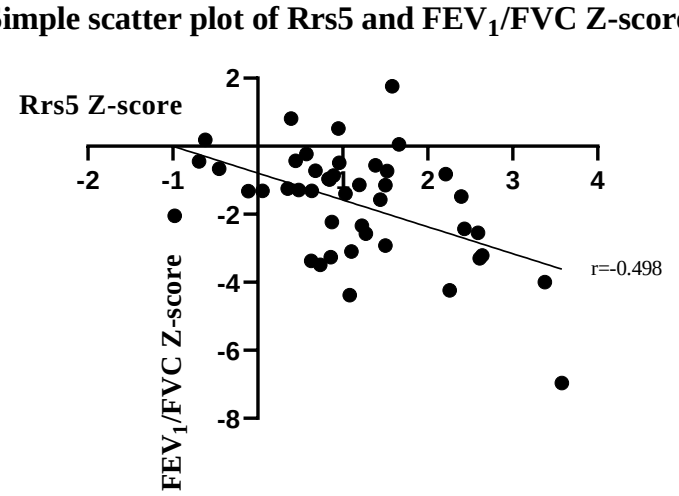
Table 6.7: Correlation between the Rrs5 Z-scores and AX Z-scores to the spirometry indices Z-scores

	Asthma with complete evidence (n=44)		Asthma with incomplete evidence (n=51)		Suspected asthma with no objective evidence (n=18)	
	r	**p-value**	***r***	**p-value**	***r***	**p-value**
Rrs5 Z-score and FEV_1 Z-score	−0.461	0.002*	−0.178	0.213	0.040	0.875
Rrs5 Z-score and FVC Z-score	−0.227	0.138	0.060	0.676	0.107	0.672
Rrs5 Z-score and FEV_1/FVC Z-score	−0.498	0.001*	−0.159	0.264	−0.225	0.370
AX Z-score and FEV_1 Z-score	−0.604	< 0.001*	−0.243	0.086	−0.116	0.646
AX Z-score and FVC Z-score	−0.399	0.007*	−0.068	0.636	0.061	0.809
AX Z-score and FEV_1/FVC Z-score	−0.454	0.002*	−0.036	0.805	−0.369	0.132

*r = correlation coefficient * statistically significant*

Spirometry and FOT were done during the same lab visit

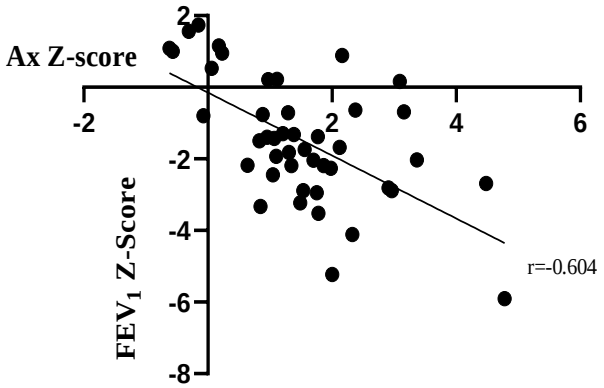
Figure 6.11 Correlation of the resistance at 5Hz (Rrs5) to the forced expiratory volume in 1 second to the forced vital capacity (FEV_1/FVC) in the group of asthma with complete evidence



The line represents the line of best fit

Legend: Note the significant negative relationship between Rrs5 Z-scores and the FEV_1/FVC Z-scores in children with asthma with complete evidence (r^2 = 0.248 and p = 0.002)

Figure 6.12 Figure 6.12: Correlation of the area under the curve (AX) to the forced expiratory volume in 1 second (FEV_1) in the group of asthma with complete evidence



The line represents the line of best fit

Legend: Note the significant negative relationship between AX Z-scores and the FEV_1 Z-scores in children with asthma with complete evidence (r^2 =0.365 and p = <0.0001)

All the correlation figures of the FOT indices to the spirometry indices Z-score are presented in the Appendix I.

6.5.3 Correlation of the Rrs5 Z-scores and to the FeNO levels in children attending the asthma clinic

A correlation between the Rrs5 Z-scores and FeNO values was conducted to assess the relationship between the FOT and the FeNO measurements in the children attending the asthma clinic. The two groups of children with asthma who had complete and incomplete evidence were combined and the correlation was run on that group in addition each group separately of asthma with complete evidence and asthma with incomplete evidence. The group of children with suspected asthma was not analysed in this part, as the FeNO readings were essential for categorisation and all FeNO readings within that particular group were normal. Data included within this part of analysis were from children who had FeNO readings. The characteristics of these groups are shown in Table 6.8.

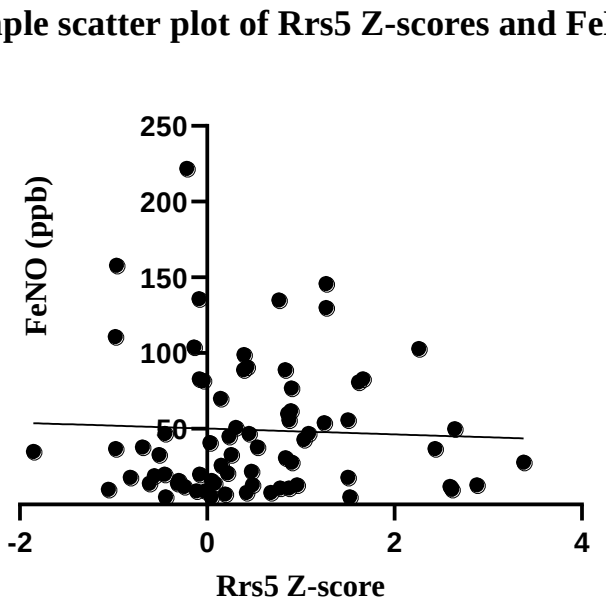
The Rrs5 Z-scores did not correlate with the FeNO values in the group with asthma and complete evidence, the group with asthma and incomplete evidence, or the combined group (Figures 6.13–6.15).

Table 6.8: Characteristics of the children with FeNO readings in the asthma with complete evidence, asthma with incomplete evidence and the combined groups

	Combined group (n=73)	**Asthma with complete evidence (n=33)**	**Asthma with incomplete evidence (n=40)**
Sex, Male (%)	46 (63%)	24 (72.7%)	22 (55%)
Age (years)	11.38 (2.36)	11.09 (2.44)	11.61 (2.31)
Height (cm)	148.4 (14.57)	145.8 (16.04)	150.6 (13.06)
Weight (kg)	44.51 (13.85)	41.38 (12.82)	47.08 (14.30)

Data presented as mean (SD) unless otherwise stated

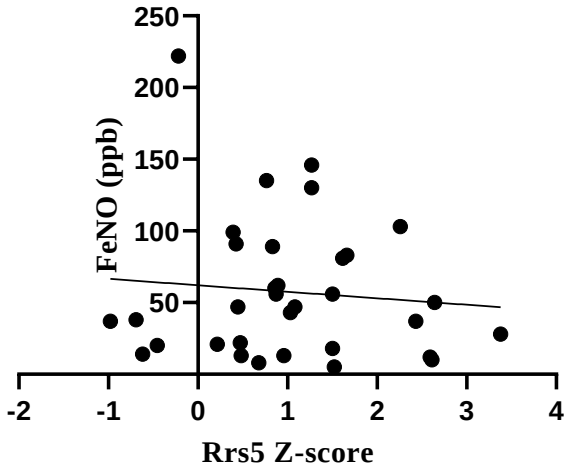
Figure 6.13: Comparing Rrs5 Z-scores with the FeNO readings in the combined group (n=73)



The line represents the line of best fit

Legend: No significant relationship between the Rrs5 Z-scores and the FeNO values in the combined group of children with asthma and complete evidence and asthma with incomplete evidence (r= 0.0453, p = 0.704)

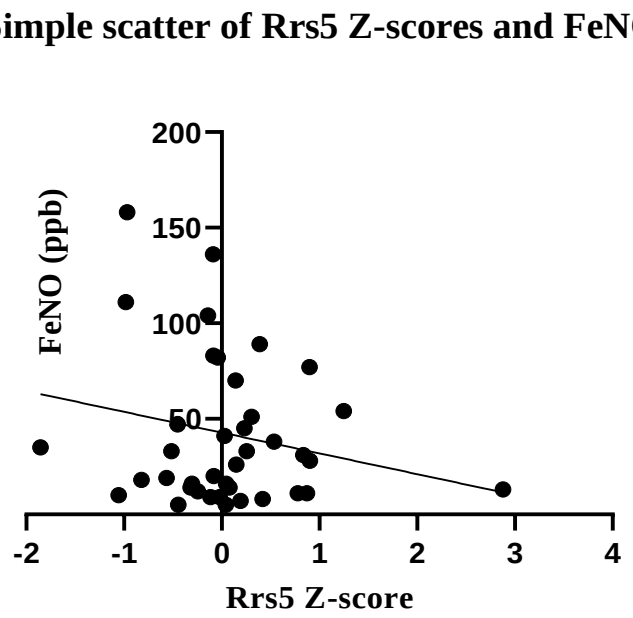
Figure 6.14: Comparing Rrs5 Z-scores with the FeNO readings in the group with asthma and complete evidence (n=33)



The line represents the line of best fit

Legend: No significant relationship between the Rrs5 Z-scores and the FeNO values in children with asthma and complete evidence (r= −0.0956, p = 0.597)

Figure 6.15: Comparing Rrs5 Z-scores with the FeNO readings in the group with asthma and incomplete evidence (n=40)



The line represents the line of best fit

Legend: No significant relationship between the Rrs5 Z-scores and the FeNO values in children with asthma and incomplete evidence (r= −0.111, p = 0.494)

6.6 Discussion

The FOT measurements of the resistance and the area under the reactance curve at the baseline were able to reflect abnormalities in children with asthma. This was shown by the mostly abnormal Z-scores of the Rrs5 and the AX values in children with asthma compared with the normal Z-scores in the children in the healthy control group. However, AX had higher sensitivity compared with the Rrs5 in children with asthma. Though Rrs5-20 suggested small airway obstruction (97,108), Rrs5-20 could not determine any abnormalities in children with asthma in this study. This could be due to the limited availability of data on the Rrs5-20 Z-scores in our study. Previously, Xrs5 was used to study the peripheral airways (108). However, it was not studied here due to technical issues with the TremeFlo machine and loss of data from the software at the data collection stage.

Our findings regarding the ability of the FOT parameters to identify asthma were in agreement with other findings of other studies in this field (88,113).The area under the reactance curve at the baseline measures was shown to be the best indicator for differentiating between children

with chronic and acute asthma compared with the healthy control group (110). This is because AX is considered to be a sensitive index of the reactance, with the ability to reflect airflow obstruction in children and adolescents (88,113). In contrast, another study reflected that the Rrs5 was the best indicator for assessing peripheral airway obstruction in children with mild to moderate asthma aged 6–17 years (112).

Seventy eight percent of the participants in the stable asthma group were using ICS treatment. Sharif et al. reported that small airway obstruction in children with asthma could be significantly reversed by ICS treatment (232). However, patients in whom small airway disease was particularly marked would be expected to show a greater response to treatment (233). IOS was also suggested to be an informative tool in determining lung mechanics in children with asthma using inhaled corticosteroids (111,139). In addition, IOS could also be used to measure the effect of the treatment on the small airways, which is not reflected by spirometry (139).

Others showed that studying bronchodilator reversibility using FOT added additional value in differentiating acute and chronic asthma from the healthy control group (110). However, there were no significant differences in the baseline measurements between healthy and asthmatic children (110). This would indicate that the bronchodilator response has better diagnostic efficacy than the baseline values of the FOT measurements. Unfortunately, only the baseline measurements were available for this study.

It was noted in our study that the Rrs5 Z-scores correlated with both FEV_1/FVC and FEV_1 at the baseline measurements. This linear association between the spirometry and FOT indices could indicate peripheral airway obstruction (157). This was supported by Lauhkonen et al. and Olaguibel et al., who showed that there was a correlation between the spirometry and IOS/FOT indices in children with asthma (157,189). A similar pattern was seen in a group of preschool children with asthma presented with a correlation of the FEV_1 to airway resistance (189). Additionally, in a group of children aged from 3.8 to 17.7 who were recruited from the asthma clinic (and were similar to the group in the current study), a significant correlation with the resistance at 8 Hz to the FEV_1 and the FEV_1/FVC was noted (157). Both studies showed a correlation with the IOS/FOT and the spirometry measurements both at the baseline and following bronchodilator administration (157,189). This was in accordance with the results of our study, although only for the baseline measurements; correlations were not taken following bronchodilator.

Both FEV_1 and FEV_1/FVC are considered reflective measures of spirometry (73), although a diagnosis of asthma depends mainly on interpreting the reduction in the FEV_1/FVC ratio, which would reflect airway obstruction (24,50,73). In contrast, a reduction in the FEV_1 could indicate large airways obstruction until a significant degree of small airway obstruction was evident (73). This could be revealed by the higher correlation that was observed between the Rrs5 and the FEV_1/FVC than with the FEV_1 Z-scores, and the significant correlation presented between the Rrs5-20 and the FEV_1/FVC ratio Z-scores, since FEV_1 and the Rrs reflect different patho-physiological characterisations of airway obstruction (187). For example, changes in airflow limitation will result in changes in the FEV_1 values. However, any changes in the calibre of the airway will be directly related to the changes in resistance (187).

Among all the FOT indices, the AX Z-scores were the only scores that correlated with all of the spirometry indices Z-scores (FEV_1, FVC and FEV_1/FVC). This could reiterate the theory that AX can be a better indicator of peripheral airway obstruction relative to the clinical presentation of a patient with asthma (168,176).

In our study, a correlation of the spirometry Z-scores with the FOT Z-scores was only evident in the group with asthma and complete evidence. However, no correlations between the FOT and the spirometry Z-scores were noticed in any of the other groups. This could be due to the different levels of airflow obstruction and the pattern of the disease seen between these groups, which would influence the spirometry flow measures, the respiratory resistive properties, and the resistance of the airways (144). In addition to that, this was affected also by the level of certainty of the diagnosis within the group of asthma. This was based on both ERS and NICE guidelines to define a confirmed asthma diagnosis based on objective testing (50,53). The severity between these groups did not differ significantly.

The FeNO values did not correlate with the FOT indices. This was in line with studies by Seo et al. and Nishida et al., who showed no significant associations between FeNO and the FOT in patients with asthma (234,235). However, it is recommended that the FeNO measurements be used in conjunction with impulse oscillometry in children with asthma. This will aid in assessing the degree of asthma as well as predicting potential asthma exacerbation (236,237). However, no correlation between FeNO and FOT was seen in this study. It is also worth adding the FeNO testing to the FOT measurements as it could support the diagnosis and subsequent monitoring of asthma in children.

This study had some limitations, the most major of which was the sample size. Using a larger sample size could decrease the incidence of type 2 errors, particularly in the population with Rrs5-20 Z-score readings. Additionally, adding bronchodilator reversibility testing would add great value for diagnosing asthma using FOT test. It may add value in differentiating healthy children from children with asthma, which is not reflected by the use of the baseline measurements solely (110).Moreover, the use of the Xrs values could serve as a better indication of obstruction in the small airways (108). This value was not collected within this study due to technical issue of the machine at the data collection stage.

In conclusion, our study showed that FOT measurements at 5–37 Hz could detect airway obstruction in children with asthma, except for the Rrs5-20 measurements. Additionally, the FOT measurements correlated with at least one of the spirometry measurements, with a particularly strong correlation noted between the FOT parameter, the FEV_1 and the FEV_1/FVC. Nevertheless, no correlation between the FeNO readings and FOT measurements was noted. However, performing FOT could be useful in diagnosing asthma in children who cannot tolerate spirometry, but it is not ideal for all children. Still, it could be used in conjunction with other methods for diagnosing asthma.

CHAPTER 7 FORCED OSCILLATION TECHNIQUE IN CHILDREN WITH ACUTE ASTHMA

7.1 Introduction and rationale

Acute asthma exacerbations are one of the most common reasons why children present to the emergency department or are admitted to the hospital (238). Clinical symptoms can include chest tightness, coughing, wheezing and shortness of breath (239). However, the signs and symptoms of acute asthma can differ from one patient to another and may not all appear at once (240). In a clinical setting, it is often difficult to estimate the severity of the airway obstruction (240). Therefore, it is important that the severity of the airway obstruction in acute asthma cases is determined objectively in order to more effectively manage and treat the disease (240). The National Asthma Education and Prevention Programme expert panel guidelines recommend the use of the physiological assessment of FEV_1 and PEF as objective tests. In children and adolescents, the predicted percentage of FEV_1, and PEF are the primary predictors of the severity of asthma exacerbation (173). However, the above-mentioned testing methods may not be comfortable for the patient and is often not possible during an asthma attack. At present, there is no specific recommended assessment tool to identify the severity of asthma exacerbations in children (83,239). The forced oscillation technique is a potentially useful diagnostic tool for children with an asthma attack because it is quick, requires minimal effort and can reflect small and large airway dynamics. Additionally, it is possible that airway dynamics as measured by FOT are altered by airways inflammation (122,137,141,168). Ducharme et al. studied the feasibility of using the FOT with acutely asthmatic children aged 2–17 and determined that the FOT could be used as an alternative method of objective testing to spirometry in younger or uncooperative children (137).

Asthma severity is usually assessed by evaluating the reflective parameters of the lungs before and after treatment (241). In adolescents and children with acute asthma, the use of short-acting beta-2 agonists (SABA) bronchodilator is usually beneficial for those with an acute asthma exacerbation (242). Using the FOT in acute asthma cases could serve as a tool in assessing the bronchodilator response and the severity of the asthma attack. FOT was studied to determine the effect of bronchodilator on the resistance and reactance of the airways at different waveform frequencies, by expressing the change from baseline (168). Different studies assessed the bronchodilator (SABA) effect on FOT measurements and determined cut-off points in healthy

children and in children with chronic but stable asthma (88,123,143,203,243,244). The cut-off for SABA percentage change was calculated to be 40% for Rrs and 65% for Xrs (244), and suspected asthma is indicated if there is a greater than 30% drop in the Rrs (168).There is still a need to assess the efficacy of FOT in assessing bronchodilator response and severity of airway obstruction in children with acute asthma.

Measurements of FOT at lower frequencies are considered to be more sensitive at reflecting airway obstruction than those measured at higher frequencies (87). However, an indirect confirmation of airway obstruction associated with asthma can be suspected when there is a positive bronchodilator response on the FOT measurements (87). Choosing the best frequency and FOT measurement to diagnose asthma in children depends on the bronchodilator effect on the FOT measurements in relation to the improvement and the percentage change of FEV_1 after the bronchodilator administration, which will reflect the best cut-off points, sensitivity, and specificity of the measurements at different frequencies (87). Hellinckx et al. reported a positive response to bronchodilator, presented as a 40% change in the resistance at 5 Hz following SABA administration (129). In contrast, Ducharme et al. suggested the use of the resistance at 8 Hz, with a 19% change after bronchodilator administration indicates a positive response (137), while Delacourt et al. recommended the use of the Rrs0 to assess airway obstruction and reversibility in children (122). The best cut-off points following SABA administration using FOT at different frequencies are still debatable.

7.2 Aims

1- To assess FOT indices using TremoFlo in children with acute asthma attending the emergency department or following admission to the children's ward.
2- To evaluate FOT parameters before and after bronchodilator administration in children with acute asthma.
3- To explore the differences between the FOT measurements at 5–37 Hz and 7–41 Hz waveform frequencies in children with acute asthma.

7.3 Hypotheses

1- The FOT measurements of resistance and reactance by TremoFlo using frequency waveforms at 5–37 Hz and 7–41 Hz (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20 and Xrs7) reflect airway obstruction in school-age children with acute asthma.
2- Most of the abnormal FOT measurements of resistance and reactance using frequency waveforms at 5–37 Hz and 7–41 Hz (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7,

Rrs7-20, Xrs7 and AX using 7–41 Hz) exhibit change after bronchodilator administration in school-age children with acute asthma.

3- The measurements of FOT using waveforms at 7–41 Hz will be more useful reflection of abnormalities than measurements at 5–37 Hz in school-age children with acute asthma.

7.4 Materials, Methods and Participants

7.4.1 Study design and participants

This was an observational prospective cohort study in school-aged children aged 5–15 years who attended the Leicester Royal Infirmary emergency department (ED) or were hospitalised. The study was conducted with the approval of the Cambridge South Research Ethics Committee and our tests were performed in addition to the patients' regular care during this period.

The parents of the children were approached either at the ED or during their hospital admission. After the initial approach, detailed information sheets were given to both the parents and children, who were then given at least 30 minutes to read the papers, with extra time provided if necessary. Before enrolling into the study, and after they had read the information sheets, the children and parents had the opportunity to ask further questions. If they subsequently agreed to join the study, a consent form was given to them to sign before they were formally enrolled.

Once they were enrolled, they filled in a respiratory questionnaire and the ACT or cACT depending on the age of the child. Then, the tests began with the FOT as a baseline measure before administration of four to ten puffs of salbutamol as prescribed by the attending physician. Repeat FOT measurements were made 15 minutes after bronchodilator administration. FeNO was attempted depending on the child's ability to perform the FeNO according to his/her clinical status.

7.4.2 Data collection and analysis

FOT was repeated until three acceptable tests were obtained. Each test lasted approximately 20 seconds and was measured at frequency ranges of 5–37 Hz and 7–41 Hz. Impedance measurements of the forced oscillation were reflected as resistance at 5 Hz (Rrs5), resistance difference of 5-20 Hz (Rrs5-20), reactance at 5 Hz (Xrs5), reactance area using 5–37 Hz (AX using 5–37 Hz), resistance at 7 Hz (Rrs7), resistance difference of 7-20 Hz (Rrs7-20), reactance at 7 Hz (Xrs7) and reactance area using 7–41 Hz (AX using 7–41 Hz). The Z-scores were recorded based on two references dataset by the TremoFlo for the intended studied group (88,133). The

best reference dataset was retrieved automatically by the TremoFlo depending on the age, height, and weight of the participant. FeNO was reported in parts per billion (ppb). The data from the FOT were reported according to the ATS/ERS guidelines (117). The guidelines used for FOT are for preschool-aged children. However, they can be applied to school-aged children even though they are intended for preschool-aged children as they were based on some studies of school-aged children. A detailed description of the procedures and the acceptance criteria is provided in Chapter 3.

7.4.3 Statistical analysis

All the participant's demographic characteristics (age, height, weight, and sex) were collected. The Z-score was used as the interpretive method for FOT, as per the recommendation of ATS/ERS since it is independent of age, height, and sex (64,117). The Z -scores were calculated as (measured – predicted mean)/ (standard deviation of the residuals) (208,209) where Z-scores of less than −1.64 or greater than + 1.64 were classified as an abnormal result (165,208). The normality of the data was tested using histograms and the Shapiro–Wilk test. Comparisons between the measurements were made using ANOVA and the Kruskal–Wallis test, followed by an unpaired t-test for parametric data and the Mann–Whitney U test for non-parametric data. A paired t-test was used to compare data before and after bronchodilator, with a significant p-value less than 0.05 denoting statistical significance for all the tests.

7.4.4 Approach to analysis

In order to study the FOT parameters in children with acute asthma, children were divided into a group of participants with FOT measurements using waveform 5–37 Hz, a group with FOT measurements using waveform 7–41 Hz and a group with FOT measurements using both waveforms. These groups were also subdivided according to the availability of the Z-scores of these measurements, which depended on the reference that was retrieved by TremoFlo (88,133).

In order to determine how the FOT parameters were presented in children with acute asthma and to evaluate the bronchodilator reversibility. The Z-scores for Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20 and Xrs7 were classified to normal and abnormal Z-scores. This was done for the group with measurements at frequency waveform 5–37 Hz and the group with measurements at 7–41 Hz. No reference values or Z-scores were available for the AX using 7–41 Hz by the machine according to the references used for the studied population. The Z-scores collected for both groups with baseline measures only and those with acceptable measures before and after the administration of the bronchodilator were classified.

Comparison between the Z-scores of the parameters (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz) were made using the Kruskal–Wallis test for the baseline and following bronchodilator measurements. Where a statistically significant difference was present, unpaired t-test and Mann–Whitney U test was also performed for the parametric data and the non-parametric data. This was also done for the Z-scores of the parameters at the oscillation waveform of 7–41 Hz, but not for AX as no reference values or Z-scores were available for the AX using 7–41 Hz by the machine according to the references used for the studied population.

The average percentage change following bronchodilator administration was calculated for Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, and Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz values. A comparison of the percentage change after bronchodilator administration of Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz was performed using an ANOVA test followed by a paired t-test to determine any statistically significant difference. This was also done to determine the percentage change after bronchodilator for Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz. A paired t-test was used for parametric data, to study the actual readings of the resistance and the reactance at 5–37 Hz and 7–41 Hz both before and after bronchodilator administration.

To explore the differences between the FOT measurements at the 5–37 Hz and 7–41 Hz waveform frequencies in detecting abnormalities and assessing bronchodilator response, the Z-scores were studied for the group with measurements at both waveform frequencies (n=15). Z-scores were classified separately as normal and abnormal for Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20 and Xrs7. No reference values or Z-scores were available for the AX using 7–41 Hz by the TremoFlo machine. The average percentage changes following bronchodilator administration was also calculated for actual readings of Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz. An unpaired t-test was used for the parametric study data. The Z-scores and the average percentage changes of the resistance and the reactance difference between the measurements at 5–37 Hz with measurements at 7–41 Hz were compared.

7.5 Results

A total of 61 school-aged children were approached to take part in the study either at the ED or on the ward. Initially, 20 families out of the 61 declined to participate. However, other participants were subsequently excluded due to reasons such as the participants either being too unwell, refusing to complete the test or not providing acceptable measurements and traces. All participants had been diagnosed with acute asthma by a physician, and the entire population is presented in the flowchart in Figure 7.1.

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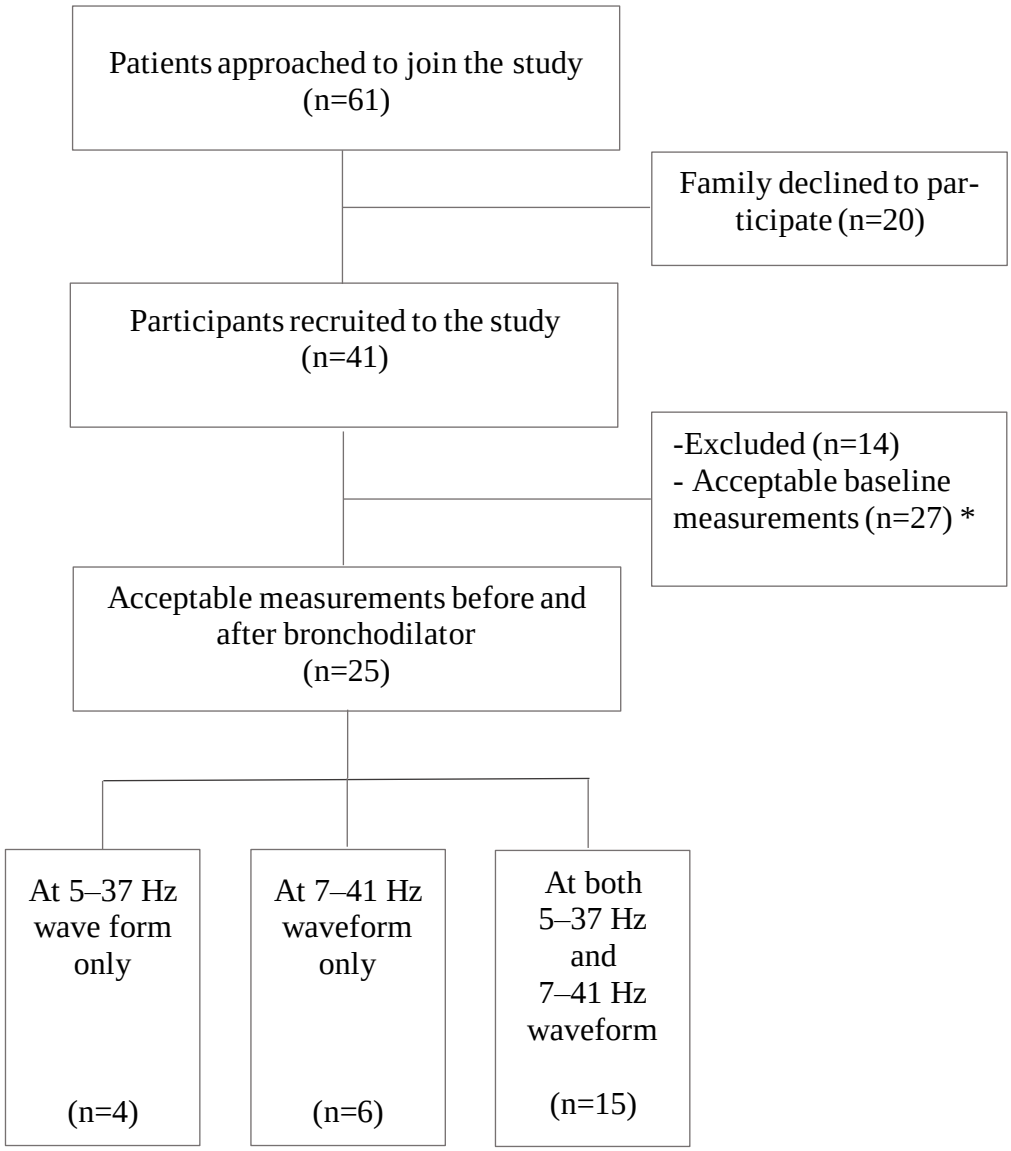
Figure 7.1: Flow chart of the entire cohort of school-aged children with acute asthma who were approached



** At 5–37 Hz wave form only (n=5), at 7–41 Hz waveform only (n=5) and at both 5–37 Hz and 7–41 Hz waveform (n=17)*

7.5.1 Evaluation of FOT parameters in children with acute asthma with acceptable baseline measurements

Among children with acute asthma, acceptable FOT measurements at baseline using waveforms of 5–37 Hz, 7–41 Hz and both were available for 27 participants (n = 5 at 5–37 Hz, n = 5 at 7–41 Hz and n = 17 at both 5–37 Hz and 7–41 Hz). Among children with FOT measurements at 5–37 Hz (n = 22), all participants had both Rrs5 and Xrs5 Z-scores, 2 had Rrs5-20 Z-scores and 20 had Z-scores for AX using 5–37 Hz. However, among children with FOT measurements at 7–41 Hz (n = 22), all participants had Rrs7 and Xrs7 Z-scores, 3 had Rrs7-20 Z-scores and none had Z-scores for AX using 7–41 Hz. Among children with readings at both 5–37 Hz and 7–41 Hz (n = 17), all 17 participants had Rrs5, Rrs7, Xrs5 and Xrs7 Z-scores, 2 had Rrs5-20 Z-scores, 2 had Rrs7-20 Z-scores, 15 had Z-scores for AX 5–37 Hz and none had Z-scores for AX using 7–41 Hz. No reference values or Z-scores were available for AX using 7–41 Hz from the machine according based on the references used for the studied population.

Comparing children with FOT measurements using waveforms of 5–37 Hz and 7–41 Hz at baseline

Baseline Z-scores for FOT at 5–37 Hz: The Z-scores for resistance at 5 Hz (Rrs5), Rrs5-20, Xrs5 and AX 5–37 Hz (mean ± SD) were 1.24 ± 1.26, 0.59 ± 0.98, 2.22 ± 3.58 and 2.18 ± 1.43, respectively. Abnormal Rrs5 Z-scores were observed in 40.9% of the participants. All Rrs5-20 Z-scores were normal. Xrs5 abnormal Z-scores were observed in 59.1% of the participants, and 50% of the Z-scores for AX using 5–37 Hz were abnormal. Eight participants had abnormal Z-scores for three measurements, three participants had abnormal Z-scores for two measurements, and two participants had abnormal Z-scores for one measurement. Nine participants had normal Z-scores for all FOT measurements in the range 5–37 Hz.

Baseline Z-scores for FOT at 7–41 Hz: Resistance at 7 Hz (Rrs7), Rrs7-20 and Xrs7 Z-scores (mean± SD) were 0.82 ± 1.06, 0.42 ± 0.57 and 1.60 ± 3.85, respectively. Resistance at 7 Hz presented with 27.3% abnormal Z-scores. All Rrs7-20 Z-scores were normal, and 68.2% abnormal Xrs7 Z-scores were observed. Four participants had abnormal Z-scores for three measurements, two participants had abnormal Z-scores for two measurements, and nine participants had abnormal Z-scores for one measurement. Seven participants had normal Z-scores for all FOT measurements in the range 7–41 Hz.

Xrs5 and Xrs7 had the highest proportion of abnormal Z-scores, followed by AX using 5–37 Hz and finally, Rrs5 and Rrs7. However, no abnormal Z-scores were observed for Rrs5-20 and Rrs7-20.

7.5.2 Evaluation of FOT parameters in children with acute asthma and bronchodilator reversibility

In our population of children with acute asthma having acceptable FOT measurements before and after bronchodilator administration using waveforms of 5–37 Hz, 7–41 Hz and both was divided according to Z-score availability. In the group of children with FOT measurements at 5–37 Hz (n = 19), all participants had both Rrs5 and Xrs5 Z-scores, 2 had Rrs5-20 Z-scores and 17 had Z-scores for AX using 5–37 Hz. However, in the group of children with FOT measurements using waveforms of 7–41 Hz (n = 21), all participants had Rrs7 and Xrs7 Z-scores, 3 had Rrs7-20 Z-scores and none had Z-scores for AX using 7–41 Hz. Among children with readings at both 5–37 Hz and 7–41 Hz (n = 15), all participants had Rrs5, Rrs7, Xrs5 and Xrs7 Z-scores, 2 had Rrs5-20 Z-scores, 2 had Rrs7-20 Z-scores, 13 had Z-scores for AX using 5–37 Hz and none had Z-scores AX using 7–41 Hz. No reference values or Z-scores were available for AX using 7–41 Hz from the machine according based on the references used for the studied population. The demographic characteristics of these groups are shown in Table 7.1.

Table 7.1: Characteristics of children diagnosed with acute asthma using FOT at frequency waveform of 5–37 Hz and 7–41 Hz

	Acute asthma 5–37 Hz (n=19)	**Acute asthma 7–41 Hz (n=21)**	**Acute asthma 5–37 Hz and 7–41 Hz (n=15)**
Sex, Male (%)	13 (68.4%)	15 (71.4%)	11 (73.3%)
Age (years)	8.42 (2.66)	8.34 (2.67)	8.47 (2.83)
Height (cm)	133.4 (15.75)	132.9 (15.63)	133.5 (15.10)
Weight (kg)	33.72 (16.46)	33.24 (15.71)	34.03 (17.17)

Data presented as mean (SD) unless otherwise stated

(There were no statistically significant differences in age, height or weight between the groups)

Comparing Z-scores among children with FOT measurements using waveforms of 5–37 Hz (n = 19) and 7–41 Hz (n = 21) before and after bronchodilator administration

Z-scores for FOT at 5–37 Hz before bronchodilator administration: The Rrs5 Z-scores were abnormal in 42% of participants with acute asthma. All Rrs5-20 Z-scores were normal. Abnormal Z-scores were also observed, with 63.2% of children having abnormal Xrs5 Z-scores and 52.9% having abnormal Z-scores for AX using 5–37 Hz. No statistically significant differences were found among the Z-scores of Rrs5, Rrs5-20, Xrs5 and AX using 5–37 Hz at baseline.

Z-scores for FOT at 7–41 Hz before bronchodilator administration: Rrs7 presented with 28.6% abnormal Z-scores. All Rrs7-20 Z-scores were normal, and 61.9% of the studied population had abnormal Xrs7 Z-scores. Statistically significant differences were only present between the Z-scores of Rrs7 and Xrs7, with a p-value of 0.022.

The highest proportion of abnormal Z-scores was observed for Xrs5 and Xrs7, followed by AX using 5–37 Hz and finally, Rrs5 and Rrs7. However, no abnormal Z-scores were observed for Rrs5-20 and Rrs7-20.

Z-scores for FOT at 5–37 Hz after bronchodilator administration: Abnormal Rrs5 Z-scores after bronchodilator administration were presented by 5.2% of the studied population. No abnormalities were observed in the Rrs5-20 Z-scores. Abnormal Xrs5 Z-scores fell slightly to 57.9% following bronchodilator, while the proportion of participants with abnormal Z-scores for AX using 5–37 Hz before and after bronchodilator remained the same at 52.9% of the studied population. Statistically significant differences were noted following bronchodilator between the Z-scores of Rrs5 and Xrs5, Rrs5 and AX using 5–37 Hz and Rrs5-20 and AX using 5–37 Hz, with p-values of 0.037, 0.011 and 0.047, respectively.

Z-scores for FOT at 7–41 Hz after bronchodilator administration: A decrease to 14.3% abnormal Rrs7 Z-scores was noted after bronchodilator, while the Rrs7-20 Z-scores remained normal. However, an abnormal Z-score for Xrs7 was observed in 66.7% of participants after bronchodilator. Statistically significant differences were only present between the Z-scores of Rrs7 and Xrs7, with a p-value of 0.008.

There were statistically significant differences in the Z-scores before and after the bronchodilator administration using 5–37 Hz for Rrs5 and AX, with p-values of 0.021 and 0.004, respectively. The Z-scores for Rrs7 and Xrs7 before and after the bronchodilator administration using 7–41 Hz were significantly different, with p-values of 0.003 and 0.023, respectively.

The Z-scores of the FOT parameters at 5–37 Hz and 7–41 Hz before and after bronchodilator are presented in Tables 7.2–7.4 and Figures 7.2 and 7.3.

Table 7.2: Forced oscillation Z-scores for Rrs5 and Rrs7 in children with doctor-diagnosed acute asthma

	Acute Asthma (Rrs5)	Acute Asthma (Rrs7)
Number of participants with Z-scores	(n=19)	(n=21)
Z-scores at the baseline, mean (SD)	1.20 (1.29)	0.81 (1.09)
Abnormal Z-scores at the baseline, n (%)	8 (42%)	6 (28.6%)
Abnormal Z-scores after bronchodilator, mean (SD)	0.67 (0.94)	0.48 (0.99)
Abnormal Z-scores after bronchodilator, n (%)	1 (5.2%)	3 (14.3%)

Table 7.3: Forced oscillation Z-score of Xrs5 and Xrs7 in children with doctor-diagnosed acute asthma

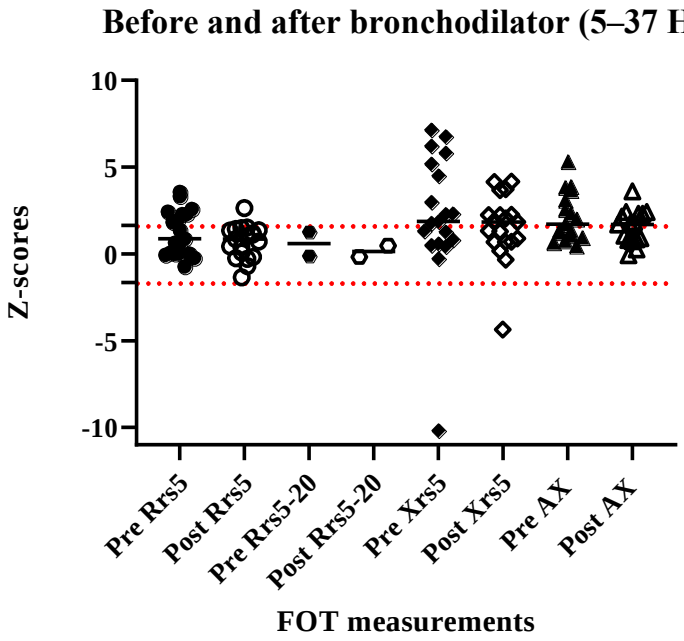
	Acute Asthma (Xrs5)	Acute Asthma (Xrs7)
Number of participants with Z-scores	n=19	n=21
Z-scores at the baseline, mean (SD)	2.18 (3.80)	1.58 (3.93)
Abnormal Z-scores at the baseline, n (%)	12 (63.2%)	13 (61.9%)
Abnormal Z-scores after bronchodilator, mean (SD)	1.54 (1.94)	1.06 (2.81)
Abnormal Z-score after bronchodilator, n (%)	11(57.9%)	14 (66.7%)

Table 7.4: Forced oscillation Z-score of AX using 5–37 Hz in children with doctor- diagnosed acute asthma

	Acute Asthma (AX using 5–37 Hz)
Number of participants with Z-scores	n=17
Z-scores at the baseline, mean (SD)	2.14 (1.39)
Abnormal Z-scores at the baseline, n (%)	9 (52.9%)
Abnormal Z-scores after bronchodilator, mean (SD)	1.52 (0.95)
Abnormal Z-scores after bronchodilator, n (%)	9 (52.9%)

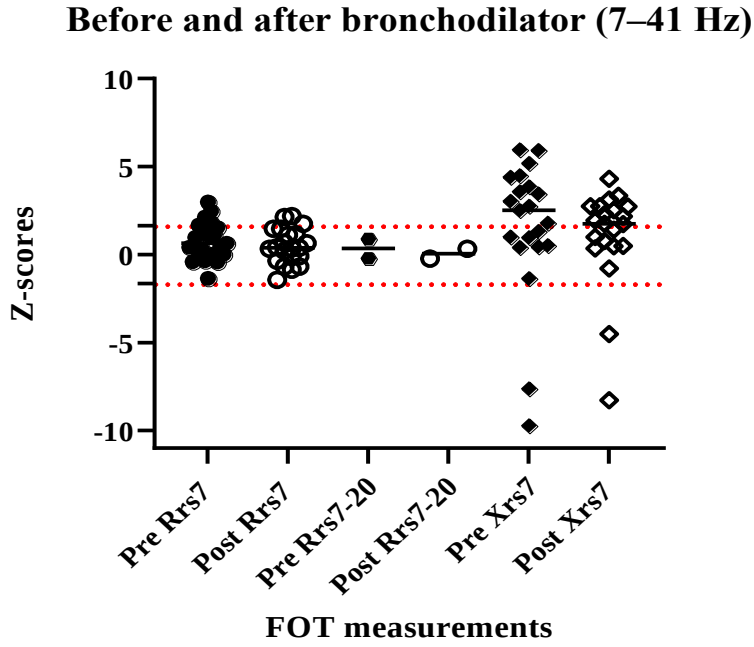
No Z-scores were available for the AX using 7–41 Hz by the machine according to the references used for the studied population

Figure 7.2: Z-scores of FOT measurements using waveform 5–37 Hz before and after administration of a bronchodilator



…… *Represents cut-off for abnormal Z-score of ≥1.64 or ≤−1.64*
Pre SABA (closed symbols), Post SABA (open symbols)

Figure 7.3: Z-scores of FOT measurements using waveform 7–41 Hz before and after administration of a bronchodilator



..... *Represents cut-off for abnormal Z-score of ≥1.64 or ≤−1.64*
Pre SABA (closed symbols), Post SABA (open symbols)

Comparing percent change in the raw data in children with FOT measurements at 5–37 Hz (n = 19) and 7–41 Hz (n = 21) before and after bronchodilator administration

FOT measurements using waveforms of 5–37 Hz before and after bronchodilator administration: An average of −9.63% improvement following bronchodilator was observed for Rrs5, with an average change of −17.30% for Rrs5-20. An average percent change of 13.55% was noted for Xrs5. The highest average percent change after bronchodilator administration among the FOT measurements at 5–37 Hz was noted for AX, at −20.07%. FOT measurements for Rrs5, Rrs5-20, Xrs5 and AX using 5–37 Hz showed statistically significant changes following bronchodilation, as shown in Table 7.5. The FOT measurements using waveforms of 5–37 Hz before and after bronchodilator are shown in the figures in Table 7.6.

When comparing the percentage change after bronchodilator administration of ΔRrs5, ΔRrs5-20, ΔXrs5 and ΔAX using 5–37 Hz, a significant difference was observed between ΔRrs5 and ΔXrs5, ΔRrs5-20 and ΔXrs5 and ΔXrs5 and ΔAX using 5–37 Hz, all with p-values < 0.0001.

Table 7.5: Paired T-test for acute asthma with FOT measurements using waveform 5–37 Hz before and after bronchodilator (n=19)

	Pre-BD	Post-BD	p-value
Rrs5 ($cmH_2O \cdot sec/L$)	8.52 (2.29)	7.49 (1.91)	0.028*
Rrs5-20 ($cmH_2O \cdot sec/L$)	3.41 (1.42)	2.66 (0.96)	0.009*
Xrs5 ($cmH_2O \cdot sec/L$)	−5.88 (2.65)	−4.62 (1.52)	0.018*
AX (cmH_2O/L)	60.88 (30.71)	44.93 (19.49)	0.004*

*Data represented mean (SD)*statistically significant*

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Table 7.6: FOT measurements using waveform 5–37 Hz before and after administration of bronchodilator

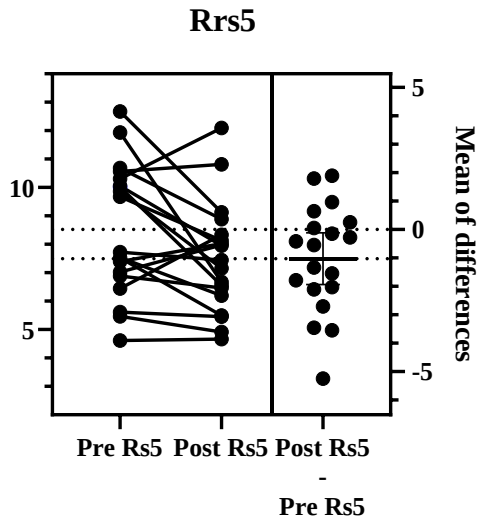
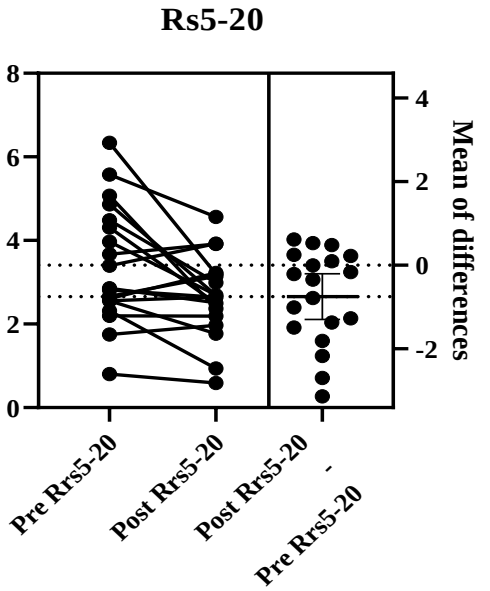
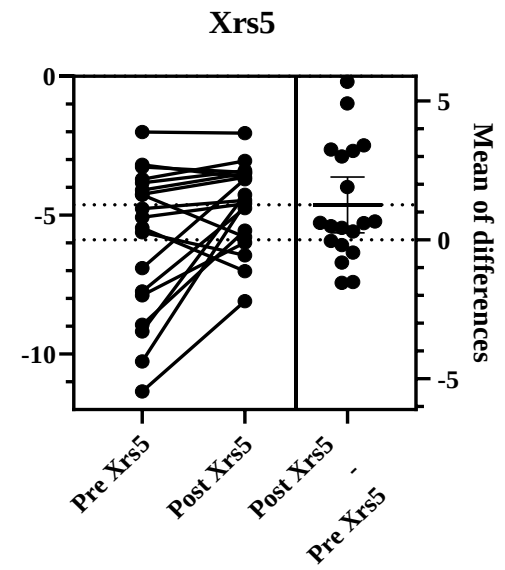
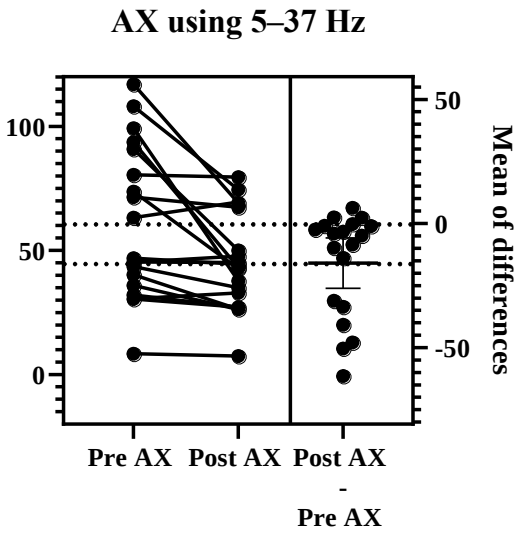
FOT measurements using 5–37 Hz	(n=19)
Rrs5 ($cmH_2O \cdot sec/L$)	
Rrs5-20 ($cmH_2O \cdot sec/L$)	

Table 7.6 (Continued)

FOT measurements using 5–37 Hz	(n=19)
Xrs5 ($cmH_2O \cdot sec/L$)	
AX (cmH_2O/L)	

FOT measurements using waveforms of 7–41 Hz before and after bronchodilator administration: The lowest average percent change following bronchodilator was noted for Rrs7, at −7.02%. An average percent change of –17.40% was observed for Rrs7-20, and similar average percent changes were observed for Xrs7 and AX using 7–41 Hz, at 14.18% and −18.32%, respectively. Statistically significant changes in the Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz readings before and after bronchodilator were also noted by the paired t-test (Table 7.7).

The percent changes after bronchodilator administration of ΔRrs7, ΔRrs7-20, ΔXrs7 and Δ AX using 7–41 Hz were also compared, and statistically significant differences were observed between ΔRrs7 and ΔXrs7, ΔRrs7-20 and ΔXrs7 and ΔXrs7 and ΔAX using 7–41 Hz, all with p-

values < 0.0001. The values of the FOT measurements before and after bronchodilator are shown in the figures in Table 7.8.

Table 7.7: Paired T-test for acute asthma with FOT measurements using waveform 7–41 Hz before and after bronchodilator (n=21)

	Pre-BD	Post-BD	p-value
Rrs7 ($cmH_2O \cdot sec/L$)	7.83 (2.20)	7.23 (2.01)	0.005*
Rrs7-20 ($cmH_2O \cdot sec/L$)	2.51 (1.10)	2.07 (1.03)	0.007*
Xrs7 ($cmH_2O \cdot sec/L$)	−5.02 (2.14)	−4.06 (1.42)	0.003*
AX (cmH_2O/L)	51.59 (25.83)	39.80 (19.08)	0.003*

*Data represented mean (SD)*statistically significant*

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Table 7.8: FOT measurements using waveform 7–41 Hz before and after bronchodilator

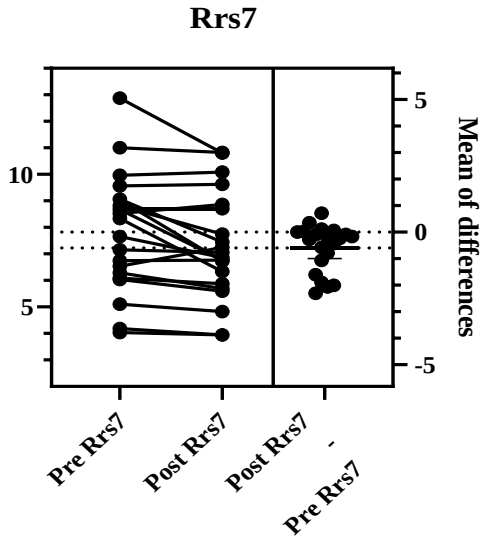
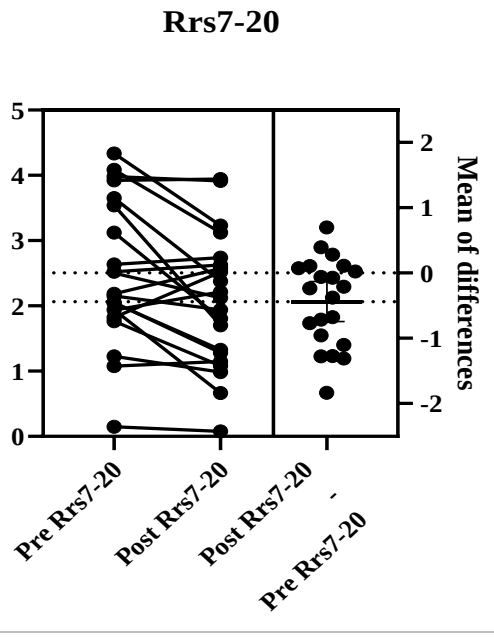
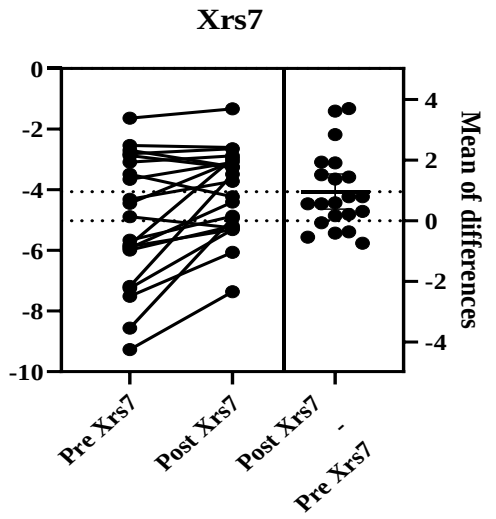
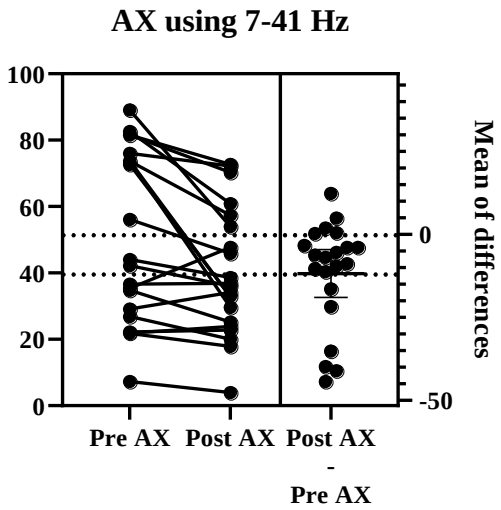
FOT measurements using 7-41 Hz	(n=21)
Rrs7 ($cmH_2O \cdot sec/L$)	
Rrs7-20 ($cmH_2O \cdot sec/L$)	

Table 7.8 (Continued)

FOT measurements using 7-41 Hz	(n=21)
Xrs7 ($cmH_2O \cdot sec/L$)	
AX (cmH_2O/L)	

7.5.3 Comparison of normal and abnormal FOT measurement Z-scores at baseline and their relation to the actual values percentage change following bronchodilator

FOT measurements, using waveforms of 5–37 Hz: For 19 participants with Rrs5 Z-scores, seven participants presented with abnormal Rrs5 Z-scores at baseline who showed a change of more than −10% of the actual values following bronchodilator administration, BDR (mean ± SD, −26.83 ±10.08), one participant showed an abnormal Rrs5 Z-score at baseline with no improvement following bronchodilator administration. However, 11 participants had normal Rrs5 Z-scores at baseline; 3 showed a percent change of more than −10 %, 3 improved by less than −10 %, BDR (mean ± SD, −18.30 ± 8.46 and −4.19 ± 1.77), and 5 showed no improvement. Regarding Rrs5-20, 2 had normal Rrs5-20 Z-scores at baseline and reflected a percent

change following bronchodilator of more than −10%. Reactance at 5 Hz (Xrs5) was found for 19 participants, 10 whom had abnormal Xrs5 Z-scores at baseline; 8 showed a change of more than 10% and 2 less than 10%, BDR (mean ± SD, 37.40 ± 14.33 and 7.94 ± 2.41). However, 2 participants had abnormal Xrs5 Z-scores of that indicated no improvement following the bronchodilator administration. Normal Xrs5 Z-scores at baseline were observed in seven participants; 3 presented a change of more than 10%, BDR (mean ± SD, 14.51 ± 3.31), while 4 participants showed no improvement. In 9 of 17 participants had AX using 5–37 Hz Z-scores, were noted to be abnormal at the baseline; 5 showed a change of more than −10 %, BDR (mean ± SD, −42.58 ± 8.19), 2 showed improvement of AX using 5–37 Hz of less than −10%, while 2 showed no improvement following bronchodilator. However, 8 participants showed normal Z-scores of AX using 5–37 Hz; 5 showed a change of more than −10 %, BDR (mean ± SD, −21.41 ± 9.53), 2 showed improvement of AX using 5–37 Hz of less than −10%, while 1 showed no improvement following bronchodilator.

FOT measurements using waveforms of 7–41 Hz: In 21 participants with Rrs7 Z-scores, 4 participants presented with abnormal Rrs7 Z-scores at baseline with a change of more than −10% of the actual values following bronchodilator administration, BDR (mean ± SD, −21.94 ±4.15). Moreover, one with an abnormal Rrs7 Z-score showed a change of less than −10%, while 1 with an abnormal Rrs7 Z-score showed no improvement following bronchodilator. However, 15 participants had normal Rrs7 Z-Scores; 4 participants presented with bronchodilation change of more than −10%, 8 with a less than −10% change, while 3 participants showed no improvement with BDR (mean ± SD, −7.36 ± 12.56, −4.52 ± 2.86 and 1.80 ± 1.98, respectively). Three participants in this group had Rrs7-20 Z-scores, two of whom were normal but presented a change of more than −10% and one who showed no improvement following bronchodilator administration. The reactance at the 7 Hz (Xrs7) Z-scores was observed for 21 participants. 14 showed abnormal Xrs7 Z-scores; 11 showed a change of more than 10%, BDR (mean ± SD 27.91± 13.98), 1 a change of less than 10%, and 2 had no improvement following bronchodilator administration. However, seven had normal Xrs7 Z-scores; 2 showed a change of more than 10%, 2 with change of less than 10 %, BDR (mean ± SD, 16.96 ± 2.48 and 6.37± 0.55, respectively), and 3 showed no improvement subsequent to bronchodilator administration. No Z-scores were available for the AX using 7–41 Hz by the machine according to the references used for the population studied.

7.5.4 Baseline readings and response to bronchodilator administration in relation to clinical condition

Studying children with acute wheezing or asthma in the ED is challenging. Most received increased doses of SABA either at home prior to admission or from the referring GP. Many children were acutely unwell with some requiring supplemental oxygen and for safety reasons these children were not studied until they were breathing room air and judged to be stable enough for FOT measurements by the attending medical team in the ED or on the ward.

Of the 25 participants with acute asthma that were tested using the FOT measurements, twelve were tested upon their arrival at the ED, and the remaining 13 were tested after admission to the ward. All participants had been given SABA in the ED and on the ward. All FOT measurements were taken at least one hour after SABA administration. Oral steroids were recorded for 60% of these participants. Asthma control test and childhood asthma control test scores were lower than 20 for 72% of the participants (Table 7.9).

Participants with close-to-normal baseline measurements of resistance and reactance and with minimal or no improvement following bronchodilator administration were found among children who received a dexamethasone dose at their ED visit and those who were tested on the children's wards. Within this category of participants, the childhood asthma control test (cACT) or asthma control test (ACT) scores were higher than in the group of participants that presented with higher resistance readings and higher percent changes following bronchodilator. Participants who showed more improvement following bronchodilator administration were tested during an ED visit, and most of them were admitted to the hospital. However, some such participant needed oxygen treatment upon admission, while others were clinically stable. The resistance at 5 Hz for one of the participants increased markedly after they underwent bronchodilator administration during the ED visit. This patient was found to have received only one dose of bronchodilator and prednisolone in the ED with no further bronchodilator treatment. No direct relationship between higher resistance and lower reactance FOT measurements and oxygen administration was noted among the children with acute asthma in our study.

Table 7.9: Clinical characteristics of children diagnosed with acute asthma using FOT at frequency waveform of 5–37 Hz and 7–41 Hz

	Acute asthma (n=25)
Characteristics	
Ethnicity	
White, n (%)	9 (36%)
Black, n (%)	1 (4%)
Asian, n (%)	6 (24%)
Mixed /other, n (%)	9 (36%)
History	
History of Eczema	
Yes, n (%)	10 (40%)
No, n (%)	15 (60%)
Age at the first wheeze	
1–3 years, n (%)	12 (48%)
4–6 years, n (%)	9 (36%)
7–10 years, n (%)	4 (16%)
Asthma exacerbation within the last year	
Yes, n (%)	12 (48%)
No, n (%)	13 (52%)
Smoking history of the family	
Yes, n (%)	9 (36%)
No, n (%)	16 (64%)
At their presentation with asthma exacerbation	
Patient using previously prescribed medication	
Corticosteroids, n (%)	7 (28%)
Combination of long acting β2 agonist and inhaled corticosteroid, n (%)	5 (20%)
No medication, n (%)	13(52%)
Oral steroids given	
Before the FOT measurements, n (%)	10 (40%)
After the FOT measurements, n (%)	5 (20%)
No oral steroids recorded, n (%)	10 (40%)
SABA given	
Before the FOT measurements, n (%)	16 (64%)
After the FOT measurements, n (%)	9 (36%)
Patient testing location	
ED, n (%)	12 (48%)
Ward, n (%)	13 (52%)
Patients was admitted after 4 hours in the ED	
Yes, n (%)	18 (72%)
No, n (%)	7 (28%)
O_2 therapy required	
Yes, n (%)	7 (28%)
No, n (%)	18 (72%)

Table 7.9 (Continued)

Acute asthma (n=25)	
At their presentation with asthma exacerbation	
ACT/cACT	
Mean (SD)	16.64 (5.84)
≤ 20, n (%)	18 (72%)
>20, n (%)	7 (28%)
POPS*	
Mean (SD)	1.68 (1.55)
Score (0-1), n (%)	15 (60%)
Score (2-3), n (%)	8 (32%)
Score (4-7), n (%)	2 (8%)

** The Paediatric Observation Priority Score is an emergency score use known- risk parameter in addition to the physiological, behavioural identifier* (245). *This early warning score consists of eight domains (background history, level of nursing concern, level of alertness, heart rate, extent of breathing difficulty, oxygen saturation, respiratory rate and temperature), each graded from 0 to 2 for a maximum score of 16* (246). *This score is used to assess the severity of the illness and guide staff in clinical decisions* (245).

7.5.5 Exploring the differences between FOT measurements at the 5–37 Hz and 7–41 Hz waveform frequencies in detecting abnormalities and assessing bronchodilator reversibility in children with acute asthma

Comparing Z-scores in children with FOT measurements at both 5–37 Hz and 7–41 Hz (n = 15) before and after bronchodilator administration

Z-scores for FOT at 5–37 Hz before bronchodilator administration: Abnormal Rrs5 Z-scores were noticed in 40% of the studied population. All Rrs5-20 Z-scores were found to be normal. Abnormal Xrs5 Z-scores were observed in 66.7% of children, and 53.8% of participants had abnormal Z-scores for AX using 5–37 Hz. No statistically significant differences were found between the Z-scores of the measurements at 5–37 Hz at baseline.

Z-scores for FOT at 7–41 Hz before bronchodilator administration: Rrs7 presented with 26.7% abnormal Z-scores. All Rrs7-20 Z-scores were normal. Moreover, 66.7% of the studied population had abnormal Xrs7 Z-scores. No statistically significant differences were found at baseline among the Z-scores of the measurements at 7–41 Hz.

Z-scores for FOT at 5–37 Hz after bronchodilator administration: Abnormal Rrs5 Z-scores after bronchodilator were presented by 6.7 % of the studied population, while no abnormalities

were observed in Rrs5-20 Z-scores. The proportion of abnormal Xrs5 Z-scores following bronchodilator fell slightly to 53.3%. The percentage of participants with abnormal Z-scores for AX using 5–37 Hz before and after bronchodilator remained the same at 53.8% of the studied population. No statistically significant differences were found among the Z-scores of the measurements at 5–37 Hz following bronchodilator administration.

Z-scores for FOT at 7–41 Hz after bronchodilator administration: The proportion of abnormal Rrs7 Z-scores decreased to 6.7% after bronchodilator administration. The Rrs7-20 Z-scores remained normal. However, an abnormal Xrs7 Z-score was observed in 66.7% of participants after bronchodilator. No statistically significant differences were found between the Z-scores of the measurements at 7–41 Hz following bronchodilator administration.

All Z-scores for Rrs5-20 and Rrs7-20 were found to be normal both before and after bronchodilator administration. The highest percentage of abnormal Z-scores was observed for both Xrs5 and Xrs7, followed by AX using 5–37 Hz. However, Rrs5 had a higher percentage of abnormal Z-scores compared with Rrs7 at baseline. Although Xrs5 and Xrs7 had the same percentage of abnormal values at baseline, the percentage remained the same for Xrs7 after bronchodilator, while it decreased for Xrs5. The percentage of abnormal Z-scores after bronchodilator remained the same for AX using 5–37 Hz. In contrast, a drop in the percentage of abnormal Z-scores for both Rrs5 and Rrs7 was observed following bronchodilator. A representation of the Z-scores for the FOT measurements is shown in Figure 7.4.

Comparing percent change in the raw data in children with FOT measurements at both 5–37 Hz and 7–41 Hz (n = 15) before and after bronchodilator administration

FOT measurements using waveforms of 5–37 Hz before and after bronchodilator administration: An average percent change of −8.99% was noted for Rrs5 following bronchodilator administration, with an average change of −10.12% in Rrs5-20. However, an average percent change of 13.48% was noted for Xrs5, and the highest average percent change after bronchodilator among the FOT measurements at 5–37 Hz was noted for AX, at −17.05%. Only Xrs5 showed statistically significant changes following bronchodilator.

Actual Rrs5 values presented a percent change of more than −10% following bronchodilator administration in 7 participants and less than −10 % in 3 participants, BDR (mean ± SD: −23.60 ± 10.96 and −4.18 ± 1.77, respectively). However, 5 participants presented with no improvement of Rrs5 following bronchodilator administration. Following bronchodilator administration, Rrs5-20 improved more than −10% in 8 participants, BDR (mean ± SD: −25.93 ± 22.59)

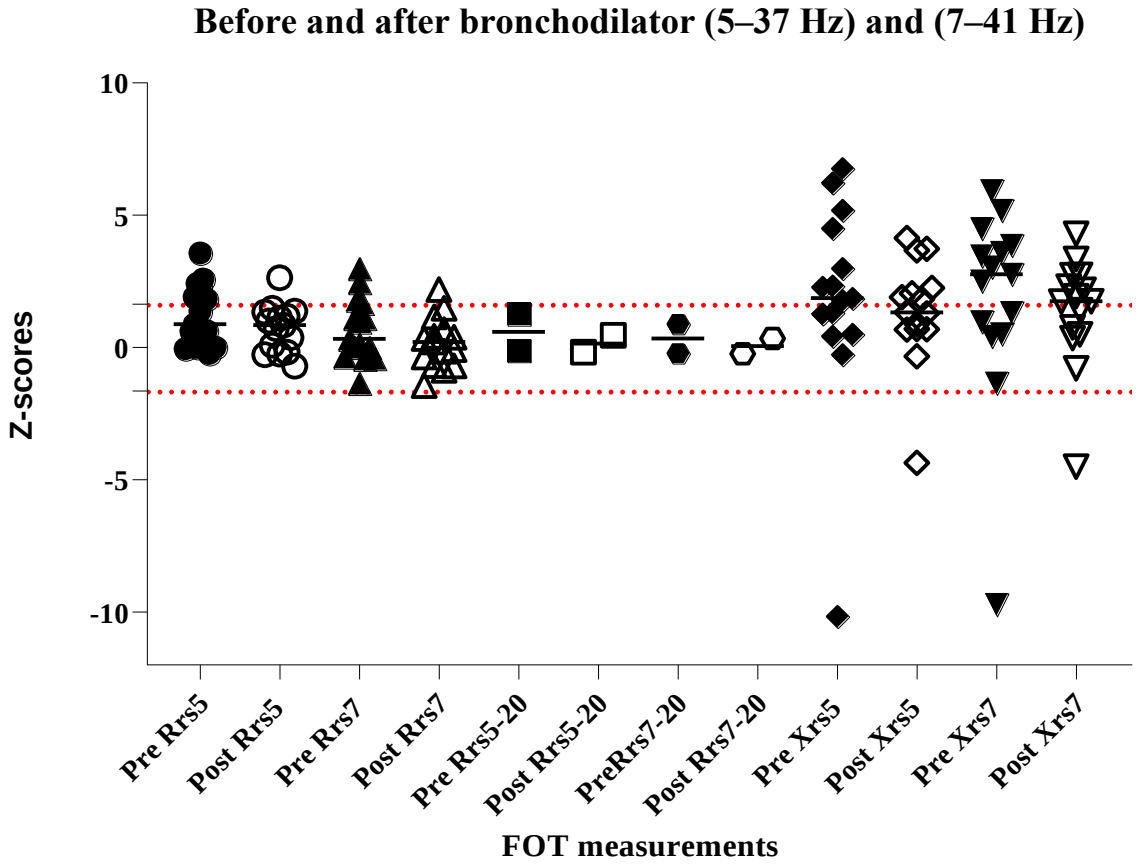
and less than −10% in 2 participants, while 5 participants had no improvement following bronchodilator. This pattern was also observed for Xrs measurements following bronchodilator administration; 8 participants showed improvements of more than 10% BDR (mean ± SD: 31.50 ± 14.97), 2 improved by less than 10% and 5 showed no improvement. However, regarding AX using 5–37 Hz values, an improvement of more than −10 % was noted in 9 participants and 3 participants showed an improvement of less than −10%, BDR (mean ± SD: −30.18 ± 18.85 and −2.38 ± 2.82, respectively), while 3 participants showed no improvement following bronchodilator administration.

FOT measurements using waveforms of 7–41 Hz before and after bronchodilator administration: The lowest average percent change after bronchodilator was noted for Rrs7, at −10.66%. An average percent change of −18.09% was observed for Rrs7-20, while that of Xrs7 was 17.98%. However, AX using 7–41 Hz had the highest average changes (−25.31%) among the measurements at 7-41 Hz. Statistically significant changes in Rrs7, Rrs7-20 and Xrs7 readings before and after bronchodilator were noted by the paired t-test.

Actual Rrs7 values presented a percent change of more than −10% following bronchodilator administration in 7 participants and less than −10 % in 6 participants, BDR (mean ± SD: −18.29 ± 5.87 and −5.54 ± 2.56, respectively). However, 2 participants presented with no improvement in Rrs7 following bronchodilator administration. Following bronchodilator administration, Rrs7-20 improved by −10 % in 10 participants, BDR (mean ± SD: −33.60 ± 12.48) and less than −10% in 1 participant, with 4 participants showing no improvement after bronchodilator. Moreover, 10 participants presented with improvements of more than 10% BDR (mean ± SD: 26.41 ± 13.89) in Xrs7 measurement following bronchodilator administration, 3 with improvements less than 10% and 2 with no improvement. However, regarding AX using 7–41 Hz values, an improvement of more −10 % was noticed in 12 participants, BDR (mean ± SD: −32.67 ± 17.43), and 3 participants showed no improvement following bronchodilator administration.

The highest average percent change in FOT measurements at 5–37 Hz following bronchodilator administration was observed for AX using 5–37 Hz followed by Xrs5, while the lowest percent change was noted for Rrs5. However, the highest average percent change among the FOT measurements at 7–41 Hz after bronchodilator administration was noted for AX using 7–41 Hz. This was followed by Rrs7-20 and Xrs7, while Rrs7 had the lowest percent change among the measurements at 7–41 Hz. Although the percent changes were higher for the measurements at 7–41 Hz compared with those at 5–37 Hz, this difference was not significant.

Figure 7.4: Z-scores of FOT measurements using waveform 5–37 and 7–41 Hz before and after bronchodilator administration in the group with both readings (n=15)



..... *Represents cut-off for abnormal Z-score of ≥1.64 or ≤−1.64*

Pre SABA (closed symbols), Post SABA (open symbols)

7.6 Discussion

Both resistance and reactance FOT parameters were used within this study to show airway dynamics in children with acute asthma, with the intention of using a lower oscillation frequency for a better overview of the peripheral airways (168). The main findings of this study showed that the reactance and the area under the curve were the best parameter to represent abnormalities in children with acute asthma at baseline, followed by airway resistance. These findings are supported by the findings of Goldman et al., who showed that the Xrs and AX gave a clearer representation of peripheral airway obstruction compared to resistance (176), and with the ability of the AX measure to differentiate between children with asthma or with small airways disease from children with healthy lungs (168). Following bronchodilator, we

found that the average percentage changes were highest for AX using 5–37 Hz and 7–41 Hz, followed by Rrs5-20 and Rrs7-20, then Xrs5 and Xrs7, and lastly Rrs5 and Rrs7. This was also seen when studying the bronchodilator response of Rrs5-20, Rrs20 and AX, showing that AX and Rrs5-20 were markedly changed compared with Rrs20 (247). Nevertheless, in some participants, Rrs presented with a higher percent change compared with AX and Xrs in the same participant following bronchodilator administration. This could be explained by the fact that the effect of SABA is mainly observed on larger airways, with no significant changes to the small airway measures in some children with asthma (248).

This study showed that individuals with higher resistance as demonstrated by the FOT and less asthma control as reflected by the ACT/cACT showed greater improvement after bronchodilator. This finding supports other studies that found a greater response to the bronchodilator in patients with asthma having lower lung functions at baseline compared with those having higher baseline function (231).

In our study, we assessed the percent change following bronchodilator administration in children with asthma, and some of our findings agree with those of other studies. However, some differences to what was observed in the field were also noted. This could be because different populations and ethnic groups of varying ages were studied using different oscillation frequency waveforms, machines, and sample sizes in addition to some studies using a healthy control group as a reference for the children with asthma and having different waiting times between bronchodilator administration and the IOS/FOT assessment. In addition, the severity of the condition in the studied children varied (88,123,143,199,203,243,244). Using the percent changes of the actual values in this chapter allowed us to compare and contrast the results with other data in the literature, as most studies report the percent change of IOS/FOT raw values following bronchodilator administration. In a study performed in children aged 2–5 years attending the outpatient asthma clinic, a 40% change in Rrs5 following bronchodilator administration suggested a positive bronchodilator response, where resistance measurements were made by IOS. However, the bronchodilator used comprised 500 µg of terbutaline, and the waiting time following bronchodilator administration was 20 min, both differing from our study (149). A similar percent change in Rrs5 was observed in young children with stable asthma based on IOS measurements at frequency range of 5–35 Hz before and after 20 min of administrating 200 µg of salbutamol (129). In children aged 4 years with asthma, a positive bronchodilator response was suggested by a change of −26.9% in Rrs5 and 35.8% in Xrs5 following the administration of 2.5 mg salbutamol over 15 minutes (105) All these studies focused on

age groups younger than the age group in our study (105,129,149). However, in a study done by Batamz et al., a similar age group to our study of children with both acute and stable asthma were included. Yet, a higher percent change of −39.05% response change in AX suggested the detection of reversibility following bronchodilator administration in that population (110) However, similar findings to our study were noted in children with asthma aged 3–18 years, suggesting bronchodilator reversibility by a decrease of 8.6% in Rrs10 following 15 min of 180 µg salbutamol administration. These measurements were performed by IOS using frequencies from 5 to 20 Hz, although this study by Komarow at al. did not include children with acute asthma (111). Data on the bronchodilator response in children with acute asthma using the FOT were also limited.

No difference in detecting abnormalities and assessing bronchodilator reversibility was noted in the measurements of FOT at the waveform frequencies of 5–37 Hz and 7–41 Hz. This could be because similar oscillations were used. However, this study had some limitations that could give a different interpretation of the findings. Within the category of the children with acute asthma, there was no other objective evidence to support the diagnosis of asthma; the diagnosis was made solely by the physician. Having more objective evidence could lead to a better reflection of the sensitivity and specificity of FOT in acute asthma cases. Additionally, we were basing the Z-score normality on other references that were used on other group ethnicities; having an adequate number of healthy control participants would allow us to use our own references and Z-scores. Also, the children in the control group did not receive ethical approval to be given a bronchodilator, meaning that no after bronchodilator measurements were performed on the healthy control group.

In our study, FOT measurements at 5–37 Hz and 7–41 Hz could detect airway abnormalities in children with acute asthma except for Rrs5-20 and Rrs7-20. However, this could be due to the limited availability of Rrs5-20 and Rrs7-20 Z-scores. Additionally, most FOT measurements at 5–37 Hz and 7–41 Hz reflected a percent change following bronchodilator, suggesting a positive bronchodilator response and airway improvement in children with acute asthma. Moreover, no significant differences were found between measurements of FOT at 7–41 Hz and 5–37 Hz in the reflection of abnormalities and assessment of the bronchodilator response.

CHAPTER 8 FORCED OSCILLATION TECHNIQUE IN CHILDREN WITH UNCONTROLLED ASTHMA

8.1 Introduction and rationale

Asthma is the most common respiratory disorder affecting children (249). Approximately 20% of patients with asthma are classified as having inadequately controlled asthma. These patients are at particular risk of asthma exacerbation, hospital admission and death (250). Appropriate treatment of asthma maintains clinical control and decreases the risks associated with the disease in the future. To reach this goal, continuous monitoring is necessary in children with asthma. Monitoring includes assessment of lung functions, inflammation and the symptoms associated with asthma (251).

Spirometry is an informative indicator of lung function, it is essential for asthma diagnosis, and it can also be used to assess the effectiveness of treatment and the risk of future adverse outcomes (252,253), which may be identified by a faster than typical decline in lung function during adulthood in patients with asthma (253). Spirometry is a recommended objective test to monitor asthma at each doctor visit (254). However, MBNW, used to determine lung clearance index (LCI), is also used to reflect the small airway disease and ventilation heterogeneity that is associated with asthma (255). Fractional exhaled nitric oxide (FeNO) is also used in children with asthma as indirect evidence of airway inflammation (256). Though, uncontrolled asthma is commonly reflected in low scores in the asthma control test (ACT) or childhood ACT (cACT) (257).

Guidelines recommend the use of the respiratory oscillometry in the diagnosis and monitoring of asthma, especially in young children (117,258). It has also been suggested that it can predict the loss of asthma control (259). With limited data on how the forced oscillation technique (FOT) presents in children with uncontrolled asthma and how it may reflect asthma control. Objective testing of spirometry, MBNW and FeNO has been chosen for the current study to test the associations between the biomarker FOT and (i) peripheral airway involvement in the disease process of asthma and (ii) airway inflammation in children with uncontrolled asthma, with consideration of the ACT/cACT scores.

Improving the health outcomes in asthma depends on adherence to the asthma management plan. Adherence is also based on the patients' understanding of the disease, and the role of reliever and maintenance therapy as long-term treatment, especially in chronic diseases. (254). Many patients do not usually take their medication as prescribed; thus, intervention to support adherence must be considered (50). Electronic monitoring devices have been suggested as useful tools to reflect the use of the medication in children with asthma, especially in children with poor adherence (260). However, further research focusing on use of an electronic monitoring device and the effect of adherence on clinical control, in combination with other objective testing of the abnormalities associated with asthma, is needed.

The use of bronchodilator reversibility (BDR) testing in children with asthma could have clinical significance beyond the diagnostic purpose (261). BDR assessment following inhaled corticosteroid treatments, is useful to assess uncontrolled asthma, as it could provide relevant information about asthma management (261). Bronchodilator response has also been shown to indicate asthma control in both adults and adolescents with asthma (262,263). In this study, the FOT was used to quantify the bronchodilator response in children with uncontrolled asthma.

8.2 Aims

1- To investigate the association between FOT indices at the frequency waveforms 5–37 Hz and 7–41 Hz using TremoFlo and spirometry parameters (forced expiratory volume in 1 second [FEV_1] and FEV_1/forced vital capacity [FEV_1/FVC]), the lung clearance index (LCI) from multiple breath nitrogen washout and airway inflammation (FeNO) in children with uncontrolled asthma.

2- To monitor changes in asthma control and clinical outcomes between two visits over a period of 2 to 4 months using the ACT or cACT and measurements of FOT at the frequency waveforms 5–37 Hz and 7–41 Hz in relation to the adherence to inhaled corticosteroids by remote monitoring using electronic smart inhalers monitoring devices in children with uncontrolled asthma.

3- To evaluate the BDR on FOT indices at the frequency waveforms 5–37 Hz and 7–41 Hz in children with uncontrolled asthma.

8.3 Hypotheses

1- FOT measurements of resistance and reactance using TremoFlo at the 5–37 Hz and 7–41 Hz oscillation waveforms (Rrs5, Xrs7, Rrs7 and Xrs7) correlate with spirometry parameters (FEV_1 and FEV_1/FVC), the LCI and the FeNO in school-age children with uncontrolled asthma.

2- FOT measurements of resistance and reactance (Rrs5, Rsr5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz) and ACT/cACT scores improve with good adherence to inhaled corticosteroids in school-age children with uncontrolled asthma.

3- FOT measurements of resistance and reactance at the frequency waveforms 5–37 Hz and 7–41 Hz (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz) exhibit a change after bronchodilator administration in school-age children with uncontrolled asthma.

8.4 Materials, Methods and Participants

8.4.1 Study design and participants

This was an observational prospective cohort study performed in school-aged children (5–15 years old) with uncontrolled asthma attending the asthma clinic at Leicester Royal Infirmary. The study was conducted under the approval of the Cambridge South Research Ethics Committee. The treatment and the clinical protocol were not changed during the study period. Tests for the study were performed in addition to the patient's regular care. The patients with uncontrolled asthma were identified by the physicians and the respiratory nurse at the clinic, if their ACT or cACT scores were <20. Once the patients were identified, the researcher was informed. Detailed information sheets were given to both the parents and the children at their clinical visit by the physician; alternatively, the information sheets were sent to their addresses by the respiratory nurse if the patients had a telephone appointment. A period of 24 hours was given for the parents and children to read the papers after they received the information sheet, and extra time was provided if needed by the parents. After they read the information sheets provided, they had time to ask questions and obtain further explanation before enrolling in the study. Once these queries were answered by the researcher, if the parents and children ultimately decided to join the study, they were invited for a respiratory physiology laboratory visit to perform relevant breathing tests including FOT. During the laboratory visit, the assent and consent forms were given to families for their approval to join the study and signature; subsequently, they filled in a respiratory questionnaire and the ACT or cACT depending on the age

of the child. The tests were then performed, starting with the performance of the FOT as a baseline measure. Next, the FeNO and the MBNW were performed. Afterward, spirometry was performed, and 400 micrograms of salbutamol was administered. Repeated FOT measurements followed by spirometry were performed 15 minutes after the bronchodilator administration. The participants were asked to bring their prescribed inhaler medication to the laboratory visits. Once the breathing tests were completed, preventer and reliever inhalers were fitted into the electronic monitoring device. Education about the usage of electronic smart inhalers and the monitoring of medication administration was provided to the parents and participants. The participants were invited for a follow-up visit that took place two to four months after the initial visit. During the follow-up visit, the same tests done in their initial visits were repeated, with the respiratory questionnaire omitted. The electronic monitoring device and adherence to the treatment were checked. In addition, parents and participants were asked to report adherence to the treatment since the initial visit.

8.4.2 Data collection and analysis

At the initial laboratory visit, FOT was performed to obtain three acceptable tests. Each test lasted 20 seconds at frequency ranges of 5–37 Hz and 7–41 Hz. Impedance measurements of the forced oscillation were reflected as resistance at 5 Hz (Rrs5), resistance difference of 5–20 Hz (Rrs5-20), reactance at 5 Hz (Xrs5), reactance area using 5–37 (AX using 5–37), resistance at 7 Hz (Rrs7), resistance difference of 7–20 Hz (Rrs7-20), reactance at 7 Hz (Xrs7) and reactance area using 7–41 Hz (AX using 7–41 Hz). Absolute values and Z-scores were recorded based on two reference datasets within TremoFlo software for the intended studied group (88,133). The most appropriate reference dataset was retrieved automatically by the TremoFlo depending on the age, height, and weight of the participant. Spirometry measurements were taken, with indices of flow limitation and lung volumes reflected as the FEV_1 and the FEV_1/FVC absolute values, in addition to predicted percentage and the Z-scores published by Quanjer PH et al. in 2012 (164). The LCI values and Z-score was reported based on the MBNW measurements (264). FeNO is reported as a number in parts per billion (ppb). A detailed description of the procedures and the acceptance criteria is provided in Chapter 3.

8.4.3 Statistical analysis

All the participants' characteristics (age, height, weight, and sex) were reported. As per the recommendation of ATS/ERS, we used the FOT Z-score because it is independent of age, height, and sex (64,117). The Z-scores were calculated as (measured – predicted mean)/

(standard deviation of the residuals) (208,209), with Z-scores of less than −1.64 or more than +1.64 classified as an abnormal result (165,208). The normality of the data was tested using histograms and the Shapiro–Wilk test of normality, for which a normal distribution is indicated by p-value > 0.05. The relationships between the FOT indices and the spirometry indices, LCI and FeNO were studied for each population using the Pearson correlation for parametric data and Spearman's correlation coefficient (r) for non-parametric data. Paired t-tests were used to compare the parametric data at the initial and follow-up laboratory visits, with p-values less than 0.05 considered significant. Paired t-tests were used for parametric data and the Wilcoxon signed-rank test was used for non-parametric data before and after the bronchodilator administration, with p-values less than 0.05 considered significant.

8.4.4 Approach to analysis

We studied the correlation of the forced oscillation technique to the spirometry, lung clearance index and fractional exhaled nitric oxide. FOT measurements were made at both 5–37 Hz and 7–41 Hz (Rrs5, Xrs5, Rrs7 and Xrs7) and correlated to the spirometry indices (FEV_1 and FEV_1/FVC) Z-scores, LCI Z-scores and the FeNO values.

We studied the association between the forced oscillation technique measurements at 5–37 and 7–41 Hz (Rrs5, Xrs5, Rrs7 and Xrs7), the spirometry indices (FEV_1 and FEV_1/FVC) actual values and Z-scores, and the ACT/cACT values. We used the Pearson correlation coefficient for parametric data and Spearman's correlation coefficient (r) for non-parametric data.

In order to compare the forced oscillation technique measurements at the initial and follow-up visits, the actual readings of the FOT measurements were used for the comparison. Normal and abnormal values were based on the upper limit of normal and the reference values that were retrieved automatically by the TremoFlo dataset depending on the age, height, and weight of the participant. A paired t-test was used to compare the parametric data at the initial and follow-up laboratory visits.

To evaluate the bronchodilator reversibility of forced oscillation technique indices using TremoFlo in children with uncontrolled asthma, the effect of short-acting beta-2 agonists (SABA) administration on FOT measurements of resistance at 5–37 Hz and 7–41 Hz (Rrs5, Rrs5-20, Xrs5, AX using 5–37 Hz, Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz) was evaluated using paired t-tests for the parametric data and the Wilcoxon signed-rank test for the non-

parametric data before and after the bronchodilator administration for both the initial and follow-up visits.

8.5 Results

Twenty school-aged children were approached at the asthma clinic. Six families declined to participate, four families subsequently could not be reached by telephone and three were not able to come to the appointments booked. Some data collected from the participants were excluded if the measurements or the traces were not acceptable. Seven participants were recruited, and six participants had a follow-up visit. A flow chart of the entire population of patients approached for the study is presented in Figure 8.1. Characteristics of the study population are presented in Table 8.1. Z-scores for the FOT, spirometry and LCI measurements are presented in Table 8.2 for the initial laboratory visit and Table 8.3 for the follow-up visit. Raw data for the FOT, spirometry and LCI measurements and ACT/cACT are presented in Table 8.4 for the initial laboratory visit and Table 8.5 for the follow-up visit.

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Figure 8.1: Flow chart of the entire cohort of school-aged children with uncontrolled asthma who were approached

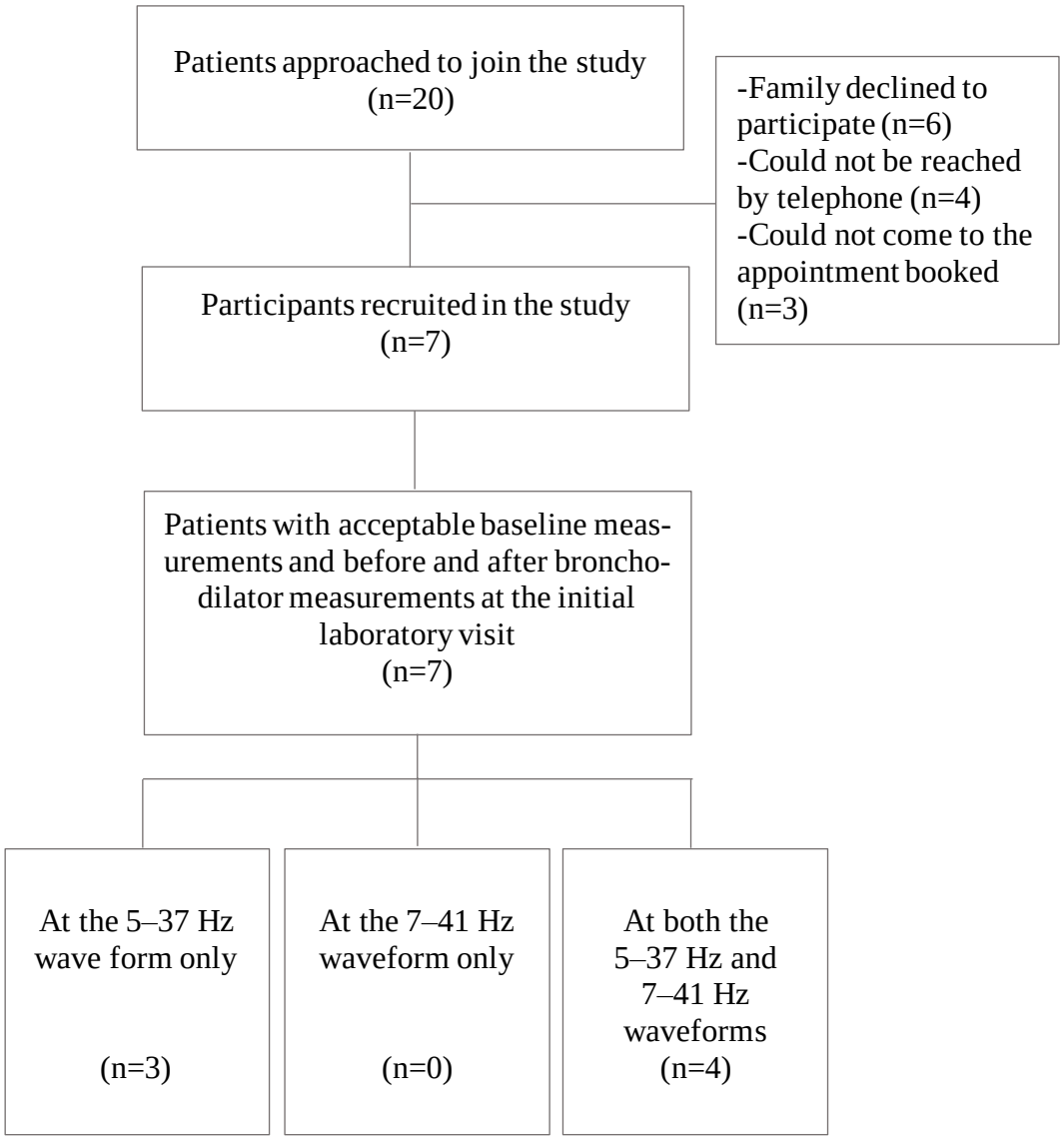

Table 8.1: Characteristics of children diagnosed with uncontrolled asthma using forced oscillation technique at frequency waveforms of 5–37 Hz and 7–41 Hz

	Uncontrolled asthma (n=7)
Sex, Male (%)	6 (85.7%)
Age (years)	11.00 (2.81)
Height (cm)	146.8 (20.25)
Weight (kg)	44.77 (18.00)
Severity according to the GINA strategy document usage of the of the medication, n (%)	Mild asthma 1 (14.3%) Moderate asthma 5 (71.4%) Severe asthma 1 (14.3%)

Data presented as mean (SD) unless otherwise stated

8.5.1 Correlation of the forced oscillation technique indices (Rrs5, Xrs5, Rrs7 and Xrs7) Z-scores to the spirometry indices (FEV_1 and FEV_1/FVC) Z-scores, lung clearance index Z-scores and fractional exhaled nitric oxide

At the initial visit, all the participants had acceptable measurements for FOT at 5–37 Hz and spirometry, four had an acceptable measurement of FOT at 7–41 Hz and four had acceptable MBNW measurements. One participant did not attend the follow-up visit. The other six participants had an acceptable FOT at 7–41 Hz, spirometry and MBNW measurements, and five of the participants had an acceptable FOT measurement at 5–37 Hz. Correlations between the Z-scores of the FOT measurements and the other measurements were evaluated for both the initial and follow-up visits.

Table 8.2: Forced oscillation, spirometry and lung clearance index Z-scores in children with uncontrolled asthma at the initial laboratory visit

	Z-scores						
	Rrs5	**Xrs5**	**Rrs7**	**Xrs7**	**FEV_1**	**FEV_1/FVC**	**LCI**
Participant 1	−0.02	0.25			-0.4	1.2	0.8
Participant 2	−0.17	−0.85			1.01	1.08	0.1
Participant 3	−0.39	−0.79			0.6	−1.00	
Participant 4	1.63	0.77	1.46	0.60	−0.06	−0.76	**10.6**
Participant 5	−0.18	0.38	0.09	−0.68	−0.26	**−3.46**	
Participant 6	1.02	−0.79	0.86	**−3.24**	**−3.02**	**−4.47**	
Participant 7	0.03	0.58	−0.26	0.38	−1.08	**−1.87**	**12.8**

Bold font indicates abnormal Z-scores

Table 8.3: Forced oscillation, spirometry and lung clearance index Z-scores in children with uncontrolled asthma at the follow-up laboratory visit

	Z-scores						
	Rrs5	**Xrs5**	**Rrs7**	**Xrs7**	**FEV_1**	**FEV_1/FVC**	**LCI**
Participant 1	1.08	−0.02	0.01	0.45	−0.91	0.11	**2.1**
Participant 2			0.40	−0.46	1.07	1.28	**1.7**
Participant 3	0.46	−0.70	0.30	−0.44	0.51	0.16	**3.6**
Participant 4	**1.91**	1.04	**1.80**	0.60	0.00	−0.86	**5.2**
Participant 5	0.12	−0.43	0.26	−1.31	−0.5	**−2.68**	**3.5**
Participant 6							
Participant 7	1.60	1.18	1.09	0.90	-0.63	−1.11	**4.8**

Bold font indicates abnormal Z-scores

Table 8.4: Forced oscillation, spirometry, lung clearance index and ACT/cACT measurements in children with uncontrolled asthma at the initial laboratory visit

	Raw data and % predicted								
	Rrs5 ($cmH_2O \cdot sec/L$)	**Xrs5** ($cmH_2O \cdot sec/L$)	**Rrs7** ($cmH_2O \cdot sec/L$)	**Xrs7** ($cmH_2O \cdot sec/L$)	**FEV_1** (L)	**FEV_1** (% predicted)	**FEV_1/FVC** (%)	**LCI**	**ACT/ cACT**
Participant 1	5.96	−2.66			1.83	96	94	6.79	13
Participant 2	5.92	−1.70			2.02	111	93	6.58	9
Participant 3	7.32	−2.82			1.23	108	87		15
Participant 4	6.99	−2.39	6.48	−1.76	2.57	99	81	11.24	16
Participant 5	3.31	−1.22	3.66	−0.96	2.70	97	66		19
Participant 6	6.15	−1.89	5.49	−2.38	2.23	64	59		22
Participant 7	4.76	−2.11	4.32	−1.47	2.42	88	74	13.04	10

Table 8.5: Forced oscillation, spirometry, lung clearance index and ACT/cACT measurements in children with uncontrolled asthma at the follow-up laboratory visit

	Raw data and % predicted								
	Rrs5 ($cmH_2O \cdot sec/L$)	**Xrs5** ($cmH_2O \cdot sec/L$)	**Rrs7** ($cmH_2O \cdot sec/L$)	**Xrs7** ($cmH_2O \cdot sec/L$)	**FEV_1** (L)	**FEV_1** (% predicted)	**FEV_1/FVC** (%)	**LCI**	**ACT/ cACT**
Participant 1	7.57	−2.38	5.89	−2.27	1.73	90	87	7.18	13
Participant 2			6.51	−1.48	2.08	112	95	7.04	8
Participant 3	8.75	−2.88	8.50	−2.41	1.24	106	93	7.63	16
Participant 4	7.32	−2.59	6.84	−1.70	2.65	100	80	8.36	19
Participant 5	3.91	−1.61	3.96	−1.26	2.91	94	71	7.71	21
Participant 6									
Participant 7	6.67	−2.65	5.72	−1.92	2.63	93	78.80	8.2	13

Correlation between the Z-scores of the forced oscillation technique measurements at 5–37 Hz (Rrs5 and Xrs5) and the spirometry Z-scores of FEV_1 and FEV_1/FVC at the initial visit and follow-up visits

All the participants at the initial visit had available data for FOT measurements at 5–37 Hz and spirometry measurement Z-scores (n=7), and for the follow-up visit, five participants had available data for Rrs5, Xrs5, FEV_1 and FEV_1/FVC Z-scores. No significant correlation was observed between any of the FOT measurements at 5–37 Hz and the spirometry measurement Z-scores in the initial laboratory visit or the follow-up visit (Table 8.6 and figures in Table 8.7).

Table 8.6: Correlation between the Rrs5 and Xrs5 Z-scores to FEV_1 and FEV_1/FVC Z-scores at the initial and follow-up visits

	Initial visit (n=7)				**Follow-up visit (n=5)**			
	FEV_1 Z-scores		**FEV_1/FVC Z-scores**		**FEV_1 Z-scores**		**FEV_1/FVC Z-scores**	
	r	**p-value**	***r***	**p-value**	***r***	**p-value**	***r***	**p-value**
Rrs5 Z-scores	−0.500	0.267	−0.071	0.906	−0.136	0.827	0.240	0.697
Xrs5 Z-scores	−0.004	0.993	0.014	0.976	−0.279	0.649	−0.094	0.881

r = correlation coefficient

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Table 8.7: Figures presenting the correlations between the Rrs5 and Xrs5 Z-scores to the FEV_1 and FEV_1/FVC Z-scores at the initial and follow-up visits

(Please note that there are differences in the scaling on the axes between pairs of comparisons)

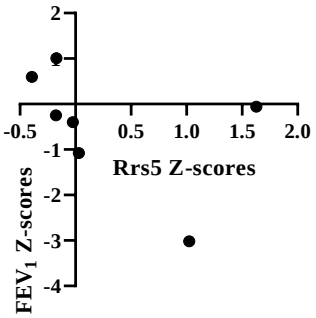
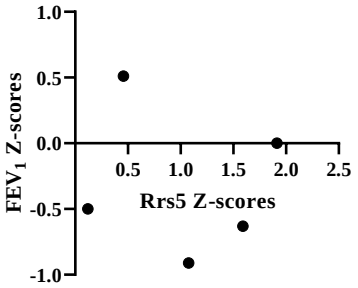
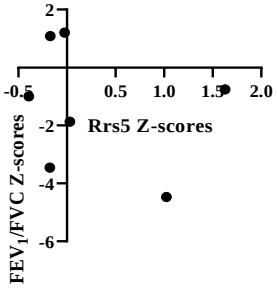
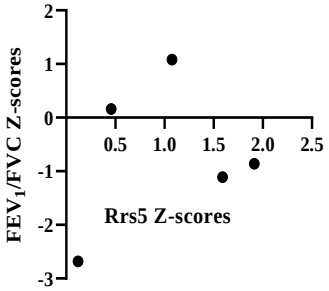
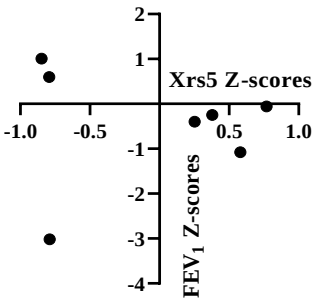
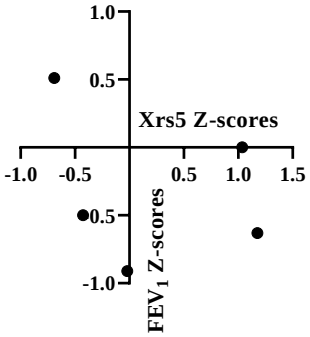
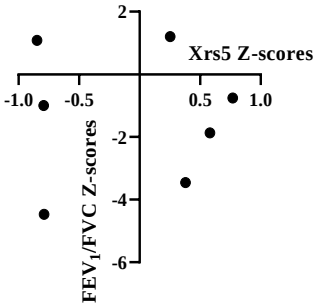
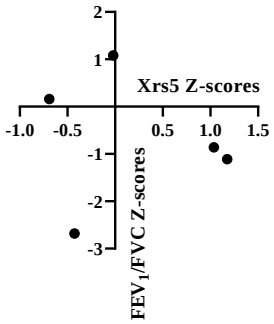
Initial visit	Follow-up visit
Correlation of the Rrs5 and FEV_1 Z-scores	**Correlation of the Rrs5 and FEV_1 Z-scores**
Simple scatter plot of Rrs5 and FEV_1 Z-scores 	**Simple scatter plot of Rrs5 and FEV_1 Z-scores** 
Correlation of the Rrs5 and FEV_1/FVC Z-scores	**Correlation of the Rrs5 and FEV_1/FVC Z-scores**
Simple scatter plot of Rrs5 and FEV_1/FVC Z-scores 	**Simple scatter plot of Rrs5 and FEV_1/FVC Z-scores** 
Correlation of the Xrs5 and FEV_1 Z-scores	**Correlation of the Xrs5 and FEV_1 Z-scores**
Simple scatter plot of Xrs5 and FEV_1 Z-scores 	**Simple scatter plot of Xrs5 and FEV_1 Z-scores** 

Table 8.7 (Continued)

Initial visit	Follow-up visit
Correlation of the Xrs5 and FEV_1/ FVC Z-scores	**Correlation of the Xrs5 and FEV_1/ FVC Z-scores**
Simple scatter plot of Xrs5 and FEV_1/FVC Z-scores 	**Simple scatter of Xrs5 and FEV_1/FVC Z-scores** 

Correlation between the Z-scores of the forced oscillation technique measurements at 7–41 Hz (Rrs7 and Xrs7) and the spirometry Z-scores of FEV_1 and FEV_1/FVC at the initial and follow-up visits

Four participants at the initial visit had available data for FOT measurements at 7–41 Hz and spirometry measurements Z-scores, and at the follow-up visit, six participants had available data for Rrs7, Xrs7, FEV_1 and FEV_1/FVC Z-scores. However, there was no significant correlation between the Z-scores of the FOT measurements at 7–41 Hz (Rrs7 and Xrs7) to the spirometry Z-scores (FEV_1 and FEV_1/FVC) at the initial visit or at the follow-up visit (Table 8.8, and figures in Table 8.9).

Table 8.8: Correlation between the Rrs7 and Xrs7 Z-scores to FEV_1 and FEV_1/FVC Z-scores at the initial and follow-up visits

	Initial visit (n=4)				**Follow-up visit (n=6)**			
	FEV_1 Z-scores		**FEV_1/FVC Z-scores**		**FEV_1 Z-scores**		**FEV_1/FVC Z-scores**	
	r	**p-value**	***r***	**p-value**	***r***	**p-value**	***r***	**p-value**
Rrs7 Z-scores	−0.018	0.982	0.236	0.765	0.001	0.999	−0.309	0.550
Xrs7 Z-scores	0.877	0.123	0.907	0.093	−0.336	0.516	0.277	0.595

r = correlation coefficient

Table 8.9: Figures presenting the correlation between the Rrs7 and Xrs7 Z-scores to FEV_1 and FEV_1/FVC Z-scores at the initial and follow-up visits

(Please note that there are differences in the scaling on the axes between pairs of comparisons)

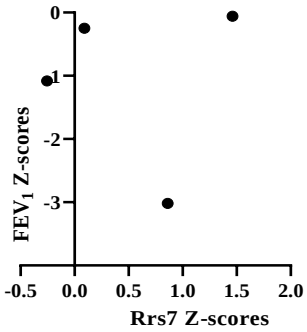
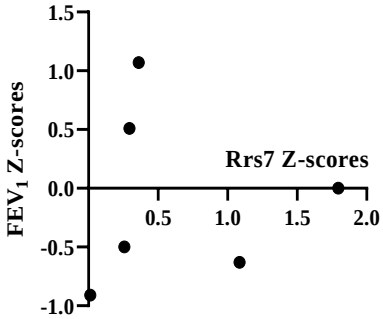
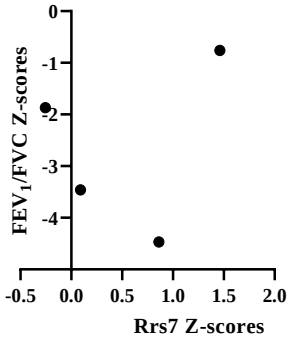
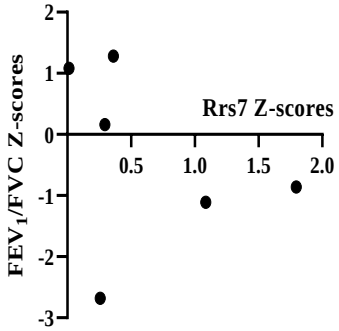
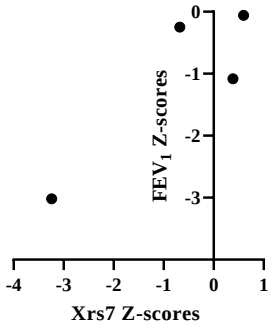
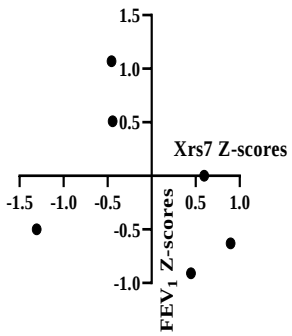
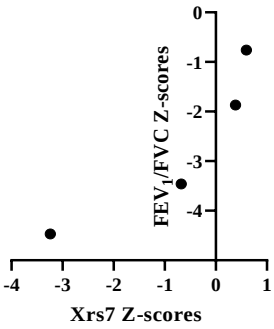
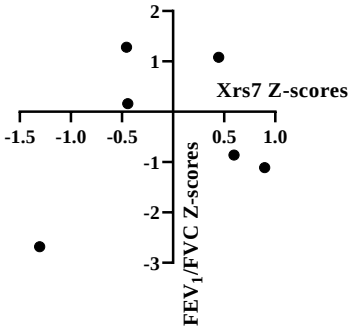
Initial visit	Follow-up visit
Correlation of the Rrs7 and FEV_1 Z-scores	**Correlation of the Rrs7 and FEV_1 Z-scores**
Simpe scatter plot of Rrs7 and FEV_1Z-scores 	**Simple scatter of Rrs7 and FEV_1Z-scores** 
Correlation of the Rrs7 and FEV_1/FVC Z-scores	**Correlation of the Rrs7 and FEV_1/FVC Z-scores**
Simple scatter plot of Rrs7 and FEV_1/FVC Z-scores 	**Simple scatter plot of Rrs7 and FEV_1/FVC Z-scores** 

Table 8.9 (Continued)

Initial visit	Follow-up visit
Correlation of the Xrs7 and FEV_1 Z-scores	**Correlation of the Xrs7 and FEV_1 Z-scores**
Simple scatter plot of Xrs7 and FEV_1 Z-scores 	**Simple scatter plot of Xrs7 and FEV_1 Z-scores** 
Correlation of the Xrs7 and FEV_1/FVC Z-scores	**Correlation of the Xrs7 and FEV_1/FVC Z-scores**
Simple scatter plot of Xrs7 and FEV_1/FVC Z-scores 	**Simple scatter plot of Xrs7 and FEV_1/FVC Z-scores** 

At the initial laboratory visit**,** all the Z-scores for the available Rrs5, Xrs5 and Rrs7 measurements were normal. However, one participant presented with abnormal Xrs7 Z-scores and had abnormal Z-scores for both FEV_1 and FEV_1/FVC. Two participants had abnormal Z-scores for FEV_1/FVC with normal Z-scores for FOT at both measurements of 5–37 Hz and 7–41 Hz. However, at the follow-up visit, almost all the participants had normal Z-scores for all the FOT measurements at both 5–37 Hz and 7–41 Hz and for the spirometry parameters; notably, one participant presented with abnormal Z-scores for the Rrs5 and Rrs7 and normal Z-scores for FEV_1 and FEV_1/FVC. However, one participant presented with abnormal FEV_1/FVC Z-scores and normal Z-scores for all other parameters of FOT.

Correlation between the Z-scores of the forced oscillation technique measurements at 5–37 Hz (Rrs5 and Xrs5) and the multiple breath nitrogen washout Z-scores of LCI at the initial and follow-up visits

For the correlation of the measurements at 5-37 Hz, there were four participants with available data for Rrs5, Xrs5 and LCI Z-scores at the initial laboratory visit, and at the follow-up visit, there were five participants with available data for FOT at 5–37 Hz and LCI Z-scores. Correlations of the FOT measurements at 5–37 Hz and LCI Z-scores are presented in Table 8.10 and figures in Table 8.11 There were no significant correlations between the FOT measurement Z-scores at 5–37 Hz and the LCI Z-scores for either the initial or the follow-up visit.

Table 8.10: Correlation between the Rrs5, Xrs5, Rrs7 and Xrs7 Z-scores and LCI Z-scores at the initial and follow-up visits

		Initial visit (n=4)		**Follow-up visit (n=5)**			**Follow-up visit (n=6)**	
		LCI Z-scores		**LCI Z-scores**			**LCI Z-scores**	
		r	**p-value**	***r***	**p-value**		***r***	**p-value**
FOT	**Rrs5 Z-scores**	0.800	0.333	0.574	0.311	**Rrs7 Z-scores**	0.825	0.043*
	Xrs5 Z-scores	0.782	0.219	0.694	0.193	**Xrs7 Z-scores**	0.400	0.432

r = correlation coefficient statistically significant*

(There were too few pairs to present data for the correlation between the Rrs7 and Xrs7 Z-scores and the LCI Z-scores at the initial laboratory *visit)*

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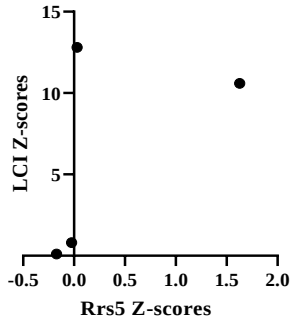
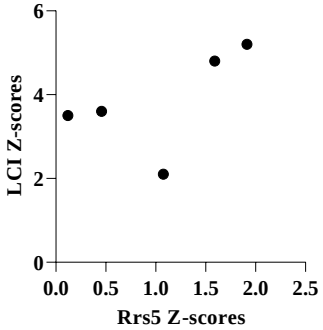
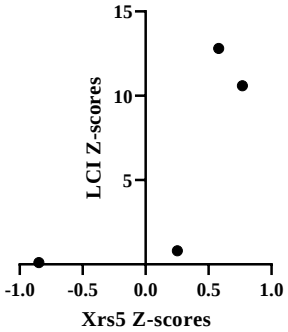
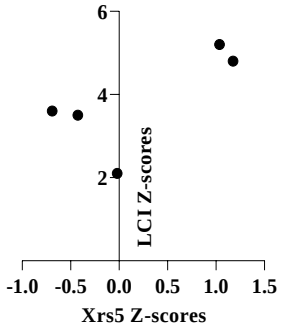
Table 8.11: Figures presenting the correlations between the Rrs5 and Xrs5 Z-scores and the LCI Z-scores at the initial and follow-up visits

(Please note that there are differences in the scaling on the axes between pairs of comparisons)

Initial visit	Follow-up visit
Correlation of the Rrs5 and LCI Z-scores	**Correlation of the Rrs5 and LCI Z-scores**
Simple scatter plot of Rrs5 and LCI Z-scores 	**Simple scatter of Rrs5 and LCI Z-scores** 
Correlation of the Xrs5 and LCI Z-scores	**Correlation of the Xrs5 and LCI Z-scores**
Simple scatter plot of Xrs5 and LCI Z-scores 	**Simple scatter of Xrs5 and LCI Z-scores** 

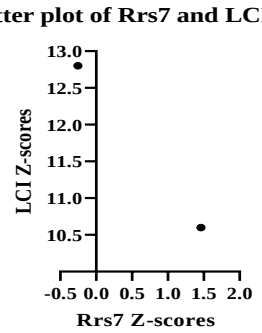
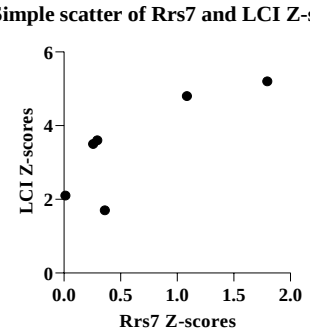
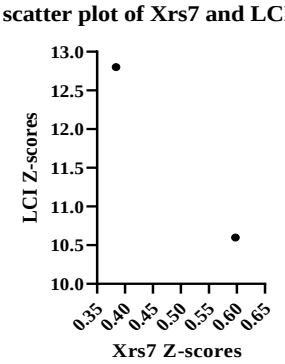
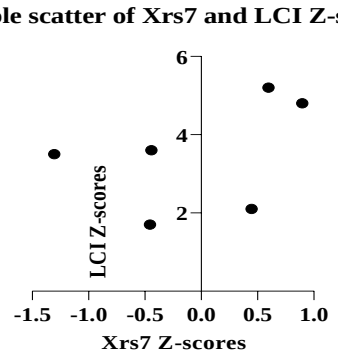
Correlation between the Z-scores of the forced oscillation technique measurements at 7–41 Hz (Rrs7 and Xrs7) and the multiple breath nitrogen washout Z-scores of LCI at the initial and follow-up visits

In attempting to evaluate correlations between the FOT Z-scores at 7–41 Hz and the LCI Z-scores at the initial laboratory visit, it was found that there were only two participants with Z-scores for both measurements, and for the follow-up visit, there were six participants with available data for the Rrs7, Xrs7 and LCI Z-scores., Table 8.10 and figures in Table 8.12 present the correlations of the FOT measurements at 7–41 Hz and the LCI Z-scores. There was a significant correlation between the Rrs7 Z-scores and the LCI Z-scores at the follow-up visit. However, no statistical analysis of the correlation between the Rrs7 and Xrs7 Z-scores and the

LCI Z-scores was performed for the initial laboratory visit due to the small sample of only two participants.

Table 8.12: Figures presenting the correlations between the Rrs7 and Xrs7 Z-scores and the LCI Z-scores at the initial and follow-up visits

(Please note that there are differences in the scaling on the axes between pairs of comparisons)

Initial visit	Follow-up visit
Correlation of the Rrs7 and LCI Z-scores	**Correlation of the Rrs7 and LCI Z-scores**
	
Correlation of the Xrs7 and LCI Z-scores	**Correlation of the Xrs7 and LCI Z-scores**
	

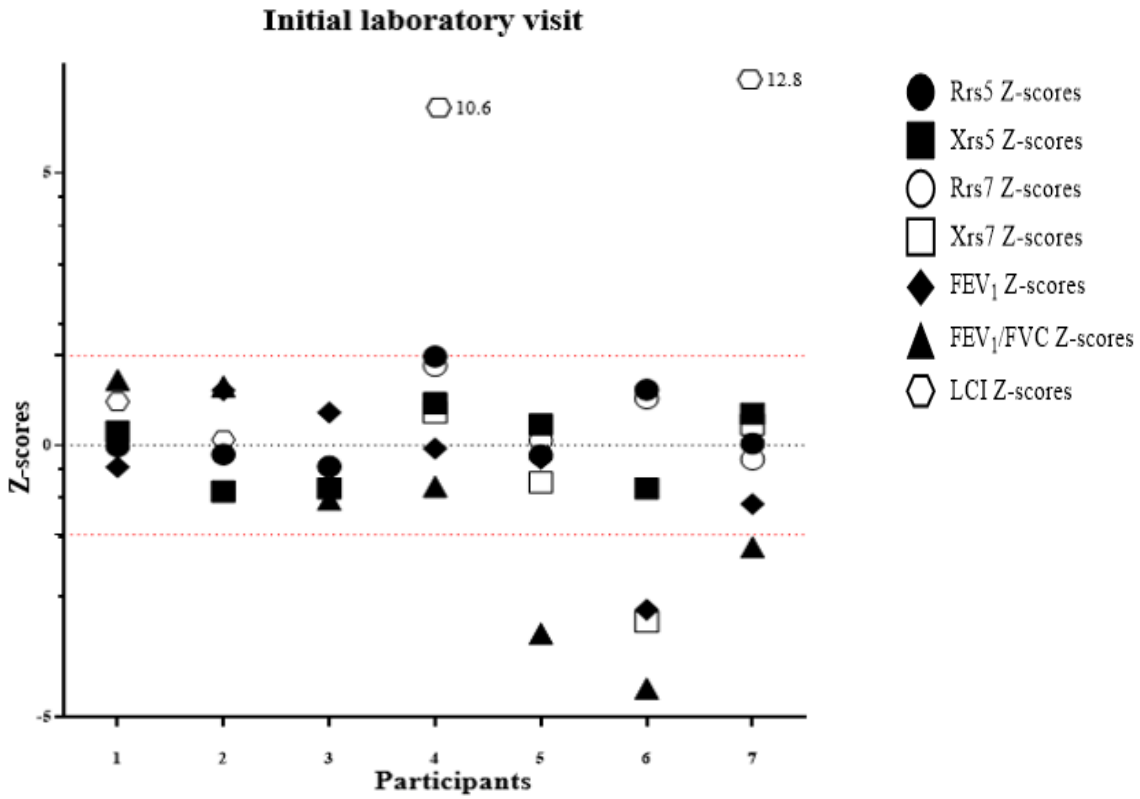
At the initial laboratory visit, data of LCI were only available for four participants. Two of the four participants had abnormal Z-scores for the LCI, with normal Z-scores for the FOT measurements at both 5–37 Hz and 7–41 Hz. However, at the follow-up visit, all the LCI Z-scores were abnormal, while only one participant presented with abnormal Z-scores for Rrs5 and Rrs7.

Comparisons of the Z-scores of the FOT measurements at 5–37 Hz and 7–41 Hz, FEV_1, FEV_1/FVC and the LCI at the initial and follow-up visits are presented in Figures 8.2 and 8.3, respectively. LCI Z-scores were mostly abnormal in the studied group of children with

uncontrolled asthma, with most of the normal Z-scores observed for the FOT and spirometry measurements.

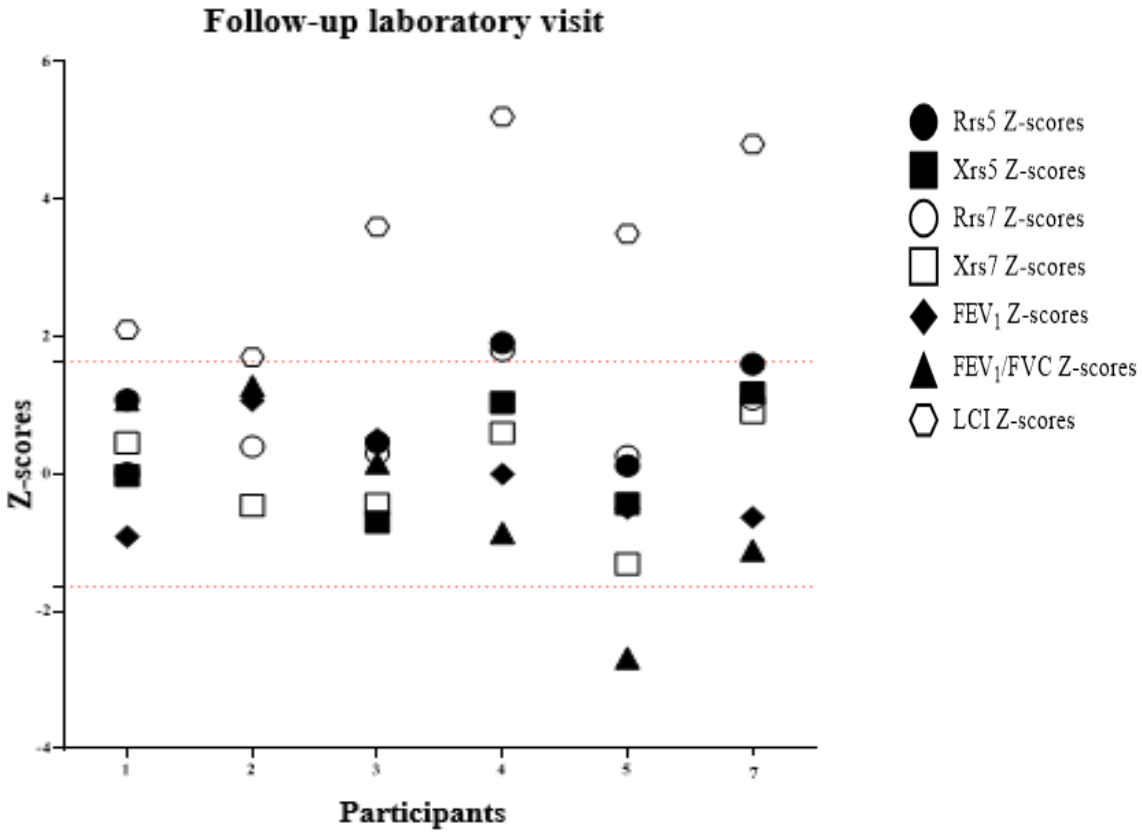
Area under the reactance curve using 5–37 Hz Z-scores were studied separately and compared to the LCI Z-scores for the participants with available Z-scores for the AX. Almost all Z-scores for the AX were normal; the exception was one participant who had the highest abnormal Z-score for LCI among the group and normal spirometry. There was a limited number of Z-scores for both Rrs5-20 and Rrs7-20; however, all the available Z-scores for these measurements were normal. No statistical analysis was performed for the correlation of the AX using 5–37 Hz, Rrs5-20 and Rrs7-20 Z-scores with the FEV_1, FEV_1/FVC and LCI Z-scores, as a limited amount of data for the Z-scores of these measurements was available.

Figure 8.2: Z-scores of the forced oscillation technique measurements at 5–37 Hz and 7–41 Hz, FEV_1, FEV_1/FVC and lung clearance index at the initial laboratory visit



……. Represents cut-off for abnormal Z-score of ≥1.64 or ≤−1.64

Figure 8.3: Z-scores of the forced oscillation technique measurements at 5–37 Hz and 7–41 Hz, FEV_1, FEV_1/FVC and lung clearance index at the follow-up laboratory visit



……. Represents cut-off for abnormal Z-score of ≥1.64 or ≤−1.64

Correlation between the Z-scores of the forced oscillation technique measurements at both 5–37 Hz and 7–41 Hz (Rrs5, Xrs5, Rrs7 and Xrs7) and the Fractional exhaled nitric oxide at the initial and follow- up visits

Six of the participants had successful FeNO readings at the initial laboratory visit, four of whom had acceptable measurements of FOT at both 5–37 Hz and 7–41 Hz; however, the other two participants only had acceptable FOT readings at 5–37 Hz. All the FeNO readings at the initial laboratory visit were more than 35 ppb. The Rrs5, Xrs5 and Rrs7 Z-scores were normal, and only one participant had abnormal Z-scores for Xrs7. There was no correlation observed between the FOT measurements and the FeNO levels.

At the follow-up visit, two participants had FeNO readings of more than 35 ppb and four had FeNO readings of less than 35 ppb. All had acceptable measurements of FOT at 7–41 Hz and five had acceptable measurements at 5–37 Hz. All participants with a higher FeNO level of more than 35 ppb had normal FOT measurements at both 5–37 Hz and 7–41 Hz. There was no correlation observed between the FOT measurements and the FeNO levels.

8.5.2 Correlation between the asthma control test (ACT) and childhood asthma control test (cACT) and the forced oscillation technique indices (Rrs5, Xrs5, Rrs7 and Xrs7) and spirometry indices (FEV_1 and FEV_1/FVC)

Correlation between the asthma control test (ACT) and childhood asthma control test (cACT) and the forced oscillation technique (Rrs5 and Xrs5) Z-scores and actual values at the initial and follow-up visits

All participants had FOT measurement data available at 5–37 Hz (n=7) from the initial visit, and five participants had Rrs5 and Xrs5 data available from the follow-up visit. No significant correlation was observed between any of the FOT measurement Z-scores or actual values at 5–37 Hz and the ACT/cACT in either the initial laboratory visit or the follow-up visit (Table 8.13).

Table 8.13:Correlation between the asthma control test (ACT) and childhood asthma control test (cACT) and the forced oscillation technique index (Rrs5 and Xrs5) Z-scores and actual values at the initial and follow-up visits

	Initial visit (n=7)				**Follow-up visit (n=5)**			
ACT/ cACT	**Rrs5 Z-scores**		**Xrs5 Z-scores**		**Rrs5 Z-scores**		**Xrs5 Z-scores**	
	r	**p-value**	***r***	**p-value**	***r***	**p-value**	***r***	**p-value**
	0.214	0.662	−0.080	0.864	−0.352	0.562	−0.240	0.697
	Rrs5 actual values		**Xrs5 actual values**		**Rrs5 actual values**		**Xrs5 actual values**	
	r	**p-value**	***r***	**p-value**	***r***	**p-value**	***r***	**p-value**
	−0.058	0.902	0.217	0.641	−0.576	0.309	0.587	0.298

r = correlation coefficient

Correlation between the asthma control test (ACT) and childhood asthma control test (cACT) and the forced oscillation technique (Rrs7 and Xrs7) Z-scores and actual values at the initial and follow-up visits

Four participants had data FOT measurement data available at 7–41 Hz from the initial visit, and six participants, had Rrs7 and Xrs7 data available from the follow-up visit. There was no significant correlation between the ACT/cACT and 7–41 Hz FOT measurement (Rrs7 and Xrs7) Z-scores or actual values at either the initial or follow-up visit (Table 8.14).

Table 8.14: Correlation between the asthma control test (ACT) and childhood asthma control test (cACT) and the forced oscillation technique index (Rrs7 and Xrs7) Z-scores and actual values at the initial and follow-up visit

	Initial visit (n=4)				**Follow-up visit (n=6)**			
ACT/ cACT	**Rrs7 Z-scores**		**Xrs7 Z-scores**		**Rrs7 Z-scores**		**Xrs7 Z-scores**	
	r	**p-value**	***r***	**p-value**	***r***	**p-value**	***r***	**p-value**
	0.453	0.547	−0.796	0.204	0.257	0.623	−0.275	0.598
	Rrs7 actual values		**Xrs7 actual values**		**Rr7 actual values**		**Xrs7 actual values**	
	r	**p-value**	***r***	**p-value**	***r***	**p-value**	***r***	**p-value**
	0.160	0.841	−0.374	0.626	−0.263	0.615	0.187	0.722

r = correlation coefficient

Correlation between the asthma control test (ACT) and childhood asthma control test (cACT) and the spirometry index (FEV_1 and FEV_1/FVC)) Z-scores and actual values at the initial and follow-up visits

All participants had spirometry data (n=7) available from the initial visit, and six participants had spirometry data available from the follow-up visit. The only significant correlation was between the ACT/cACT and the FEV_1/FVC Z-scores at both the initial and follow-up visit. (Table 8.15).

Table 8.15: Correlation between the asthma control test (ACT) and childhood asthma control test (cACT) and the spirometry index (FEV_1 and FEV_1/FVC) Z-scores and actual values at the initial and follow-up visits

	Initial visit (n=7)				Follow-up visit (n=6)			
ACT/ cACT	FEV_1 Z-scores		FEV_1/FVC Z-scores		FEV_1 Z-scores		FEV_1/FVC Z-scores	
	r	p-value	*r*	p-value	*r*	p-value	*r*	p-value
	−0.611	0.145	−0.782	0.038*	−0.390	0.445	−0.826	0.043*
	FEV_1 actual values		FEV_1/FVC actual values		FEV_1 actual values		FEV_1/FVC actual values	
	r	p-value	*r*	p-value	*r*	p-value	*r*	p-value
	0.230	0.620	−0.615	0.142	0.401	0.431	−0.731	0.099

r = correlation coefficient statistically significant*

8.5.3 Comparing the forced oscillation technique measurements at the initial and follow-up visits

Five participants had acceptable measurements of FOT at 5–37 Hz at both the initial and follow-up laboratory visits. However, only three participants presented with acceptable FOT measurements at 7–41 Hz at both visits. ACT or cACT scores were obtained for all participants at both the initial and follow-up laboratory visits.

FOT measurements using waveforms of 5–37 Hz: The FOT measurements at 5–37 Hz, for all the participants showed an increase in the Rrs5 and AX values at their follow-up visit compared to their initial laboratory visit. Though the Rrs5 and AX values remained within the normal levels for most of the participants, one participant had an increase to the abnormal level for Rrs5 and AX. The Rrs5-20 increased for all the participants except one who presented a drop in Rrs5-20 between the visits. Reactance at 5 Hz tended to be more negative for most of the participants; however, for one participant, the value moved toward zero. However, no significant change was observed for the FOT measurements at 5–37 Hz between the two visits, with

the exception of Rrs5 (p = 0.018). The comparison between the two visits and the paired t-tests are presented in figures in Table 8.16 and Table 8.17, respectively.

Table 8.16: Forced oscillation technique measurements using waveform 5–37 Hz at the initial and follow-up laboratory visits

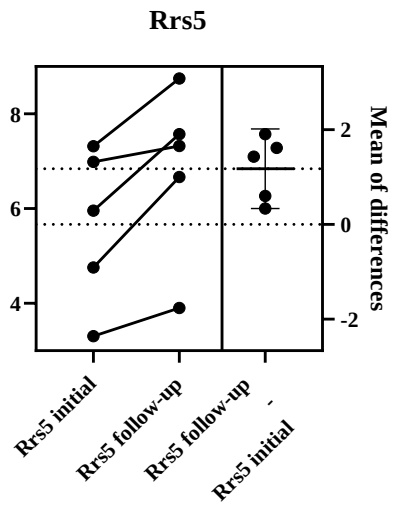
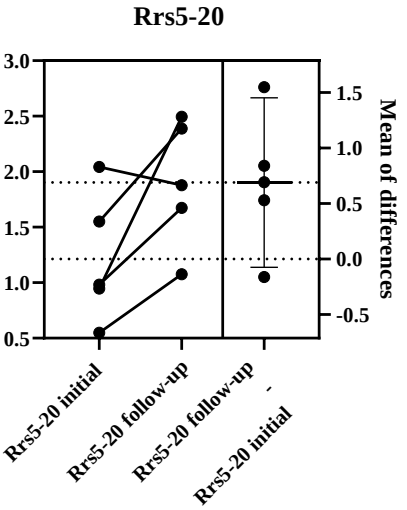
FOT measurements using 5–37 Hz	(n=5)
Rrs5 ($cmH_2O \cdot sec/L$)	
Rrs5-20 ($cmH_2O \cdot sec/L$)	

Table 8.16 (Continued)

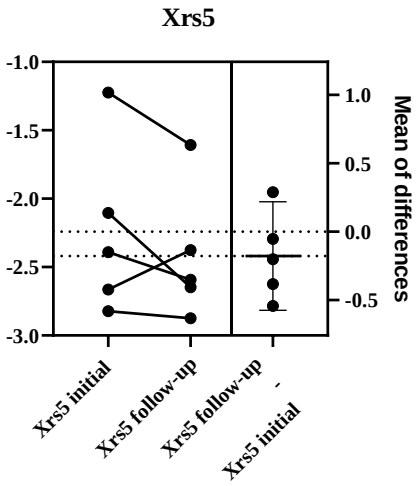
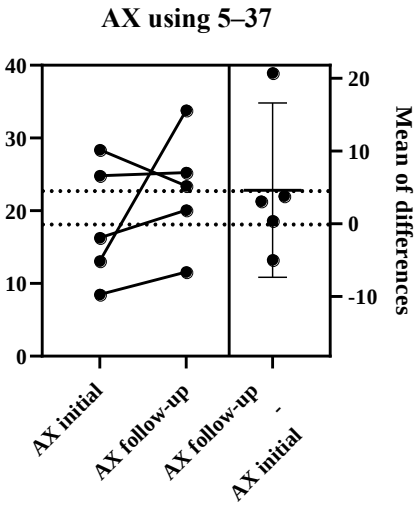
FOT measurements using 5–37 Hz	(n=5)
Xrs5 ($cmH_2O \cdot sec/L$)	
AX (cmH_2O/L)	

Table 8.17: Paired t-test for uncontrolled asthma with forced oscillation technique measurements using waveform 5–37 Hz at the initial and follow-up laboratory visits (n=5)

	Initial visit	**Follow-up visit**	**p-value**
Rrs5 ($cmH_2O \cdot sec/L$)	5.67 (1.66)	6.84 (1.81)	0.018*
Rrs5-20 ($cmH_2O \cdot sec/L$)	1.21 (0.59)	1.90 (0.58)	0.067
Xrs5 ($cmH_2O \cdot sec/L$)	−2.24 (0.63)	−2.42 (0.49)	0.280
AX (cmH_2O/L)	18.22 (8.25)	22.83 (8.07)	0.345

*Data represent mean (SD) *statistically significant*

FOT measurements using waveforms of 7–41 Hz: Comparing the FOT measurements at 7–41 Hz between the initial and follow-up visits for the three participants with available data showed that all Rrs7 values increased at the follow-up, with only one showing an increase to the abnormal level. However, two participants presented an increase, and one presented a decrease in Rrs7-20. The Xrs7 values became more negative in the follow-up visit for two of the participants and remained almost the same for one of the participants. AX using 7–41 Hz varied between the participants: the AX values remained the same for one of the participants, another participant exhibited a decrease in the AX values and the third participant exhibited an increase in the AX values. The comparison between the two visits and the paired t-tests are presented in figures in Table 8.18 and Table 8.19, respectively.

Table 8.18: Forced oscillation technique measurements using waveform 7–41 Hz at the initial and follow-up laboratory visits

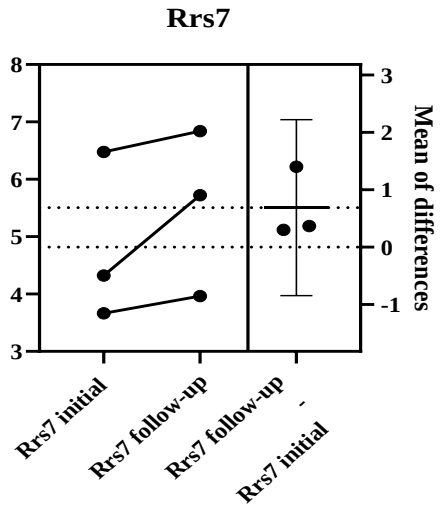
FOT measurements using 7–41 Hz	**(n=3)**
Rrs7 ($cmH_2O \cdot sec/L$)	

Table 8.18 (Continued)

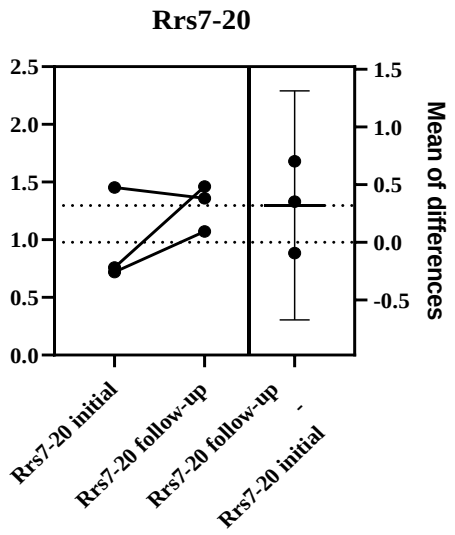
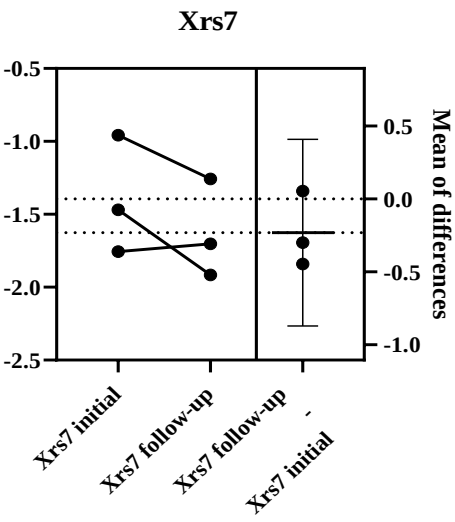
FOT measurements using 7–41 Hz	(n=3)
Rrs7-20 ($cmH_2O \cdot sec/L$)	
Xrs7 ($cmH_2O \cdot sec/L$)	

Table 8.18 (Continued)

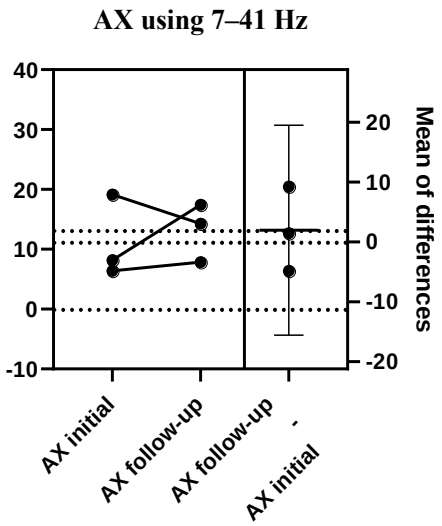
FOT measurements using 7–41 Hz	(n=3)
AX (cmH_2O/L)	

Table 8.19: Paired t-test for uncontrolled asthma with forced oscillation technique measurements using waveform 7–41 Hz at the initial and follow-up laboratory visits (n=3)

	Initial visit	Follow-up visit	p-value
Rrs7 (cmH2O·sec/L)	4.82 (1.47)	5.51 (1.45)	0.194
Rrs7-20 (cmH2O·sec/L)	0.98 (0.41)	1.30 (0.20)	0.299
Xrs7 (cmH2O·sec/L)	−1.39 (0.40)	−1.63 (0.34)	0.261
AX (cmH2O/L)	11.25 (6.91)	13.19 (4.88)	0.681

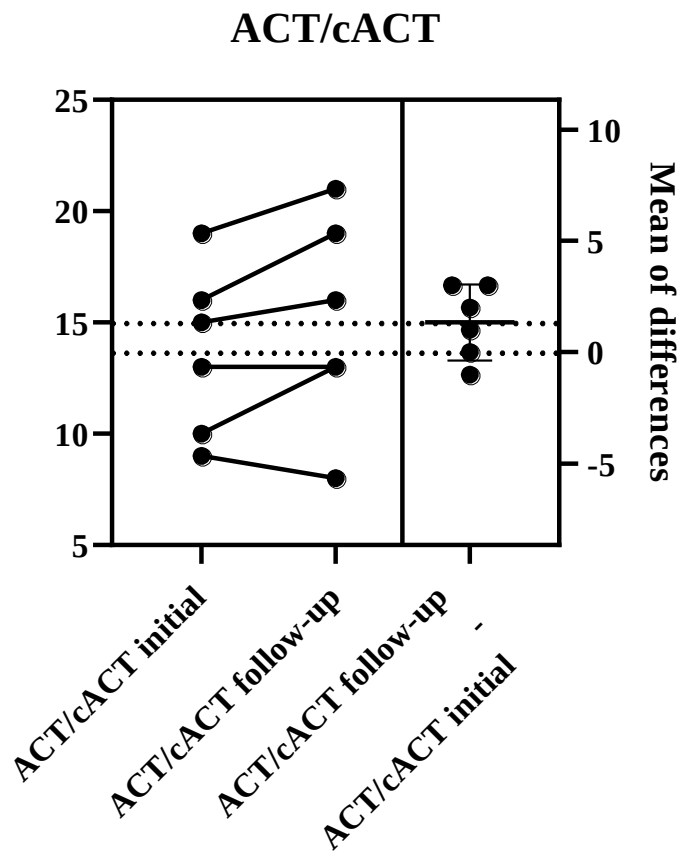
Data represent mean (SD)

8.5.4 Monitoring adherence to the treatment

We intended to monitor the medication usage by the participants through the electronic monitoring devices. However, this was not possible due to some technical issues, as families were not able to synchronize the electronic monitoring devices to their smart phones because of some Bluetooth issues, or the administration of the medication was not able to be detected through the device. These technical issues did not allow us to review accurate records of medication usage through the portal. Overall, the parents and participants reported good adherence to the medication; however, one participant reported good adherence while the parent reported the opposite. ACT/cACT scores increased slightly in four of the participants, remained the same

in one and decreased slightly in one, with no statistically significant change observed (Figure 8.4). Though the ACT/cACT scores increased at the follow-up visit overall, most of the FOT measurements did not show improvements. However, the FeNO levels dropped at the follow-up visit for all the participants except for one participant.

Figure 8.4: Asthma control test scores at the initial and follow-up laboratory visits



8.5.5 Evaluation of bronchodilator reversibility of forced oscillation technique indices in children with uncontrolled asthma

FOT measurements using waveforms of 5–37 Hz: For the initial laboratory visit, seven participants had acceptable measurements for Rrs5, Rrs5-20, Xrs5 and AX using 5–37 Hz before and after the administration of the bronchodilator. However, only five participants had acceptable FOT measurements at 5–37 Hz at the follow-up visit. Figures in Table 8.20 presents the FOT parameters before and after the bronchodilator administration.

Table 8.20: Forced oscillation technique measurements using waveform 5–37 Hz before and after bronchodilator administration at the initial and follow-up laboratory visits

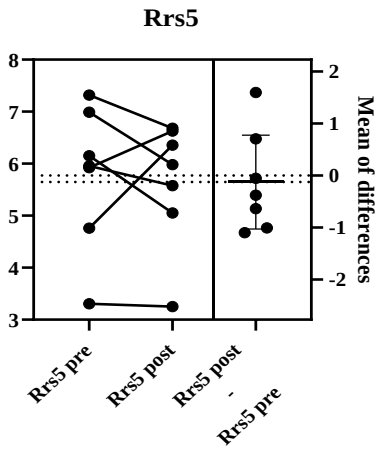
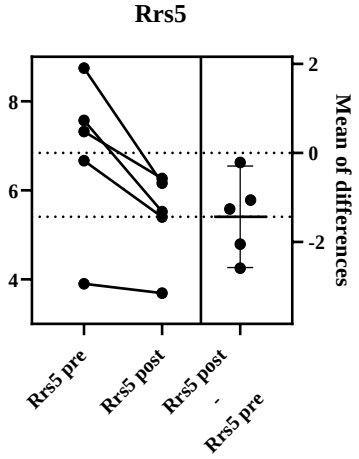
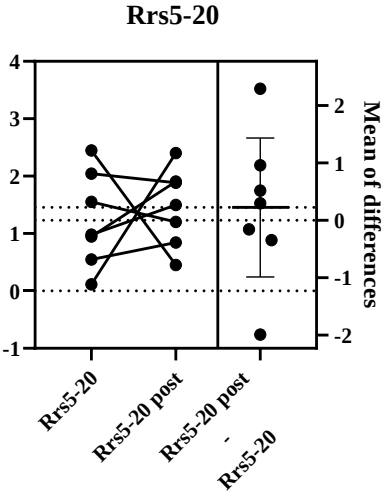
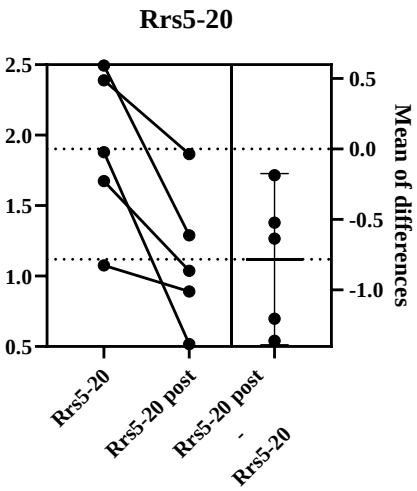
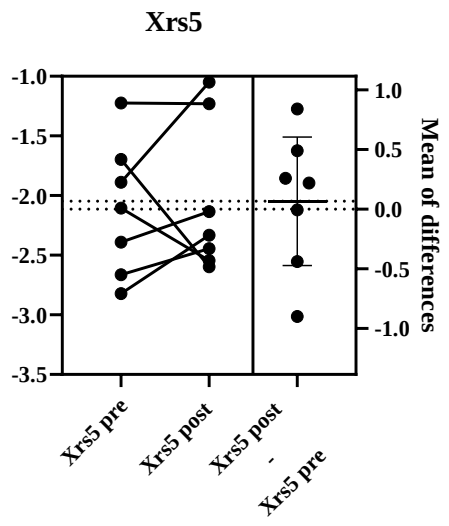
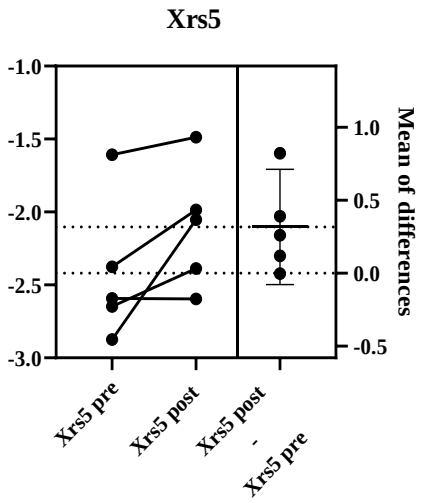
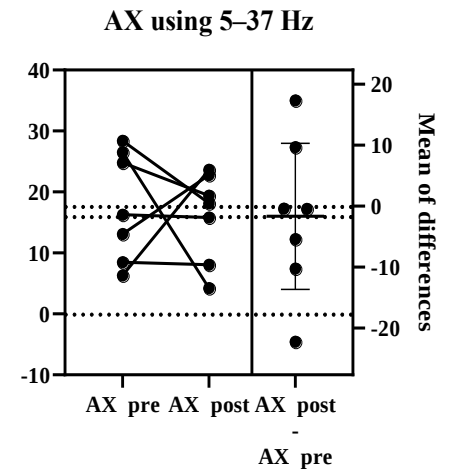
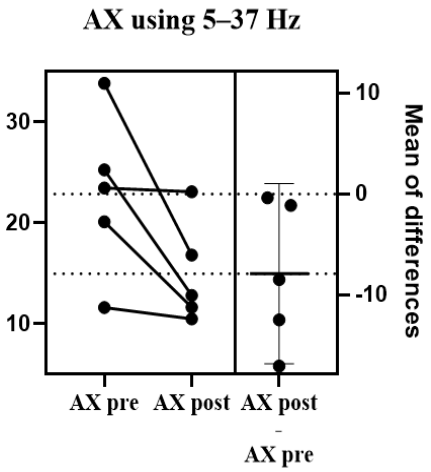
FOT measurements using 5–37 Hz	Initial visit (n=7)	Follow-up visit (n=5)
Rrs5 ($cmH_2O \cdot sec/L$)		
Rrs5-20 ($cmH_2O \cdot sec/L$)		

Table 8.20 (Continued)

FOT measurements using 5–37 Hz	Initial visit (n=7)	Follow-up visit (n=5)
Xrs5 (cmH2O·sec/L)		
AX (cmH2O/L)		

At the initial visit, the Rrs5 dropped in four participants, remained almost the same in one participant and increased in two participants following the bronchodilator administration. One of the participants exhibited a huge increase in Rrs5-20 and three participants had a slight increase in Rrs5-20 values following the bronchodilator. A decrease in the Rrs5-20 readings was noticed in three participants after the bronchodilator; two with a minor change and the other participant with a huge drop. Following the bronchodilator administration, the Xrs5 shifted toward zero in four participants, did not change for one participant and became more negative in two participants. However, the AX values dropped in three participants, increased in two participants and remained almost the same in the other two participants after the bronchodilator. The highest increase in Rrs5-20 after the bronchodilator was aligned with the increase in the AX values in the same participants, although this was not reflected in the Rrs5 for these

participants. Despite these changes before and after the bronchodilator administration at the initial lab visit, none of these changes were a statistically significant. The Rrs5-20 average percent changes did not exhibit an improvement following the bronchodilator. However, Rrs5 and Xrs5 had very minimal percent changes at the initial laboratory visit before and after the bronchodilator administration. Moreover, AX using 5–37 showed an improvement following the BDR by average (28.4%).

At the follow-up visit, all the Rrs5 and Rrs5-20 values decreased following the bronchodilator administration for the five participants for whom data were available, with statistically significant differences ($p = 0.025$ and $p = 0.023$, respectively). With the exception of one participant, for whom a minimal change in Xrs5 was observed, all the Xrs5 values moved toward zero. The AX also trended toward a decrease in four of the participants and remained the same for one of the participants. However, none of the changes in Xrs5 and AX were statistically significant. The average percent change after bronchodilator administration was highest for the Rrs5-20, followed by the AX using 5–37 and the Rrs5 and the lowest percent change was seen for the Xrs5 (mean ± SD, −39.61±22.20, −30.63±23.22, −19.10±9.76 and 12.42±10.80, respectively). The highest percent changes following the bronchodilator administration were all observed in the same participant, who had a high resistance measure of the FOT at 5–37 Hz.

FOT measurements using waveform 7–41 Hz: The measurements of FOT at 7–41 Hz before and after the bronchodilator administration were compared for four participants at the initial laboratory visit and six participants at the follow-up visit. Figures in Table 8.21 presents the FOT measurements at 7–41 before and after the bronchodilator administration at the two visits.

Table 8.21: Forced oscillation technique measurements using waveform 7–41 Hz before and after the bronchodilator administration at the initial and follow-up laboratory visits

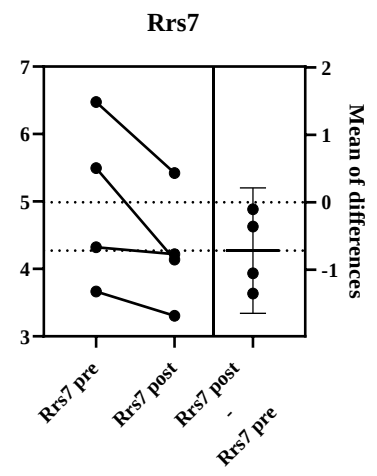
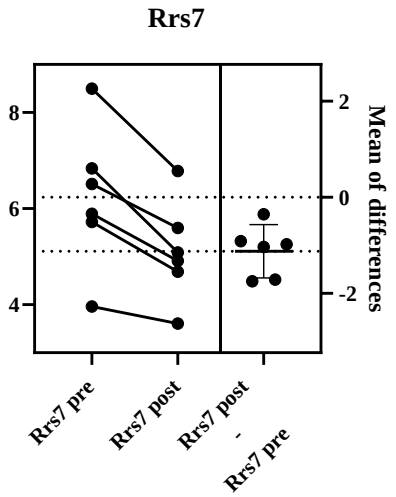
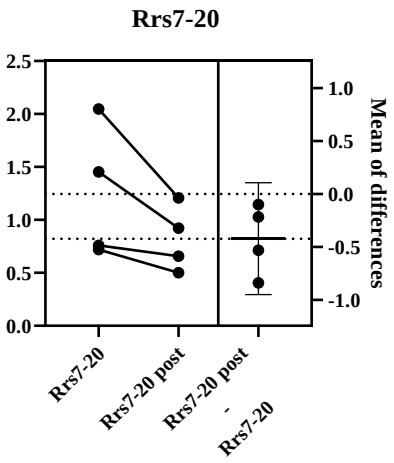
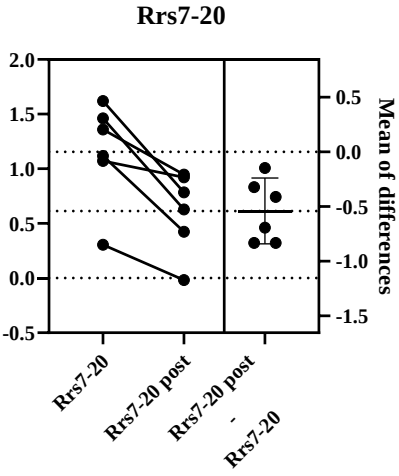
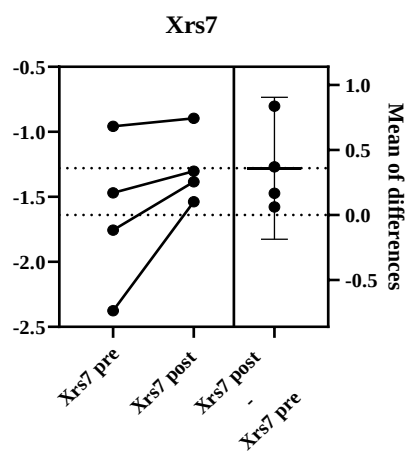
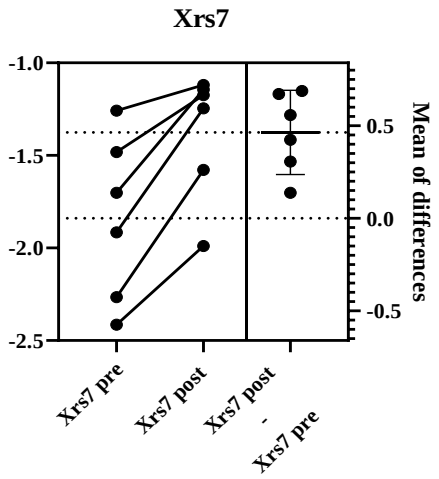
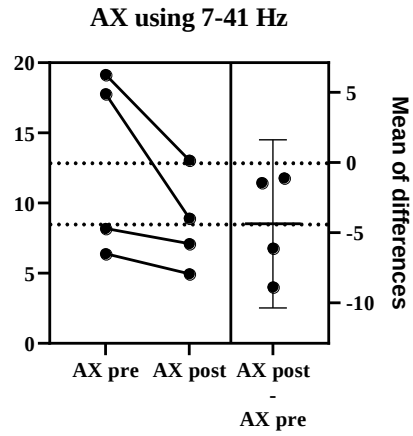
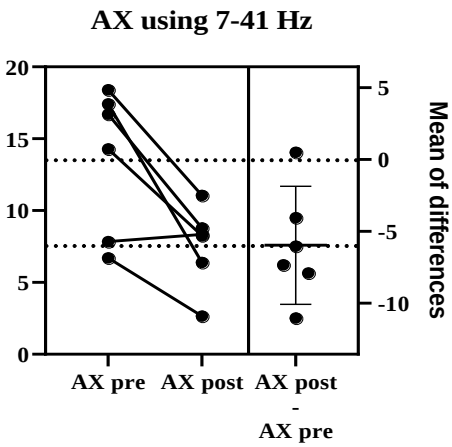
FOT measurements using 7–41 Hz	Initial visit (n=4)	Follow-up visit (n=6)
Rrs7 ($cmH_2O \cdot sec/L$)		
Rrs7-20 ($cmH_2O \cdot sec/L$)		

Table 8.21 (Continued)

FOT measurements using 7–41 Hz	Initial visit (n=4)	Follow-up visit (n=6)
Xrs7 ($cmH_2O \cdot sec/L$)		
AX (cmH_2O/L)		

At the initial laboratory visit, three of the four participants with acceptable measurements exhibited a decrease in the Rrs7 values following the bronchodilator administration, and the fourth had Rrs7 reading similar to that observed at baseline. However, the Rrs7-20 and AX values decreased in all four participants, with a huge decline in two and a minimal decrease in the other two participants. The reactance at 7 Hz moved toward zero in three of the participants following the bronchodilator administration, while a minimal change was observed in one of the participants. No significant differences in any of the measurements of FOT at 7–41 were observed before and after the administration of bronchodilator at the initial laboratory visit. However, all the Rrs7, Rrs7-20, Xrs7 and AX using 7–41 Hz measurements showed an improvement following bronchodilator administration at the initial laboratory visit, as reflected by the average of the percent change before and after the bronchodilator. The highest percent change was observed for the Rrs7-20 measurements, followed by the AX and the Xrs7

measurements, with the lowest percent change observed for the Rrs7 measurements (mean ± SD, −30.27 ±12.15, −29.30±15.64, 18.59 ±12.66 and −13.28 ±9.48, respectively).

The Rrs7, Rrs7-20 and Xrs7 measurements improved in all six participants following the bronchodilator at the follow-up visit. Measurements of the resistance at 7 Hz decreased, with an increase in the level of the reactance observed after the bronchodilator administration. However, the AX using 7–41 Hz decreased in five participants after the bronchodilator administration, while one participant had similar readings. These changes before and after the bronchodilator were statistically significant. All measurements of the Rrs7-20, AX using 7–41 Hz, Xrs7 and Rrs7 showed an improvement following the bronchodilator administration, with an average percent change following the bronchodilator of −53.5%, −41.1%, 24.6% and −17.2%, respectively.

Though the measurements of FOT at 7–41 Hz showed a larger improvement after the bronchodilator administration for both the initial and follow-up visits, a comparison to the group with the FOT measurements at 5–37 was not possible due to the difference in the sample studied at each visit for each frequency range.

8.6 Discussion

Previous studies have shown that FOT measures at multiple frequencies (5, 11 and 19 Hz) in a group of children and adults aged 13–39 years with controlled and uncontrolled asthma and in healthy controls were similarly informative as spirometry measures (147). However, this was not reflected in our study, as no correlation was observed between the FOT and spirometry measures in children with uncontrolled asthma. Notably, when FOT was studied for its relevance in the diagnosis of asthma, studies supported the correlation between FOT and spirometry measures (122,135). Delacourt et al. demonstrated a correlation between the spirometry indices (FEV_1, maximal expiratory flow at 50% MEF50) and the resistance measure of FOT extrapolated at 0 HZ (Rrs0) in a group of children with asthma aged 2.7–12.7 years (122). Additionally, the resistance measure by FOT correlated to the FEV_1 reflected by the spirometry in children with asthma (135). However, it is important to note that these studies were conducted with a population with stable asthma; in contrast, our present study included children with uncontrolled asthma. We also did not observe any correlation between FOT and FeNO levels. This is consistent with the findings of Seo et al., who showed that FeNO does not correlate with the IOS variables in children with asthma (234). This could be attributed to the fact that these tests evaluate two independent and different aspects of the disease (265). Also, no association was observed between the spirometry and FeNO levels in groups of children and

adults with asthma (147,265) . In our study, the LCI was found to be a better parameter to reflect small airway abnormalities compared to the FOT parameters This could be explained by the LCI having been shown to have a significant role in the assessment of small airways in children with asthma (248). Also, LCI has been established to be a more sensitive measure for reflecting small airways disease than other objective evidence, as it can reflect ventilation inhomogeneity when small airway obstruction persists, and spirometry is still normal (255). However, the findings of our study were based mainly on the analysis of the relationship between the Rrs5 and Xrs5 and the LCI that was performed. In our findings, the evaluation properties of FOT measures differ from what is seen for the LCI, the Rrs5 represents the total respiratory resistance and the Xrs5 mainly reflects the elastic properties of the small airways (97).

Adherence to treatment has been shown to play a role in improving clinical outcomes and quality of life, as well as in improving lung function (266). Most of the participants demonstrated an increase in the resistance and a decrease in the reactance measures of FOT in the follow-up visit. Though, adherence to the use of the inhalers was determined only by reports from the parents and participants; thus, adherence cannot be guaranteed, since there was no accurate method to assess and reflect upon the adherence by the participants. Some flaws with the use of the electronic monitoring devices arose during the study; these included technical issues with the electronic monitoring device and the connection to the families' smart phones that impeded the full and accurate review of the medication taken through the smart inhaler portal.

All the FOT measurements revealed improvements following the bronchodilator administration, except for the FOT measurements at 5–37 Hz in the initial visit. A persistent BDR is considered to be associated with low asthma control or with poor compliance with treatment (258). However, measurements of the FOT in the follow-up visit exhibited a higher percent change following the bronchodilator administration compared to those performed in the initial laboratory visit. This could be due to the higher values of the resistance and the lower reactance values of the FOT in the follow-up visit compared to the initial laboratory visit, which could be indicative of the higher percent change following the bronchodilator administration. This change is also notable with lower baseline readings of lung function in children with asthma (231).

In groups of children with uncontrolled asthma, measurements of FOT mostly did not correlate to either of the spirometry, LCI, ACT/cACT and the FeNO. Nevertheless, FOT measurements were able to exhibit percent changes following the bronchodilator administration as stated, and

this was mainly seen in measurements of FOT using 7–41 Hz. Though these findings focus on patients with uncontrolled asthma, it is still considered essential as an initial observation noticed in the children with asthma. Even though the statistical power is low given the small sample, these initial findings could be supported and extended in further studies, since the need to study the role of the FOT in children with uncontrolled asthma remains crucial.

CHAPTER 9 CONCLUSIONS AND FUTURE WORK

This chapter concludes the thesis by summarising how the study's findings align with its aims. It also discusses the study's limitations and avenues for future research.

9.1 Summary of key research findings

This thesis aimed to investigate the role of the forced oscillation technique (FOT) in the diagnosis and monitoring of asthma in school-aged children. The results and interpretation of findings have been discussed in previous chapters. This chapter summarises the key messages of this study.

The thesis began with a systematic review of the literature on the role of the IOS/FOT in asthma diagnosis and assessment using bronchodilator reversibility testing and spirometry. The analysis of the three studies included in the systematic review identified a correlation between the IOS/FOT and the spirometry measurements. However, IOS/FOT may be useful to differentiate between children and adolescents with asthma and healthy children and adolescents. This was mainly represented in the measurements of the resistance at 5, 8 and 10 Hz in addition to the area under the reactance curve. As a result, the IOS/FOT tool could be used to support the diagnosis of asthma and the assessment of bronchodilator responses in children and adolescents. Nevertheless, the types of devices, frequency waveforms and populations studied in these works differed from the intended focus of study in this thesis.

We studied healthy children using the FOT at 5–37 Hz and 7–41 Hz to determine how the measurements of this control population related to reference values from other populations. In addition, we studied the relationships between anthropometric characteristics and the resistance and reactance FOT measurements. Most of the FOT measurements from the study's 22 healthy participants aligned with other reference values dataset of the prediction equations used in the TremoFlo software. However, these raw measurements cannot be directly compared with the reference data, whose values depend on the characteristics of the studied population and the applied frequency, which differed from those used in this study. Nevertheless, relationships between FOT measurements and anthropometry can be compared and are valid. Correlations were observed between FOT measurements and height, weight, and age. In particular, there was a strong negative correlation between height and FOT resistance.

The results presented in chapter 6 indicate that FOT measurements allowed us to distinguish children with stable asthma (with complete or incomplete evidence) from those without asthma. This was mainly achieved using the AX and Rrs5 measurements. However, such distinctions

were not observed in the Rrs5-20 measurements, which at the baseline measure appeared normal for children both with and without asthma. In addition, FOT measurements at 5–37 Hz were highly correlated with the spirometry measurements of FEV_1 and FEV_1/FVC. However, the findings from this study did not entirely support our hypotheses, as there was no correlation between FeNO and the FOT indices in our study sample. This could be because these evaluate two distinct, independent aspects of the disease.

In chapter 7, we discussed how FOT indices – primarily AX, Xrs and Rrs measurements – reflected airway abnormalities in children diagnosed with acute asthma who were recruited from the emergency department or hospital wards. Moreover, bronchodilator reversibility reflected significant improvements in the FOT indices of children with acute asthma following bronchodilator administration. There was no significant difference, however, between the extents to which measurements at 5–37 Hz and 7–41 Hz reflected abnormalities within the study sample.

Finally, in seven participants with uncontrolled asthma, no correlation was observed between the FOT measurements and spirometry, MBNW, FeNO measurements, or the ACT/cACT scores. However, amongst these participants, the FOT measurements revealed the reversal of bronchoconstriction following bronchodilator administration.

9.2 Strengths and limitations

To our knowledge, this is the first study to investigate the use of the FOT through the TremoFlo device to assess children with different types of asthma across a variety of clinical settings. This study included children with stable asthma, uncontrolled asthma, and acute asthma. Children were recruited from the asthma clinic, the emergency department and hospital wards. The study also included a control group of healthy children in the same age group.

This study had several limitations. Due to the coronavirus pandemic and the disruption it caused, this work included only a limited number of children with acute and uncontrolled asthma. In addition, the 7–41 Hz frequency waveforms were introduced in a second stage of data collection, because the 5–37 Hz frequency waveform was found to interfere with breathing in a number of asthmatic participants aged 2–4 years in another study that was conducted whilst our study was ongoing. However, it had less effect on older children aged 5-15 years. Moreover, the reference values used were obtained from a population different to the studied population, originating from research conducted using different equipment, software and measurement procedures. Further, time constraints inhibited the data collection process, resulting in a small sample size.

In children with acute asthma, the diagnosis of asthma was based exclusively on physician diagnoses, without considering additional objective evidence. We were unable to perform spirometry or measure participants' lung function in the emergency department due to COVID-19 restrictions and participants' physical conditions. Had they been obtained, these results would have provided a benchmark for the FOT measurements.

Another limitation of this study was the difficulty of conducting spirometry measurements in children, as not all the children were able to perform spirometry satisfactorily.

Furthermore, no bronchodilator reversibility testing was conducted for the children in the control group, as the Research Ethics Committee did not support the administration of bronchodilator to these children. Additionally, bronchodilation reversibility was not tested for the children with stable asthma.

Type I errors (false positives) usually arise due to chance or improper research technique; however, Type II errors (false negatives) largely occur due to low statistical power. Within this project the significance level that was chosen was $p \leq 0.05$. Nevertheless, raising the confidence threshold would increase the test accuracy and decrease the type I error rate. Using a larger sample size would decrease the incidence of type II errors, especially in children where no Z-scores could be calculated. However, a larger sample size was not possible due to the impact of Covid-19 on this project.

9.3 Clinical implications and directions for future research

Future clinical studies with larger sample sizes and greater statistical power could adopt the aims of this study and continue to use the FOT to measure lung function in children and adolescents with asthma.

In addition, it would be beneficial to study bronchodilation reversibility in children with stable asthma, as reversibility testing would aid the diagnosis of children with reversible airway obstruction and help detect asthma in children with normal lung function.

Further, studying a larger sample of the healthy population would allow for the creation of appropriate reference values and prediction equations specific to the sample population. Studying bronchodilator responses in healthy children would allow for sensitivity and specificity measurements with the use of the ROC and AUC to represent the optimal cut-off points for per cent change in bronchodilator within the study sample.

Lastly, studying the FOT measurements in acute asthma cases post-discharge and during follow-up visits could provide insight into changes in lung function and pathophysiology.

9.4 Learning techniques

Research, especially that within this project and in developing the thesis, helped me to gain a deeper vision of the scientific process. This ranged from the development of the research questions and hypotheses, processing of the ethical approval and the data collection periods (which included dealing with patients and their parents). In addition to formulating the quality standard and the acceptability criteria for the measurements. These were an important learning aspect within my research that aided in reflecting a high quality and accuracy for the data collected and the results.

Recruiting participants with acute asthma was the most challenging aspect of the project due to the restricted time available and due to the nature of work in the emergency department. However, during this part of the study, I learned how to identify potential participants, make initial contact with them (or their family), obtain informed consent and test subsequent participants in an organised manner. In addition, working with children from different age groups extended my experience in dealing with children. Some initial difficulties with younger children were overcome in time, as I learnt different techniques to work with children. In general, this research has widened my clinical experience in various ways.

As a result of interacting with children and their families. I have become more aware of the impact of asthma on their daily lives, to the point where I learned what it is like to be a patient with asthma or the parent of a child with asthma

9.5 Conclusion

We found that FOT measurements provide useful information about the airways of asthmatic children but are more helpful for differentiating between children who do or do not have asthma. Of the FOT indices, the AX provides the most valuable information, as it reflects the state of the peripheral airways and most accurately identified children with asthma.

Based on the findings of this thesis, it can be concluded that the FOT, after further careful evaluation, could constitute a useful, objective tool for the diagnosis, assessment, and monitoring of children with asthma.

APPENDICIES

APPENDIX A: Service Improvement Project Audit Documents (invitation letter, information sheets)

University Hospitals of Leicester NHS
NHS Trust

Caring at its best

Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW

Tel: 0300 303 1573
Switchboard Fax: 0116 258 7565

Dear Parent or Carer,

We need your help with a service improvement project.

The British Thoracic Society recommends the use of lung function tests in children requiring hospital treatment for asthma or wheeze to grade severity.

This is rarely done because of time constraints and children sometimes find active blowing tests difficult to perform during an asthma/wheezy attack. In young children, typically those under 5 years no tests are performed at all due to the difficulty in performing blowing tests.

A new technique has been developed called The Forced Oscillation Technique (FOT). This test is quick, painless and does not require any active blowing. All your child has to do is close her/his lips around a small hollow tube and the instrument sends tiny soundwaves into the airways for 10 seconds. The test can be done in all children from 2 years of age and the equipment is fully licensed for clinical use.

We want to test the equipment in the emergency department and on the children's wards to find out if it can replace active blowing tests. It could then potentially be introduced at UHL as a routine test.

We will only do the test when your child is stable and no longer needs extra oxygen.

It is up to you to decide whether or not to take part. A decision to take part or withdraw does not affect any treatment you may be receiving from your doctor or the hospital.

Thank you for taking the time to read this invitation letter

Dr Erol Gaillard

Consultant in Paediatric Respiratory Medicine

Children's Hospital, Leicester Royal Infirmary

Telephone: (0116) 252 3262 / (0116) 258 5691

University Hospitals of Leicester NHS
NHS Trust

Leicester Childrens Hospital
Leicester Royal Infirmary
Leicester
LE1 5WW

Tel: 0116 258 5691

Database for Lung Research in Children

Brief information sheet for young children (5 to 10 years) with acute wheeze/asthma

We are trying to find out what happens in the lungs of children with breathing problems, such as asthma or wheezing. We would like you to help us understand more about what causes these lung problems. Your parent(s) will have some information too, so you can talk to them about it. Please take your time to read this information.

Why?

Doctors want to find out what is different between the lungs of children with lung problems (such as asthma) and those without lung problems. This is called **research**. We are asking children with lung problems and without lung problems to take part.

How?

You can take part in 2 ways. It is up to you if you want to take part or not.

1. If you come to the hospital to see a doctor about your lungs or breathing, we would like to see some of the results of the tests you do. Doctors can then use these results for their research.

2. We may also ask you if you want to take part in some of our research studies. This means that we may ask you may come to the hospital to do some tests. The tests may be breathing tests or answering some questions about how you feel. We will send you a letter asking you if you want to take part in the study.

What next?

If your parent(s) and you are happy to take part then your parent(s) will sign a form called a 'consent form' and say which part of the research you would like to take part in. The important thing is that you do not have to take part if you do not want to.

Any questions?

You can ask your parents if you have any questions and or

Dr Erol Gaillard

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University Hospitals of Leicester NHS
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Leicester Childrens Hospital
Leicester Royal Infirmary
Leicester
LE1 5WW

Tel: 0116 258 5691

Database for Lung Research in Children

Brief information sheet for young people (11 to 15 years) with acute wheeze/asthma

We are asking you whether you would like to take part in our research. We are trying to find out what happens in the lungs of young people with breathing problems, such as asthma or wheezing. We would like you to help us understand more about what causes these lung problems. Your parent(s) will have some information too, so you can talk to them about it. Please take your time to read this information, and decide whether or not you want to take part.

Why?

Many children and young people have wheezing and asthma. Doctors want to find out what causes these lung problems, and want to find out what is different between the lungs of people with lung problems (such as asthma) and those without lung problems. We are asking children and young people with and without lung problems to take part.

How?

You can take part in 2 ways. It is up to you if you want to take part or not.

1. If you come to the hospital to see a doctor about your lungs or breathing, we would like to see some of the results of the tests you do. Doctors can then use these results for their research.

2. We may also ask you if you want to take part in some of our research studies. This means that we may ask you may come to the hospital to do some tests. The tests may be breathing tests or answering some questions about how you feel. We will send you a letter asking you if you want to take part in the study.

Doctors, scientists and researchers will use your information to find out more about breathing problems in children and young people and how best to treat them.

What next?

If your parent(s) and you are happy to take part then your parent(s) will sign a form called a 'consent form' and say which part of the research you would like to take part in. The important thing is that you do not have to take part if you do not want to. If you do decide to take part but later change your mind you can stop at any point without giving a reason.

Any questions?

If you have any questions then please contact us on these details

Dr Erol Gaillard

Telephone: 0116 258 5691

APPENDIX B: Ethical Approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Erol Gaillard
PO Box 65
University of Leicester,
Department of Respiratory Sciences
Robert Kilpatrick Clinical Sciences Building
Leicester Royal Infirmary
LE2 7LX

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

04 March 2021 Updated 12/03/21

Dear Dr Gaillard

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Monitoring asthma in children using the forced oscillation technique**
IRAS project ID:	**278875**
Protocol number:	**UOL 0802**
REC reference:	**21/EE/0026**
Sponsor	**University of Leicester**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **278875**. Please quote this on all correspondence.

Yours Sincerely
Beverley Mashegede

Email: approvals@hra.nhs.uk

Copy to: *Dr Cat Taylor, Sponsor Contact*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
GP/consultant information sheets or letters	1	12 January 2021
HRA Schedule of Events	1	11 January 2021
IRAS Application Form [IRAS_Form_07012021]		07 January 2021
IRAS Application Form XML file [IRAS_Form_07012021]		07 January 2021
IRAS Checklist XML [Checklist_01032021]		01 March 2021
Letter from sponsor [Sponsor Letter]	N/A	04 December 2020
Organisation Information Document	1.0	03 December 2020
Other [Funding letter - Afnan]		14 December 2020
Other [Funding letter - Afnan]		03 May 2019
Other [University of Leicester - TWIMC 2020 - Clinical Trials]		12 August 2020
Other [University of Leicester - TWIMC 2020 – PI]		07 August 2020
Other [peer review 1]		15 May 2019
Other [Peer Review 2]		04 July 2019
Other [Answers to ethics committee comments]		
Other [Answers to the comments]		
Other [Poster acute asthma]	1	11 September 2020
Other [Poster for the control]	1	11 September 2020
Other [Protocol]	2	19 February 2021
Other [Assent form for children with asthma (6-9 years) cc]	2	19 February 2021
Other [Assent form for children control (6-9 years) cc]	2	19 February 2021
Other [Info sheet for parent CC]	2	19 February 2021
Other [Info sheet 5 years and younger control CC]	2	19 February 2021
Other [Info sheet 5 years and younger wheeze CC]	2	19 February 2021
Other [Parent Info sheet attacks CC]	2	19 February 2021
Other [Parent Info sheet control CC]	2	19 February 2021
Other [PIS (6-9) clinic, acute CC]	2	19 February 2021
Other [PIS (6-9) control CC]	2	19 February 2021
Other [PIS (10-15) control CC]	2	19 February 2021
Other [PIS (10-15) Acute asthma CC]	2	19 February 2021
Other [PIS (10-15) asthma, clinic CC]	2	19 February 2021
Participant consent form [FOT_Parent_consent form Attacks]	1.0	26 October 2020
Participant consent form [FOT_Parent_consent form_asthma clinic]	1.0	26 October 2020
Participant consent form [FOT_Participant Assent form Controls aged 10-15 years]	1.0	26 October 2020
Participant consent form [FOT_Participant_assent form attacks aged 10-15 years]	1.0	26 October 2020
Participant consent form [FOT_Participant_assent form_asthma clinic aged 10-15 years]	1.0	26 October 2020
Participant consent form [FOT_Parent consent form controls]	1.0	26 October 2020
Summary CV for Chief Investigator (CI) [Erol CV]		22 October 2019
Summary CV for student [CV for Afnan]		04 February 2021
Summary CV for student [CV for Malak]		05 January 2021

Summary CV for supervisor (student research) [CV for Caroline Sarah Beardsmore]		05 November 2019
Validated questionnaire [Questionnaire<14]	1.0	26 October 2020
Validated questionnaire [Questionnaire>14]	1.0	26 October 2020

IRAS project ID	278875

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
Single centre study.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	No funds will be provided to the participating organisation to support this study.	A PI is expected at the participating organisation.	All study activities will be undertaken by local staff employed by the NHS organisation. Therefore, no honorary research contracts or letters of access are expected for this study.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated they do not intend to apply for inclusion on the NIHRCRN Portfolio.

Gallagher

Insurance | Risk Management | Consulting

1st August 2021

TO WHOM IT MAY CONCERN

We, the undersigned Insurance Brokers, hereby certify that the following described insurance:

VERIFICATION OF INSURANCE

Unique Market Reference:	B1262FI0675321
Type:	Errors and Omissions
Insured:	University of Leicester and/or subsidiaries
Period:	From: 1st August 2021 To: 31st July 2022 Both days inclusive at Local Standard Time.
Interest:	This Policy will indemnify/Cover the insured in respect of their Legal Liabilities arising out of the Insured's activities and as more fully disclosed within the Policy Wording.
Limit of Indemnity:	GBP 10,000,000 Any One Claim and GBP 10,000,000 in the Aggregate, including costs and expenses
Excess:	GBP 10,000 Each and Every Claim, other than United States of America Jurisdiction where USD 25,000 each and every Claim shall apply
Underwriter:	100.0000% Newline Syndicate 1218 in respect of Non-EEA 100.0000% Lloyds insurance Company S.A NMWL 5320 in respect of EEA

This document is for information only and does not make the person or organisation to whom it is issued an additional Insured, nor does it modify in any manner the Contract of Insurance between the Insured and the Insurers. Any amendment, change or extension to such Contract can only be affected by specific endorsement attached thereto.

Should the above mentioned Contract of Insurance be cancelled, assigned or changed during the above policy period in such manners as to affect this document, no obligation to inform the holder of this document is accepted by the undersigned or by the Insurers. The information provided is correct at the date of signature.

Authorised Signatory
Arthur J Gallagher

Gallagher

Insurance | Risk Management | Consulting

1st August 2021

TO WHOM IT MAY CONCERN

We, the undersigned Insurance Brokers, hereby certify that the following described insurance:

VERIFICATION OF INSURANCE

Unique Market Reference:	B1262 FI0675321
Type:	Legal Liability for Human Clinical Trials
Insured:	University of Leicester
Period:	From: 1st August 2021 To: 31st July 2022 Both days inclusive at Local Standard Time.
Interest:	This Policy will indemnify/Cover the insured in respect of their Legal Liabilities arising out of the Insured's activities and as more fully disclosed within the Policy Wording.
Limit of Indemnity:	GBP 10,000,000 Any One Claim and GBP 10,000,000 in the Aggregate, Legal Costs in Addition
Excess:	GBP 2,500 Each and Every Claim, other than United States of America Jurisdiction where USD 25,000 each and every Claim shall apply
Underwriter:	100.0000% Newline Syndicate 1218 in respect of Non-EEA 100.0000% Lloyds Insurance Company S.A NWL 5320 in respect of EEA

This document is for information only and does not make the person or organisation to whom it is issued an additional Insured, nor does it modify in any manner the Contract of Insurance between the Insured and the Insurers. Any amendment, change or extension to such Contract can only be affected by specific endorsement attached thereto.

Should the above mentioned Contract of Insurance be cancelled, assigned or changed during the above policy period in such manners as to affect this document, no obligation to inform the holder of this document is accepted by the undersigned or by the Insurers. The information provided is correct at the date of signature.

Authorised Signatory
Arthur J Gallagher

APPENDIX C: Parent Information Sheets

INFORMATION SHEET FOR PARENTS - Children (2-15 years) attending University Hospitals Leicester with an asthma attack.

Study Title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

We are inviting your child to take part in a research study. Before deciding, it is important for them and the family to understand why the research is being done and what it would involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Our contact details are at the end of this leaflet. Take time to decide whether or not you wish to take part.

Who is conducting the study?

This study is being conducted as part of PhD research being undertaken by Afnan AlRaimi and Malak Alshlowi at the University of Leicester. The study is being supervised by Dr Erol Gaillard and Dr Caroline Beardsmore, both of whom are researchers at the University of Leicester.

What is the purpose of the study?

Asthma is the most common chronic illness in children. Children and young people with asthma often experience asthma attacks. We know that these attacks are worrying and distressing. We want to understand more about asthma attacks and what happens in the lungs. Breathing tests are one way in which we do this. We plan to include 86 children with asthma and 60 children who do not have asthma for comparison. This study may help us in the future to develop treatments or strategies to prevent asthma attacks in children and young people in the future. The purpose of this study is to investigate the role of a novel painless test called the Forced Oscillation Test (FOT).

Why has your child been invited?

Your child is attending University Hospitals Leicester with an asthma attack.

Does your child have to take part?

It is up to you and your child to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form and your child will be asked to sign an assent form. If you decide to take part you can withdraw at any time, without giving a reason. A decision to take part or withdraw does not affect any treatment your child may be receiving from your doctor or the hospital.

What will happen to your child if he/she takes part?

Standard care: We will ask you and your child to complete a questionnaire about their asthma. After this we will perform some routine lung function tests including spirometry and exhaled nitric oxide testing as we always do at every asthma outpatient clinic visit. **Spirometry** is a test where the child takes a maximal breath in and then blows out as hard as possible into a machine that measures how much and how fast they can blow out. It is repeated several times

and we choose the best result. **Exhaled nitric oxide** testing requires a big breath in and then a slow, steady breath out into the hand-held machine. This gives a measure of the level of any inflammation in the lungs. These tests are usually only attempted in children aged three years and above.

Study procedures: We will then carry out the **Forced Oscillation Technique.** This requires your child to simply breathe normally through a mouthpiece into a hand-held machine. The machine sends small vibrations through the airways to measure their stiffness. Tests are usually repeated three or four times. This is not uncomfortable, and the testing takes no more than 5 minutes.

All the tests are painless breathing tests.

Following the tests, we will give your child a standard dose of 4 puffs (400mcg) of salbutamol from an inhaler and repeat the spirometry and FOT tests 15 minutes later.

Following this we will invite your child to perform an optional measurement (called **multibreath nitrogen washout**) of how efficiently each breath of fresh air is distributed throughout the lungs, which involves steady breathing into a machine for couple of minutes. This test is not offered to very young children who may find it difficult to co-operate for the time required.

If your child needs to be admitted to hospital we may invite them to repeat the breathing tests, including the optional multibreath|nitrogen washout, a maximum of twice before they are finally discharged home.

We would then like to invite you and your child back to our specialist children's asthma service on two or possibly three occasions. Each visit will last approximately 2 hours. The first occasion will be when your child has fully recovered from the asthma attack, typically after 2 weeks, when we will repeat the breathing tests, give you some asthma education, provide you with a personalised written asthma action plan, and fit an electronic monitor to your child's inhaler in order to track inhaler use. The monitor records whenever the inhaler is used, so we can see the number of times your child has used it, and the days and times it has been activated.

At the second laboratory visit, approximately 3 months later, we will repeat the breathing tests and review the inhaler use to see how the control of your child's asthma has progressed. For some families this will be the final part of their involvement in the study. If there is evidence that asthma control can be further improved, we will discuss how this might be achieved with the family and the asthma action plan updated if necessary. The electronic monitoring will be continued until the third laboratory visit approximately three months later. At this visit the breathing tests will be repeated and the inhaler use reviewed. The asthma action plan will be discussed with the family. This will be the final visit for any family remaining in the study and there will be no further electronic monitoring of inhaler use. After this we will continue to collect clinical data about your child's health until either she or he reaches their 16th birthday, or until five years after the final laboratory visit by any child in the study.

How will we use information about your child?

The University of Leicester will need to use information from your child's medical records for this research project.

This information will include your child's NHS number/ name/ contact details/ medical history. People will use this information to do the research or to check your child's records to make sure that the research is being done properly.

People who do not need to know who your child is will not be able to see your child's name or contact details. Your child's data will have a code number instead. We will keep all information about your child's safe and secure on hospital or University secure systems.

What are your choices about how your child's information is used?
Your child can stop being part of the study at any time, without giving a reason, but we will keep information about your child that we already have. If your child choose to stop taking part in the study, we would like to continue collecting information about your child's health from your child's NHS records. If you or your child do not want this to happen, tell us and we will stop. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your child's information is used?
Further information on how data is used in research is available on the University of Leicester website; if you would like a printed copy of the guidance please ask a study team member:

You can find out more about how the University of Leicester use your information or ask questions via:

Web: https://le.ac.uk/ias
Telephone: 0116 229 7945

Email: ias@le.ac.uk

**A PDF that can be printed containing further information is available here:

https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/template-wording-for-generic-information-document/

What are the possible side effects of this study and will your child feel any discomfort during the tests?
There are minimal identified risks to taking part in this research. Spirometry may cause some shortness of breath and coughing, but these occur rarely and tend to be short lasting and resolve fairly quickly. Spirometry is performed at every clinic visit and you and your child may well be familiar with it. The additional breathing tests do not cause any discomfort.

What are the possible benefits of taking part?
We will learn more about asthma and your child's asthma in particular. This may influence the way we diagnose and monitor asthma in the future using breathing and breath tests. Your child will be closely observed, and you may learn to understand your child's asthma better.

Will I/my child be paid for taking part?
Participants in this study will not be paid for taking part. We will reimburse reasonable travel costs, car parking and mileage up to the value of £10 per visit (original receipts must be provided). Refreshments (drinks and light snacks) will be offered if appropriate.

What if we identify that your child has a new condition/illness?
As part of this study, we may uncover medical conditions not previously recognised. If this happens, we will assess your child's condition and manage their health accordingly. This may mean referring them to other specialist teams or back to their GP for further investigations.

What if something goes wrong?
It is very unlikely that your child will be harmed by taking part in this type of research trial. However, if you wish to complain or have any concerns about the way you have been approached or treated in connection with the trial, you should ask to speak to the local trial team via the details provided below who will do their best to answer your questions. If you remain unhappy and wish to address your concerns or complaints on a formal basis you should contact the Patient Information & Liaison Service or local complaints number on Freephone: 0808 178 8337; Fax: 0116 258 8661; Email: pils@uhl-tr.nhs.uk.

If something does go wrong and your child is harmed during research and this is due to someone's negligence then you may have grounds for legal action for compensation against the University of Leicester but you may have to pay your legal costs. The normal NHS complaints service will still be available to you (if appropriate).

Will your child taking part in this study will be kept confidential?
Yes. All the results are confidential.

The study team will use your/ your child's name, NHS number (if available) and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care and to oversee the quality of the trial. Individuals from the University Sponsor, the NHS Trust who are hosting the study, and regulatory organisations may look at your medical and research records to check the accuracy of the research trial.

The study team will pass these details to the University Sponsor, along with the information collected from you and your medical records. The only people from the University Sponsor who will have access to information that identifies you will be people who need to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your / your child's name, NHS number, or contact details. The hospital where you are treated will keep identifiable information about you for 10 years after the study has finished.

When you agree for your child to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this and other organisations if you consent to this. Other organisations may be universities, NHS

organisations or companies involved in health and care research in this country or abroad. Please be aware that the laws in countries outside of the UK and the European Economic Area (EEA) may not provide the same level of data protection as in the UK and may not stop Trial Data from being shared with others. However, rest assured that all Trial Data that is transferred will be coded, so your identity is masked or made anonymous.

What will happen to the results of the research study?
The results of the study will be presented at national and international scientific meetings and published in the medical literature in due course. In practice, publication takes about 1-2 years from the end of a study. You will not be identified in any report or publication.

Who is organising and funding the research?
This is a research project organised by the Department of Respiratory Sciences. Sponsored by the University of Leicester, and funded by Royal Embassy of Saudi Arabia Cultural Bureau. None of the trial doctors will be paid for including you in the study.

Who has reviewed the study?
All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be granted a favourable opinion by an NHS Research Ethics Committee before it goes ahead. Favourable opinion does not guarantee that your child will not come to any harm if you take part. However, it means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision. This study has been reviewed by Cambridge South Research Ethics Committee.

Contact for further information:
Please contact the following number to speak to or leave a message for any one of the other research team members.

Research team	Erol Gaillard	Caroline Beardsmore	Afnan AlRaimi	Malak Alshlowi
Telephone From 9:00 am to 5:00 pm	(0116) 2525881	(0116) 2525811	(0116) 2525881	(0116)2525881
E-mail	eag15@le.ac.uk	csb@le.ac.uk	aa1060@le.ac.uk	Mosa1@le.ac.uk
Fax	(0116) 252 3282	(0116)252 3282	(0116) 252 3282	(0116)2523282

Thank you for taking the time to read this information leaflet

You will be given a copy of the information sheet and a signed consent form to keep

Dr Erol Gaillard
Consultant in Paediatric Respiratory Medicine
Children's Hospital, Leicester Royal Infirmary

INFORMATION SHEET FOR PARENTS - Children (2-15 years) attending University Hospitals Leicester Paediatric Asthma/Respiratory Clinics

Study Title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

We are inviting your child to take part in a research study. Before deciding, it is important for them and the family to understand why the research is being done and what it would involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Our contact details are at the end of this leaflet. Take time to decide whether or not you wish to take part.

Who is conducting the study?

This study is being conducted as part of PhD research being undertaken by Afnan AlRaimi and Malak Alshlowi at the University of Leicester. The study is being supervised by Dr Erol Gaillard and Dr Caroline Beardsmore, both of whom are researchers at the University of Leicester.

What is the purpose of the study?

Asthma is the most common chronic illness in children. Children and young people with asthma often experience asthma attacks. We know that these attacks are worrying and distressing. We want to understand more about asthma attacks and what happens in the lungs. Breathing tests are one way in which we do this. We plan to include 86 children with asthma and 60 who do not have asthma for comparison. This study may help us in the future to develop treatments or strategies to prevent asthma attacks in children and young people in the future. The purpose of this study is to investigate the role of a novel painless test called the Forced Oscillation Test (FOT).

Why has your child been invited?

Your son or daughter is attending a clinic or having telephone reviews at UHL NHS Trust for children and young people with **uncontrolled** asthma.

Does your child have to take part?

It is up to you and your child to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form and your child will be asked to sign an assent form. If you decide to take part you can withdraw at any time, without giving a reason. A decision to take part or withdraw does not affect any treatment your child may be receiving from your doctor or the hospital.

What will happen to your child if he/she takes part?

You and your child will be invited to attend up to 3 separate appointments our specialist children's lung function laboratory. Each visit will last approximately 2 hours. At the first laboratory visit we will ask you and your child to complete a questionnaire about their asthma, including questions on recent asthma attacks, treatments and medical and family history.

Standard care: We will then perform the routine spirometry and exhaled nitric oxide testing as we always do at every outpatient clinic visit. **Spirometry** is a test where the child takes a maximal breath in and then blows out as hard as possible into a machine that measures how much and how fast they can blow out. It is repeated several times. **Exhaled nitric oxide** testing requires a big breath in and then a slow, steady breath out into the hand-held machine. This gives a measure of the level of any inflammation in the lungs. These tests are usually only attempted in children aged three years and above because younger children cannot usually co-operate with testing.

Study procedures: We will then carry out the **Forced Oscillation Technique.** This requires your child to breathe normally through a mouthpiece into a hand-held machine. The machine sends small vibrations through the airways to measure their stiffness. Tests are usually repeated three or four times. This is not uncomfortable, and the testing takes no more than 5 minutes in total.

Following the tests, we will give your child a standard dose of 4 puffs (400mcg) of salbutamol from an inhaler and repeat the spirometry and FOT tests 15 minutes later.

We will then perform a measurement of how efficiently each breath of fresh air is distributed throughout the lungs, which involves steady breathing into a machine for couple of minutes. This is called **multibreath nitrogen washout**. This test is not offered to very young children (below three years) who may find it difficult to co-operate for the time required. When we have completed and reviewed the questionnaire and breathing tests we will provide you with a personalised written asthma action plan, and then fit an electronic monitor to your child's inhaler in order to track inhaler use. The monitor records whenever the inhaler is used, so we can see the number of times your child has used it, and the days and times it has been activated.

At the second laboratory visit, approximately 3 months later, we will repeat the breathing tests and review the inhaler use to see how the control of your child's asthma has progressed. For some families this will be the final part of their involvement in the study. If there is evidence that asthma control can be further improved, we will discuss how this might be achieved with the family and the asthma action plan updated if necessary. The electronic monitoring will be continued until the third laboratory visit approximately three months later. At this visit the breathing tests will be repeated and the inhaler use reviewed. The asthma action plan will be discussed with the family. This will be the final visit for any family remaining in the study and there will be no further electronic monitoring of inhaler use. After this we will continue to collect clinical data about your child's health until either she or he reaches their 16th birthday, or until five years after the final laboratory visit by any child in the study.

How will we use information about your child?

The University of Leicester will need to use information from your child's medical records for this research project.

This information will include your child's NHS number/ name/ contact details/ medical history. People will use this information to do the research or to check your child's records to make sure that the research is being done properly.

People who do not need to know who your child is will not be able to see your child's name or contact details. Your child's data will have a code number instead. We will keep all information about your child's safe and secure on hospital or University secure systems.

What are your choices about how your child's information is used?
Your child can stop being part of the study at any time, without giving a reason, but we will keep information about your child that we already have. If your child choose to stop taking part in the study, we would like to continue collecting information about your child's health from your child's NHS records. If you or your child do not want this to happen, tell us and we will stop. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your child's information is used?
Further information on how data is used in research is available on the University of Leicester website; if you would like a printed copy of the guidance please ask a study team member:

You can find out more about how the University of Leicester use your information or ask questions via:

Web: https://le.ac.uk/ias
Telephone: 0116 229 7945

Email: ias@le.ac.uk

**A PDF that can be printed containing further information is available here:

https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/template-wording-for-generic-information-document/

What are the possible side effects of this study and will your child feel any discomfort during the tests?
There are minimal identified risks to taking part in this research. Spirometry may cause some shortness of breath and coughing, however these occur rarely and tend to be short lasting and resolve fairly quickly. Spirometry is performed at every clinic visit and you and your child may well be familiar with it. The additional breathing tests do not cause any discomfort.

What are the possible benefits of taking part?
We will learn more about asthma and your child's asthma in particular. This may influence the way we diagnose and monitor asthma in the future using breathing and breath tests. Your child will be closely observed, and you may learn to understand your child's asthma better.

Will I/my child be paid for taking part?
Participants in this study will not be paid for taking part. We will reimburse reasonable travel costs, car parking and mileage up to the value of £10 per visit (original receipts must be provided). Refreshments (drinks and light snacks) will be offered if appropriate.

What if we identify that your child has a new condition/illness

As part of this study, we may uncover medical conditions not previously recognised. If this happens, we will assess your child's condition and manage their health accordingly. This may mean referring them to other specialist teams or back to their GP for further investigations.

What if something goes wrong?
It is very unlikely that your child will be harmed by taking part in this type of research trial. However, if you wish to complain or have any concerns about the way you have been approached or treated in connection with the trial, you should ask to speak to the local trial team via the details provided below who will do their best to answer your questions. If you remain unhappy and wish to address your concerns or complaints on a formal basis you should contact the Patient Information & Liaison Service or local complaints number on Freephone: 0808 178 8337; Fax: 0116 258 8661; Email: pils@uhl-tr.nhs.uk.

If something does go wrong and your child is harmed during research and this is due to someone's negligence then you may have grounds for legal action for compensation against the University of Leicester but you may have to pay your legal costs. The normal NHS complaints service will still be available to you (if appropriate).

Will your child taking part in this study will be kept confidential?
Yes. All the results are confidential.

The study team will use your/ your child's name, NHS number (if available) and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care and to oversee the quality of the trial. Individuals from the University Sponsor, the NHS Trust who are hosting the study, and regulatory organisations may look at your medical and research records to check the accuracy of the research trial.

The study team will pass these details to the University Sponsor, along with the information collected from you and your medical records. The only people from the University Sponsor who will have access to information that identifies you will be people who need to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your / your child's name, NHS number, or contact details. The hospital where you are treated will keep identifiable information about you for 10 years after the study has finished.

When you agree for your child to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this and other organisations if you consent to this. Other organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Please be aware that the laws in countries outside of the UK and the European Economic Area (EEA) may not provide the same level of data protection as in the UK and may not stop Trial Data from being shared with others. However, rest assured that all Trial Data that is transferred will be coded, so your identity is masked or made anonymous.

What will happen to the results of the research study?

The results of the study will be presented at national and international scientific meetings and published in the medical literature in due course. The data collected may also be used, in part or in whole, for the writing of educational projects such as a Master's Degree or a PhD. In practice, publication takes about 1-2 years from the end of a study. You will not be identified in any report or publication.

Who is organising and funding the research?
This is a research project organised by the Department of Respiratory Sciences. Sponsored by the University of Leicester, and funded by Royal Embassy of Saudi Arabia Cultural Bureau. None of the trial doctors will be paid for including you in the study.

Who has reviewed the study?
All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be granted a favourable opinion by an NHS Research Ethics Committee before it goes ahead. Favourable opinion does not guarantee that your child will not come to any harm if you take part. However, it means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision. This study has been reviewed by Cambridge South Research Ethics Committee.

Contact for further information:

Please contact the following number to speak to or leave a message for any one of the other research team members.

Research team	Erol Gaillard	Caroline Beardsmore	Afnan AlRaimi	Malak Alshlowi
Telephone From 9:00 am to 5:00 pm	(0116) 2525881	(0116) 2525811	(0116) 2525881	(0116)2525881
E-mail	eag15@le.ac.uk	csb@le.ac.uk	aa1060@le.ac.uk	Mosa1@le.ac.uk
Fax	(0116) 252 3282	(0116)252 3282	(0116) 252 3282	(0116)2523282

Thank you for taking the time to read this information leaflet

You will be given a copy of the information sheet and a signed consent form to keep

Dr Erol Gaillard
Consultant in Paediatric Respiratory Medicine
Children's Hospital, Leicester Royal Infirmary

INFORMATION SHEET FOR PARENTS - Children (2 to 15 years) attending University Hospitals Leicester without wheezing or asthma

Study title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

We are inviting your son or daughter to take part in a research study. Before deciding, it is important for them and the family to understand why the research is being done and what it would involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Our contact details are at the end of this leaflet. Take time to decide whether or not you wish to take part.

Who is conducting the study?

This study is being conducted as part of PhD research being undertaken by Afnan AlRaimi and Malak Alshlowi at the University of Leicester. The study is being supervised by Dr Erol Gaillard and Dr Caroline Beardsmore, both of whom are researchers at the University of Leicester.

What is the purpose of the study?

Children and young people with asthma may require hospital treatment for an asthma attack. We know that these attacks are worrying and distressing. We want to understand more about the causes of severe asthma attacks in children and what happens inside the lungs when an attack occurs. For this reason we also want to involve children who do NOT have asthma. We plan to include 86 children with asthma and 60 who do not have asthma for comparison. This may help us in the future to develop treatments or strategies to prevent severe asthma attacks in children and young people. In order to get information on inflammation and function of the breathing tubes inside the lung, we would like to complete a questionnaire and carry out some simple breathing and blowing tests. Some of these tests are optional, and some tests need more co-operation and are not suitable for the youngest children in the study. Overall, the purpose of this study is to investigate the role of a novel painless test called the Forced Oscillation Test (FOT).

Why has your child been invited?

Your son or daughter is free of asthma or wheezing and their lung function is expected to be normal. This would make them suitable to compare with children who do suffer from asthma.

Does your child have to take part?

It is up to you and your child to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form and your child will be asked to sign an assent form. If you decide to take part you can withdraw at any time, without giving a reason. A decision to take part or withdraw does not affect any treatment your child may be receiving from your doctor or the hospital

What will happen to your child if he/she takes part?

This study will require one visit to our lung function laboratory taking up to two hours, but we can tie this in with another routine appointment you may have so that you do not have additional visits to the hospital.

We will invite you and your child for a visit to our lung function laboratory and ask you questions about your child's medical history, family history and medications. We will then measure their height and weight and invite your child to perform several simple and painless breathing tests.

Breathing tests:
Standard care: We will first perform **spirometry** and **exhaled nitric oxide testing**. These are common investigations that we perform for any child who attends a respiratory outpatient clinic visit. Spirometry is a test where the child takes a maximal breath in and then blows out as hard as possible into a machine that measures how much and how fast they can blow out. It is repeated several times. Exhaled nitric oxide testing requires a big breath in and then a slow, steady breath out into the hand-held machine. This gives a measure of the level of any inflammation in the lungs. These tests are usually only attempted in children aged three years and above because younger children cannot usually co-operate with testing.

In addition we will invite your child to do the following **study procedures**:

Forced Oscillation Technique: We will ask your child to breathe normally through a mouth piece into a hand-held machine. In this new test the machine will send small vibrations through the airways to measure their stiffness. This is not uncomfortable, and it takes no more than 5 minutes for several measurements.

For children aged 3 years and over, we will also invite your child for an additional optional specialist breathing test, **Multiple Breath Nitrogen Washout**. For this breathing test your child will breathe in and out of a machine for around 5 minutes and this test will tell us how efficiently each breath of fresh air is distributed throughout the lungs. Again, this is not uncomfortable. This test is repeated 3 or 4 times with rests in between each one.

How will we use information about your child?
The University of Leicester will need to use information from your child's medical records for this research project.

This information will include your child's NHS number/ name/ contact details/ medical history. People will use this information to do the research or to check your child's records to make sure that the research is being done properly.

People who do not need to know who your child is will not be able to see your child's name or contact details. Your child's data will have a code number instead. We will keep all information about your child's safe and secure on hospital or University secure systems.

What are your choices about how your child's information is used?
Your child can stop being part of the study at any time, without giving a reason, but we will keep information about your child that we already have. If your child choose to stop taking part in the study, we would like to continue collecting information about your child's health from your child's NHS records. If you or your child do not want this to happen, tell us and we will stop. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your child's information is used?
Further information on how data is used in research is available on the University of Leicester website; if you would like a printed copy of the guidance please ask a study team member:

You can find out more about how the University of Leicester use your information or ask questions via:

Web: https://le.ac.uk/ias
Telephone: 0116 229 7945

Email: ias@le.ac.uk

**A PDF that can be printed containing further information is available here:

https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/template-wording-for-generic-information-document/

What are the possible side effects of this study and will your child feel any discomfort during the tests?
There are minimal identified risks to taking part in this research. Some of the breathing tests may cause some shortness of breath and coughing, but these occur rarely and tend to be short lasting and resolve fairly quickly.

What are the possible benefits of taking part?
There will not be any direct benefit to your child, although she or he may find it interesting to take part. We will learn more about asthma and the differences between children with and without asthma. This may influence the way we diagnose and monitor asthma in the future using breathing tests.

Will I/my child be paid for taking part?
Participants in this study will not be paid for taking part. We will reimburse reasonable travel costs, car parking and mileage up to the value of £10 per visit (original receipts must be provided). Refreshments (drinks and light snacks) will be offered if appropriate.

What if we identify that your child has a new condition/illness?
As part of this study, we may uncover medical conditions not previously recognised. If this happens, we will assess your child's condition and manage their health accordingly. This may mean referring them to other specialist teams or back to their GP for further investigations.

What if something goes wrong?
It is very unlikely that your child will be harmed by taking part in this type of research trial. However, if you wish to complain or have any concerns about the way you have been approached or treated in connection with the trial, you should ask to speak to the local trial team via the details provided below who will do their best to answer your questions. If you remain unhappy and wish to address your concerns or complaints on a formal basis you should contact the Patient Information & Liaison Service or local complaints number on Freephone: 0808 178 8337; Fax: 0116 258 8661; Email: pils@uhl-tr.nhs.uk.

If something does go wrong and your child is harmed during research and this is due to someone's negligence then you may have grounds for legal action for compensation against the University of Leicester but you may have to pay your legal costs. The normal NHS complaints service will still be available to you (if appropriate).

Will your child taking part in this study will be kept confidential?
Yes. All the results are confidential.

The study team will use your/ your child's name, NHS number (if available) and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care and to oversee the quality of the trial. Individuals from the University Sponsor, the NHS Trust who are hosting the study, and regulatory organisations may look at your medical and research records to check the accuracy of the research trial.

The study team will pass these details to the University Sponsor, along with the information collected from you and your medical records. The only people from the University Sponsor who will have access to information that identifies you will be people who need to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your / your child's name, NHS number, or contact details. The hospital where you are treated will keep identifiable information about you for 10 years after the study has finished.

When you agree for your child to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this and other organisations if you consent to this. Other organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Please be aware that the laws in countries outside of the UK and the European Economic Area (EEA) may not provide the same level of data protection as in the UK and may not stop Trial Data from being shared with others. However, rest assured that all Trial Data that is transferred will be coded, so your identity is masked or made anonymous.

What will happen to the results of the research study?
The results of the study will be presented at national and international scientific meetings and published in the medical literature in due course. The data collected may also be used, in part or in whole, for the writing of educational projects such as a Master's Degree or a PhD. In practice, publication takes about 1-2 years from the end of a study. You will not be identified in any report or publication.

Who is organising and funding the research?
This is a research project organised by the Department of Respiratory Sciences. Sponsored by the University of Leicester, and funded by Royal Embassy of Saudi Arabia Cultural Bureau. None of the trial doctors will be paid for including you in the study.

Who has reviewed the study?
All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be granted a favourable opinion by an NHS Research Ethics Committee before it goes ahead. Favourable opinion does not guarantee that your child will not come to any harm if you take part. However, it means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision. This study has been reviewed by Cambridge South Research Ethics Committee.

Contact for further information:
Please contact the following number to speak to or leave a message for any one of the other research team members.

Research team	Erol Gaillard	Caroline Beardsmore	Afnan AlRaimi
Telephone	(0116) 2525881	(0116) 2525811	(0116) 2525881
E-mail	eag15@le.ac.uk	csb@le.ac.uk	aa1060@le.ac.uk
Fax	(0116) 252 3282	(0116) 252 3282	(0116) 252 3282

Thank you for taking the time to read this information leaflet

You will be given a copy of the information sheet and a signed consent form to keep.

Dr Erol Gaillard
Consultant in Paediatric Respiratory Medicine
Children's Hospital, Leicester Royal Infirmary

APPENDIX D: Patient Information Sheets

Participant information sheet for young people (10 to 15 years) attending University Hospitals Leicester with an asthma attack.

Study Title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

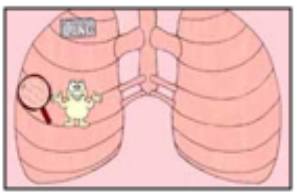
We are inviting you to take part in a research study. Before you decide, it is important for you and your family to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Who is doing this research?

Dr Gaillard and Dr Beardsmore, who work at the University of Leicester and with the children's asthma service at Leicester Hospitals, supervise the team doing this research study.

Why are we doing this research?

Many children and young people of your age have wheezing and asthma attacks. There is much that we do not understand about asthma attacks in young people.
We want to find out more about what happens inside your lungs during an asthma attack. This information could help us to treat children and young people with asthma better in the future.



Why have I been invited?

You have been invited because you are attending hospital with an asthma attack.

What will happen to me if I take part?

During your hospital treatment, we will do some routine painless breathing and blowing tests as we always do at every asthma clinic visit. **Spirometry** is the test where you take a big breath in and then blow out as hard as possible into a machine that measures how much and how fast you can blow out. **Exhaled nitric oxide** testing requires a big breath in and then a slow, steady breath out into a machine. This measures a chemical in breath that tells us if your lungs are inflamed.

Study tests: We will then do the **Forced Oscillation Technique.** All you have to do is breathe normally through a tube connected to a machine. The machine sends small vibrations into your lungs to measure their stiffness. All the tests are painless and none takes more than 5 minutes in total.

After this, we will ask you to take a dose of your salbutamol (from a blue inhaler) and repeat the spirometry and forced oscillation tests 15 minutes later. Following this we will invite you to perform one more breathing test that requires steady breathing into a machine for a couple of minutes. Again, this test is painless and optional. It does give detailed information of how the deep parts of your lungs work.

If you are admitted to the hospital we will invite you to repeat the breathing tests up to twice more while you are in hospital. All children and young people who have an asthma attack will be invited with their families to our specialist service for a review. You will be invited to repeat the breathing tests when you are better and fully recovered from your asthma attack. We will

provide you with written asthma information and monitor your inhaler use so that we can review your progress.

All the breathing tests are all quite simple and many children find them interesting. Someone from your family will be with you all the time.

Duration of the laboratory visit: The visit to the laboratory will not exceed 2 hours.

Do I have to take part?
It is up to you to decide whether or not you are happy to take part in this study. You may keep this information sheet. If you decide to take part but later change your mind, you can stop at any point without giving a reason. This will not affect how we treat you in hospital.

Are there any risks of taking part?
No, all the tests are very safe.

What are the possible benefits of taking part?
We will learn more about the lungs of young people with asthma. This may help us to treat asthma better in the future.

What will happen to the results of the research study?
The results of the study will be analysed and shared with other children's asthma doctors at scientific meetings. We will published the results in medical newspapers. Your name and other personal information will be private and not shared with others.

Keeping your information private
It is important that we share what we learn with others, so that as many children as possible can be helped. However, your name and personal details will never be shared, so that nobody will be able to identify you from any information made available to others.

Thank you very much for your time taken to read this information leaflet.

Any questions?

Please ask the researcher if you have any questions.

Dr Erol Gaillard
Consultant in Paediatric Respiratory Medicine
Children's Hospital, Leicester Royal Infirmary

Participant information sheet for young people (10 to 15 years) attending University Hospitals Leicester Paediatric Asthma/Respiratory Clinics.

Study Title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

We are inviting you to take part in a research study. Before you decide, it is important for you and your family to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Who is doing this research?

Dr Gaillard and Dr Beardsmore, who work at the University of Leicester and with the children's asthma service at Leicester Hospitals, supervise the team doing this research study.

Why are we doing this research?

Many children and young people of your age have wheezing and asthma. There is much that we do not understand about asthma in young people.

We want to find out more about what happens inside your lungs during an asthma attack. This information could help us to treat children and young people with asthma better in the future.

Why have I been invited?

You have been invited because you are attending hospital for an asthma clinic review.

What will happen to me if I take part?

You will be invited to attend our specialist children's lung function laboratory, where we will ask you and your parent or carer to fill in a questionnaire about your asthma. We will then perform the routine spirometry and exhaled nitric oxide testing as we always do at every outpatient clinic visit. **Spirometry** is the test where you take a big breath in and then blow out as hard as possible into a machine that measures how much and how fast you can blow out. **Exhaled nitric oxide** testing requires a big breath in and then a slow, steady breath out into a machine. This measures a chemical in breath that tells us if your lungs are inflamed.

Study tests: We will then do the **Forced Oscillation Technique.** All you have to do is breathe normallythrough a tube connected to a machine. The machine sends small vibrations into your lungs to measure their stiffness. All the tests are painless and none takes more than 5 minutes in total.

After this, we will ask you to take a dose of your salbutamol (from a blue inhaler) and repeat the spirometry and forced oscillation tests 15 minutes later. Following this we will invite you to perform one more breathing test that requires steady breathing into a machine for a couple of minutes. Again, this test is painless and optional. It does give detailed information of how the deep parts of your lungs work.

We will give you and your family some written information on how to manage your asthma at home and an electronic monitor for your inhaler. By doing this we hope to improve your asthma.

We will invite you to return to the laboratory on one or sometimes two occasions, when we will ask you to repeat the breathing tests. We will review your asthma and the written asthma plan on each occasion.

All the breathing tests are all quite simple and many children find them interesting. Someone from your family will be with you all the time.

Duration of the laboratory visit: The visit to the laboratory will not exceed 2 hours

Do I have to take part?
It is up to you to decide whether or not you are happy to take part in this study. You may keep this information sheet. If you decide to take part but later change your mind you can stop at any point without giving a reason. This will not affect how we treat you in hospital.

Are there any risks of taking part?
No, all the tests are very safe.

What are the possible benefits of taking part?
We will learn more about the lungs of young people with asthma. This may help us to treat asthma better in the future.

What will happen to the results of the research study?
The results of the study will be analysed and shared with other children's asthma doctors at scientific meetings. We will published the results in medical newspapers. Your name and other personal information will be private and not shared with others.

Keeping your information private
It is important that we share what we learn with others, so that as many children as possible can be helped. However, your name and personal details will never be shared, so that nobody will be able to identify you from any information made available to others.
Thank you very much for your time taken to read this information leaflet.

Any questions?

Please ask the researcher if you have any questions.

Dr Erol Gaillard
Consultant in Paediatric Respiratory Medicine
Children's Hospital, Leicester Royal Infirmary

Information sheet for young people (10 to 15 years) who do not have wheezing/asthma

Study title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

We are inviting you to take part in a research study. Before you decide, it is important for you and your family to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Many children and young people of your age have breathing problems like asthma.
You do not have asthma and we want to find out more about what is different about your healthy lungs compared to children with asthma. This information could help us to treat children and young people with asthma better in the future.

Who is doing this research?

Dr Gaillard and Dr Beardsmore, who work at the University of Leicester and with the children's asthma service at Leicester Hospitals, supervise the team doing this research study.

Why have I been invited?

You have been invited because you are in hospital and you have healthy lungs.

What will happen to me if I take part?

We will invite you for one visit to our children's lung function laboratory ask you and your family a few questions and then ask you to do several quick and painless breathing tests.

Breathing Test 1: This test is called **spirometry.** It requires you to take a deep breath in and then blow out as hard and fast as possible.

Breathing test 2: The **Exhaled nitric oxide** test requires a big breath in, followed by a steady breath out into a hand-held machine. This test measures a chemical in the breath that is present in people with asthma. It will be useful to measure this in your breath even though you do not have asthma.

Breathing Test 3: The **forced oscillation technique.** We will ask you to breathe normally through a mouth piece into a hand-held machine. In this new test the machine will send small vibrations through the airways to measure their stiffness. This is not uncomfortable, and it takes no more than 5 minutes for several measurements.

Breathing Test 4: We will ask you to breathe in and out of a machine for around 5 minutes. This test is called **multiple breath washout**. Again, this is not uncomfortable and the test will tell us much about what happens in the deep part of your lung. It is usually repeated 2-3 times, with a short rest between each test.

All the breathing tests are all quite simple and many children find them interesting. Someone from your family will be with you all the time.

Duration of the laboratory visit: The visit to the laboratory will not exceed 2 hours

Do I have to take part?
It is up to you to decide whether or not you are happy to take part in this study. You may keep this information sheet. If you decide to take part but later change your mind, you can stop at any point without giving a reason. This will not affect how we treat you in hospital.

Are there any risks of taking part?
No, all the tests are very safe.

What are the possible benefits of taking part?
We will learn more about the lungs of young people with asthma. This may help us to treat asthma better in the future.

What will happen to the results of the research study?
The results of the study will be analysed and shared with other children's asthma doctors at scientific meetings. We will published the results in medical newspapers. Your name and other personal information will be private and not shared with others.

Keeping your information private
It is important that we share what we learn with others, so that as many children as possible can be helped. However, your name and personal details will never be shared, so that nobody will be able to identify you from any information made available to others.

Thank you very much for your time taken to read this information leaflet.

Any questions?

Please ask the researcher if you have any questions.

Dr Erol Gaillard
Consultant in Paediatric Respiratory Medicine
Children's Hospital, Leicester Royal Infirmary

Information sheet for young children (6 to 9 years) attending University Hospitals Leicester Paediatric Asthma/Respiratory Clinics, with wheeze/asthma OR attending University Hospitals Leicester with an asthma attack

Study title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

We want to find out what happens inside your lungs. You can help us by doing some simple blowing tests. Are you happy to do this?

Why?

You sometimes get a little breathless. We want to find out what happens inside your lungs.

How?

You can help by doing some simple blowing tests. The blowing tests are quick and will not hurt you. We will learn how your lungs work. You can decide if you want to take part and choose the blowing tests you are happy to do.

We will invite you back later to do the blowing tests again.

Problems?

All the tests are very safe and simple.

What next?

If your parent(s) and you are happy to do the blowing tests your parent(s) will sign a "Consent form". The important thing is that you do not have to do the blowing tests if you do not want to, and you can change your mind at any time.

Dr Erol Gaillard
Consultant in Paediatric Respiratory Medicine
Children's Hospital, Leicester Royal Infirmary

Information sheet for children (6 to 9 years) who have never wheezed/do not have asthma attending hospital

Study title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

We want to find out what happens inside your healthy lungs. You can help us by doing some simple blowing tests. Are you happy to do this?

Why?

We want to find out how your healthy lungs work.

How?

You can help by doing some simple blowing tests. The blowing tests are quick and will not hurt you. We will learn how your lungs work. You can decide if you want to take part and choose the blowing tests you are happy to do.

Problems?

All the tests are very safe and simple.

What next?

If your parent(s) and you are happy to do the blowing tests your parent(s) will sign a "Consent form". The important thing is that you do not have to do the blowing tests if you do not want to, and you can change your mind at any time.

Dr Erol Gaillard
Consultant in Paediatric Respiratory Medicine
Children's Hospital, Leicester Royal Infirmary

Participant information sheet for children (2-5 years) who have wheezed or have asthma and are attending hospital

Study Title: Monitoring Asthma using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

Koala and his lungs

I am 3 years and older

I am less than 3 years

I'm Koala, colour me in!

Hello, my name is Koala

Today I'm going to see a doctor to have a look at my lungs.

The doctor would like to do some tests to see how my lungs work.

Would you like to come, too?

I'll show you around. I'm here with my parents.

First, a doctor will ask a few questions about me

Now the doctor will see how well my lungs and breathing tubes are working with his magic machine called FOT

He will ask me to breathe quietly and normally.

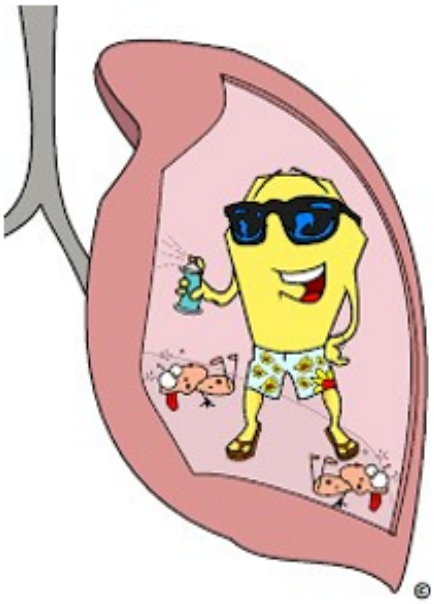
Then, if I am 3 years or older…

There is a fun test to see how big my lungs are. The doctor will ask me to take a big breath in and then blow out hard

Also, there is an easy test to see if my lungs are sore!

The doctor will ask me to breathe out strongly.

There are other tests if I am still interested and not too tired! These will tell the doctor more about how well my lungs are working.



It is up to me whether I do the tests or not, and I can choose which ones I am happy to do.

All finished time to get home now

Goodbye everyone. It was lots of fun!

Don't forget to colour me in and bring me along to your visit!

Participant information sheet for children (2-5 years) who have never wheezed/do not have asthma attending hospital (healthy control)

Study Title: Monitoring Asthma using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

Koala and his lungs

I am 3 years and older

I am less than 3 years

I'm Koala, colour me in!

Hello, my name is Koala

Today I'm going to see a doctor to have a look at my lungs.

I am not poorly. The doctor would like to do some tests to see how my lungs work.

Would you like to come, too?

I'll show you around. I'm here with my parents.

First, a doctor will ask a few questions about me

Now the doctor will see how well my lungs and breathing tubes are working with his magic machine called FOT

He will ask me to breathe quietly and normally.

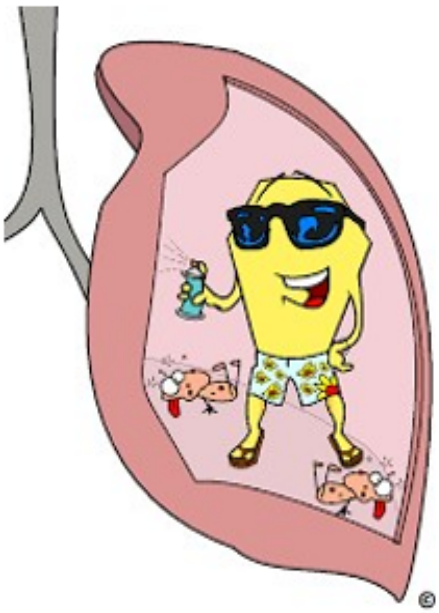
Then, if I am 3 years or older …

There is a fun test to see how big my lungs are. The doctor will ask me to take a big breath in and then blow out hard

Also, there is an easy test to see if my lungs are sore!

The doctor will ask me to breathe out strongly.

There are other tests if I am still interested and not too tired! These will tell the doctor more about how well my lungs are working.



It is up to me whether I do the tests or not, and I can choose which ones I am happy to do.

All finished time to get home now

Goodbye everyone. It was lots of fun!

Don't forget to colour me in and bring me along to your visit!

APPENDIX E: Consent and Assent

University Hospitals of Leicester NHS
NHS Trust

CONSENT FORM

Children and young people attending Emergency Department with wheeze/asthma

Study Number: 0802

Participant Identification Number:

Study Title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

	Please initial box
1. I confirm that I have read and understand the Parent Information Sheet dated 19.02.2021 .Version 2 for the above study and have had the opportunity to ask questions.	☐
2. I understand that my child's participation is voluntary and that my child is free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected.	☐
3. I understand that relevant sections of my child`s medical notes and/or data may be looked at by responsible individuals from the study team, the Sponsor, NHS Trust or from regulatory authorities where it is relevant to my child`s taking part in the research. I give permission for these individuals to access my child`s records and for data collected as part of the study to be stored securely in University of Leicester and University Hospitals of Leicester secure systems	☐
4. I give permission for my child`s GP to be informed about my child`s participation in this study and of any clinically significant findings	☐
5. I agree to the study team accessing my child's medical record up to the age of 16 (optional)	Yes ☐ No ☐
6. I agree on behalf of my child for forced oscillation technique to be taken and analysed for the purpose of this study.	☐
7. I agree on behalf of my child for spirometry to be taken and analysed for the purpose of this study	☐
8. I agree on behalf of my child for fractional exhaled nitric oxide to be taken and analysed for the purpose of this study	☐
9. I agree on behalf of my child for multibreath nitrogen washout to be taken and analysed for the purpose of this study	☐
10. I agree to my child's inhaler being fitted with an electronic monitor to track inhaler use	☐
11. I agree that my child's research data may be stored for future ethically approved research	Yes ☐ No ☐
12. I agree that my child's pseudonymised research data may be shared with other research collaborators in other academic institutions and industry partners inside and outside of the UK for future research	Yes ☐ No ☐

13. I agree to my child`s taking part in the above study. ☐

14. I would like to receive a copy of the final study report ☐ Yes ☐ No

Name of participant

_____

Name of Parent	Date	Signature
_____	_____	_____

Name of researcher taking consent	Date	Signature
_____	_____	_____

1 for participant; 1 for researcher (original), 1 for patient notes

CONSENT FORM

Children and young people attending University Hospitals Leicester Paediatric Asthma/Respiratory Clinics with wheeze/asthma (including telephone reviews)

Study Number: 0802

Participant Identification Number:

Study Title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

Please initial box

1. I confirm that I have read and understand the Parent Information Sheet dated 19.02.2021 .Version 2 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my child's participation is voluntary and that my child is free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected. ☐
3. I understand that relevant sections of my child`s medical notes and/or data may be looked at by responsible individuals from the study team, the Sponsor, NHS Trust or from regulatory authorities where it is relevant to my child`s taking part in the research. I give permission for these individuals to access my child`s records and for data collected as part of the study to be stored securely in University of Leicester and University Hospitals of Leicester secure systems ☐
4. I give permission for my child`s GP to be informed about my child`s participation in this study and of any clinically significant findings ☐
5. I agree to the study team accessing my child's medical record up to the age of 16 (optional) Yes ☐ No ☐
6. I agree on behalf of my child for forced oscillation technique to be taken and analysed for the purpose of this study. ☐
7. I agree on behalf of my child for spirometry to be taken and analysed for the purpose of this study ☐
8. I agree on behalf of my child for fractional exhaled nitric oxide to be taken and analysed for the purpose of this study ☐
9. I agree on behalf of my child for multibreath nitrogen washout to be taken and analysed for the purpose of this study ☐
10. I agree to my child's inhaler being fitted with an electronic monitor to track inhaler use ☐
11. I agree that my child's research data may be stored for future ethically approved research. Yes ☐ No ☐
12. I agree that my child's pseudonymised research data may be shared with other research collaborators in other academic institutions and industry partners inside and outside of the UK for future research. Yes ☐ No ☐

13. I agree to my child`s taking part in the above study. ☐

14. I would like to receive a copy of the final study report ☐ Yes ☐ No

Name of participant

_____

Name of Parent	Date	Signature
_____	_____	_____

Name of researcher taking consent	Date	Signature
_____	_____	_____

1 for participant; 1 for researcher (original), 1 for patient notes

CONSENT FORM

Children and young people attending hospital not diagnosed with wheeze/asthma (healthy control)

Study Number: 0802

Participant Identification Number:

Study Title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

Please initial box

1. I confirm that I have read and understand the Parent Information Sheet dated 19.02.2021 .Version 2 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my child's participation is voluntary and that my child are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected. ☐
3. I understand that relevant sections of my child`s medical notes and/or data may be looked at by responsible individuals from the study team, the Sponsor, NHS Trust or from regulatory authorities where it is relevant to my child`s taking part in the research. I give permission for these individuals to access my child`s records and for data collected as part of the study to be stored securely in University of Leicester and University Hospitals of Leicester secure systems ☐
4. I give permission for my child`s GP to be informed about my child`s participation in this study and of any clinically significant findings ☐
5. I agree to the study team accessing my child's medical record up to the age of 16 (optional) Yes ☐ No ☐
6. I agree on behalf of my child for forced oscillation technique to be taken and analysed for the purpose of this study. ☐
7. I agree on behalf of my child for spirometry to be taken and analysed for the purpose of this study ☐
8. I agree on behalf of my child for fractional exhaled nitric oxide to be taken and analysed for the purpose of this study ☐
9. I agree on behalf of my child for multibreath nitrogen washout to be taken and analysed for the purpose of this study ☐
10. I agree that my child's research data may be stored for future ethically approved research. Yes ☐ No ☐
11. I agree that my child's pseudonymised research data may be shared with other research collaborators in other academic institutions and industry partners inside and outside of the UK for future research. Yes ☐ No ☐
12. I agree to my child`s taking part in the above study. ☐

13. I would like to receive a copy of the final study report

Yes	No

Name of participant

_____

Name of Parent	Date	Signature
_____	_____	_____

Name of researcher taking consent	Date	Signature
_____	_____	_____

1 for participant; 1 for researcher (original), 1 for patient notes

University Hospitals of Leicester NHS
NHS Trust

ASSENT ('CONSENT') FORM

Children and young people attending Emergency Department with wheeze/asthma

Study Number: 0802

Participant Identification Number:

Study Title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

Please initial box

1. I confirm that I have read and understand the Patient Information Sheet for Young People Aged 10-15 years with Acute Asthma dated 19.02.2021 .Version 2 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and/or data may be looked at by responsible individuals from the study team, the Sponsor, NHS Trust or from regulatory authorities where it is relevant to my taking part in the research. I give permission for these individuals to access my records and for data collected as part of the study to be stored securely in University of Leicester and University Hospitals of Leicester secure systems ☐
4. I give permission for my GP to be informed about my participation in this study and of any clinically significant findings ☐
5. I agree to the study team accessing my medical record up to the age of 16 (optional) Yes ☐ No ☐
6. I agree for forced oscillation technique to be taken and analysed for the purpose of this study. ☐
7. I agree for spirometry to be taken and analysed for the purpose of this study ☐
8. I agree for fractional exhaled nitric oxide to be taken and analysed for the purpose of this study ☐
9. I agree for multibreath nitrogen washout to be taken and analysed for the purpose of this study ☐
10. I agree to my inhaler being fitted with an electronic monitor to track inhaler use ☐
11. I agree that my research data may be stored for future ethically approved research Yes ☐ No ☐
12. I agree that my pseudonymised research data may be shared with other research collaborators in other academic institutions and industry partners inside and outside of the UK for future research Yes ☐ No ☐

13. I agree to take part in the above study. ☐

14. I would like to receive a copy of the final study report

Yes	No
☐	☐

Name of participant	Date	Signature
_____	_____	_____

Name of researcher taking assent	Date	Signature
_____	_____	_____

1 for participant; 1 for researcher (original), 1 for patient notes

ASSENT ('CONSENT') FORM

Children and young people attending University Hospitals Leicester Paediatric Asthma/Respiratory Clinics with wheeze/asthma (including telephone reviews)

Study Number: 0802

Participant Identification Number:

Study Title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

Please initial box

1. I confirm that I have read and understand the Participant Information Sheet for Young People aged 10-15 years Attending Clinic dated 19.02.2021 .Version 2 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and/or data may be looked at by responsible individuals from the study team, the Sponsor, NHS Trust or from regulatory authorities where it is relevant to my taking part in the research. I give permission for these individuals to access my records and for data collected as part of the study to be stored securely in University of Leicester and University Hospitals of Leicester secure systems ☐
4. I give permission for my GP to be informed about my participation in this study and of any clinically significant findings ☐
5. I agree to the study team accessing my medical records up to the age of 16 (optional) ☐ Yes ☐ No
6. I agree for forced oscillation technique to be taken and analysed for the purpose of this study. ☐
7. I agree for spirometry to be taken and analysed for the purpose of this study ☐
8. I agree for fractional exhaled nitric oxide to be taken and analysed for the purpose of this study ☐
9. I agree for multibreath nitrogen washout to be taken and analysed for the purpose of this study ☐
10. I agree to my inhaler being fitted with an electronic monitor to track inhaler use ☐
11. I agree that my research data may be stored for future ethically approved research. ☐ Yes ☐ No
12. I agree that my pseudonymised research data may be shared with other research collaborators in other academic institutions and industry partners inside and outside of the UK for future research. ☐ Yes ☐ No

13. I agree to take part in the above study. ☐

14. I would like to receive a copy of the final study report ☐ Yes ☐ No

Name of participant	Date	Signature
_____	_____	_____

Name of researcher taking assent	Date	Signature
_____	_____	_____

1 for participant; 1 for researcher (original), 1 for patient notes

ASSENT ('CONSENT') FORM

Children and young people attending hospital not diagnosed with wheeze/asthma (healthy control)

Study Number: 0802

Participant Identification Number:

Study Title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

	Please initial box
1. I confirm that I have read and understand the Participant Information Sheet for young People (10-15 years) – Controls dated 19.02.2021 .Version 2 for the above study and have had the opportunity to ask questions.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that relevant sections of my medical notes and/or data may be looked at by responsible individuals from the study team, the Sponsor, NHS Trust or from regulatory authorities where it is relevant to my taking part in the research. I give permission for these individuals to access my records and for data collected as part of the study to be stored securely in University of Leicester and University Hospitals of Leicester secure systems	☐
4. I give permission for my GP to be informed about my participation in this study and of any clinically significant findings	☐
5. I agree to the study team accessing my medical record up to the age of 16 (optional)	Yes ☐ No ☐
6. I agree for forced oscillation technique to be taken and analysed for the purpose of this study.	☐
7. I agree for spirometry to be taken and analysed for the purpose of this study	☐
8. I agree for fractional exhaled nitric oxide to be taken and analysed for the purpose of this study	☐
9. I agree for multibreath nitrogen washout to be taken and analysed for the purpose of this study	☐
10. I agree that my research data may be stored for future ethically approved research.	Yes ☐ No ☐
11. I agree that my pseudonymised research data may be shared with other research collaborators in other academic institutions and industry partners inside and outside of the UK for future research.	Yes ☐ No ☐
12. I agree to take part in the above study.	☐

13. I would like to receive a copy of the final study report

Yes	No

Name of participant	Date	Signature
_____	_____	_____

Name of researcher taking assent	Date	Signature
_____	_____	_____

1 for participant; 1 for researcher (original), 1 for patient notes

Assent form for children (6-9 years) attending University Hospitals Leicester Paediatric Asthma/Respiratory Clinics, with wheeze/asthma OR attending University Hospitals Leicester with an asthma attack

Study title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

Participant Identification Number:

We want to find out what happens inside your lungs. You can help us by doing some simple blowing tests. Are you happy to do this? Please answer the questions below, and write your name at the bottom of the page.

1. I have read the information given to me, and talked to my parents about it	Yes	No
2. I have asked any questions I wanted	Yes	No
3. I am happy to try the breathing tests	Yes	No
4. I know I don't have to do anything I don't want to do	Yes	No
5. I know that I can stop when I want	Yes	No

We do not mind if you do not want to get involved, but if you would like to join in, please write your name below.

Assent form for children (6-9 years) who have never wheezed/do not have asthma attending hospital

Study title: Monitoring Asthma in Children using the Forced Oscillation Technique

Principal Investigator: Dr Erol Gaillard

Participant Identification Number:

We want to find out what happens inside your healthy lungs. You can help us by doing some simple blowing tests. Are you happy to do this? Please answer the questions below, and write your name at the bottom of the page.

1. I have read the information given to me, and talked to my parents about it	Yes	No
2. I have asked any questions I wanted	Yes	No
3. I am happy to try the breathing tests	Yes	No
4. I know I don't have to do anything I don't want to do	Yes	No
5. I know that I can stop when I want	Yes	No

We do not mind if you do not want to get involved, but if you would like to join in, please write your name below.

APPENDIX F: Questionnaires and Poster

Questionnaire on breathing problems in children aged 14 years and over

Your First Name: **Number:**

⇨ **Please fill in these questions yourself. We promise that your answers are confidential. They will not be shown to *anyone* that you know. The answers will only be seen by the research team.**

⇨ **Date questionnaire completed** day _____ month _____ year _____ *(please fill in today's date)*

Wheezing

By wheezing we mean breathing that makes a squeaky whistling sound from the chest, not the throat.

1. Have you had **wheezing or whistling in the chest** in the last 12 months? yes ☐ no☐

2. Have you had **chest tightness with cough** in the last 12 months? yes ☐ no☐

⇨ *if you answered "**no**" to **both questions** please skip to question* (16)

3. When was the **last occasion** that you were **wheezy**?
this week ☐ last week ☐ more than a week, but less than a month ago ☐ more than a month ago ☐

*In the next questions we will ask you about things that make you wheeze, or have chest tightness with cough. We will ask questions about the times you have **attacks of wheeze**, or chest tightness with cough **lasting for more than one day**, then, in the next section, about the shorter attacks which **last for less than a day** (only minutes or hours).*

First**, we will ask you about **attacks** of **wheeze or chest tightness with cough** which last **more than one day.

4. Do you have attacks of wheeze or chest tightness which? yes ☐ no☐

⇨ *if you answered "**no**" please skip to question* (11)

5. **How many attacks like this** have you had in the last year?
none ☐ 1 to 3 ☐ 4 to 12 ☐ more than 12 ☐

6. How **bad** were these attacks **at their worst** in the last year?

- caused difficulty sleeping or kept you awake at night yes ☐ no☐
- caused you to miss school yes ☐ no☐
- limited the amount of exercise you do yes ☐ no☐
- bad enough to stop you talking normally yes ☐ no☐

7. Do you have these attacks **only when you have a cold**? yes, only with colds ☐ no, also without colds ☐

8. Do these attacks cause you to be **short of breath**? yes ☐ no☐

9. Tick all the **things** that you think **cause** these **attacks lasting for more than one day**

• colds or flu	yes ☐	no ☐	don't know ☐
• running or sports	yes ☐	no ☐	don't know ☐
• laughing, crying, excitement	yes ☐	no ☐	don't know ☐
• pollen (grass, hay, trees, flowers)	yes ☐	no ☐	don't know ☐
• pet (dogs, cats, or other)	yes ☐	no ☐	don't know ☐
• house dust	yes ☐	no ☐	don't know ☐
• cigarette smoke from others	yes ☐	no ☐	don't know ☐
• food or drinks	yes ☐	no ☐	don't know ☐
• other	yes ☐	no ☐	don't know ☐

• if other, what _____

10. Tick all the **symptoms** which you have **during** these **attacks lasting for more than one day**

• cough	yes ☐	no ☐	don't know ☐
• chest tightness	yes ☐	no ☐	don't know ☐
• difficult breathing	yes ☐	no ☐	don't know ☐
• wheezing	yes ☐	no ☐	don't know ☐
• other	yes ☐	no ☐	don't know ☐

• if other, what _____

***Next**, we will ask you about **shorter attacks** of **wheeze or chest tightness with cough** lasting for **less than a day** (only minutes or hours).*

(11) Do you have **short** attacks of wheeze or chest tightness **lasting for less than a day**? yes ☐ no ☐

⇨ *if you answered "**no**" please skip to question* (16)

12. How often do you have attacks of wheeze or chest tightness **lasting for less than a day?**
every day ☐ several times a week ☐ about once per week ☐ once per month or less ☐ never ☐

13. Do these attacks cause you to be **short of breath**? yes ☐ no ☐

14. Tick all the **things** that you think **cause** these **attacks lasting for less than a day**

• colds or flu	yes ☐	no ☐	don't know ☐
• running or sports	yes ☐	no ☐	don't know ☐
• laughing, crying, excitement	yes ☐	no ☐	don't know ☐
• pollen (grass, hay, trees, flowers)	yes ☐	no ☐	don't know ☐
• pet (dogs, cats, or other)	yes ☐	no ☐	don't know ☐
• house dust	yes ☐	no ☐	don't know ☐
• cigarette smoke from others	yes ☐	no ☐	don't know ☐
• food or drinks	yes ☐	no ☐	don't know ☐
• other	yes ☐	no ☐	don't know ☐

• if other, what _____

Coughing

15. Tick all the **symptoms** that you have during these attacks lasting for less than a day

- cough yes ☐ no ☐ don't know ☐
- chest tightness yes ☐ no ☐ don't know ☐
- difficult breathing yes ☐ no ☐ don't know ☐
- wheezing yes ☐ no ☐ don't know ☐
- other yes ☐ no ☐ don't know ☐
- if other, what _____

16. **Do you think that** you **cough more than other children**? yes ☐ no ☐

17. Do you usually **cough with colds**? yes ☐ no☐

Smoking

18. Have you ever smoked **cigarettes or roll-ups** (or any other form of tobacco)? yes ☐ no ☐

19. Have you ever been a **regular smoker** (smoking at least daily for a period of more than 3 month yes ☐ no☐

20. In **what form** do you or did you, usually smoke? *(tick as many as apply)*

- Cigarette with tobacco ☐
- Roll-ups ☐
- Other ☐
- If other please specify _____

21. **How old** were you when you **started smoking**? _____yrs _____months

22. Are you still **smoking**? yes ☐ no☐

If no, how **old** were you when you **stopped smoking**? _____yrs _____months

23. **How many cigarettes** (or equivalent) do (did) you usually smoke **per day**? ☐ *(please fill in a number)*

Thank you very much for helping us again to study and improve health in children and young people!

Questionnaire on breathing problems in children aged under 14 years

First Name of Child: **Number:**

⇨ **Person completing questionnaire:** Mother ☐ Father ☐ Other ☐ If other who? _____

⇨ **Date questionnaire completed** day _____ month _____ year _____ *(please fill in today's date)*

Wheezing

By wheezing we mean breathing that makes a squeaky whistling sound from the chest, not the throat.

1. Has your child ever had **wheezing or whistling in the chest** at any time in the past? yes ☐ no☐

2. Has your child had **wheezing or whistling in the chest** in the last 12 months? yes ☐ no☐

⇨ *If you answered "**no**" to **both questions** please skip to question* **(19)**

3. In which of the last 12 months, was your child's wheeze **particularly bad**? *(tick off which apply)*
   Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sep ☐ Oct ☐ Nov ☐ Dec ☐

4. In the last 12 months, was the wheezing **worse during a particular time of day**?
   no ☐ yes, during the day ☐ yes, in the evening before falling asleep ☐ yes, at night ☐

5. In the last 12 months, has your child had wheezing or whistling in the chest **during or soon after a cold or flu**?
   yes ☐ no ☐

6. In the last 12 months, has your child had wheezing or whistling in the chest even **without** having a cold or flu?
   yes ☐ no ☐

7. **How many attacks of wheezing** has your child had during the last 12months?
   none ☐ 1 to 3 ☐ 4 to 12 ☐ more than 12 ☐

8. Do these attacks cause him/her to be **short of breath**? yes, always ☐ yes, occasionally ☐ no, never ☐

9. **How many** of these attacks **lasted for more than one day, and needed extra inhaler treatment**?
   none ☐ 1 ☐ 2 ☐ 3 ☐ 4 to 6 ☐ more than 6 ☐

10. In the last 12 months, has your child's chest sounded wheezy during or after exercise? yes ☐ no ☐
    If yes: when does it happen? Only, during a cold, flu or temperature ☐ even without a cold ☐

11. In the last 12 months, how often, on average, has your child's sleep **been disturbed due to wheezing**?
    never woken with wheezing ☐ less than one night per week ☐ one or more nights per week ☐

12. In the last 12 months, has wheezing ever been severe enough to limit your **child's speech** to only one or two words at a time between breaths? yes ☐ no ☐

13. **How old** was he/she when the **first attack** of wheezing occurred? _____yrs

14. If the wheezing has now stopped, at **what age did it stop**? _____yrs

15. In the last 12 months, **did the following things cause any wheezing** in your child?

- **exercise** (running, sports) yes ☐ no ☐ don't know ☐
- **laughing, crying, excitement** yes ☐ no ☐ don't know ☐
- **pollen** (grass, hay, trees, flowers) yes ☐ no ☐ don't know ☐
- **house dust** yes ☐ no ☐ don't know ☐
- **contact with pets** or other animals yes ☐ no ☐ don't know ☐
- **Food or drink** yes ☐ no ☐ don't know ☐ If yes: which food or drinks?

_____

16. In the last 12 months, how much did wheezing interfere with your child's daily activities?
not at all ☐ a little ☐ a moderate amount ☐ a lot ☐

17. Looking back at the last 12 months how severe was your child's wheezing or asthma?
very mild ☐ mild ☐ moderate ☐ severe ☐

18. During the last 12 months, did your child **miss school** because of **asthma or wheezing or bronchitis**?
yes ☐ no ☐
If yes: how much time did your child miss during the past 12 months (all missing days counted together)?
Less than 1 week ☐ 1 to 2 weeks ☐ 3 to 4 weeks ☐ more than 4 weeks ☐

19. Have you ever been told by **a doctor or a nurse** that your child has **asthma**? yes ☐ no ☐

Coughing

20. Do you think that your child **coughs more than other children**? yes ☐ no ☐

21. Does your child usually **cough with colds**? yes ☐ no ☐

22. Does your child have a cough even without **having a cold**? no, never, ☐ yes, sometimes ☐ yes, always ☐
If yes: is the cough worse at a particular time of the day?
no ☐ yes, during the day ☐ yes, in the evening before falling asleep ☐ yes, at night ☐

Ears, nose, throat and skin

23. In the last 12 months, **how many times** has your child had **a cold or flu**?
never ☐ 1 to 3 times ☐ 4 to 6 times ☐ 7 to 10 times ☐ more than 10 times ☐

24. In the last 12 months, has your child had a problem with **sneezing, or a runny or blocked nose** when he/she did NOT have a cold or the flu? yes ☐ no ☐

⇨ *If you answered "**no**" please skip to question* **27**

25. In the last 12 months, has this nose problem been accompanied by **itchy-watery eyes**? yes ☐ no ☐

26. In which of the last 12 months did this **nose problem** occur? (tick off which apply)
Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sep ☐ Oct ☐ Nov ☐ Dec ☐

27. In the last 12 months, has your child had **hay fever**? yes ☐ no ☐

28. Has your child ever had **eczema**? yes ☐ no ☐
If yes: has your child had **eczema** in the past 12 months? yes ☐ no ☐

Treatment

29. **How often did your child see the GP for coughing or** wheezing during the last 12 months?
never ☐ once ☐ 2 to 3 times ☐ 4 to 6 times ☐ 7 or more times ☐

30. In the last 12 months, **because of wheezing or asthma**, has your child?
- been referred to a **consultant in hospital** yes ☐ no ☐
- been admitted **to hospital** yes ☐ no ☐
- attended the casualty **(A and E)** department yes ☐ no ☐
- attended (or called) the **GP in an emergency** yes ☐ no ☐

31. **Did your child take any of the following drugs** during the last 12 months?
- Salbutamol, Ventolin, Bricanyl or other **blue** inhaler yes ☐ no ☐ don't know ☐
  Pulmicort, Flixotide, Becotide, Qvar or other **brown or orange** inhaler yes ☐ no ☐ don't know ☐
- Serevent or Oxis (a **green** or green-white inhaler) yes ☐ no ☐ don't know ☐
- Seretide or Symbicort (a **violet** or **red**-white inhaler) yes ☐ no ☐ don't know ☐
- Singulair tablets (Montelukast) yes ☐ no ☐ don't know ☐
- Steroid tablets (prednisolone) **for attacks** yes ☐ no ☐ don't know ☐

32. If your child has used **a brown, orange, violet or red inhaler,** please answer also the following two questions:
- Did he/she use it regularly (every day for at least 2 months in a row)? yes ☐ no ☐
- In total, how many months in the last year did he/she use it (adding up all episodes)?
  _____months

Family and household

33. Does the child's **mother smoke cigarettes** (in or out of the house)? yes ☐ no ☐
- **If yes:** how many per day? 1 to 10 ☐ 11 to 20 ☐ more than 20 ☐

34. Does **any other household member smoke at all** (in or out of the house)? yes ☐ no ☐
- **If yes:** how many per day? 1 to 10 ☐ 11 to 20 ☐ more than 20 ☐
  (please add up all cigarettes which are smoked by everybody except the mother)

35. Does your child have any **brothers** and **sisters (including half-siblings)** yes ☐ no ☐
- **If yes:** (a) how **many brothers?** ☐
  What years were they born _____ _____ _____ _____ _____
  (b) how **many sisters?** ☐
  What years were they born _____ _____ _____ _____ _____

You can also write any other comments you might have in this space below.

Thank you very much for helping us again to study and improve health in children and young people!

Asthma Control Test™ for teens 12 years and older. Know the score.

If your teen is 12 years or older have him take the test now and discuss the results with your doctor

Step 1 Write the number of each answer in the score box provided.

Step 2 Add up each score box for the total.

Step 3 Take the test to the doctor to talk about your child's total score.

1. In the past **4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time	
1	2	3	4	5	☐

2. During the past **4 weeks**, how often have you had shortness of breath?

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all	
1	2	3	4	5	☐

3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness, or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	2 or 3 nights a week	Once a week	Once or twice	Not at all	
1	2	3	4	5	☐

4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all	
1	2	3	4	5	☐

5. How would you rate your **asthma** control during the past **4 weeks**?

Not controlled at all	Poorly controlled	Somewhat controlled	Well controlled	Completely controlled	
1	2	3	4	5	☐

AMERICAN LUNG ASSOCIATION®

The American Lung Association supports the Asthma Control Test and wants everyone 12 years of age and older with asthma to take it.

Total ☐

What does it mean if my child scores 19 or less?

- If your child's score is 19 or less, it may be a sign that your child's asthma is not under control.
- Make an appointment to discuss your child's asthma score with their doctor. Ask if you should change your child's asthma treatment plan.
- Ask your child's doctor about daily long-term medications that can help control airway inflammation and constriction, the two main causes of asthma symptoms. Many children may need to treat both of these on a daily basis for the best asthma control.

asthma.com

Patient's Name: _____

Today's Date: _____

Childhood Asthma Control Test for children 4 to 11 years

Know your score.

Parent or Guardian: The Childhood Asthma Control Test* is a way to help your child's healthcare provider determine if your child's asthma symptoms are well controlled. Take this test with your child (ages 4 to 11). Share the results with your child's healthcare provider.

Step 1: Have your child answer **the first four questions (1 to 4).** If your child needs help, you may help, but let your child choose the answer.

Step 2: Answer the last **three questions (5 to 7)** on your own. Don't let your child's answers influence yours. There are no right or wrong answers.

Step 3: Write the number of each answer in the score box to the right.

Step 4: Add up each score box for the total.

Step 5: Take the COMPLETED test to your child's healthcare provider to talk about your child's total score.

19 or less

IF YOUR CHILD'S SCORE IS 19 OR LESS, **Your child's asthma symptoms may not be as well controlled as they could be. No matter what the score, bring this test to your child's healthcare provider to talk about your child's results.**

NOTE: If your child's score is 12 or less, his or her asthma may be very poorly controlled. Please contact your child's healthcare provider right away.

Have your child complete these questions.

1. How is your asthma today?

SCORE
0 Very bad
1 Bad
2 Good
3 Very good

2. How much of a problem is your asthma when you run, exercise or play sports?

SCORE
0 It's a big problem, I can't do what I want to do.
1 It's a problem and I don't like it.
2 It's a little problem but it's okay.
3 It's not a problem.

3. Do you cough because of your asthma?

SCORE
0 Yes, all of the time.
1 Yes, most of the time.
2 Yes, some of the time.
3 No, none of the time.

4. Do you wake up during the night because of your asthma?

SCORE
0 Yes, all of the time.
1 Yes, most of the time.
2 Yes, some of the time.
3 No, none of the time.

Please complete the following questions on your own.

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

SCORE
5 Not at all
4 1-3 days
3 4-10 days
2 11-18 days
1 19-24 days
0 Everyday

6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

SCORE
5 Not at all
4 1-3 days
3 4-10 days
2 11-18 days
1 19-24 days
0 Everyday

7. During the last 4 weeks, how many days did your child wake up during the night because of the asthma?

SCORE
5 Not at all
4 1-3 days
3 4-10 days
2 11-18 days
1 19-24 days
0 Everyday

TOTAL

*The Childhood Asthma Control Test was developed by GSK.

This material was developed by GSK.

UNIVERSITY OF LEICESTER

ASTHMA RESEARCH IN CHILDREN (2-15 years old)

HEALTHY VOLUNTEERS NEEDED

We are studying new ways to diagnose asthma in children using a novel non-invasive breathing test.

What is involved: Simple and painless breathing tests to study lung function.

We would like to talk you about the study:

Afnan AlRaimi (PhD student) aa1060@le.ac.uk /

Malak Alshlowi (PhD student)mosa1@le.ac.uk

Dr. Erol Gaillard (Children's Asthma Consultant at UHL) eag15@leicester.ac.uk

APPENDIX G: Additional documents; Honorary Contract and certificates for Good Clinical Practice (GCP) training, consent training and site file training

RESEARCH. & INNOVATION

University Hospitals of Leicester NHS
NHS Trust

Research & Development Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

DIRECTORATE OF RESEARCH & DEVELOPMENT

Director: **Professor Nigel Brunskill**
Assistant Director: **Dr David Hetmanski**
Head of Research Operations: **Carolyn Maloney**

Direct Dial: (0116) 258 4199
Fax No: (0116) 258 4226

4th July 2018

Ms Afnan Al-Raimi
University of Leicester
Infection, Immunity and Inflammation department.
Leicester Royal Infirmary
Leicester
LE1 5WW

Dear Afnan,

This letter confirms your right of access to conduct research through **University Hospitals of Leicester NHS Trust** for the purpose and on the terms and conditions set out below. This right of access commences on **4th July 2018** and ends on **3rd July 2021** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at **University Hospitals of Leicester NHS Trust** has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to **University Hospitals of Leicester NHS Trust** premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through University Hospitals of Leicester NHS Trust, you will remain accountable to your Employer **Leicester University** but you are required to follow the reasonable instructions of **Dr Erol Gaillard** in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with **University Hospitals of Leicester NHS Trust** policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with **University Hospitals of Leicester NHS Trust** in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on **University Hospitals of Leicester NHS Trust** premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

University Hospitals of Leicester NHS Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Lisa Wann
R&I Manager

cc: **Copy to Bristol University HR**
Tina Larder HR UHL
Copy for File
Dr Erol Gaillard UHL

DIRECTORATE OF RESEARCH & INNOVATION

Director: Professor Nigel Brunskill

Assistant Director: Dr David Hetmanski

Head of Research Operations: Carolyn Maloney

Direct Dial: (0116) 258 8351

Research & Innovation Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

23rd April 2021

Ms Afnan Al-Raimi
University of Leicester
PhD Student
Childrens
Leicester Royal Infimary
Leicester
LE1 5WW

Dear Afnan,

Honorary research contract issued by University Hospitals of Leicester NHS organisation.

RE: EDGE ID 136058 - Forced oscillation and childhood asthma.

I am pleased to offer you an honorary research contract in **University Hospitals of Leicester,** the previous Letter of Access is now obseolete. I should be grateful if you would sign the attached two contracts, keep one yourself and return the other two to **Research & Innovation Office, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW**. We will send a copy of the contract to your substantive employer.

The contract if accepted by you begins on **23rd April 2021** and ends on **22nd April 2024** unless terminated earlier in accordance with the clauses in the contract. Please note that you cannot start the research until the Principal Investigator has received a letter from us giving permission to conduct the project.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and the organisation OH prior to commencing your research role at the Trust.

We will not reimburse any expenses you incur in the course of your research unless we have agreed to do so by prior arrangement. Similarly, we accept no responsibility for damage to or loss of personal property.

Your Research Passport Form may be subject to random checks carried out by us within the lifetime of the project. The information it contains must therefore remain up to date and accurate.

If your circumstances change in relation to your health, criminal record, suitability to work with adults or children, professional registration or any other aspect that may impact on your suitability to

conduct research, or your role in research changes, you must inform your employer through its normal procedures. You must also inform your nominated manager in this NHS organisation.

You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this honorary research contract is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Once you have signed and returned two of the attached contracts, you should contact the HR Department of this organisation, who will arrange for you to be issued with an ID badge.

Yours sincerely

Lisa Wann
R&I Manager
University Hospitals of Leicester

cc:
UoL HR Department
Tina Larder HR UHL
Erol Gaillard UHL
Copy for File

(A copy of the signed honorary research contract must be sent to the substantive employer/academic supervisor.

HONORARY RESEARCH CONTRACT BETWEEN

NHS organisation(s): University Hospitals of Leicester NHS Trust

AND

Name: Afnan Al-Raimi

Employer:
OR Place of Study: Leicester University

Report To:
(Principal Investigator/Head of Department)

PERIOD of AGREEMENT

From: **23rd April 2021** To: **22nd April 2024**

OR
Fixed term
contract for: years months Effective Date:

SIGNATURES

Researcher: Date: 23.04.2021

Name: Afnan AlRaimi

On behalf of the NHS organisation(s)

Date: 23.04.2021

Name: Lisa Wann

Whereas

A. The Researcher named in this Agreement ("the Researcher") is employed by the employing organisation named in this Agreement ("the Employer") to undertake research, during the course of which the Researcher requires access to the organisation/s named in this Agreement their premises, patients, their clinical samples, and clinical and personal information ("the Facilities"). Where independent contractors and their premises are involved with research activity, the Agreement is issued by the host organisation/team on behalf of the independent contractors.

OR

The Researcher named in this Agreement ("the Researcher") is studying at the place of study named in this Agreement ("the Place of Study") to undertake research, during the course of which the Researcher requires access to the organisations named in this Agreement, their premises, patients, their clinical samples, and clinical and personal information ("the Facilities"). Where independent contractors and their premises are involved with research activity, the Agreement is issued by the host organisation/team on their behalf of the independent contractors.

B. The organisation(s) provide healthcare services to NHS patients, including patients who are protected by the criminal record disclosure arrangements.

C. The organisation(s)Trust(s) and Researcher have entered into this agreement whereby the Researcher can have access to the Facilities of the organisation(s) to conduct such research as confirmed in writing in the letter of permission for research from this organisation, subject to the conditions below.

1. Status

The title and status of this Honorary Research Contract does not create an employment relationship and attracts no remuneration from the organisation(s). Its award will be subject to: a satisfactory criminal record disclosure if the research position is eligible for a check; checks against the Disclosure and Barring Service(DBS) barred lists, where this is a legal requirement; confirmation of registration with the GMC or other appropriate professional body if the Researcher is required to maintain such professional registration; and confirmation that the Researcher's health does not constitute a risk to patients of the organisation(s), employees of the organisation(s) or visitors to the organisation(s).

2. Reporting Arrangements

The Researcher shall report to the Principal Investigator/Head of Department named in this Agreement whilst conducting research under this Agreement.

3. Policies and Procedures

3.1. The terms and conditions of employment of the Researcher including applicable policies and procedures are determined by the Employer and the Researcher will be carrying out duties at the organisation(s) in accordance with the contract of employment with the Employer

OR

The rules governing the Researcher's period of study including applicable policies and procedures are determined by the Place of Study and the Researcher will be carrying out duties at the organisation(s) in accordance with those rules.

3.2. In carrying out research under the terms of this Agreement, the Researcher agrees to act at all times in accordance with the policies and procedures of the organisation(s) including the Research Governance Framework, copies of which are available upon request.

3.3. The Researcher is required to co-operate with the organisation(s) in discharging relevant duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of himself/herself and others while on the premises of the organisation(s). The Researcher must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and the premises as is expected of any other contract holder and must act appropriately, responsibly and professionally at all times.

3.4. The Researcher agrees to accept any variation to this Agreement necessitated by changes to research and development guidance issued by the Department of Health.

3.5. In the event of sickness or unavoidable absence, the Researcher must notify her/his line manager and/or the organisation(s) immediately. The Researcher must report any accident or injury, arising out of or in the course of her/his activities at the organisation(s) and make appropriate records and statements as required.

3.6. Adverse events or incidents arising from the research should be reported immediately in compliance with the policies of the organisation(s).

4. Confidentiality

Information concerning the Facilities is confidential and must not be disclosed under any circumstances. The Researcher must treat all material connected with her/his presence in the organisation(s) in accordance with the NHS Confidentiality Code of Practice and the Data Protection Act 2018 (which covers information concerning individuals stored in any systems belonging to the organisation(s)). Unauthorised disclosure could lead to prosecution under the terms of the Act.

5. Legal Claims

5.1. The research sponsor and provider organisation(s) agree to indemnify the Researcher for any claims in negligence in respect of those patients of the organisation(s) to whom the Researcher provides care and treatment when performing duties in accordance with this Agreement.

5.2. The organisation(s) takes/take no responsibility for any claims against the Researcher arising from her/his negligent acts or omissions in undertaking agreed programmes of research using the Facilities of the organisation(s) where these are covered by warranties or conditions of any third party contracts signed by the Employer/Place of Study.

5.3. The Researcher is advised either to ensure that the Employer/Place of Study maintains adequate indemnity arrangements or, if not, maintains membership of

her/his medical defence organisation or has other professional indemnity arrangements in place before starting to use the Facilities of the organisation(s).

5.4. The organisation(s) accepts/accept no responsibility for damage to or loss of the Researcher's personal property.

5.5. The organisation(s) accepts/accept no legal liability in respect of any decision it/they may take to terminate this contract pursuant to section 9 below.

6. Complaints and misconduct

6.1. The Researcher should raise any complaints against the organisation(s) with the Employer/Place of Study.

6.2. Complaints or allegations against the Researcher will be dealt with in accordance with the policies and procedures of the Employer/Place of Study. Partnership between the organisation(s) and the Employer/Place of Study will be assured.

6.3. The Researcher agrees to comply with any requests for data, information or documents from the organisation(s) or the Employer/Place of Study as part of any investigation of a complaint or of suspected misconduct.

7. Intellectual Property

The organisation(s) is/are required by the Department of Health to protect and manage intellectual property arising from Research and Development funded by the NHS. The organisation(s) has/have arrangements in place with the Employer/Place of Study relating to ownership and exploitation of intellectual property. All intellectual property outputs from the Researcher's research activity in the organisation(s), both commercially and non-commercially exploitable, should be declared to the Research and Development office of this organisation for our records, e.g. peer-reviewed papers or patents.

8. Audit

The Researcher agrees that all research undertaken by him/her may be subject to audit and/or monitoring. The organisation(s) will ensure that all data, records and other materials are kept confidential. The Researcher also agrees that the information about her/his research activity may be listed by the organisation(s) on relevant national databases and incorporated into the Annual Research Report of the organisation(s). This Agreement will be subject to random checks as part of the research and development audit activity of the organisation(s).

9. Duration and Termination

9.1. The organisation(s), the Researcher or the Employer/Place of Study may request that this Agreement is reviewed in order to confirm the Researcher's status as a Researcher.

9.2. Subject to 9.3 and 9.4 below, the organisation(s) reserves/reserve the right to terminate this Agreement upon giving one month's written notice.

9.3. In the event that the Researcher fails to comply with the requirements of this Agreement, the organisation(s) reserves/reserve the right to:

9.3.1. terminate the Agreement forthwith without notice and refuse the Researcher access to the Facilities of the organisation(s); or

9.3.2. require the Researcher to submit to an agreed training programme as a condition of being allowed to continue to have access to the Facilities of the organisation(s); or

9.3.3. require that this Agreement is suspended subject to investigation by the Employer/Place of Study in conjunction with the organisation(s). The Employer/Place of Study and the organisation(s) will endeavour to complete the investigation within 20 working days and the Researcher will be notified regarding termination or reinstatement of the contract.

9.4. In the event that the researcher ceases to be suitable for undertaking regulated activity, the Employer/Place of Study undertakes to withdraw the researcher from their activity and terminate their access to the facilities. The organisation also reserves the right to terminate this Agreement forthwith without notice and refuse the Researcher access to the Facilities of the organisation(s).

9.5. The organisation(s) agrees/agree that no later than five working days prior to terminating the Agreement in accordance with 9.2 or 9.3 or 9.4 above, it will inform the Employer/Place of Study of its intention to do so.

9.6. The organisation(s) reserves/reserve the right to exclude the Researcher at any time from its premises for whatever reason, pending a decision upon whether it wishes to terminate this Agreement.

9.7. It is the obligation of the Researcher to disclose any mitigating circumstances that may affect the Agreement such as a change in criminal record, registration, employment or occupational health status.

10. The Researcher warrants that she/he has the relevant skills and expertise to undertake the research for which she/he is permitted to use the Facilities of the organisation(s) and is supported through suitable professional development programmes or training by the Employer/Place of Study or research sponsor, to ensure that she/he is suitable to undertake research.

UNIVERSITY OF LEICESTER

Certificate of Achievement

Issued to

Afnan Alraimi

For the completion of the University of Leicester

Researcher Training for Non-CTIMP Studies (incorporating the principles of GCP)

Training and Assessment on

19th April 2018

Authorised on behalf of the University of Leicester

Dr Diane Delahooke & Dr Cat Taylor

Valid Until 18th April 2021

NIHR | National Institute for Health Research

Issued by:
Clinical Research Network
Coordinating Centre

CERTIFICATE OF ACHIEVEMENT

Afnan AlRaimi

has completed the course:

Good Clinical Practice (GCP) Refresher eLearning

March 12, 2021

Modules Completed

- Good Clinical Practice (GCP) Refresher: Revisiting Key Concepts
- GCP Refresher Hot Topics
- Good Clinical Practice (GCP) Refresher: Reflecting on your own practice and experience

This course is worth 3 CPD Credits

CPD®
The CPD Certification Service

Version: Nov 2020

Training Certificate

Issued to

Afnan Alraimi

For completion of the University Hospitals of Leicester NHS Trust

Consent for Research Training on the 16th May 2018

Authorised on behalf of the University Hospitals of Leicester

Julie James
Aldona Kirkham
Anne Moore
Clinical Trial Monitors and Trainers

Valid for 24 months

Updated October 2014


Certificate of Achievement
University Hospitals of Leicester
NHS
NHS Trust
This is to certify that:
Afnan Alraimi (aa1060@leicester.ac.uk)
Successfully completed:
Consent Training for Research Studies REFRESHER (OCB - eLearning)
Sessions Notes:
None
Date: Thursday August 13, 2020
Valid for: 36 Months

Certificate of Attendance

Issued to

Afnan Alraimi

For

Site File Management Training

on the

19th June 2019

Authorised on behalf of the University Hospitals of Leicester

Julie James
Aldona Kirkham
Anne Moore
Clinical Trial Monitors and Trainers

Version 1 23/05/2017

APPENDIX H: Systematic review database search strategies

Database Ovid Medline (14.04.2021)

Number	Key word	Number of the articles
1.	"Forced oscillation*".mp.	1309
2.	"impulse oscillometry*".mp.	574
3.	FOT.mp.	535
4.	IOS.mp.	1762
5.	"Respiratory resistance".mp.	1205
6.	"Airway resistance".mp.	16110
7.	"Respiratory impedance".mp.	490
8.	"respiratory reactance".mp.	3
9.	"airway impedance".mp.	42
10.	"Airway reactance".mp.	16
11.	"peripheral airway*".mp.	1690
12.	"peripheral lung*".mp.	2543
13.	"small airway*".mp.	4742
14.	"distal airway*".mp.	1106
15.	"distal lung*".mp.	830
16.	Asthma*.mp.	185507
17.	wheez*.mp.	14269
18.	Bronchoconstriction.mp. or Bronchoconstriction/	9408
19.	Bronchial Spasm/ or broncospasm.mp.	4324
20.	"pulmonary function".mp.	32226
21.	"respiratory function".mp.	56945
22.	"lung function".mp.	35589
23.	spirometry.mp. or Spirometry/	31538
24.	BDR.mp.	426
25.	Bronchodilator*.mp.	27868
26.	"Bronchodilator response*".mp.	1026
27.	"Airway reversibility".mp.	70
28.	"Reversibility test".mp.	150
29.	Spiromet*.mp.	35342
30.	Bronchodilation*.mp.	2457
31.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	19220
32.	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	204652
33.	20 or 21 or 22 or 23 or 29	121642
34.	24 or 25 or 26 or 27 or 28 or 30	29275
35.	31 and 32 and 33 and 34	492
36.	limit 35 to ("all child (0 to 18 years)" and english)	175

Database EBSCO (14.04.2021)

Number	Key word	Number of the articles
1.	"forced oscillation*"	161
2.	"impulse oscillometry*"	144
3.	"FOT"	80
4.	"IOS"	514
5.	"Respiratory resistance"	118
6.	"Airway resistance"	1646
7.	"Respiratory impedance"	50
8.	"respiratory reactance"	7
9.	"airway impedance"	5
10.	"Airway reactance"	5
11.	"peripheral airway*"	184
12.	"peripheral lung*"	363
13.	"small airway*"	723
14.	"distal airway*"	144
15.	"distal lung*"	68
16.	"Asthma*"	47102
17.	"wheez*"	3608
18.	"Bronchoconstriction"	1008
19.	"Bronchial Spasm"	1686
20.	“Bronchospasm”	2073
21.	"pulmonary function"	7219
22.	"respiratory function"	12375
23.	"lung function"	7785
24.	"spirometry"	8994
25.	"Spiromet*"	9155
26.	"BDR"	63
27.	"Bronchodilator*"	7701
28.	"Bronchodilation*"	406
29.	"Bronchodilator response*"	219
30.	"Airway reversibility"	12
31.	"Reversibility test"	17
32.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	2393
33.	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	51255
34.	S21 OR S22 OR S23 OR S24 OR S25	27007
35.	S26 OR S27 OR S28 OR S29 OR S30 OR S31	7944
36.	S32 AND S33 AND S34 AND S35	71
37.	S32 AND S33 AND S34 AND S35 with the limit of All child and English	33

Database SCOPUS (14.04.2021)

Number	Key word	Number of the articles
1.	"forced oscillation*"	14734
2.	"impulse oscillometry*"	1825
3.	fot	5419
4.	ios	125922
5.	"Respiratory resistance"	4819
6.	"Airway resistance"	31661
7.	"Respiratory impedance"	2356
8.	"respiratory reactance"	107
9.	"airway impedance"	340
10.	"Airway reactance"	23
11.	"peripheral airway*"	9272
12.	"peripheral lung*"	13961
13.	"small airway*"	23465
14.	"distal airway*"	4943
15.	"distal lung*"	5348
16.	Asthma*	650928
17.	wheez*	62019
18.	Bronchoconstriction	35978
19.	"Bronchial Spasm"	3891
20.	broncospasm	14
21.	"pulmonary function"	133892
22.	"respiratory function"	104237
23.	"lung function"	208496
24.	spirometry	67751
25.	Spiromet*	81948
26.	BDR	7788
27.	Bronchodilator*	55261
28.	Bronchodilation*	8543
29.	"Bronchodilator response*"	5263
30.	"Airway reversibility"	173
31.	"Reversibility test"	485
32.	1-2-3-4-5-6-7-8-9-10 OR	178363
33.	11-12-13-14-15-16-17-18-19-20 OR	703429
34.	21-22-23-24-25 OR	356223
35.	26-27-28-29-30-31 OR	66649
36.	32-33-34-35 AND	3456
37.	36 with the limit to children and English	38

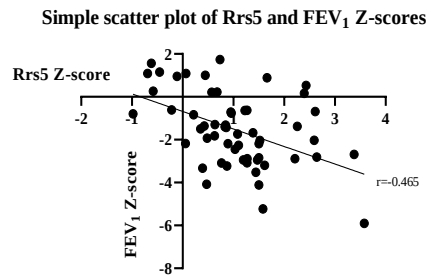
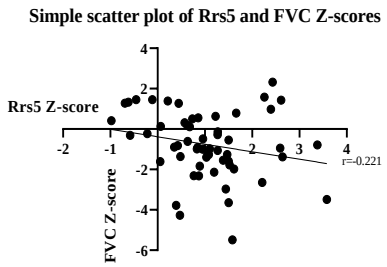
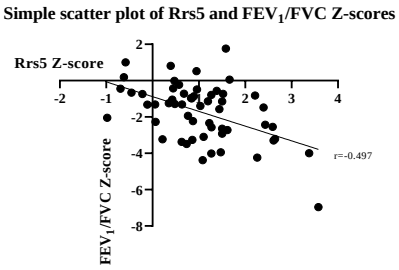
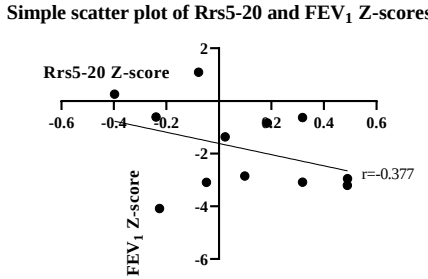
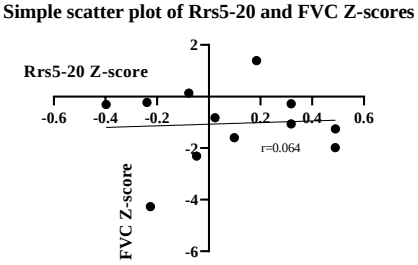
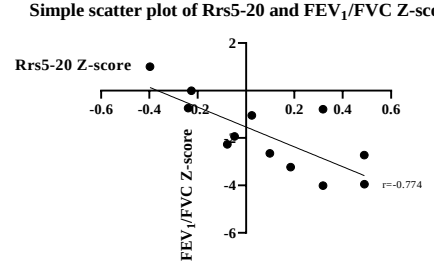
Database Web of science (14.04.2021)

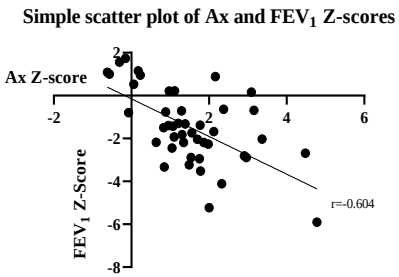
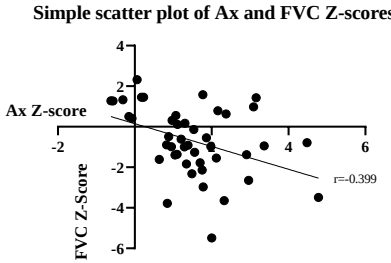
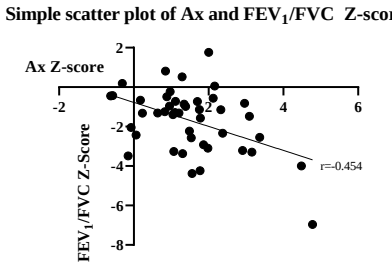
Number	Key word	Number of the articles
1.	(Forced oscillation*)	34853
2.	(impulse oscillometry*)	950
3.	(FOT)	1867
4.	(IOS)	26872
5.	(Respiratory resistance)	38204
6.	(Airway resistance)	14218
7.	(Respiratory impedance)	3882
8.	(respiratory reactance)	626
9.	(airway impedance)	1673
10.	(Airway reactance)	471
11.	(peripheral airway)	7432
12.	(peripheral lung*)	40487
13.	(small airway*)	17087
14.	(distal airway*)	3069
15.	(distal lung*)	10536
16.	Asthma*	247136
17.	wheez*	14139
18.	Bronchoconstriction	10218
19.	(Bronchial Spasm)	137
20.	(broncospasm)	6
21.	(pulmonary function)	110097
22.	(respiratory function)	109910
23.	(lung function)	206003
24.	(Spirometry)	18466
25.	(Spiromet*)	23056
26.	(BDR)	1552
27.	(Bronchodilator*)	13584
28.	(Bronchodilation*)	2337
29.	(Bronchodilator response*)	3369
30.	(Airway reversibility)	918
31.	(Reversibility test)	4701
32.	Child	2126823
33.	(school age)	989833
34.	(adolescent*)	535206
35.	Children	1876151
36.	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	109791
37.	#20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11	315904
38.	#25 OR #24 OR #23 OR #22 OR #21	308183
39.	#31 OR #30 OR #29 OR #28 OR #27 OR #26	19614
40.	#35 OR #34 OR #33 OR #32	3183333
41.	#40 AND #39 AND #38 AND #37 AND #36	275
42.	#40 AND #39 AND #38 AND #37 AND #36 Refined by: LANGUAGES: (ENGLISH)	83

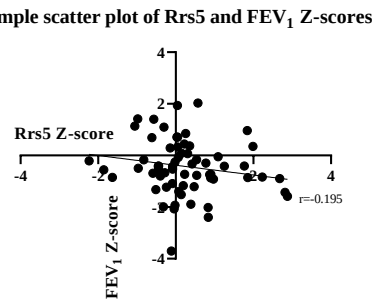
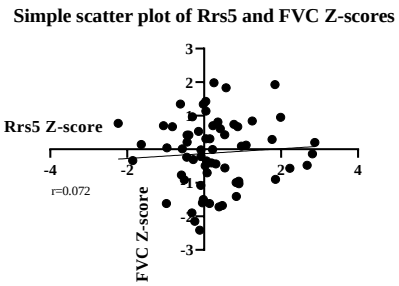
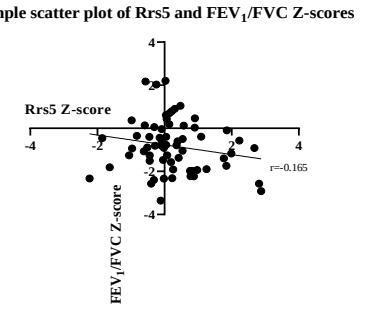
Database Cochrane (14.04.2021)

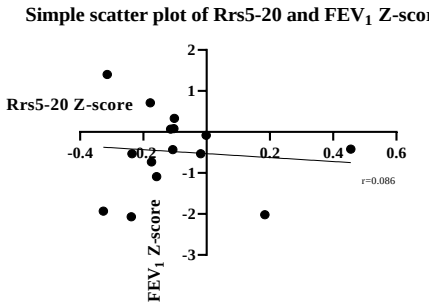
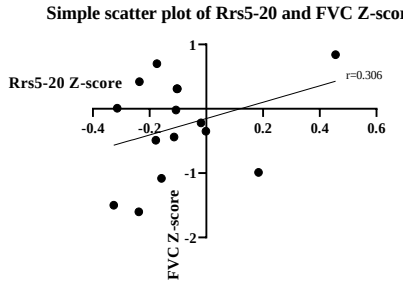
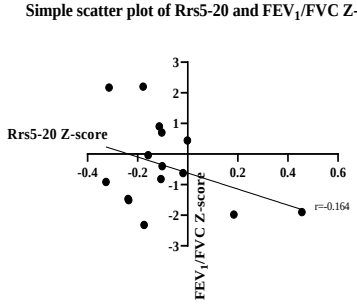
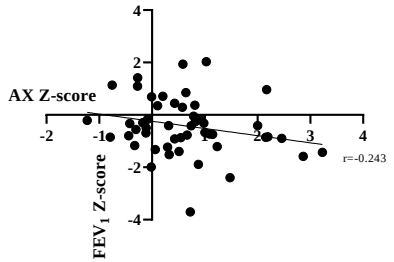
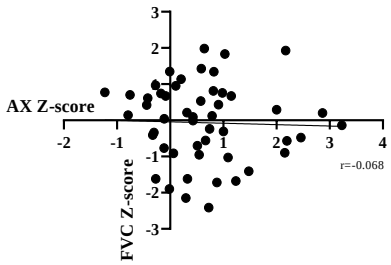
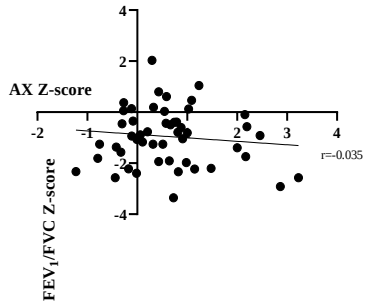
Number	Key word	Number of the articles
1.	"forced oscillation*"	172
2.	"impulse oscillometry*"	240
3.	FOT	133
4.	IOS	675
5.	"Respiratory resistance"	201
6.	"Airway resistance"	2174
7.	"Respiratory impedance"	47
8.	"respiratory reactance"	4
9.	"airway impedance"	10
10.	"Airway reactance"	9
11.	"peripheral airway*"	115
12.	"peripheral lung*"	181
13.	"small airway*"	242
14.	"distal airway*"	33
15.	"distal lung*"	18
16.	Asthma*	37239
17.	wheez*	3072
18.	Bronchoconstriction	2304
19.	"Bronchial Spasm"	518
20.	broncospasm	3
21.	"pulmonary function"	7852
22.	"respiratory function"	6291
23.	"lung function"	13305
24.	spirometry	6927
25.	Spiromet*	8060
26.	BDR	84
27.	Bronchodilator*	9289
28.	Bronchodilation*	1517
29.	"Bronchodilator response*"	442
30.	"Airway reversibility"	47
31.	"Reversibility test"	87
32.	Child*	183841
33.	Children	171030
34.	"school age"	1578
35.	"adolescent*"	133877
36.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	3197
37.	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	39334
38.	#21 OR #22 OR #23 OR #24 OR #25	26682
39.	#26 OR #27 OR #28 OR #29 OR #30 OR #31	9993
40.	#32 OR #33 OR #34 OR #35	267706
41.	#36 AND #37 AND #38 AND #39 AND #40	92

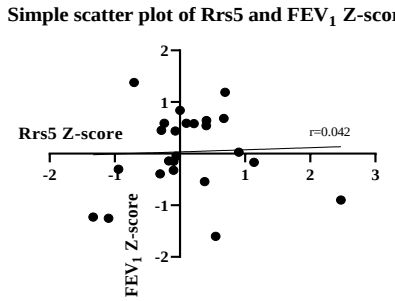
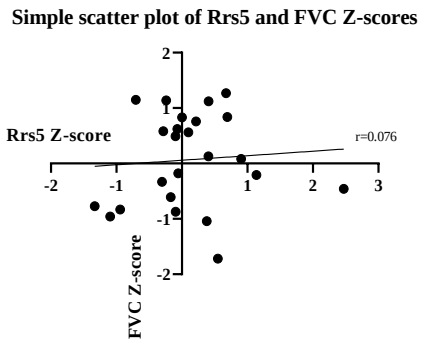
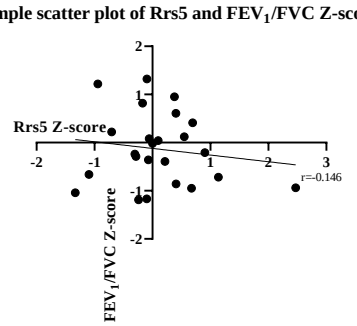
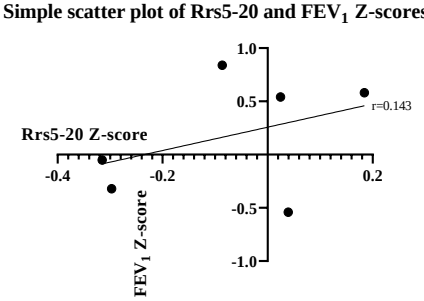
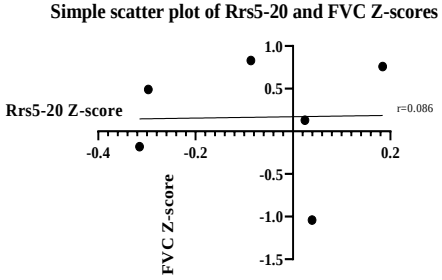
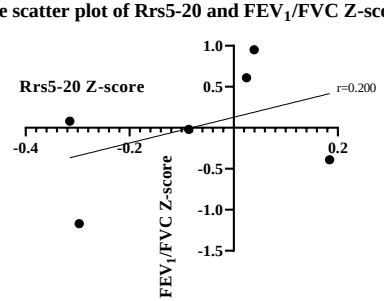
APPENDIX I: Correlations of the FOT parameters (Rrs5, Rrs5-20 and AX) Z-scores with the spirometry parameters (FEV_1, FVC and FEV_1/FVC) Z-scores

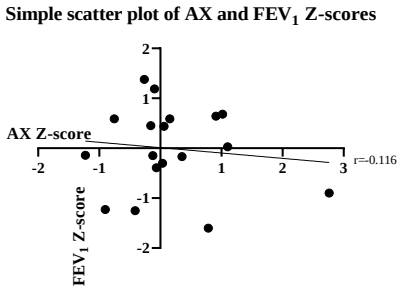
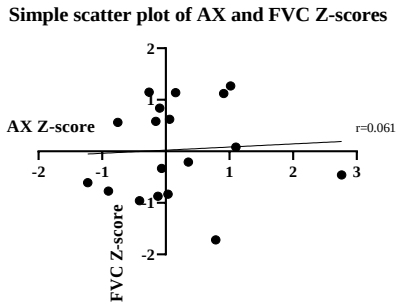
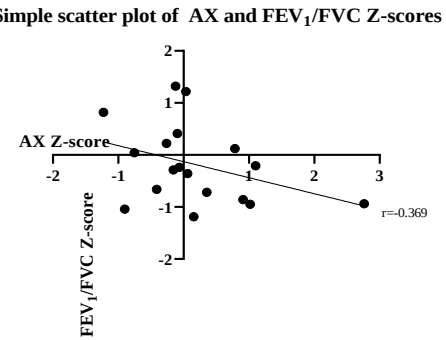
	Asthma with complete evidence (n=56)		
With Rrs5 Z-scores (n=56)	Correlation of the resistance at 5Hz (Rrs5) to the forced expiratory volume in 1 second (FEV_1)	Correlation of the resistance at 5Hz (Rrs5) to the forced vital capacity (FVC)	Correlation of the resistance at 5Hz (Rrs5) to the ratio of the forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC)
			
With Rrs5-20 Z-scores (n=12)	Correlation of the resistance at 5-20 Hz (Rrs5-20) to the forced expiratory volume in 1 second (FEV_1)	Correlation of the resistance at 5-20 Hz (Rrs5-20) to the forced vital capacity (FVC)	Correlation of the resistance at 5-20 Hz (Rrs5-20) to the ratio of the forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC)
			

	Asthma with complete evidence (n=56)		
With AX Z-scores (n=44)	Correlation of the area under the curve (AX) to the forced expiratory volume in 1 second (FEV_1)	Correlation of the area under the curve (AX) to the forced vital capacity (FVC)	Correlation of the area under the curve (AX) to the ratio of the forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC)
			

	Asthma with incomplete evidence (n=66)		
With Rrs5 Z-scores (n=66)	Correlation of the resistance at 5Hz (Rrs5) to the forced expiratory volume in 1 second (FEV_1)	Correlation of the resistance at 5Hz (Rrs5) to the forced vital capacity (FVC)	Correlation of the resistance at 5Hz (Rrs5) to the ratio of the forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC)
			

	Asthma with incomplete evidence (n=66)		
With Rrs5-20 Z-scores (n=15)	**Figure:** Correlation of the resistance at 5-20 Hz (Rrs5-20) to the forced expiratory volume in 1 second (FEV_1)	**Figure:** Correlation of the resistance at 5-20 Hz (Rrs5-20) to the forced vital capacity (FVC)	**Figure:** Correlation of the resistance at 5-20 Hz (Rrs5-20) to the ratio of the forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC)
			
With AX Z-scores (n=51)	Correlation of the area under the curve (AX) to the forced expiratory volume in 1 second (FEV_1)	Correlation of the area under the curve (AX) to the forced vital capacity (FVC)	Correlation of the area under the curve (AX) to the ratio of the forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC)
			

	Suspected asthma with no evidence (n=24)		
With Rrs5 Z-scores (n=24)	Correlation of the resistance at 5Hz (Rrs5) to the forced expiratory volume in 1 second (FEV_1)	Correlation of the resistance at 5Hz (Rrs5) to the forced vital capacity (FVC)	Correlation of the resistance at 5Hz (Rrs5) to the ratio of the forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC)
			
With Rrs5-20 Z-scores (n=4)	Correlation of the resistance at 5-20 Hz (Rrs5-20) to the forced expiratory volume in 1 second (FEV_1)	Correlation of the resistance at 5-20 Hz (Rrs5-20) to the forced vital capacity (FVC)	Correlation of the resistance at 5-20 Hz (Rrs5-20) to the ratio of the forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC)
			

	Suspected asthma with no evidence (n=24)		
With AX Z-scores (n=18)	Correlation of the area under the curve (AX) to the forced expiratory volume in 1 second (FEV_1)	Correlation of the area under the curve (AX) to the forced vital capacity (FVC)	Correlation of the area under the curve (AX) to the ratio of the forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC)
			

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