CHILDHOOD ASTHMA MANAGEMENT IN PRIMARY CARE – IMPLEMENTATION OF EXHALED NITRIC OXIDE AND SPIROMETRY TESTING

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by

David Kwok Hai Lo

MB ChB, MSc, MRCPCH

Department of Respiratory Sciences

University of Leicester

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ABSTRACT

Childhood **A**sthma **M**anagement in **P**rimary Care: **I**mplementation **o**f Exhaled **N**itric Oxide and **S**pirometry (**CHAMPIONS** study)

David Kwok Hai Lo

The National Institute for Health and Care Excellence recommends spirometry and exhaled nitric oxide (eNO) testing in children from five years for diagnosis, and spirometry for asthma monitoring. However, there is limited paediatric spirometry and eNO data in UK primary care to support this.

Using the principles of a type 3 hybrid study design, this was a prospective observational study with the dual objectives of exploring the implementation and clinical outcomes related to provision of spirometry and eNO testing for children in general practice. Firstly, to quantify the training and capacity requirements needed in general practice to deliver routine spirometry and eNO testing for children, and secondly to explore what additional information these tests provide and how they relate to current symptoms and asthma attacks.

Ten general practices (GP) participated. GP staff were trained to perform and interpret spirometry and eNO. Children aged 5-16 with suspected or doctor-diagnosed asthma were invited to attend a review. Spirometry and eNO data, Asthma Control Test (ACT) scores, and number of UHAs in the previous six months were recorded. Follow up ACTs were sent out, and patient records were reviewed, six months later.

We demonstrated that it is possible to train GP staff to obtain quality spirometry and eNO data from most children in the GP setting, and that the tests are acceptable to staff and families.

Of the 612 children recruited, 24% had abnormal spirometry and 36% had raised eNO. 54% of children reporting good asthma control had abnormal spirometry or raised eNO, whilst 49% of children reporting poor control had normal tests.

We conclude that abnormal lung function is prevalent in children managed for asthma in primary care, and assessing asthma based on symptoms' alone is inadequate. The role of objective test targeted children's asthma management in primary care warrants further study.

ACKNOWLEDGEMENTS

I would like to thank my supervisors Dr. Erol Gaillard, and Prof. Andy Wilson for their guidance and encouragement throughout this project; Dr. Caroline Beardsmore for providing me with the necessary skills to perform lung function testing; Mrs. Lesley Danvers for all her support in running this study day-to-day; all my collaborators for sharing with me their expertise; Health Education East Midlands, the Midlands Asthma and Allergy Research Association, and Circassia Pharmaceuticals for providing the necessary funding to make this study possible.

Thanks also goes to all the general practice staff, and families I have had the privilege of working with, for their enthusiasm and patience with this project.

Most of all, I would like to thank my parents, my sister, and in particular my wife Jo, and son Joshua, for their understanding, unquestioning support, and unwavering belief in me over the course of my training.

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LIST OF ABBREVIATIONS

ACT	Asthma Control Test
AHR	Airway Hyper Responsiveness
ARTP	Association for Respiratory Technology and Physiology
ASM	Abnormal Smooth Muscle
ATS	American Thoracic Society
BDR	Bronchodilator Response
BLF	British Lung Foundation
BMI	Body Mass Index
BTS	British Thoracic Society
CACT	Children's Asthma Control Test
CAN	Canadian
CCG	Clinical Commissioning Group
CHAMPIONS	Childhood Asthma Management in Primary Care: Implementation of Nitric Oxide and Spirometry
CLAHRC	Collaborations for Leadership in Applied Health Research and Care
COM-B	Capability, Opportunity, Motivation, and Behaviour Model
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRN	Clinical Research Network
CRN-EM	Clinical Research Network – East Midlands
ECRHS	European Community Respiratory Health Survey
EfH	Education for Health
eNO	Exhaled Nitric Oxide
eNOS	Endothelial Nitric Oxide Synthases
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GAN	Global Asthma Network
GCP	Good Clinical Practice
GDG	Guideline Development Group

GINA	Global Initiative for Asthma
GLI	Global Lung Initiative
GP	General Practitioner
HCA	Health Care Assistant
HDM	House Dust Mite
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
iNOS	Inducible Nitric Oxide Synthases
IRAS	Integrated Research Application System
ISAAC	International Study of Asthma and Allergies in Childhood
L	Litres
LLN	Lower Limit of Normal
LPT	Leicester Partnership Trust
MAARA	Midlands Asthma and Allergy Research Association
MDI	Metered Dose Inhaler
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung, and Blood Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NO	Nitric Oxide
NOS	Nitric Oxide Synthases
NP	Nurse Practitioner
nNOS	Neuronal Nitric Oxide Synthases
NPV	Negative Predictive Value
NRAD	National Review of Asthma Deaths
PEF	Peak Expiratory Flow
PFL	Pulmonary Function Laboratory
PIS	Patient Information Sheet
PN	Practice Nurse
PPB	Parts Per Billion

PPV	Positive Predictive Value
QOF	Quality and Outcomes Framework
RCP	Royal College of Physicians
R+D	Research and Development
REC	Research Ethics Committee
RfCQ	Readiness for Change Questionnaire
SABA	Short Acting Beta Agonist
SD	Standard Deviation
SPT	Skin Prick Test
STAT6	Signal Transducer and Activator of Transcription 6
Th2	T Helper 2
UAE	United Arab Emirates
UHA	Unplanned Healthcare Attendance
UK	United Kingdom
US	United States
WHO	World Health Organisation

STATEMENT OF WORK PERSONALLY PERFORMED

I applied for ethical approval, co-designed and amended the research protocol, and contacted potential practices to participate in this study. All initial face-to-face meetings were conducted by myself and the research nurse. I designed all data entry forms, consent forms, patient information leaflets, the spirometry and eNO training package, the readiness for change questionnaire, feedback questionnaires, and created the study database. I was responsible for the maintenance of the site files and all research paperwork in accordance to GCP and sponsor guidance.

I personally delivered at least 80% of the training to GP staff, attended at least 50% of clinics, and obtained written informed consent from at least 50% of families. The rest of training and recruitment were conducted by the research nurse. I collated all data from the readiness for change questionnaires and online practice demographics data.

I performed 20% of the data entry; the research nurse entered the rest of the data. I personally undertook all data analysis and interpretation.

PUBLICATIONS ARISING FROM THIS THESIS

Papers

Published

Lo DKH, Beardsmore CS, Roland D, Richardson M, Yang Y, Danvers L, Wilson A, Gaillard EA. Lung function and asthma control in school age children managed in UK primary care: a cohort study. Thorax. 2020;75(2):101-7.

Danvers L, Lo DKH, Gaillard EA. The role of objective tests to support a diagnosis of asthma in children. Paediatr Respir Rev. 2019.

Andrews G, Lo DKH, Richardson M, Wilson A, Gaillard EA. Prospective observational cohort study of symptom control prediction in paediatric asthma by using the Royal College of Physicians three questions. NPJ Prim Care Respir Med. 2018;28(1):39.

Lo DKH, Gaillard DE, Gaillard DB, Bullous L. Diagnosis and management of childhood asthma in primary care. Independent Nurse. 2016;2016(18):16-22.

Submitted

Lo DKH, Beardsmore CS, Roland D, Richardson M, Yang Y, Danvers L, Wilson A, Gaillard EA. Spirometry and FeNO for children's asthma in primary care: an observational study.

Lo DKH, Gaillard EA. Asthma misdiagnosis in children: Is it that common and are objective tests the solution?

Lo DKH, Beardsmore CS, Roland D, Richardson M, Yang Y, Danvers L, Wilson A, Gaillard EA. Risk Factors for Asthma Attacks and Poor Control in Children.

Abstracts

Lo DKH, Beardsmore CS, Roland D, Richardson M, Yang Y, Danvers L, Wilson A, Gaillard EA. Raised FeNO is associated with lower FEV_1 and FEV_1/FVC in children with asthma. European Respiratory Journal. 2019;54(suppl 63):PA5423.

Lo DKH, Beardsmore CS, Roland D, Richardson M, Yang Y, Danvers L, Wilson A, Gaillard EA. Spirometry, FeNO, and asthma control in children managed for asthma in primary care. European Respiratory Journal. 2019;54(suppl 63):OA5423.

Lo DKH, Beardsmore CS, Roland D, Richardson M, Yang Y, Danvers L, Wilson A, Gaillard EA. Misdiagnosis of children's asthma is common in UK primary care and can be improved with objective tests. European Respiratory Journal. 2018;52(suppl 62):PA1314.

Lo DKH, Beardsmore CS, Roland D, Richardson M, Yang Y, Danvers L, Wilson A, Gaillard EA. Asthma reviews in primary care which include spirometry lead to improved asthma control in children. European Respiratory Journal. 2018;52(suppl 62):PA5444.

Lo DKH, Harcombe N, Beardsmore CS, Roland D, Richardson M, Yang Y, Danvers L, Wilson A, Gaillard EA. High prevalence of abnormal lung function is seen in children managed for asthma in primary care. European Respiratory Journal. 2017;50(suppl 61):PA4499.

CHAPTER 1: INTRODUCTION

Asthma is the most common chronic disease of childhood, but despite this, there remains no agreed gold standard test to diagnose the condition with absolute certainty.

It is a complex, heterogeneous disorder characterised by variable airflow limitation (obstruction), bronchial smooth muscle hyper-responsiveness, and chronic inflammation; resulting from an incompletely understood interplay between intrinsic host factors and extrinsic environmental triggers.

Clinically, people with asthma complain of episodes of wheeze, breathlessness and cough, which are typically worse at night; and can be triggered by aeroallergens, viruses, exercise, or stress. Temporary relief can be obtained with inhaled bronchodilators, whilst symptom control and reduction of asthma attacks are usually achieved with regular inhaled corticosteroids.

Across many care settings, including primary care, asthma is a clinical diagnosis based on history, physical examination, and response to treatment, without evidence from objective testing. This, at least in part, may explain why misdiagnosis (both over- and under-) is increasingly recognised as a problem in adults and children.

Getting the diagnosis right in children is important because children have the highest asthma hospital admission rates of any age group, and under-diagnosis is associated with poor asthma control. In addition, inappropriate treatment of children who do not have asthma can result in increased healthcare costs, and unnecessary side effects including decreased growth velocity caused by long-term inhaled corticosteroid use.

A recent guideline issued by the UK National Institute for Health and Care Excellence (NICE, 2017) recommends the use of objective tests including spirometry and exhaled nitric oxide (eNO) testing in all healthcare settings for the diagnosis and monitoring of asthma in adults, and children from the age of five years. Implementation of these recommendations would represent a major change in the way that childhood asthma is diagnosed and monitored in

primary care in the UK, but has the potential to improve diagnostic accuracy, management, and clinical outcomes.

The resource and training requirements to provide these tests in UK primary care are not known. Furthermore, it is unclear whether making these tests available to community health providers can provide any useful additional information which would impact on their ability to manage childhood asthma.

Therefore the objectives of the CHAMPIONS (**CH**ildhood **A**sthma **M**anagement in **P**rimary care: **I**mplementation **O**f **N**itric oxide and **S**pirometry) study were two fold. Firstly, to evaluate the training and capacity requirements needed in general practice to deliver routine spirometry and eNO testing for children, and secondly to explore the additional information these tests provide and how to they relate to current symptoms and asthma attacks.

This thesis will begin with providing an overview of asthma in terms of its definition, prevalence, pathophysiology and cost to society. Following this, I will present a focused literature review looking at the extent of asthma misdiagnoses, the diagnostic tools recommended in the most recent asthma guidelines and the evidence supporting these tests. The methodology, results and discussion of findings are then presented.

CHAPTER 2: ASTHMA OVERVIEW

2.1 Definition

Asthma is a chronic condition characterised by variable airflow obstruction associated with an episodic combination of symptoms including breathlessness, wheeze, cough, and chest tightness. Different descriptions of the condition may include factors which trigger symptoms, airway hyperresponsiveness and the type of inflammatory cells involved (BTS, 2019, GINA, 2019, NHLBI, 2014, WHO, 2017).

2.2 Epidemiology

Historically, accurate estimates of asthma prevalence have been difficult to obtain due to a lack of a standardised definition or measure. Common measures for counting and defining those with asthma have included: those with asthma symptoms (wheeze, cough, night-waking etc.), people who have been told they have asthma, and those being treated by GPs for asthma. Moreover, counts based on these indicators may relate to different periods of time, ranging from “ever” to “current”.

Each of these potential definitions have different meanings and often different sources, resulting in different estimates. Ideally, to make comparisons of the prevalence of asthma between different geographical locations and periods of time, standardised measurements should be used (i.e. measurements done in the same way at different places and times).

Significant epidemiological studies with global surveillance data for asthma include the International Study of Asthma and Allergies in Childhood (ISAAC) – for children, and the European Community Respiratory Health Survey (ECRHS) and World Health Survey – for adults.

2.2.1 Prevalence

Globally, 334 million people are estimated to have asthma (GAN, 2014). In the UK, 8 million people (over 12% of the population) either have a current asthma diagnosis or have been given a previous asthma diagnosis (BLF, 2017). Although this figure is plateauing (Figure 1), asthma is still the most common respiratory condition and one of the most common chronic conditions by a considerable margin (Figure 2). According to Asthma UK, 5.4 million people are currently actively receiving treatment for asthma (www.asthma.org.uk, 2017).

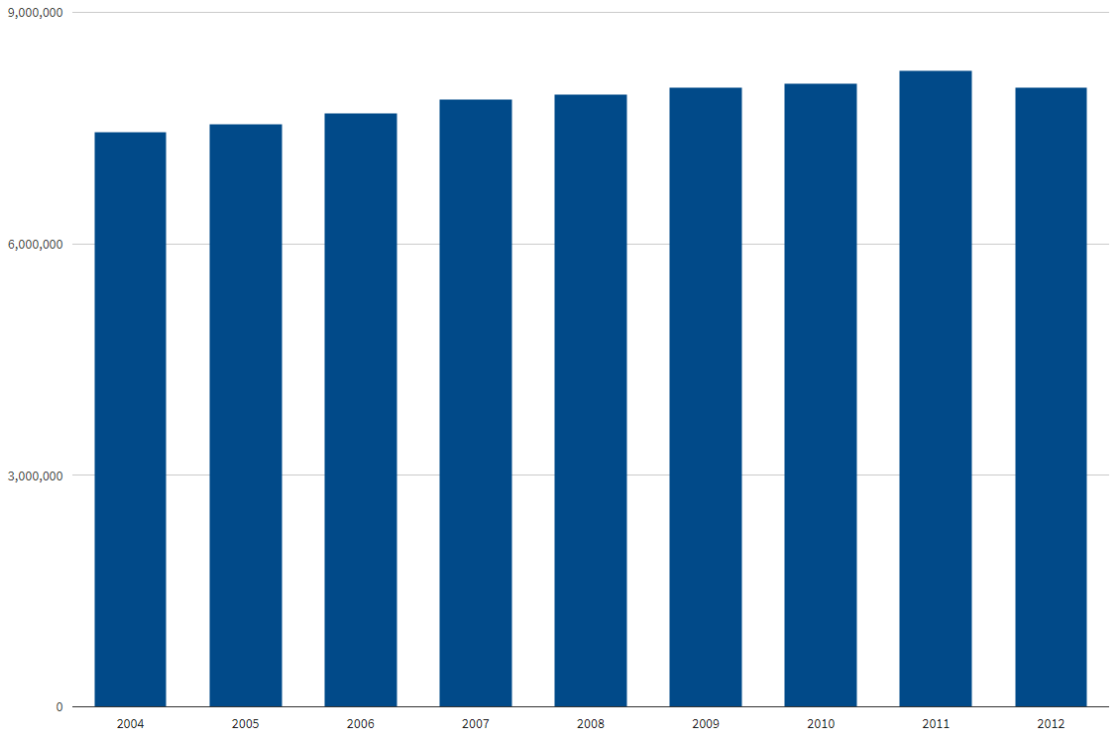


Figure 1. Estimated number of people ever diagnosed with asthma in the UK 2004-12 (Source: https://statistics.blf.org.uk/asthma)

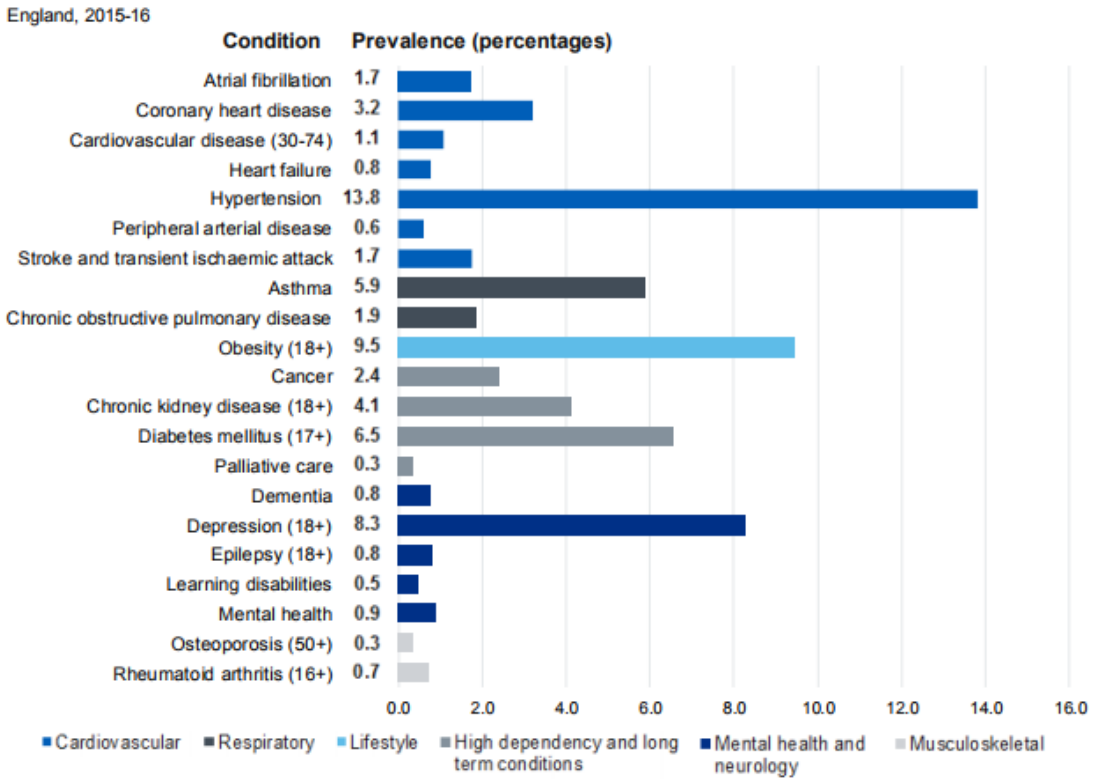


Figure 2. Quality and Outcomes Framework (QOF) Recorded Condition in 2015-16 (Source: http://www.content.digital.nhs.uk/catalogue/PUB22266/qof-1516-rep-v2.pdf)

In children, the International study of asthma and allergies in children (ISAAC) found that about 14% of the world's children were likely to have had asthmatic symptoms in the last year. This finding resulted from ISAAC surveying a representative sample of 798,685 children aged 13-14 years in 233 centres in 97 countries (a younger group of children (6-7 years) was also studied with similar findings). Importantly, the prevalence of childhood asthma varies substantially between countries (Figure 3) and within countries (Figure 4).

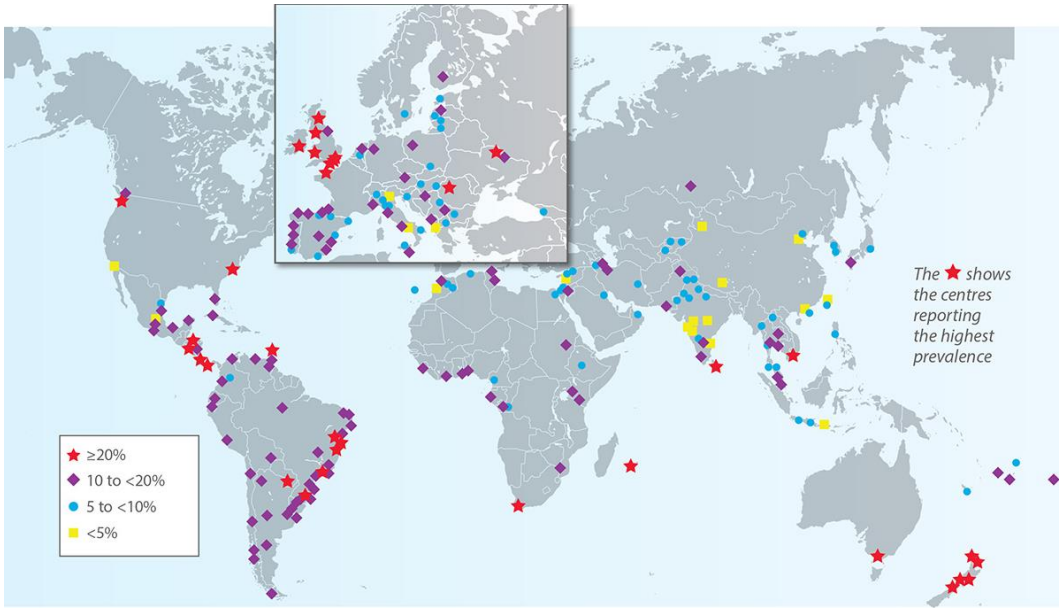


Figure 3. Prevalence of asthma symptoms among 13-14 year olds (Source: ISAAC)

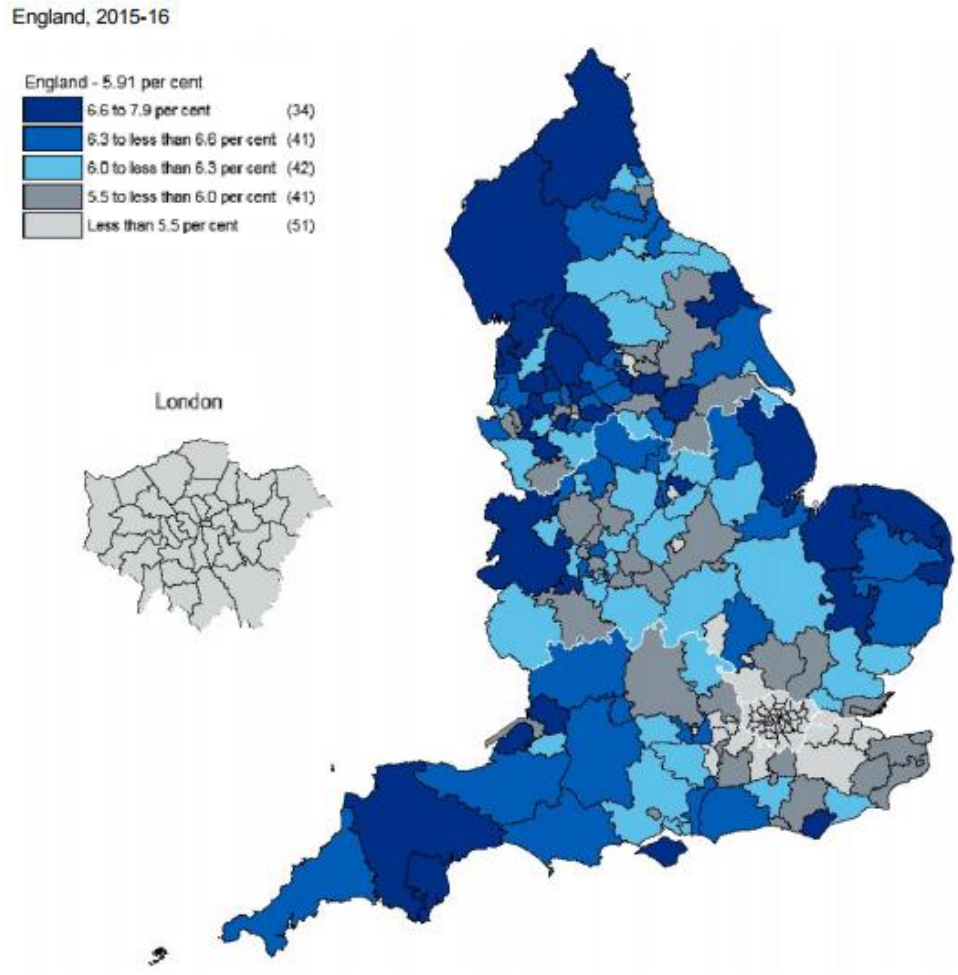


Figure 4. Asthma prevalence in England by CCG (adults and children) (Source: NHS Digital)

The traditionally held view of asthma being an illness of high-income countries is no longer appropriate, since most people affected are now from low to middle-income countries. The ISAAC team have reported the phase III results of their study (a repeat of the phase I survey after 5-10 years). They concluded that increases in the prevalence of childhood asthma in Africa, Latin America, and parts of Asia indicate that the global burden of asthma is continuing to rise, however corresponding decreases in prevalence in English speaking countries and Western Europe have meant that global differences in prevalence between countries are decreasing (Pearce et al., 2007).

2.2.2 Hospital Admissions

In the UK, asthma accounted for 60 000 acute hospital admissions and 200 000 bed days per year between 2008 and 2012 (BLF, 2017), without including those who attended the emergency department for treatment but who did not require admission (Figure 5). In the paediatric population, it is estimated that a child is admitted to hospital every 20 minutes because of an asthma attack (www.asthma.org.uk, 2017).

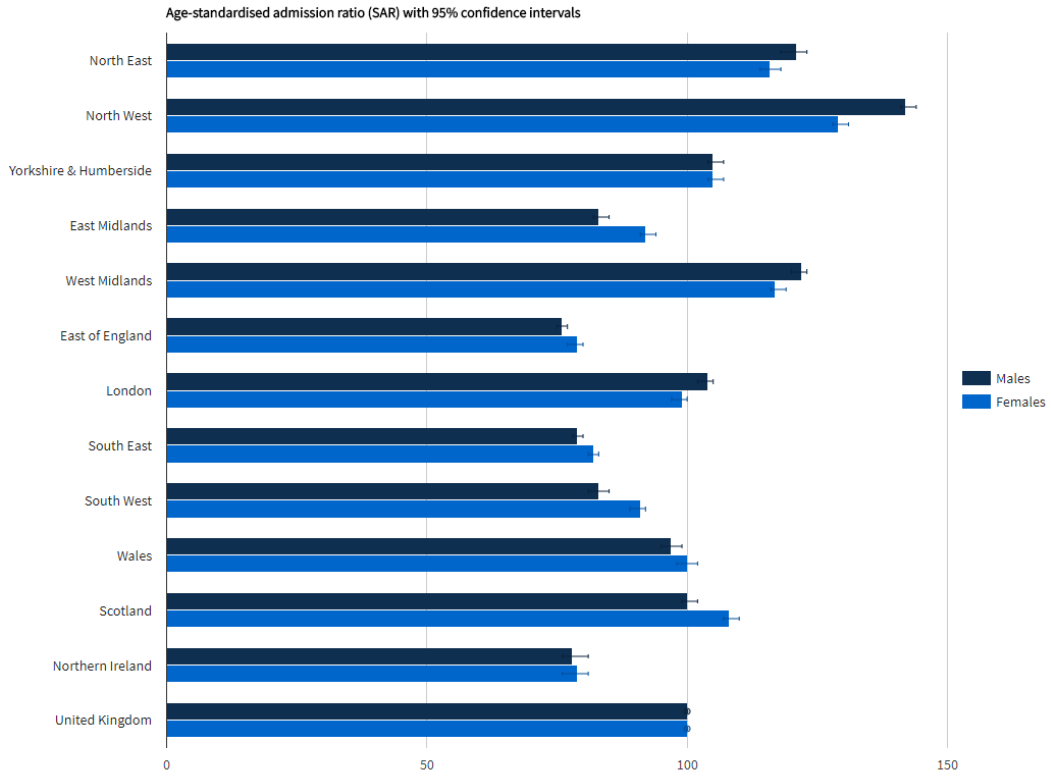


Figure 5. UK Asthma hospital admission ratios (male and female) in each UK region 2008-12 (Source: https://statistics.blf.org.uk/asthma)

International hospital admission statistics are mainly limited to high-income countries in Europe, North America and Australasia. In Europe, amongst all age groups, asthma accounts for 0.6% of all hospital admissions and 0.4% of all inpatient bed-days.

Although the rates of hospital admission for asthma has plateaued in England and Wales (Figure 6), following a steady rise between the 1950s to 1980s, the UK still has one of the highest rates of admissions among European countries (Figure 7).

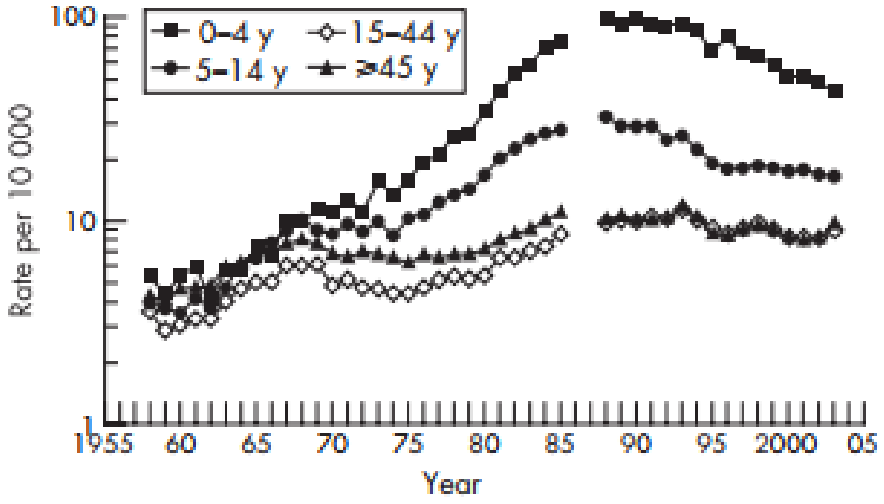


Figure 6. Hospital admissions for asthma by age, England and Wales 1958-2003 (Source: Anderson et al. 2007)

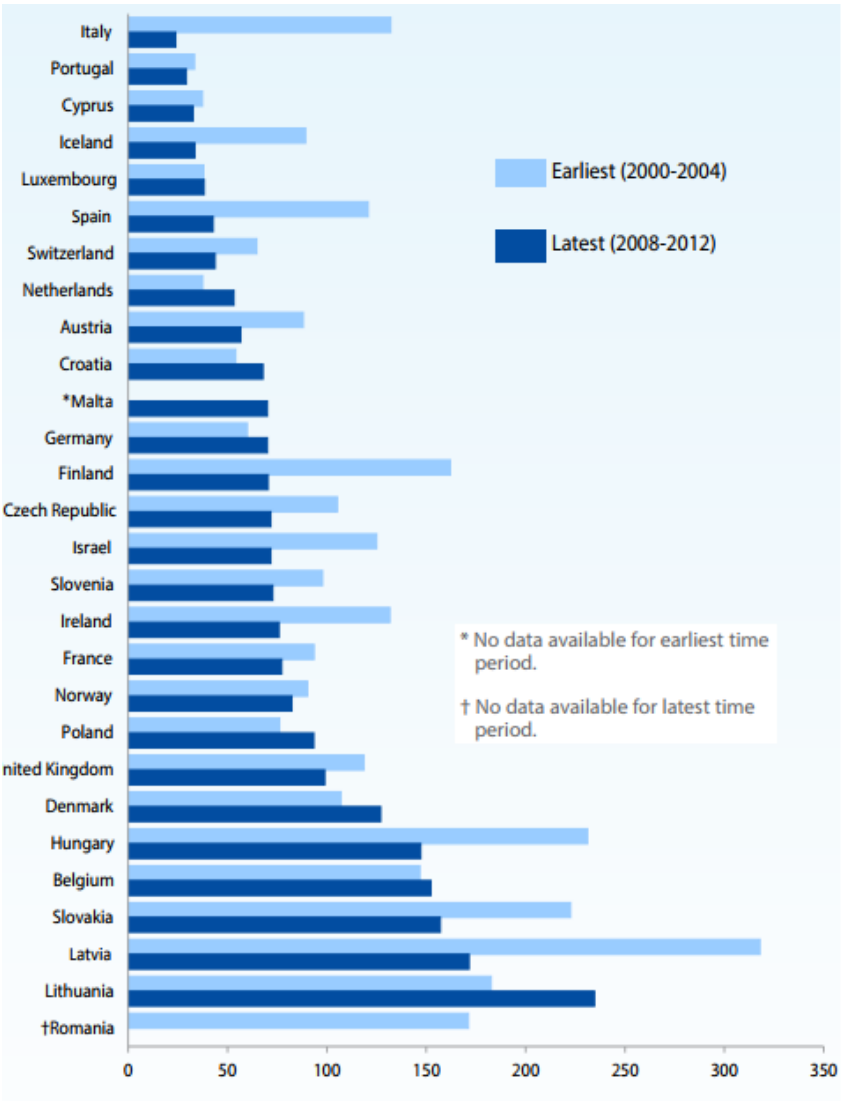


Figure 7. Age standardised admission rates for asthma for earliest and latest available year in European countries ordered by admission rate (Source: Global Asthma Report 2014)

Admission to hospital with an asthma attack may indicate the first presentation of disease or a failure of preventive care for diagnosed asthma. Either way, hospital admissions are a burden to both patients and healthcare infrastructure and represent a target for improvement in care.

2.2.3 Asthma Mortality

The number of people dying from asthma in the UK has fluctuated over the past 50 years (Figure 8), with a peak in the 1960s followed by a steady rise

from the 1980s until the mid-1990s. Even though asthma deaths have since plateaued in the UK to around 1200 people per year (RCP, 2014a), it still has one of the highest numbers of recorded asthma deaths amongst high income countries (Figure 9).

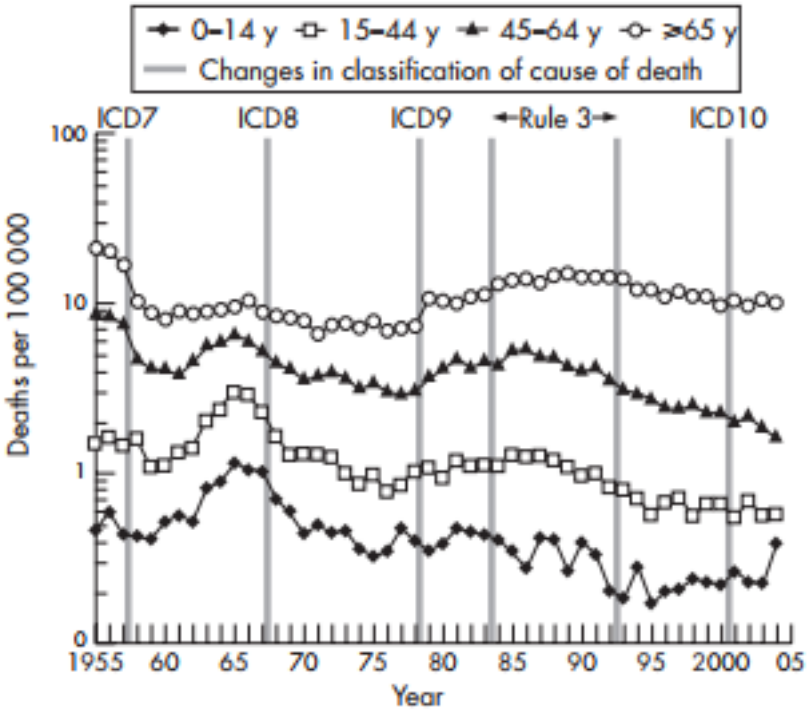


Figure 8. Mortality from asthma by age, England and Wales, 1955-2004 (Source: Anderson et al. 2007)

In a recent comprehensive review of UK asthma deaths, a number of avoidable factors were identified. The UK National Review of Asthma Deaths (NRAD 2014) reviewed 195 deaths which occurred in 2012-2013, of which 28 (14%) were young people below the age of 20. The majority of people who died from asthma (112, 57%) were not recorded as being under specialist supervision during the 12 months prior to death. Furthermore, only one-quarter had been provided with a personal asthma action plan, there was evidence of excessive prescribing of short-acting reliever medication, under-prescribing of preventer medication, and there was no evidence that an asthma review had taken place

in general practice in the last year before death for 84 (43%) of the 195 people who died (RCP, 2014b).

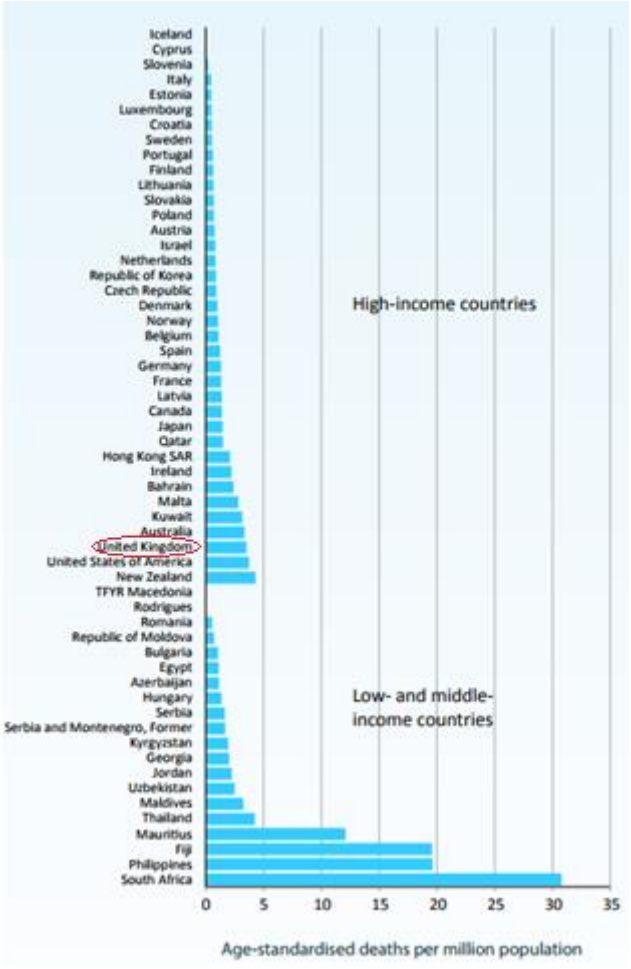


Figure 9. Age standardised mortality rates for 5-34 year olds, 2001-2010 (Source: Global Asthma Report 2014). UK highlighted in red.

2.2.4 Cost of Asthma

Economic loss because of asthma can be attributed to both direct and indirect costs. Direct costs through consumption of resources (hospitalisations, GP visits, prescribed medications) or indirectly through loss of productivity (parent taking time off work to care for unwell child). Quantifying the monetary cost attributable directly to asthma is challenging since people may have more than

one medical condition, utilise health care resources differently, and asthma itself may be over- or under- diagnosed within a population (GAN, 2014).

A recent large UK-wide study aiming to investigate the economic impact of asthma estimated an annual cost of at least £1.1 billion, with the majority arising in primary care (74%); of which community prescribing accounted for 81% of primary care expenditure (Mukherjee et al., 2016).

Globally reported annual estimated costs vary from less than US$150/patient per year in the UAE to more than US$3000/patient per year in the US (Ehteshami-Afshar et al., 2016). In Europe, recent estimates range from 1183 Euros/year in Italy (Dal Negro et al., 2016) to 580 Euros/year in Cyprus (Zannetos et al., 2017).

Importantly, asthma related treatment costs have consistently been shown to be higher (up to 3-fold) in those with severe compared to mild-moderate asthma (Barry et al., 2017, Turktas, 2014, Chastek, 2016, Sullivan et al., 2017).

In terms of indirect costs, school absenteeism for asthma in the UK is thought to account for 252 days/1000 children per year, equivalent to 2.8 million absences. Work absenteeism for asthma symptoms accounted for 79 days/1000 adults per year, equivalent to 4.1 m workdays lost (Mukherjee et al., 2016). A Canadian study estimated that a person with uncontrolled asthma would avoid CAN$185 (GBP£110 in 2017) in productivity loss over a week by achieving clinical control (Sadatsafavi et al., 2014). This is supported by a study from Singapore which found that although patients with good asthma control had higher drug costs, they also had significantly lower total asthma costs (direct and indirect) (Nguyen et al., 2017).

Potential economic savings do not only relate to improving control in those with poorly managed asthma, but also to identifying people who have been misdiagnosed with asthma. Of 540 randomly selected patients with physician diagnosed asthma in Canada, 150 (28%; 95%CI 19-37%) did not have asthma when objectively studied with lung function tests. 71% of those misdiagnosed were on some asthma medications. The study team estimated the average cost

saving per 100 individuals screened to be CAN$35,141 (95%CI $4,588-$69,278) (Pakhale et al., 2011).

Controlled asthma results in far less of an economic burden than uncontrolled asthma. Strategies aimed towards improving the way that asthma is diagnosed and monitored could potentially be effective in reducing both the direct and indirect costs of asthma in the UK.

2.3 Pathophysiology

Our understanding of the mechanism of disease in asthma has evolved over the last twenty years, allowing the development of specific treatments which can better target the dysregulated immune processes seen in asthma (Loo and Wark, 2016).

The pathophysiology of asthma is still incompletely understood, but is known to be a heterogeneous disease characterised by varying levels of bronchoconstriction, airway hyper-responsiveness, mucus hypersecretion, and chronic inflammation (Olin and Wechsler, 2014). Airway inflammation may be chronic or acute, airflow obstruction may be secondary to mucus hypersecretion or airway oedema, whilst hyper-responsiveness may present in response to numerous different exogenous and endogenous stimuli in different people. All this has led to an increasing recognition that asthma may not be a single disease state, but instead a complex of multiple phenotypes, each with its own natural history, severity and treatment response pattern (Gauthier et al., 2015). To quote the recent Lancet commission on asthma, we need to –

> "*Evolve from the use of umbrella terms to disease labels that allow for treatment guidelines to be more precise. What asthma do I have?"* (Pavord et al., 2018)

This section will provide a brief overview of our current understanding of asthma pathophysiology.

2.3.1 Inflammation

Asthma has traditionally been viewed as a Th2 lymphocyte mediated, eosinophil driven disease of airway inflammation (Gemou-Engesaeth V, 1994). However, although the presence of airway eosinophils has been shown to be present in bronchoscopic samples from children with asthma (Barbato et al., 2003), only up to 50% of all asthma cases are thought attributable to eosinophilic airway inflammation (Douwes J, 2002).

Adult studies suggest that patients may fall into one of several phenotypic and inflammatory profile clusters: 1) early onset disease with prominent T helper type 2 cell (Th2) activation, high levels of eosinophils, mast cells, IgE and exhaled nitric oxide levels (eNO), 2) late onset asthma with absence of other allergic diseases, Th2 pathway and eosinophils predominate, 3) exercise induced 4) minimal Th2 pathway involvement and associated with obesity, and 5) minimal Th2 response with sputum neutrophilia (Wenzel, 2006, Carolan and Sutherland, 2013).

Likewise, in children, asthma is not a single phenotype but appears to be heterogeneous (Just et al., 2014). Attempts at clustering children into different asthmatic phenotypes have similarly identified distinct groups based on disease severity, lung function, presence of atopy and degree of eosinophilic inflammation (Cabral et al., 2017, Chang et al., 2014, Fitzpatrick et al., 2011, Just et al., 2014).

Whilst phenotypes can describe the visible characteristics of asthma, in terms of clinical, physiological, biochemical, and treatment response, they do not necessarily describe the underlying disease process. An emerging concept in asthma is that of the “endotype”, which is proposed to be a subtype of asthma defined by a distinct functional or pathophysiological mechanism (Lotvall et al., 2011).

Different asthma endotypes show variable degrees of inflammation, bronchial hyper-reactivity, mucus production, and remodelling (Olin and Wechsler, 2014), which are mediated by different cells and cell signalling molecules.

2.3.2 Airway inflammation and asthma control

The relationship between airway inflammation and clinical control is not straightforward, however people with uncontrolled asthma generally appear to have evidence of raised Th2 inflammatory biomarkers compared to people with good control (Tillie-Leblond et al., 2009). Previous studies in children with diagnosed asthma have reported that poor symptom control is associated with higher eNO levels compared to in children with good symptom control, however the correlation between eNO and asthma control scores were low, and demonstrated significant overlap (Lee et al., 2019, Piacentini et al., 2009). In adults, increased sputum eosinophils, but not eNO, is reportedly associated with poor symptom control (Quaedvlieg et al., 2009); however, sputum eosinophils cannot be reliably used to distinguish between patients with controlled and uncontrolled asthma (Pavord, 2009).

2.3.3 Inflammation and risk of attacks

The link between airway inflammation and the risk of an asthma attack in children is similarly unclear. In a recent meta-analysis, which combined the individual patient data from seven randomised controlled trials where eNO was used to guide asthma treatment in children, a 50% increase in eNO from baseline at three months was associated with an increased risk of loss of asthma control but not with asthma attacks (Fielding et al., 2019).

Nevertheless, indirect evidence from clinical trials involving biological therapies would suggest that Th2 inflammation is related to future risk of attacks. Trials of therapies targeting IgE (Busse et al., 2001), IL5 (Gupta et al., 2019), and IL4 and IL13 (Wenzel et al., 2013) have all demonstrated improvements in asthma control, and reduction in asthma attacks during follow up. Moreover, a systematic review of studies which evaluated the efficacy of eNO-directed asthma management in children versus management without the use of eNO, reported a significant reduction in the number of asthma attacks in the eNO-directed treatment group but found no difference in clinical control (Petsky et al., 2016b).

The role of airway inflammation, though substantiated, appears to vary considerably between asthma patients. Although it is estimated that only approximately 50% of patients with asthma exhibit a Th2 endotype (Woodruff et al., 2009) , Th2 inflammation appears to play an important role in both the pathophysiology and the clinical presentation of patients with asthma.

These phenotypic and endotypic differences may determine treatment response and highlights the importance of accurate diagnosis and workup.

2.3.4 Hyper-responsiveness

Airway hyper-responsiveness (AHR) describes an exaggerated response to exogenous or endogenous stimuli, and can be defined as the predisposition of the airways of patients to narrow excessively in response to triggers that would produce little or no effect in healthy people (Chapman and Irvin, 2015) (Figure 10).

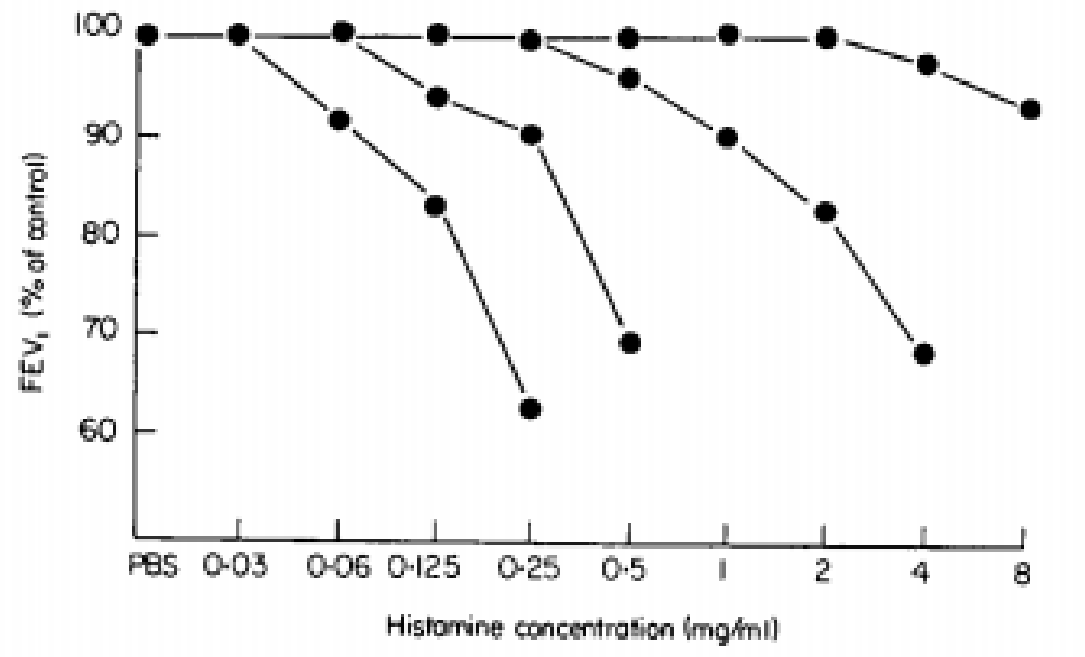


Figure 10. Histamine challenge dose response curve in a person without asthma (far right) and three people with asthma (source: Cockcroft 1977).

Due to the multitude of pathophysiological changes associated with asthma, there is still uncertainty surrounding the mechanisms underlying AHR. Given its key role in asthma, inflammation is thought to play a part. Indeed, severity of AHR has been positively correlated with the number of sputum eosinophils (Porsbjerg et al., 2013, Kirby JG, 1987), and the number of mast cells (Brightling et al., 2002) in airway smooth muscle. However, studies on the relationship between AHR and airway inflammation are not always in agreement (Brusasco et al., 1998) and the underlying mechanisms are unlikely to be due to active inflammation alone.

Abnormal smooth muscle (ASM) function would seem to be another obvious candidate cause for excessive bronchial hyperresponsiveness. Although evidence has not been conclusive, the rapid bronchoconstrictor response, and its subsequent reversal with bronchodilators, seen during bronchial challenge testing suggests that ASM contraction is involved (Berend et al., 2008). AHR may be abnormal due to *intrinsic* abnormalities of the ASM itself or to the *extrinsic* pro-inflammatory asthmatic environment it inhabits.

As a diagnostic tool, bronchial provocation tests are used to assess the presence of AHR, and can be clinically useful aids to help diagnose asthma in people with a suggestive clinical history but normal spirometry (Brannan and Lougheed, 2012).

Whilst for asthma monitoring, studies comparing treatment strategies using AHR to monitor asthma against strategies using guideline recommendations alone have reported a reduction in asthma exacerbations and improvement in pre-bronchodilator FEV_1 in adults (Sont et al., 1999), and improvement in pre-bronchodilator FEV_1, but not symptoms, in children (Nuijsink et al., 2007).

Although airway hyper-responsiveness may have a role in asthma diagnosis, classification of severity, and monitoring, it is associated with variable phenotypes, and different underlying mechanisms between patients. It is therefore important to recognize that the severity, and even presence, of AHR is not stable (Chapman and Irvin, 2015).

2.3.5 Airway remodelling

Airway remodelling is the term used to describe the collective structural changes that are associated with asthma.

Chronic inflammation in asthmatic airways can eventually lead to irreversible airway remodelling and fixed airway obstruction, with increasingly prominent changes as the disease takes on a more severe and chronic phenotype (Cho SH, 1996). Of note, changes are associated with disease severity and not duration, as thickening of the basement membrane has been noted even in preschool children with recurrent wheeze (Saglani et al., 2007).

Overall, these structural changes alter the protective functions of the airways by affecting mucociliary clearance and increase the risk of infections and exacerbations (Bonsignore et al., 2015, Thomas et al., 2010).

2.3.6 Pathophysiology and Lung Function Testing

The differing endotypes and phenotypes by which asthma can present makes both asthma diagnosis and asthma monitoring difficult. However, non-invasive outpatient based tests, such as spirometry and bronchodilator reversibility testing, provides a useful means to identify variable airflow obstruction and bronchial lability resulting from the mechanisms described above; and eNO measurements can provide indirect evidence for the presence of eosinophilic airways inflammation (discussed in more detail later). When used together, it is thought that spirometry and eNO testing can assist clinicians to diagnose asthma more accurately, and potentially improve the way in which asthma in children is monitored. However, there is limited evidence to justify their routine use in children in the community setting.

CHAPTER 3: ASTHMA DIAGNOSIS AND MONITORING

3.0.1 Asthma Diagnosis

Many doctors consider the diagnosis of asthma to be a clinical one and opinions differ on how a diagnosis should best be confirmed. The absence of a consistent and accepted gold-standard diagnostic criterion means that it is not possible to make unequivocal evidence-based recommendations on how to make a diagnosis of asthma in children or adults (BTS, 2019).

However, recent published guidelines (BTS, 2019, GINA, 2019, NAEPP, 2007, NICE, 2017) are generally in agreement that diagnosis based on symptom history alone is inadequate.

Both the National Asthma Education and Prevention Program (NAEPP, 2007) expert review panel report and latest Global initiative for asthma (GINA, 2019) guideline recommends that a diagnosis of asthma should be made on the basis of episodic symptoms consistent with asthma, exclusion of an alternative diagnosis AND objective evidence of airflow obstruction reversibility with SABA or over time.

The BTS guideline (BTS, 2019) takes a more pragmatic approach and recommends using a structured clinical assessment (Figure 11) to stratify patients as having a high, intermediate or low probability of asthma. Historical records of objective tests (FEV_1 or PEF) are listed as part of the structured review, but not mandated unless there is only an intermediate probability of asthma.

In children with a high probability of having asthma, a trial of treatment is suggested (without the need for objective testing) but response should be assessed objectively either with lung function (ideally FEV_1) or a validated scoring system. Those with a good response to treatment can be documented as confirmed asthma without further testing. Spirometry and reversibility testing are recommended first-line for those with an intermediate or low probability where other diagnoses have been excluded.

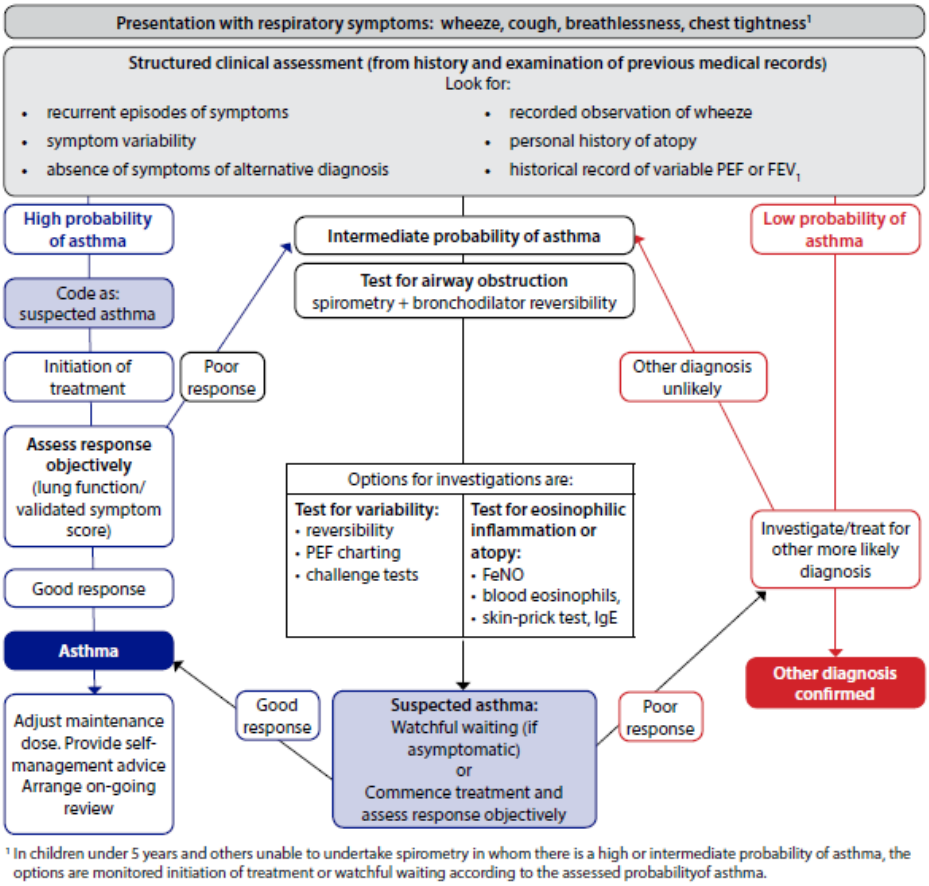


Figure 11. BTS 2019 Asthma Diagnosis Guideline

By contrast, the 2017 NICE guideline (NICE, 2017) advocates stricter criteria for diagnosis, stating that not only should an asthma diagnosis NOT be made based on symptoms alone, but also not based on any single test. The proposed paediatric diagnostic algorithm, which would apply across health sectors, specifies the use of spirometry, bronchodilator reversibility, exhaled nitric oxide (eNO) and peak flow (PEF) variability over 2-4 weeks as the first line objective tests (Figure 12) to help confirm a diagnosis.

3.0.2 Asthma Monitoring

In terms of asthma monitoring, there is broad consensus on the need to assess both current asthma control and the future risk of adverse asthma related outcomes (BTS, 2019, GINA, 2019, NAEPP, 2007, NICE, 2017). Whilst the

BTS asthma guideline does not specifically recommend the need for regular objective tests as part of monitoring, both the NAEPP and GINA guidelines recommend using spirometry to inform future risk. The NICE guideline development group (GDG) also agreed that spirometry should be the preferred objective test measured at every asthma review; however, as no evidence was identified comparing monitoring using spirometry versus PEF in general practice, the GDG made the consensus recommendation that either spirometry or PEF should be measured at every review to monitor control in children from the age of five years. No guideline recommend the use of eNO as part of asthma monitoring.

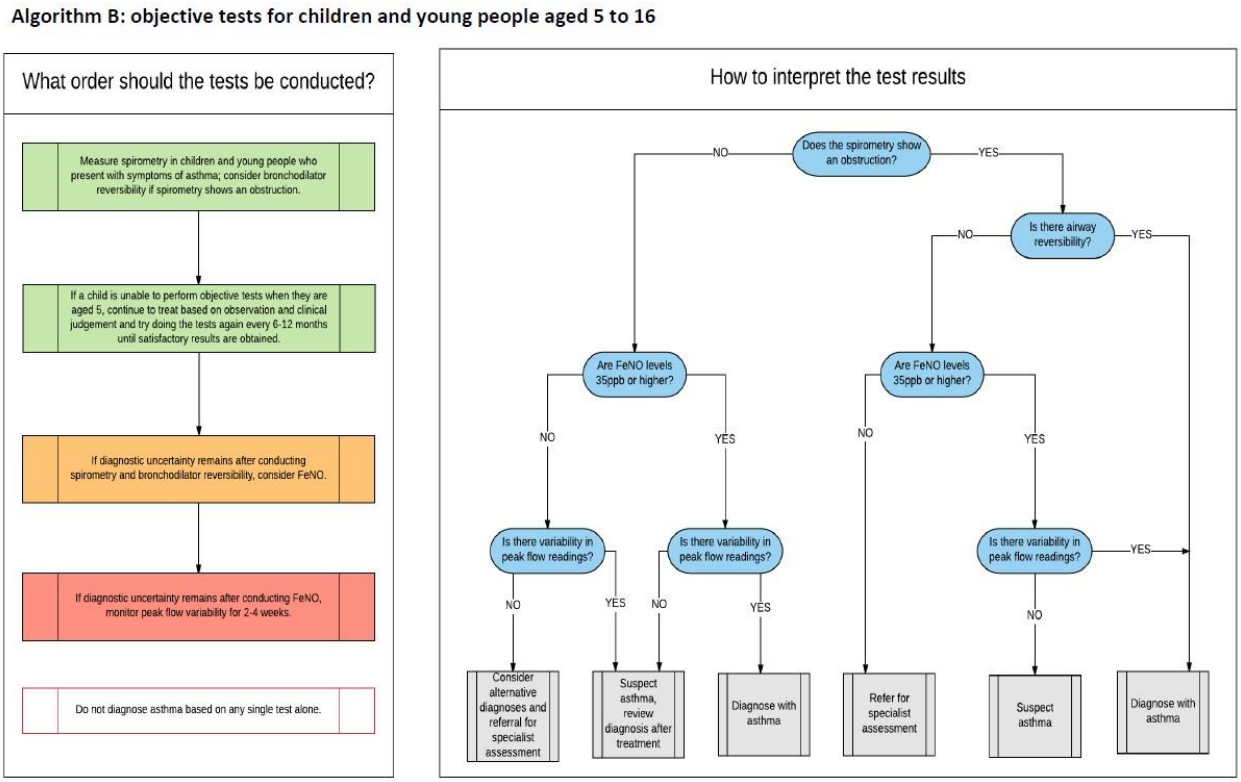


Figure 12 – NICE asthma diagnostic algorithm for children aged 5-16

Although on face value there are some key differences between these guidelines, particularly between the two main UK guidelines (NICE, 2017, BTS, 2019); under closer scrutiny, they share much in common (White et al., 2018).

This is chiefly because they broadly share the same evidence base, and any differences in recommendations are a result of differences in how the evidence is interpreted and the onus placed on health economics versus clinical efficacy. One key message from all four guidelines is that accurate diagnosis and monitoring of asthma is not straightforward, and no single test or measure can be relied upon on its own. Hence the multiple tiers of objective testing recommended by the latest NICE asthma guideline for diagnosis.

The potential implications for implementing this guideline into routine general practice has raised concerns amongst GP stakeholders (NICE, 2013, Nash, 2015, Price, 2015, Price, 2017), particularly on the issues of cost, training, clinic burden and clinical usefulness.

The following sections will present findings from a focused literature review to summarise the available evidence regarding the prevalence of asthma misdiagnosis in children, the evidence for the use of spirometry and eNO in asthma diagnosis and in asthma monitoring, and their current role in primary care. Finally, I will discuss some of the challenges and controversies in using objective tests for asthma diagnosis and monitoring.

3.1 Asthma Misdiagnosis

Studies from the 1980s and 1990s have reported under-diagnosis of asthma in children and adults in the UK and Europe (Frank P, 1996, Speight ANP, 1983, Siersted et al., 1998). Thirty years on, it might be assumed that recognition and correct diagnosis of asthma will have improved. Indeed it has been argued that asthma is now diagnosed too readily and that over-diagnosis, not under-diagnosis, has become the problem (Bush and Fleming, 2016).

A number of studies from the past 20 years have attempted to quantify the prevalence of asthma misdiagnosis. Only a few studies have concentrated on reporting misdiagnosis in children (Table 1), with most studies focused on asthma misdiagnosis in adults (Table 2).

Adult studies have reported overdiagnosis rates of 26-56% (Aaron et al., 2008, Heffler et al., 2015, Jain et al., 2015, Scott et al., 2012, Aaron et al., 2017, Heffler et al., 2018, LindenSmith et al., 2004). All seven studies, from Europe and North America, employed objective lung function tests (including spirometry, BDR, and bronchoprovocation tests) to confirm or reject a diagnosis of asthma.

Interestingly, even though over-diagnosis of asthma was found to be common amongst obese adults (Scott et al., 2012), the rate of misdiagnosis was not found to be different between obese or non-obese adults (Aaron et al., 2008). A greater proportion of adults who had asthma excluded were found to be on regular asthma medications compared with those who had asthma confirmed; suggesting that over-diagnosis may also lead to over treatment (Heffler et al., 2015), presumably because symptoms do not go away when patients are given asthma medications incorrectly and thus are not weaned off. Importantly, a lack of spirometry testing has been identified as an independent risk factor for asthma misdiagnosis (Jain et al., 2015).

There were however a number of limitations to these studies (summarised in Tables 1 and 2) and the reported over-diagnosis rates are likely overestimated. Each study was subject to a degree of selection bias, potentially favouring a cohort of patients in whom a diagnosis of asthma was less certain.

Two studies (Heffler et al., 2015, Heffler et al., 2018) excluded asthma based on a single objective test only. Since there is no single test for asthma with a 100% sensitivity, this criterion was likely to have excluded patients with controlled asthma at the time of testing. Similarly, two studies excluded asthma using multiple tests (LindenSmith et al., 2004, Scott et al., 2012) however, these tests were performed at a single time point only and may have inappropriately excluded asthma in patients who were well controlled on medications, or who were in remission at the time of testing.

Three studies adopted a study protocol which performed sequential lung function testing whilst weaning off asthma medications until asthma was either confirmed or excluded (Aaron et al., 2008, Aaron et al., 2017, Jain et al., 2015).

These studies reported over-diagnosis rates of 26 to 33%. Two of these studies also included a follow up period of 6 to 12 months for participants in whom asthma had been excluded and medications stopped. In the 2008 Canadian study (Aaron et al., 2008) 34.5% of participants resumed their asthma medications during a mean follow up period of 7.5 months, and 7.7% had an unscheduled healthcare visit with respiratory symptoms. Whilst, on repeat objective testing, the 2017 Canadian study (Aaron et al., 2017) reported positive methacholine challenge tests in 11% of their cohort during follow up after asthma medications were stopped. These studies highlight the challenge of excluding a diagnosis of asthma even when a structured protocol including repeat objective testing is used.

In children, a 2016 Dutch primary care study (Looijmans-van den Akker et al., 2016) reported that 53% of children were likely to have been misdiagnosed as having asthma; leading to headline claims of “up to half a million [British] children with asthma may not actually have the condition” (Knapton, 2016). The children from this study did not undergo a rigorous protocol of objective testing (diagnosis was excluded on the basis of electronically recorded symptom history and medication usage), and the majority of children included in the over-diagnosis category, were actually classified as “asthma unlikely” and included those who were prescribed up to two short acting bronchodilator inhalers per year. These may include those who either had mild intermittent asthma symptoms only, or those who did not seek medical reviews appropriately, thus overestimating the rate of over-diagnosis. However, a previous UK epidemiological study also found no evidence of bronchial hyper-responsiveness in 50% of children with GP diagnosed asthma (Cornish et al., 2014), providing some objective support for the Dutch study.

Underdiagnosis rates of 19-70% have been reported in adult studies from Europe, Australia, and Colombia (Table 2), with figures for adults above 64 years of age increasing to 80% (Gonzalez-Garcia et al., 2015). Of note, whilst most studies have addressed physician misdiagnosis only, Van Schayck et al. (2006) also recruited participants who hadn’t previously sought medical help for respiratory symptoms. Only 34% of their cohort who had both history and

objective lung function test results suggestive of asthma had consulted a GP. This suggests an under-presentation rate of 66% of asthma patients and highlights an important area to target beyond improving clinical diagnosis pathways alone.

All five studies were cross sectional in design and participation was voluntary. Selection bias is possible for participants with symptomatic but unconfirmed asthma, which may overestimate the rate of underdiagnosis.

In two studies (Gonzalez-Garcia et al., 2015, Magnoni et al., 2015) asthma diagnosis was based on responses to questionnaire data, which is subject to recall bias and may over- or underestimate the prevalence of asthma amongst their study population. Although Gonzalez-Garcia *et al.* included FEV_1/FVC ratio ≥ 70% as part of their definition for asthma (to exclude COPD); this may have included healthy adults with no respiratory condition at all.

Van Schayck and colleagues' defined asthma based on clinical history and low FEV_1, but did not test for airflow reversibility. Differentiating between asthma and COPD in adults can be difficult, and their definition for asthma may have included those with COPD and not asthma.

Two studies (Adams et al., 2003, Backer et al., 2007) used tests for variable airflow obstruction (BDR or methacholine challenge) as part of their research protocol. These studies reported the rate of underdiagnosis in the range of 19 to 51%. However, a pre-existing physician diagnosis of asthma was based on participant self-reporting which may not be accurate and result in over-or underestimates of underdiagnosis.

In children, underdiagnosis rates of between 24-50% have been reported (Brozek et al., 2013, Oluwole et al., 2017) in studies from Poland and Nigeria. Oluwole and colleagues diagnosed asthma based on questionnaire data only and may have overestimated the prevalence of asthma and rate of underdiagnosis. Although the Polish study (Brozek et al., 2013) included objective tests to confirm asthma, these tests were only performed in a subgroup of participants following initial screening by questionnaire. A higher proportion of children reporting asthma symptoms but no diagnosis took part in

clinical testing compared with children with an existing diagnosis. This would bias the cohort in favour of those with an unclear asthma diagnosis.

Importantly however, children with undiagnosed asthma were found to have poorer symptom control (Annesi-Maesano et al., 2012) compared with those with a pre-existing physician diagnosis.

Few studies have actively sought to identify the prevalence of both under- and over- diagnosis of asthma. A 2013 Dutch study recruited 86 obese adult patients undergoing pre-operative assessment for bariatric surgery, with or without physician diagnosed asthma. All patients underwent clinical assessment, spirometry, bronchodilator reversibility and methacholine challenge testing. Confirmed asthma was defined as presence of asthma symptoms and either positive response to reversibility or challenge testing. Over-diagnosis was reported in 41% of adult patients, and under-diagnosis in 31%. At least in obese adult patients, asthma diagnosis cannot be made on symptoms alone (van Huisstede et al., 2013).

A similar study was published in 2017 involving a Canadian paediatric cohort. Two-hundred and three children (9-12 years) were recruited from the community, either with or without an existing asthma diagnosis. Again, each child underwent clinical assessment, spirometry, reversibility and methacholine challenge testing. Over-diagnosis was found in 45% of children and under-diagnosis in 10%. Notably, only 18% of the cohort had undergone previous lung function testing (Yang et al., 2017).

Neither of these studies included a follow up period for their patients to see if asthma symptoms or abnormal lung function recurred over time following exclusion of asthma and stopping of treatment. Moreover, enrolment in the adult study was only 39% of eligible participants, potentially biasing the cohort towards those with an unclear or questionable diagnosis.

Reported asthma misdiagnosis rates in both adults and children vary considerably between studies, and confounded by limitations in study designs, particularly from selection bias or testing at a single time point only. Even when asthma is excluded on the basis of normal repeated objective testing,

recurrence during follow up is possible. However, despite these limitations, the multiple reports of asthma misdiagnosis from a large number of studies would suggest that misdiagnosis is a significant and genuine problem.

Table 1. Paediatric Studies Reporting Asthma Misdiagnosis				
Study	**Details**	**Reference Standard for asthma diagnosis**	**Main Findings**	**Notes**
Overdiagnosis Reported				
Looijmans-van den Akker 2016	Setting: Primary care, Netherlands Design: Retrospective analysis of medical records. Children classified as overdiagnosed if they had an existing asthma diagnosis label, but who fell into the "unlikely" or "no asthma" categories of reference standard. Population: 652 children aged 6-18 years with diagnosis of asthma or on chronic inhaled asthma medications	Confirmed: recurrent symptoms with reversible airflow limitation confirmed by spirometry +/- histamine challenge Probable: suggestive history or taking regular asthma medications (no objective testing) Unlikely: no symptoms and on little or no medications (no testing) No asthma: asthma excluded by pulmonary specialist based on history and lung function tests	**Overdiagnosis** reported in 349 (**54%**) children: 391 classified as "unlikely asthma", and 5 as "no asthma"	Exclusion of asthma was based on review of primary care medical records only, with no direct assessment of the patient. Only five patients had asthma excluded following lung function testing. Children in "unlikely asthma" category included those prescribed up to two SABA inhalers per year. Therefore, overdiagnosis likely overestimated as many of these children may have mild intermittent symptoms or have not sought medical reviews appropriately.
Underdiagnosis Reported				
Brozek 2013	Setting: Random sample of primary school children from Poland Design: Cross sectional study using questionnaires to screen for children with self-reported "asthma diagnosis", "respiratory symptoms but no asthma diagnosis", and "no symptoms and no diagnosis". A subgroup	Confirmation of asthma by pulmonologist blinded to the questionnaire data, based on clinical history and spirometry +/- indirect challenge test.	From questionnaire, 5.4% of cohort reported asthma diagnosis. Based on further clinical evaluation, prevalence of asthma estimated at 10.8%.	Participation in clinical assessment following the questionnaire was voluntary, with a higher proportion of children attending from the "respiratory symptoms but no diagnosis group." Selection bias leading to potential overestimate of underdiagnosis rate amongst general population

	of children were then invited for further evaluation. Population: 1822 children aged 6-12 years completed the questionnaire. A subgroup of 456 children completed further clinical evaluation.		Therefore, **underdiagnosis rate of 50%** reported by authors.	
Oluwole 2017	Setting: Sample of children from 16 schools in Rural Nigeria Design: Cross sectional study using modified ISAAC questionnaire Population: 1690 school pupils aged 6-21 years.	Physician-diagnosed asthma was defined as a positive response on the questionnaire to: 1) child had a history of physician-diagnosed asthma, 2) child had any episode of asthma in the past 12 months, and 3) child had taken prescribed asthma medication in the past 12 months. Possible asthma was defined as a positive response to wheeze or whistling symptoms in the chest, dry cough, and activity limitation, but who had never been diagnosed with asthma by a physician or other health professional.	Based on the questionnaire responses, 2.2% of children had diagnosed asthma, and 24.4% had possible asthma. Authors concluded that difference found between diagnosed and possible asthma suggests **underdiagnosis.**	Study limited by use of questionnaires only to establish diagnosis of asthma without a formal clinical assessment and without use of objective testing. Prevalence of possible asthma likely overestimated.
Both Over- and Underdiagnosis Reported				
Yang 2017	Setting: Community based cohort in Toronto, Canada. Design: Nested case control study. Subjects recruited randomly from 231 public schools who had originally participated in a population based cohort study.	Asthma was diagnosed if the participant had both a positive clinical diagnosis and objective evidence of reversible airway obstruction (either a positive methacholine challenge or a significant bronchodilator response).	Of the 203 participants, 102 had a parent-reported diagnosis of asthma, 52 were symptomatic controls, and 49 were asymptomatic controls.	Underdiagnosis Rate of underdiagnosis was lower in this study compared to other reports. This study only included children aged 9-12 years. Asthma may be more difficult to diagnose in children at the extremes of childhood.

	Three groups were recruited. Based on questionnaire data: asthma cases had a parental report of physician diagnosed asthma, symptomatic controls had respiratory symptoms without a diagnosis of asthma, and asymptomatic controls had no respiratory symptoms. All participants assesses by asthma physician (before testing) and performed the following tests: spirometry, methacholine challenge test and allergy skin prick testing. Population: 203 children aged 9-12 years.	If the objective tests were normal, asthma was excluded.	Of the 197 subjects with complete data, **overdiagnosis** was reported in **45%** of participants with parent reported physician diagnosis, and **underdiagnosis** in **10%** of the symptomatic control group. All subjects in the asymptomatic control group were correctly classified.	Study conducted in higher income population with better access to healthcare. Overdiagnosis Asthma was excluded on the basis of objective tests performed at a single point in time, and children were electively invited i.e. not presently acutely unwell. Due to the variable nature of asthma, a normal test result may be a result of a participant with asthma being well controlled. Excluding asthma based on objective tests alone is likely to overestimate the rate of overdiagnosis.

Table 2. Adult Studies Reporting Asthma Misdiagnosis				
Study	**Details**	**Reference Standard for asthma diagnosis**	**Main Findings**	**Notes / Limitations**
Overdiagnosis Reported				
Aaron 2008	Setting: Community based cohort in Canada Design: Longitudinal cohort study of adults with physician diagnosed asthma. Cohort divided in obese and non-obese participants based on body	A diagnosis of current asthma excluded if participant had no acute worsening of symptoms, reversible airflow obstruction, or bronchial hyperresponsiveness despite weaning off asthma medications.	**Overdiagnosis** of asthma was reported in 31.8% of obese and 28.7% of non-obese participants. No significant difference between	During follow up, 34% of patients in whom asthma had been excluded, needed to recommence asthma medications. 7.7% had an unscheduled healthcare visit due to respiratory symptoms. Of the 9282 potential participants identified, only 540 agreed to participate,

	mass index. The study protocol involved sequential visits where spirometry, bronchodilator reversibility testing, and methacholine challenge tests were performed. Visits continued until patients weaned off medications or asthma was confirmed based on a positive test result or worsening of symptoms during weaning of medications. Population: 496 adults selected by random-digit dialling		rate of overdiagnosis between groups.	and 496 completed the study. This may bias the cohort, selecting for those where the diagnosis of asthma was in doubt.
Aaron 2017	Setting: Community based cohort in Canada Design: Prospective cohort study of adults with self-reported physician diagnosed asthma within past 5 years. All participants assessed with home PEF and symptom monitoring, spirometry, and serial methacholine challenge tests. Medications were tapered off over 4 study visits. Patients with asthma excluded were followed up for 12 months with repeat symptoms assessment and challenge testing at 6 and 12 months. Population: 613 adults selected by random-digit dialling	Current asthma excluded if participant had no acute worsening of symptoms, reversible airflow obstruction, or bronchial hyperresponsiveness despite weaning off asthma medications, and after an alternative diagnosis established by pulmonologist.	Current asthma excluded in 203 (33.1%) participants suggesting **overdiagnosis**. After 12 months follow up, 181 (29.5%) continued to have no clinical symptoms or objective evidence of asthma	24 out of 203 (11.8%) participants where asthma excluded, had previous objective evidence of asthma. 22/203 (10.8%) had positive challenge test during follow up. Only 68.3% of eligible participants consented to take part in the study, introducing selection bias.

Heffler 2015	Setting: Allergy clinic in Italy Design: Retrospective study of adults referred by GP with suspected asthma but who had normal baseline spirometry. All had methacholine challenge testing. Population: 226 adults	Positive methacholine test	56.2% had negative challenge test. 51.2% of these participants were already on asthma medications. **Overdiagnosis** suggested in significant proportion but not quantified	Methacholine test performed at single point in time only and half of participants with negative result were on asthma medications. These patients may be well controlled on their medications or in remission and not necessarily overdiagnosed. Cohort excluded those with abnormal spirometry, therefore selecting for patients with better lung function. Also, cohort included only patients who were referred from their GP where an asthma diagnosis was unclear, introducing selection bias.
Heffler 2018	Setting: Lung function hub in Italy Design: Prospective study of the first 300 patients referred to the lung function hub by their GP. Spirometry and bronchodilator reversibility were measured. Population: 300 adults aged 16-87 years referred for lung function testing by their GP	Asthma diagnosis supported by positive bronchodilator reversibility.	128 out of 300 participants had existing doctor-diagnosed asthma. 89 out of 128 (69.5%) had objective evidence to support asthma. **Overdiagnosis** suggested in significant proportion but not quantified	Asthma confirmed on basis of significant BDR, but this test has low sensitivity. Test only performed at single time point. Included patients which were referred for lung function testing by their GP. Potential selection bias of patients with more unclear diagnosis.
Jain 2015	Setting: Medical centre in California, USA Design: All participants underwent baseline spirometry and BDR testing. If no evidence of airflow obstruction, asthma	Asthma or COPD diagnosis confirmed by two pulmonologists based on history and evidence from objective testing.	Overall **overdiagnosis** for asthma and COPD reported in 26% of participants.	Unclear from manuscript on proportion with overdiagnosis of asthma versus COPD. No follow up period after asthma treatments discontinued to identify relapse of symptoms and/or airflow limitation.

	medications were tapered off and serial spirometry performed over an average of 10 months. Methacholine challenge was performed if diagnosis remained in doubt. Population: 333 adults with physician diagnosed asthma or COPD with history of two or more ED or hospitalisations in previous 12 months			
Scott 2012	Setting: Secondary care, UK Design: Cohort study of adults with physician diagnosed asthma. All subjects were tested using methacholine challenge or bronchodilator reversibility. Population: 91 adults recruited from outpatient clinics or by poster advertisement with BMI ≥ 30 kg/m^2 on asthma medication, and current non-smokers.	Asthma confirmed on basis of positive methacholine challenge or BDR test.	**Overdiagnosis** reported in 36.3% on basis of normal objective tests	Tests performed at single time point only. All patients were on asthma medications. Normal test results may be due to good current control on treatment or current remission. Patient self-selected based on response to poster advert. Potential bias leading to recruitment of patients in which asthma was questioned.
LindenSmith 2004	Setting: Community sample in Canada Design: Cohort study. All participants completed symptoms questionnaire and underwent spirometry +/- PEF for two weeks +/- methacholine challenge testing	Asthma diagnosis based on clinical history either: 1) Positive BDR on spirometry 2) PEF variability 3) Positive methacholine challenge	41% did not meet diagnostic criteria for asthma suggesting **overdiagnosis**	Recruitment based on self-referral in response to poster advert. Potential selection bias favouring participants with questionable asthma diagnosis. Testing performed at single time point only

	Population: 90 adults self-referring to a tertiary centre with physician labelled asthma			
Underdiagnosis Reported				
Gonzalez-Garcia 2015	Setting: Five cities in Colombia Design: Cross sectional study population based study using questionnaire data and spirometry testing. Population: 5539 adults aged 40-93 years.	Definitions used: 1) Wheezing: affirmative answer to the question ‘‘Have you ever had two or more attacks of wheezes causing you to feel short of breath?’’ 2) Asthma: wheezing definition plus a post-bronchodilator FEV_1/FVC ratio ≥ 70%. Asthma underdiagnosis was considered when participants had wheezing or asthma definitions without a self-reported physician diagnosis of asthma.	**Underdiagnosis** reported to be 69.9% of those meeting definition for asthma (wheezing and spirometry without obstruction)	Asthma defined epidemiologically only, based on two episodes of wheeze ever with associated breathlessness and normal lung function (to differentiate with COPD). This is likely to include a large number of healthy individuals without asthma or who may have had symptoms as a child or younger person. Underdiagnosis rate likely overestimated.
Magnoni 2015	Setting: Community sample in Italy Design: Cross sectional study of patients registered at GP surgery with at least three prescriptions of inhaled steroids in previous 12 months. All participants invited to attend GP surgery for interview and completion of European Community Respiratory Health Survey (ECRHS). Population: 2090 adults. 991 of which had existing physician diagnosis of asthma.	Asthma diagnosis based on questionnaire responses: wheeze, nocturnal chest tightness, attack of breathlessness after activity at rest or at night, or one asthma attack.	Asthma suspected in 33.2% of participants without existing diagnosis based on ECRHS questionnaire suggesting **underdiagnosis**.	Excluded patients on LABA, theophyllines, leukotriene antagnosists, anticholinergics, sodium cromoglycate, and nedocromil thus biasing towards cohort with potentially milder symptoms or uncertain diagnosis. Asthma diagnosis based on questionnaire data only and may over or underestimate true prevalence of asthma in this cohort.

Van Schayck 2000	Setting: Community sample in the Netherlands Design: Cross sectional study. Each participant screened for symptoms using questionnaire and lung function (FEV_1). Participants with low FEV_1 during screening, had it repeated within a 4-month period. Number of previous GP consultations for asthma symptoms were recorded from GP records. Population: 1155 adults aged 25-70 years from the general population.	Asthma confirmation based on supportive clinical history and obstructed airflow using FEV_1.	**Underdiagnosis** reported in **21%** of participants who had presented to their GP with respiratory symptoms. Of the 86 participants meeting criteria for asthma, 66% had not previously consulted a GP with their symptoms suggesting **under-presentation**	Diagnosis based on symptoms and low FEV_1 in adult population, where COPD is also a possibility. Therefore not all patients meeting this criteria necessarily had asthma.
Adams 2003	Setting: Community sample in Australia Design: Cross sectional study. Households were selected at random from telephone directory and invited to participate. Participants completed symptom questionnaires and spirometry and BDR. Self-reported physician diagnosis of asthma was recorded. Population: 2523 (74%) adults agreed to participate out of 3422	Asthma diagnosis was based on positive BDR. Underdiagnosis defined as those with positive BDR but no physician diagnosis of asthma.	**Underdiagnosis** reported in 19.2%	Physician diagnosis based on patient self-reporting. Some patients may be unaware or unclear of their diagnosis. Also asthma diagnosis was based on a positive BDR only which does not have 100% PPV, therefore underdiagnosis may be overestimated.
Backer 2007	Setting: Community sample in Denmark	Asthma defined by asthma symptoms and positive methacholine test or BDR.	493 participants met criteria for asthma. Of these,	Only ~10% of original sample included into study for clinical evaluation. This leads to

	Design: Cross sectional study. Random sample of 10877 people contacted by letter and questionnaire. Those with respiratory symptoms evaluated with objective tests. Population: 1149 adults aged 16-44 years reporting respiratory symptoms.		249 (50.5%) had not previously been diagnosed suggesting **underdiagnosis.**	potential selection bias for participants with an uncertain diagnosis.
Both Over- and Underdiagnosis Reported				
Van Huisstede 2013	Subjects: Secondary care in the Netherlands Design: Participants recruited during pre-operative screening for bariatric surgery. Symptom questionnaire, spirometry and methacholine challenge were performed. If initial challenge test was negative, this was repeated six weeks later. Subjects were asked to voluntary stop their ICS six weeks prior to challenge test. Physician diagnosis was based on self-reporting. Population: 86 obese adult patients with BMI ≥ 35 kg/m^2. 222 were eligible to participate, but 136 declined.	Asthma defined as positive symptoms and either positive BDR or methacholine challenge test.	Overdiagnosis reported in 41%. Underdiagnosis reported in 31%.	Participation rate only 39% and participants not included consecutively leading to potential bias towards participants in whom a diagnosis was uncertain or questioned. No long term follow up of participants in whom ICS discontinued therefore overdiagnosis may be over-estimated. Existing diagnosis was based on patient self-reporting and may have been over or under-estimated.

3.2 Asthma Management

Getting the diagnosis right is clearly not straightforward, but what about getting the treatment right? In the US, figures of between 17% and 65% of adults and children with mild to severe persistent asthma but who were not on regular inhaled corticosteroids have previously been reported (Halterman et al., 2002, Wolfenden et al., 2003).

More recently, a Dutch study (Caudri et al., 2011) reported that 30% of their cohort of 8 year-old children with parental-reported severe current asthma symptoms were not prescribed regular inhaled corticosteroids. As this was a survey based study, it is possible that current symptoms were overestimated or wrongly attributable to asthma; however even in those children with doctors' diagnosed asthma, only 70-80% of current wheezers were reportedly using inhaled corticosteroids. Conversely, 50% of children without a history of wheeze for the previous 2 years, were on regular inhaled steroids, suggesting both under- and over- treatment. The authors did acknowledge that the lack of symptoms may be attributable to regular inhaled steroids, but argued that because asymptomatic children should be reviewed regularly and have their treatment stepped down, children with inhaled steroids for two consecutive years without a single episode of wheeze were probably over-treated.

Under-treatment may be a consequence of under-recognition or under-reporting of asthma symptoms and severity. A 2006 French study, involving 13,493 adults with persistent asthma, sought to identify the prevalence of nocturnal asthma symptoms (Raherison et al., 2006) using both a patient questionnaire and GP assessment. A total of 7989 adults with nocturnal symptoms had complete data from both the patient and GP. Only 48% had perfect agreement between patients' reported nocturnal symptoms by questionnaire, and GP assessed symptoms. In 10%, nocturnal symptoms were reported by the adult patients but not recognised by their GPs (under-recognised severity). In contrast, 42% of adults in the study did not self-report nocturnal symptoms, but were assessed by their GPs to be symptomatic (under-reporting by patients).

The proportion of patients on regular treatment for their asthma has been found also to correlate with physician assessed severity. In their cohort of 4000 adults, Wolfenden *et al.* (2003) found that only 35% of patients with mild asthma were prescribed daily inhaled steroids, but this increased to 53% of patients with moderate asthma and 68% with severe asthma. Even though regular treatment increases with increasing severity, this still represents up to a third of patients being under-treated.

Of particular note, there is evidence to show that monitoring based on symptom history alone under-recognises severity. In a Japanese study, 50% of adults and 35% of children classified as having mild to moderate asthma based on reported symptoms alone, were found to have moderate (FEV_1 60-80% predicted) to severe (FEV_1 < 60% predicted) airflow limitation when spirometry was performed (Tomita et al., 2009). Comparing the study participants' actual asthma treatment with optimal treatment based on a combined symptom-FEV_1 classification, the authors concluded that 49% of adults and 35% of children were over-treated, and 30% of adults and 40% of children were under-treated. The prevalence of reported overtreatment in this study should be interpreted with some scepticism however, since it may represent patients who are not over treated but well controlled on their current medications.

The current evidence demonstrates that both under- and over- diagnosis, and under-and over- treatment of asthma is prevalent amongst children and adults. Additionally, the issue is further complicated by underreporting of symptoms by patients. Current guidelines have attempted to standardise the way in which asthma is diagnosed and monitored through the routine use of objective measures of airflow limitation. The following sections will review the evidence in support of two of the objective tests recommended in current asthma guidelines – spirometry and exhaled nitric oxide.

3.3 Spirometry

Spirometry is a non-invasive physiological test which measures the volume and flow rate of air during inhalation and exhalation. The most commonly reported parameters are FEV_1 (forced expiratory volume in 1 second) and FVC (forced vital capacity) and the ratio of FEV_1 to FVC (FEV_1/FVC). All parameters are measured during a forced expiratory manoeuvre – a patient is asked to inhale to total lung capacity and forcefully expire down to residual volume.

The FEV_1 represents the volume of air (litres) expired in the first second and the FVC (litres) is the total volume of air expired from the start of the manoeuvre to the end. A reduced FEV_1 to FVC ratio indicates obstruction, as it represents a prolonged expiratory time secondary to narrowed/obstructed airways.

A standardised procedure for performing spirometry has been published jointly by the European Respiratory Society (ERS) and American Thoracic Society (ATS) (Miller et al., 2005). Depending on the equipment used, the primary recorded signal may be flow or volume, with extrapolation of the remaining parameter.

Though originally invented in the 1840s by John Hutchinson (Hutchinson, 1846) as a means to measure vital capacities, time-dependent volumes (such as FEV_1) were not introduced until the 1940s and bronchodilator responsiveness testing until the 1950s (Gauthier et al., 2015).

Multi-ethnic reference values for people aged 3-95 have only been available since 2012 (Quanjer et al., 2012), with publication of a study comprising over 150 000 spirometry data points, from 74,187 healthy non-smokers from 41 countries across 5 continents. There are still some gaps in data from certain ethnic groups however. Most notably missing from the global lung initiative (GLI) reference equations are data from the African continent, South Asia (Indian sub-continent) and Latin America.

The main limitation of spirometry is that results are both operator and patient dependent, requiring good cooperation and coordination from the patient,

and clear instructions and encouragement from the operator. This makes the test technically challenging, particularly in young children. However, with appropriate coaching, children as young as 5 years of age are often able to perform acceptable spirometry (Eigen et al., 2001). Therefore most national and international guidelines advocate the use of spirometry to investigate suspected asthma in children from 5 years (BTS, 2019, NICE, 2017, GINA, 2019, NAEPP, 2007).

3.3.1 Diagnostic accuracy of Spirometry

Confirmation of asthma requires both a suggestive history and demonstration of variable airflow obstruction. Spirometry is the investigation of choice for identification of airflow obstruction (BTS, 2019); so in a patient with a history suggestive of asthma, with obstructive spirometry and bronchodilator reversibility, the diagnosis is clear cut (Levy, 2016).

However, diagnostic tests are often only performed at a single time point whereas asthma symptoms can vary over time (BTS, 2019). Whilst one child may have daily persistent symptoms associated with abnormal lung function, another child may only experience seasonal symptoms, or is symptom free with normal lung function in between asthma attacks. In other words, a normal spirogram in a patient when they are asymptomatic cannot rule out asthma (Ringsberg et al., 2014, Greiver et al., 2002, Melbye et al., 2011). Almost half of children seen in secondary care with severe persistent asthma, as defined by NAEPP (NAEPP, 2007), have normal FEV_1 to FVC ratios (Bacharier et al., 2004); and up to 71% of adult patients presenting to primary care for the first time with symptomatic asthma may have normal spirometry (Schneider et al., 2009a).

The diagnostic accuracy of spirometry in asthma has recently been reviewed in a NICE document (NICE, 2017).

To expand on some of the statistical measures used: the sensitivity of a test (also called the true positive rate) is defined as the proportion of people with the disease who will have a positive result; whilst the specificity of a test (the

true negative rate) is the proportion of people without the disease who will have a negative result. An alternative way of measuring test accuracy is by calculating the positive predictive (PPV) and negative predictive (NPV) values. The PPV is the probability of patients who have a positive test result actually having the disease; and the negative predictive value is the probability that people who get a negative test result truly do not have the disease.

Using a definition for obstruction as either a $FEV_1/FVC < 70\%$ or FEV_1 predicted < 80%, NICE identified 5 adult studies and 1 paediatric study addressing the question of diagnostic accuracy. In adults, the reported sensitivity, specificity, PPV and NPV are shown in the Table 3.

Due to the low sensitivity of the test, the GDG agreed that spirometry should not be used in isolation for asthma diagnosis.

Table 3. Diagnostic Accuracy of Abnormal Spirometry for Asthma

	Sensitivity	Specificity	PPV	NPV
Adults	23-47%	31-100%	45-100%	18-73%

(Source: NICE 2017 evidence tables)

Children have a higher normal FEV_1/FVC compared with adults, which decreases with age (Quanjer et al., 2012). Using an arbitrary cut-off for FEV_1/FVC of 70% results in under-recognition of airflow obstruction in children and young adults where the lower limit of normal (LLN) for FEV_1/FVC is well above 70% (Figure 13). It is therefore not surprising that no studies were identified using a 70% cut-off for FEV_1/FVC in children.

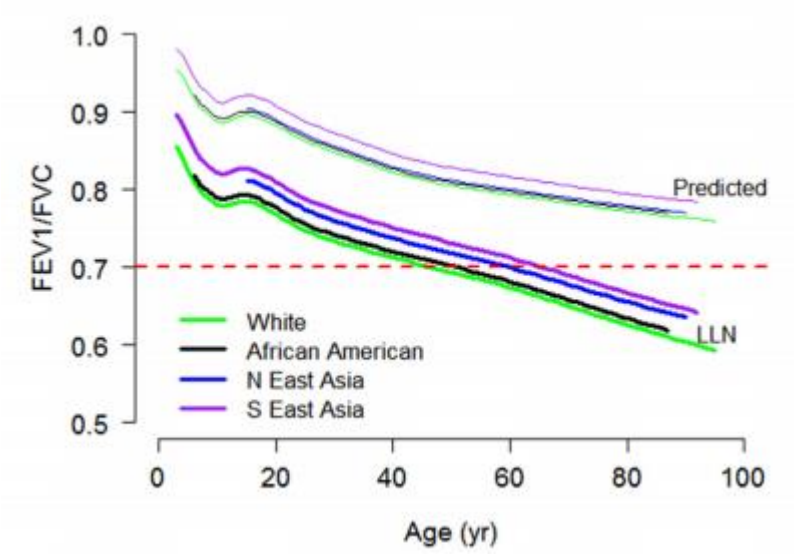


Figure 13 . Predicted FEV_1/FVC and lower limit of normal (LLN) in healthy females of different ethnicities (Source: Quanjer 2012).

Sivan *et al.* (Sivan et al., 2009) performed spirometry, exhaled nitric oxide (eNO) and sputum eosinophil percentage cell (eos%) counts in 150 children referred to a paediatric respiratory outpatient clinic with non-specific respiratory symptoms before following their progress over 18 months. A diagnosis of asthma was made during the follow up period based on clinical history (two or more clinical exacerbations, dyspnoea or cough relieved by bronchodilators) and documented variability in $FEV_1 \geq 15\%$ in response to bronchodilators (BDR), or documented variability of $FEV_1 \geq 15\%$ over time with or without controller medications. Using this criteria, they reported the diagnostic accuracy of spirometry, at the time of initial presentation, using a fixed cut-off for FEV_1 of less than 80% predicted at time of recruitment (Table 4).

Table 4. Diagnostic Accuracy of Spirometry for Children (Using FEV_1 < 80% Predicted)

	Sensitivity	Specificity	PPV	NPV
Children	52%	72%	75%	48%

(Source: NICE 2017 Evidence Tables)

Likewise in a study involving 61 children (6-16 years) monitored for 2 weeks at home with twice daily FEV_1 measurements, the diagnostic accuracy using diurnal variation in FEV_1 (using 95^{th}-centile for FEV_1 variation in healthy school children) versus diagnosis by a paediatric pulmonologist (reference standard) showed similar values for sensitivity (45%) and PPV (75%), but better values for specificity (92%) and NPV (77%) (Brouwer et al., 2010).

In practice, the availability of FEV_1% predicted in assessing children presenting with respiratory symptoms has been shown to influence clinical management. A US study of 56 children presenting to a community health centre initially asked clinicians to base their treatment plans on clinical assessment alone, before spirometry was performed. Approximately 2/3 of patients had abnormal FEV_1 values and nearly one third of patients had their treatment plans revised after clinicians viewed their spirometry results (Holt et al., 2006).

However, since FEV_1 varies with lung volume, it is argued that a documented reduced FEV_1/FVC is a better index of airflow limitation; since FEV_1/FVC is intrinsically corrected for lung capacity by using FVC as a proxy. Reportedly, using the lower limit of normal for FEV_1/FVC as the reference index (as opposed to a fixed cut off), the assumption that there is airways obstruction if $FEV_1 < 80\%$ predicted leads to a 42–56% false detection rate (Quanjer and Weiner, 2014); where the false detection rate is the ratio of false positives to true positives expressed as a percentage.

3.3.2 Diagnostic Accuracy of the Bronchodilator Reversibility Test

Performing spirometry pre- and post- inhalation of bronchodilator medicine is a test of bronchial lability, a hallmark of asthma, which can readily be performed in the clinic setting without the need for additional specialist equipment. Moreover, increased bronchodilator response (BDR) in asthmatic patients is associated with poor clinical outcomes, increased airway

inflammation and response to inhaled corticosteroids (Kerstjens et al., 1993, Tantisira et al., 2006).

Nevertheless, there is no clear consensus as to what constitutes positive reversibility in terms of: the ideal measured lung function parameter, the drug and dose of bronchodilator to use, and what magnitude of change is significantly greater than random variation (Pellegrino et al., 2005). Attempts to standardise the test procedure and interpretation of results have led to publication of standardised guidance (Pellegrino et al., 2005, Miller et al., 2005).

The diagnostic accuracy of bronchodilator reversibility testing (BDR) for diagnosing asthma has previously been reviewed (BTS, 2019, NICE, 2017) which included studies measuring the percentage change in FEV_1 (L) pre- and post- bronchodilation (Table 5).

Table 5. Diagnostic Accuracy of Bronchodilator Response in Adult Asthma

	Sensitivity	Specificity	PPV	NPV
Adults	17-69%	55-81%	53-82%	22-68%

(Source: NICE 2017 data tables)

All four studies included in these reviews (BTS, 2019, NICE, 2017) were performed in adults, and the population of all included studies were people with either asthma or COPD, with the aim of assessing the diagnostic accuracy of BDR in distinguishing between these conditions. None of the studies included children. A positive BDR test in these adult studies was defined as an increase in initial FEV_1(L) of at least 12% or 200ml post-bronchodilator; which is consistent with ERS/ATS recommendations (Pellegrino et al., 2005), and supported by a large international adult study (Tan et al., 2012) which reported the mean (95% confidence interval) bronchodilator response in 3922 healthy adults (over 40 years old) as an increase in initial FEV_1(L) of 12.0% (11.2% to 12.8%).

In children, the validity of the 12% cut-off has been questioned by previous paediatric studies which have reported the mean change in FEV_1 (L) post-bronchodilator to be 2.2-2.7% from baseline in healthy children (Galant et al., 2007, Tse et al., 2013); compared with 8.6-10.7% in those with a history of asthma. The reported values for sensitivity and specificity using a 12% cut-off in children is 35-36% and 90-98% respectively (Dundas et al., 2005, Tse et al., 2013)

A lower cut-off of 9% increase in absolute FEV_1 (L) post-bronchodilator for children has been proposed, which differentiates between health and disease with a sensitivity of 43-50% and specificity of 78-86% (Dundas et al., 2005, Galant et al., 2007, Vilozni et al., 2016, Tse et al., 2013). The Tse *et al.* study, which involved 1041 children (5-13yrs) with mild-moderate asthma and 250 healthy controls, further calculated the sensitivity and specificity values using cut-offs between 5-12% for each 1% interval (Table 6).

Table 6. Diagnostic accuracy of BDR using different cut-off points for FEV_1 (L) increase from baseline

BDR cut-off (%)	Sensitivity (%)	Specificity (%)
12	35.6	89.5
11	40.1	86.5
10	45.2	81.0
9	49.1	78.0
8	54.4	76.5
7	61.1	73.0
6	67.6	66.5
5	73.6	63.5

Source: Tse et al 2013

This study demonstrates that whilst sensitivity of the BDR test in diagnosing children with asthma can be increased by lowering the cut-off threshold, this has the effect of reducing specificity and potentially result in over-diagnosis. Conversely, given the low associated sensitivity, insisting on a threshold cut-

off of 12% for FEV_1 (L) will result in under-diagnosis and under-treatment of asthma.

Furthermore, the clinical utility of the BDR test is influenced by the prevalence of asthma in any given population and the pre-test probability. Using a cut-off of 9% for FEV_1 (L), the Dundas (2005) study reported the positive and negative predictive values for the BDR test for different pre-test probabilities (Table 7).

Table 7. Predictive values of a positive BDR of 9%

Pre-test Probability (estimated prevalence)	PPV	NPV
10%	29%	94%
30%	61%	80%
50%	78%	63%

Source: Dundas et al 2005

Used in isolation, the BDR is an imperfect test and depending on the threshold cut-off used, can both over- and under- diagnose asthma. The pre-test probability of asthma, based on a thorough clinical assessment, should be considered when interpreting the BDR test result.

3.3.3 Role of Spirometry in Asthma Monitoring

Current guidelines recommend the use of spirometry for asthma diagnostic and monitoring purposes, emphasising the aim of achieving both good symptom control and normal lung function in children's asthma management (BTS, 2019, GINA, 2019, NAEPP, 2007).

The justification for this recommendation is two-fold. Firstly, children with long standing asthma perceive symptoms less well (Rietveld and Walter,

2000), normalise higher levels of asthma symptoms and have higher self-treatment thresholds (Mammen et al., 2017).

Secondly, the relationship between lung function and current asthma control is unclear. Whilst some authors have reported concordance between FEV_1 (Waibel et al., 2012) and FEV_1/FVC (Bacharier et al., 2004) with clinical severity based on frequency of symptoms, others have reported no association (Green et al., 2013, Schifano et al., 2014). Moreover, children with asthma can have significant airflow obstruction without reporting any symptoms (Clough and Holgate, 1994).

Taken together, this means that a symptom based assessment alone may under-recognise severity and result in suboptimal management. This may partially explain why the severity of asthma was underestimated in around two-thirds of children reviewed in the National Review of Asthma Deaths (NRAD) report between 2012 and 2013 (RCP, 2014a).

In children, clinical symptoms reportedly underestimates asthma severity determined using spirometry in 31-36% of children (Cowen et al., 2007, Schifano et al., 2014). By contrast, spirometry assessment alone was found to underestimate clinician-determined severity (without spirometry) in 40% of children (Cowen et al., 2007).

It could be argued that the emphasis of asthma management should be on achieving symptom control, and reacting to abnormal lung function in the context of an asymptomatic child may lead to over-treatment. However, there is evidence that reduced lung function has both short and long term implications for the child. Airflow obstruction during childhood is associated with reduced FEV_1 in adulthood (Roorda et al., 1994, Tai et al., 2014a, Belgrave et al., 2018, Bui et al., 2018), and ongoing asthma symptoms as adults (Jenkins et al., 1994).

Although a recent systematic review to identify risk factors for asthma attacks in children reported that the evidence supporting the role of spirometry is inconclusive (Buelo et al., 2018), there is some evidence from longitudinal cohort studies that low lung function may be associated with an

increased risk of future asthma attacks in children and adults (Kitch et al., 2004). Children with an FEV_1 < 60% predicted are twice as likely to have an asthma "attack" (defined as an episode of wheezing or shortness of breath) in the subsequent 12 months (Fuhlbrigge et al., 2001) compared to those with an FEV_1 > 80% predicted. In terms of "serious exacerbations" (need for oral steroids, emergency department visits, and hospitalisations) compared to children with an FEV_1 > 100% predicted, children with FEV_1 of 80% to 99%, 60% to 79%, and < 60% predicted are respectively 1.3, 1.8, and 4.8 times more likely to have a serious asthma exacerbation over the next 4 months (Fuhlbrigge et al., 2006). All three of these studies were however limited by their reliance on patient self-reporting to identify asthma attacks.

In summary, spirometry parameters do not always correlate well with current clinical symptoms, but may have a role in asthma attack risk stratification. Moreover, unrecognised low lung function as a child appears to have implications for adult lung function trajectories. A management approach based on either symptom or spirometry assessments alone may therefore provide an incomplete assessment of a child's asthma.

3.3.4 Longitudinal Lung Function in Asthma

Children with early onset, transient or persistent, asthma symptoms before the age of four years have been shown to have significantly lower FEV_1 and FEV_1/FVC by age eight years when compared with children without a history of asthma symptoms, regardless of whether they continued to experience symptoms after their fourth birthday (Hallberg et al., 2010). Furthermore, a history of asthma during childhood is associated with reduced lung function persisting into early adulthood associated with an increased rate of decline during adult life (James et al., 2005).

Factors associated with poorer lung function and a greater rate of lung function decline in people with asthma include: high BMI (Chu et al., 2009), smoking (James et al., 2005), in-utero and/or passive smoke exposure (McEvoy and Spindel, 2017, Venners et al., 2001, Vanker et al., 2017), high

sputum eosinophil count variability (Newby et al., 2014), and poor symptom control (Bai et al., 2007, Matsunaga et al., 2014).

This raises the question of whether improving symptom control and reducing inflammation can improve long term lung function? Certainly in adults, treatment with inhaled corticosteroids (ICS) compared with no ICS is associated with a significantly reduced decline in FEV_1 over a 10-year period (Lange et al., 2006). By contrast, in children, no difference in FEV_1 was found between an ICS treated group compared with placebo over 4-6 years of follow up (CAMP, 2000). However, the ICS treated group of children did have a smaller decline in FEV_1/FVC, lower airway responsiveness (to methacholine), fewer hospitalisations and healthcare visits, and less frequent need for short acting bronchodilators (SABA).

Further support for regular lung function monitoring is provided by a recent study which retrospectively compared the current spirometry of 46 asymptomatic adults with asthma, with spirometry performed five years previously. Even though all 46 adults had normal lung function as defined by the lower limit of normal (LLN) (Quanjer et al., 2012), approximately 28% of their cohort, with apparently well-controlled asthma, showed an FEV_1 decline beyond what would be physiologically expected with age (Sposato, 2016). The authors concluded that basing management on symptoms only would underestimate and possibly undertreat a proportion of apparently “well-controlled” people with asthma.

3.3.5 Spirometry Use in the Community

In adults, office based spirometry is feasible in the community (Jones, 1995, Lusuardi et al., 2006, Lei Burton et al., 2015), and can assist primary care physicians to differentiate between asthma and COPD (Griffiths et al., 1999, Metting et al., 2015). Despite this, routine use of spirometry by primary care providers has been reported at only between 14-67% for adults in Australia and the US (Blain and Craig, 2009, Finkelstein et al., 2000, Johns et al., 2006). In Wales, 86% of surveyed GP practices reportedly used spirometry

routinely for COPD management, however only 58% of GP practices reportedly felt confident with its use and 34% confident with interpretation (Bolton et al., 2005). More recently, the National Welsh COPD audit, which included 63% of Welsh General Practices, found that only 19% of patients on the QOF COPD register had a post-bronchodilator FEV_1/FVC recorded on their electronic records. Although the absence of an electronically coded FEV_1/FVC ratio does not necessarily mean that this test had not been performed, the authors argue that this does suggest that the importance of spirometry in accurate diagnosis is "not at the forefront of clinicians' management strategies" (Fisk et al., 2019).

Fewer studies have investigated spirometry use in children managed within primary care. A survey of 360 office based family physicians and paediatricians in the US found that only 21% used spirometry as per asthma guideline recommendations, and 25-50% did not feel comfortable interpreting spirometry test results (Dombkowski et al., 2010). This would suggest lack of training to be a major barrier against the routine use of spirometry in primary care for children and adults.

Previous reports suggest an increase in use of spirometry amongst primary care practitioners following formal training (Johansen, 2007, Licskai et al., 2012). Although results obtained by practice nurses were found to be lower than those obtained in a pulmonary function laboratory (Akhtar and Wilson, 2005), follow up training to solidify learning can improve quality (Borg et al., 2010).

Aside from training, studies which have sought to specifically address the question of why spirometry use within the community is generally low have identified additional barriers including: increased clinic time, lack of equipment, insufficient remuneration, staff unfamiliarity with equipment, and lack of staffing to perform the tests (Johns et al., 2006, Dombkowski et al., 2010, Walters et al., 2005, Poels et al., 2006). Furthermore, there is evidence that spirometry as an investigation for respiratory complaints is undervalued by clinicians who do not have a specific respiratory interest (Roberts et al., 2011), with uncertainty of what impact the test actually has

on clinical management (Kaminsky et al., 2005). Amongst US community practitioners, the belief that spirometry is necessary for accurate asthma diagnosis is associated with higher usage (O'Dowd et al., 2003).

Any attempt to implement spirometry for children in general practice must first seek to identify staff training needs, demonstrate clinical usefulness, ascertain locally perceived barriers and provide sufficient ongoing support and resources to practices.

3.3.6 Spirometry Training

Quality spirometry is very dependent on the provider administering the test and needs to be performed by trained, experienced, and preferably certified personnel (Levy et al., 2009). In a previous adult study, spirometry results obtained by practice nurses and those obtained within a hospital pulmonary function laboratory (PFL) within one month of each other, were compared in 45 patients with stable chronic obstructive pulmonary disease (COPD). It was found that both FEV_1 and FVC were underestimated by practice nurses compared with measurements obtained within a PFL (Akhtar and Wilson, 2005). Although five out of six participating nurses had received spirometry training previously (between one to five years ago), only one course was formally accredited; which may go some way in explaining the discrepancy in results.

A recent document published by Education for Health (EfH), along with a number of asthma stakeholders, sets out a competency assessment framework with the aim of improving the quality of diagnostic spirometry in adults over 16 years old (Education for Health, 2016). This document essentially sets out the framework by which all providers of adult spirometry need to comply in order to be accredited, and includes registration onto a national adult spirometry register.

The Association for Respiratory Technology and Physiology (ARTP) are the "guardians of quality spirometry in the UK" (www.artp.org.uk). Although the EfH framework does not mandate that training needs to be provided directly

by the ARTP (currently £500), only ARTP accredited providers can undertake competency assessments. This is to ensure that quality of spirometry is standardised across the UK, and is to be commended. However, the current framework being rolled out (2017 to 2021) only applies to adults, and does not apply to spirometry performed in children under the age of 16 years. This is due to the recognition that performing spirometry in children is different, and training requirements needs to reflect this. Unfortunately, there is currently limited evidence to inform the amount of training required in order to ensure accurate quality assured spirometry in the five to 16 years age group.

3.4 Exhaled Nitric Oxide

Though previously considered only as an environmental pollutant released from combusting fossil fuels and cigarette smoke (IFC, 1998), nitric oxide (NO) has since been recognised as an important cell signalling molecule in mammals.

In humans, NO is produced by nitric oxide synthases (NOS) through the metabolism of the amino acid L-arginine to L-citrulline. NOS can exist in three isoforms: neuronal (nNOS), endothelial (eNOS) and inducible (iNOS). The nNOS and eNOS, termed constitutive NOS, are active under normal physiological conditions, constantly produce NO at low concentrations, and have homeostatic roles in maintaining low vascular and smooth muscle tone, prevention of platelet adherence to vascular walls, and in neurotransmission (Prado et al., 2011).

By contrast, the inducible form of NOS (iNOS) is expressed predominantly in inflammatory and epithelial cells, and is activated by inflammatory cytokines during inflammation. The major determinant of increased NO concentration in the exhaled breath of people with asthma is increased epithelial iNOS expression (Lane et al., 2004), consequent to upregulation of signal transducer and activator of transcription 6 (STAT6) by IL-4 and IL-13. Although STAT6 is necessary for normal immune function, it has been

implicated in a number of pathologic inflammatory features of asthma, including airway eosinophilia, epithelial mucus production, smooth muscle changes, Th2 cell differentiation, IgE production and iNOS activation (Pernis and Rothman, 2002, Walford and Doherty, 2013).

The possibility of measuring endogenous nitric oxide produced from exhaled breath was first reported in 1993 (Borland et al., 1993), and later noted to be raised in both adults (Alving et al., 1993) and children (Nelson et al., 1997) with asthma. Subsequent studies have demonstrated that eNO levels correlate moderately well with sputum and blood eosinophil counts in asthmatic patients (Warke et al., 2002, Piacentini et al., 1999, Payne et al., 2001, Berry et al., 2005); suggesting a role for using eNO as an indirect marker of eosinophilic inflammation, and raising the possibility of its use as a biomarker in asthma management.

However, it should be noted that eNO levels can be affected by a number of other clinical variables (Table 8) besides asthma.

Table 8. Factors affecting eNO levels

Increased:	Decreased:
• In people with allergic rhinitis exposed to allergen • By rhinovirus infection in healthy individuals • In men and tall people • By dietary nitrates	• In children • In cigarette smokers • By inhaled or oral steroids • In patients with cystic fibrosis • In patients with primary ciliary dyskinesia

Source: BTS 2016

Studies which have investigated the clinical utility of measuring eNO in asthma management have yielded conflicting results and conclusions (Turner, 2015). Nevertheless, the possibility of being able to diagnose and monitor asthma using a non-invasive biomarker is appealing, and interest in eNO is still very much alive (Bjermer et al., 2014).

Documents aiming to standardise the measurement of eNO are available (American Thoracic and European Respiratory, 2005, Dweik et al., 2011), which provide guidance on the technical aspects of the procedure itself, along with suggestions for how to interpret results. Like spirometry, implementation of eNO into primary care for children would represent a radical change to current practice. The evidence for eNO's role in asthma diagnosis and management is discussed below.

3.4.1 Diagnostic accuracy of exhaled nitric oxide

Existing asthma guidelines have included a discussion of the use of exhaled nitric oxide (eNO) as a marker of T-helper 2 cell type (Th2) or eosinophilic airway inflammation; suggesting that a raised eNO level supports a diagnosis of asthma (BTS, 2019, NAEPP, 2007, GINA, 2019), without providing clear guidance on how it should influence clinical decision making, or when it should be used. The recent NICE asthma guideline (NICE, 2017) includes eNO measurement within its proposed algorithm for asthma diagnosis (in children and adults), and recently reviewed the diagnostic accuracy of eNO for adult asthma (Table 9).

Table 9. Diagnostic Accuracy of eNO for Asthma

	Sensitivity	Specificity	PPV	NPV
Adults	43-88%	60-92%	54-95%	65-93%

Source: NICE 2017 Data Tables

The six adult studies included in the NICE review (NICE, 2017) compared the accuracy of eNO against a physician diagnosis plus another objective test for asthma; using a positive cut-off for eNO of between 20-50 parts per billion (ppb). Based on the authors' findings, they recommended that eNO testing should be offered to all adults (> 16 years) with suspected asthma using a positive threshold for eNO of 40ppb. By contrast, in children (16 years and younger) the NICE guideline only recommends eNO testing where

there is diagnostic uncertainty (normal spirometry or negative BDR). Only one study was included for children in the NICE review (Woo et al., 2012), which included 245 Korean children (8-16 years) referred to secondary care with suspected asthma. Diagnostic accuracy of eNO was compared against a relevant asthma history with objective evidence of either BDR or AHR. The best cut-off threshold for eNO was found to be 22ppb, which offered a sensitivity of 57%, specificity of 87%, PPV 91% and NPV 49%. NICE concluded that, in children, eNO only offered a moderate sensitivity and therefore did not recommend its use for all children, unlike for adults.

In a separate review (Tang et al., 2016), which included eight studies in children evaluating the accuracy of eNO in asthma diagnosis, the pooled estimates for sensitivity and specificity were higher than those reported by NICE, at 79% (95% CI 64-89%) and 81% (95% CI 66-90%) respectively, using thresholds for eNO ranging from 19 to 25ppb. It should be noted however, that not all studies included in this review used objective testing as the reference standard to confirm asthma, i.e. physician diagnosis based on clinical history was used instead.

Nevertheless, the optimal threshold reported in all these studies were lower than the 35ppb suggested in the proposed NICE guidance.

Interestingly, in the Woo *et al.* (2012) study, eNO was low in non-atopic children regardless of asthma status, a finding supported by an earlier Norwegian study (Sachs-Olsen et al., 2010). A raised eNO was only observed in children with atopy. Furthermore, whilst the highest eNO was seen in children with atopy and asthma, 28% of these children still had eNO levels below their suggested threshold of 22ppb (Woo et al., 2012).

In summary, a raised eNO value can help to discriminate asthma from non-asthmatic conditions. However, a normal eNO level cannot be used to exclude asthma, particularly in the absence of atopy.

3.4.2 Role of eNO in Asthma Monitoring

Current asthma guidelines do not recommend routine eNO monitoring to guide management in children or adults (NAEPP, 2007, GINA, 2019, BTS, 2019, NICE, 2017). The question of whether regular eNO monitoring confers clinical benefit is unanswered, and current evidence is unclear.

In both children and adults, eNO levels have been shown to correlate with patient reported symptoms and physician assessed control, albeit only weakly (Green et al., 2013, Park et al., 2016). Although children with eNO levels < 20 ppb have been observed to have higher asthma control test scores and baseline FEV_1% predicted than those with eNO levels ≥ 20ppb (Soto-Ramos et al., 2013), the difference in asthma control test score (23 vs 21) is minimal and there is significant overlap between groups. Interestingly, the absolute eNO level also does not appear to reflect acute severity during exacerbations, and the initial eNO (measured on arrival to hospital) is similar between children who were admitted or sent home following assessment (Nelson et al., 2011).

The relationship between sputum eosinophils, another biomarker for airway inflammation, and day-to-day asthma control is also unclear from the existing literature.

In a paediatric study of patients with asthma, the relationship between sputum eosinophil cell count and current symptom control was reported in a group of 50 children recruited from specialist clinics. The authors found no significant difference in sputum eosinophil counts between children with controlled or current symptomatic asthma (Cai et al., 1998). A larger study involving 146 children with asthma, did observe higher levels of sputum eosinophils in current symptomatic versus current asymptomatic children, however, there was considerable overlap between groups and, on an individual level, poor relationship between the number of symptom free days in the past year and sputum eosinophil levels. The authors did however, observe that higher sputum eosinophil levels were associated with more frequent asthma attacks over the prior 12 months (Gibson et al., 2003).

Taken together, this suggests that airway inflammation may not correlate well with day-to-day symptoms, but may reflect longer term control in terms of frequency of exacerbations.

Green *et al.* conducted a randomised controlled trial to investigate whether an eosinophilic inflammation targeted asthma management strategy versus standard guideline based management could reduce asthma exacerbations. The authors reported significantly fewer asthma exacerbations over 12 months in the sputum eosinophils targeted management group compared to control (35 vs 109; p = 0·01), but no difference in symptom control scores (Green et al., 2002).

However, in a more recent study, Demarche *et al.* investigated the relationship between fluctuations in sputum eosinophils over time and changes in asthma control (Demarche et al., 2017). The authors retrospectively collected data from 187 adults with asthma who had at least 2 sputum samples collected as part of routine investigations in a specialist asthma clinic. Asthma control was observed to be associated with changes in sputum eosinophils in individual patients over time; an increase in sputum eosinophils was associated with worsening of asthma control, whilst a decrease in sputum eosinophils was associated with an improvement control. Similarly, as discussed earlier in this thesis, a number of studies investigating the efficacy of biologic treatments targeting specific inflammatory pathways have demonstrated improvements in both frequency of asthma attacks and in asthma control scores in patients receiving active treatment versus controls (Busse et al., 2001, Gupta et al., 2019, Wenzel et al., 2013).

Compared with spirometry and airway hyper responsiveness (AHR) testing, eNO responds earliest to initiation of inhaled corticosteroids (ICS) in steroid-naïve patients; decreasing at the start of treatment, and increasing when ICS are stopped (Mehta et al., 2009). As such, eNO may be able to differentiate between children taking ICS or not, and have a potential role in adherence monitoring (Beck-Ripp et al., 2002). In adults, the demonstration of eNO suppression (~43%) following five days of directly observed high dose ICS

has been shown to distinguish between adults who are adherent or non-adherent to their asthma treatment (McNicholl et al., 2012).

Additionally, eNO measurements have been shown to predict ICS response. In an adult study, which included children 14 years and older, asthma patients with eNO levels > 47ppb were significantly more likely to respond to ICS treatment in terms of improved symptom control, lung function, and reduced AHR (Smith et al., 2005b). Moreover, when ICS doses are adjusted over a 12-month period according to symptoms alone or symptoms and eNO levels, the average daily ICS dose was found to be lower in the eNO group without affecting symptom control, exacerbation rate or lung function (Smith et al., 2005a).

Once control has been achieved and ICS is stepped down, serial monitoring of eNO may predict relapse of asthma symptoms. Two small studies in children found that an increased eNO level is a significant predictor of failed treatment reduction (Pijnenburg et al., 2005b, Zacharasiewicz et al., 2005). An eNO level of ≥ 49 ppb 4-weeks after discontinuation of ICS had a sensitivity of 71% and specificity of 93% for predicting asthma relapse within 24 weeks.

Although eNO does not appear to correlate strongly with current asthma control, there is a potential role for eNO monitoring in asthma management. Including with identifying those at an increased risk of asthma attacks, to identify patients more likely to respond to ICS treatment, to help with adherence monitoring, and potentially to predict failure of stepping down asthma treatment.

3.4.3 Longitudinal eNO Levels in Asthma

As discussed above, eNO measurement has emerged as a potentially clinically useful tool in asthma management. However, compared with spirometry, there have been fewer studies investigating how eNO varies over time in individuals with asthma and whether this relates to other clinical parameters.

Longitudinal studies in children have provided mixed conclusions. Some have found no relationship between changes in eNO levels over time and clinical symptoms, corticosteroid use or quality of life (de Bot et al., 2013, Elmasri et al., 2014). Furthermore, when the cohorts of children in these studies were sub-grouped by atopic and rhinitis status, no difference was found in eNO levels between those with a positive history of atopy/rhinitis regardless of whether they had asthma or not. It has been argued, therefore, that eNO is more a marker of atopy rather than asthma. Further support for this argument is provided by a Korean study, which serially measured (at least 10 times) eNO in asthmatic children over a 2-year period; only house dust mite (HDM) sensitization was significantly correlated with frequency of eNO levels > 21ppb (Lee et al., 2015).

Likewise, although eNO is widely regarded as a surrogate marker of sputum eosinophilia (Berry et al., 2005), when multiple paired (eNO and induced sputum) samples are taken over a 12-month period, almost half of all children did not have a concordant relationship between eNO and sputum eosinophils (Fleming et al., 2013). This serves as a reminder that although both eNO and sputum eosinophils are associated with airway inflammation, each biomarker reflects a different part of the Th-2 pathway. Using eNO to predict sputum eosinophilia is likely to both overestimate and underestimate sputum eosinophilia overtime as treatments which suppress eNO may only partially suppress eosinophils, and medications which act on cytokines involved with stimulation of eosinophils may have little or no effect on inducible nitric oxide synthases.

Conversely, other studies have found a positive association between levels of eNO and asthma outcomes during longer term follow up. In adults, low eNO (< 30-34ppb) at the initial hospital outpatient visit was found to predict better control and fewer exacerbations during follow up (Michils et al., 2008, Yang et al., 2015b). In children, when serial measurements of eNO over a 2-year period are performed, a single eNO of > 37 ppb had a sensitivity of 91% and specificity of 60% for predicting future exacerbations; whilst a single eNO of > 47ppb increased specificity to 96% but reduced sensitivity to 70% (Yang et al., 2015b).

3.4.4 Exhaled Nitric Oxide Use in the Community

Delivering eNO testing in the community is an attractive option to provide objective evidence of airway inflammation, which can facilitate asthma diagnosis and monitoring. A German study involving 160 adults comparing eNO results from primary care with laboratory AHR testing concluded that a eNO cut-off of 46 ppb could “diagnose asthma” with a sensitivity of 32%, specificity of 93%, PPV of 80%, and NPV of 61% when compared with a positive methacholine challenge performed in a lung physiology laboratory (Schneider et al., 2009b).

Although no articles were identified which reported on the prevalence of eNO use within the community setting, measurement of exhaled nitric oxide has been shown to be possible within primary care, and is acceptable to staff and patients (Gruffydd-Jones et al., 2007). Moreover, an eNO directed treatment strategy within primary care may reduce inhaled steroid use and medication costs, without compromising on symptom control (Hewitt et al., 2009, Honkoop et al., 2015). However, these studies were either conducted in adults only, or only included very small numbers of children.

3.4.5 Exhaled Nitric Oxide Training

At the time of writing, there is no formal course for performing exhaled nitric oxide testing in children in the UK. A short training session is provided by the manufacturers either face to face, or via online webinars. Three devices have been evaluated by NICE and recommended for clinical use – the NIOX MINO, and NIOX VERO (Circassia Pharmaceuticals plc, UK), and the NObreath (Bedfont Scientific Ltd, UK) (NICE, 2019). All three devices are suitable for children, the NIOX VERO and MINO from as young as four years depending on the compliance of the child. Both the VERO and MINO offer a 6 second mode for children under ten years, and a 10 second mode for adults. The NObreath has a 12 second mode for adults and a 10 second mode for children. The cost per test depends on which machine is used and varies from between £4.82 to £7.07 (NICE, 2017). Practitioners need to be

shown how to use the machine and to be taught what the different eNO measurements mean (Robinson, 2015).

3.5 Are Objective Tests the Solution?

Through their recommendations, the latest NICE asthma guideline has proposed a number of portable objective tests, including spirometry and eNO, which may be useful in asthma diagnosis and monitoring. However, even if these tests were available within primary care, there remains a number of challenges faced by clinicians during asthma diagnosis, and limited evidence that the use of objective testing can improve asthma related outcomes. These issues are discussed further below.

3.5.1 Challenges in Diagnosis

It is important to recognise that people with respiratory symptoms may not seek a medical review in the first place. In a Dutch study, a random sample of 1155 adults were screened using a questionnaire and measurements of FEV_1. Eighty-six were identified as having asthma based on obstructed airflow (FEV_1 < 1.64 standard deviations) and a suggestive history. Only 29 of these adults had ever presented to their GP with their symptoms, suggesting an under-presentation rate of 66% (van Schayck et al., 2000). In children, a Danish study reported that only 31% of their cohort of 12 to 15 year old children with undiagnosed asthma had previously reported their symptoms to a doctor. In this study, undiagnosed asthma was defined as the co-existence of asthma symptoms (based on questionnaire data) plus one or more obstructive airflow abnormalities, including low FEV_1/FVC, positive challenge test to exercise or methacholine, or positive peak flow variability (over two weeks) in the absence of a patient reported physician diagnosis of asthma (Siersted et al., 1998).

Reasons for under presentation are multifactorial. Risk factors identified in children include low physical activity, high body mass index, serious family problems (self-reported), passive smoking, and the absence of symptoms of

rhinitis (Siersted et al., 1998). Whilst in both adults and children, poor perception of dyspnoea has been proposed as a possible explanation for under presentation to doctors (van Schayck et al., 2000, van Gent et al., 2007).

Even when patients do seek a medical consultation for their symptoms, clinical features of asthma often overlap with other conditions. This is particularly challenging at the extremes of age (Akindele et al., 2019) when "classic" asthma symptoms such as cough, wheezing, and breathlessness may be due to viral episodic wheeze in young children or chronic obstructive pulmonary disease in older adults. Moreover, children presenting with isolated symptoms, such as chronic cough, are unlikely to have asthma (Bush and Fleming, 2015) and represents a broad range of differential diagnoses (Chang et al., 2012). To complicate things further, the term "wheeze" is often used to describe a range of different respiratory noises by patients, such that parental reporting of wheeze has been found to be unreliable (Cane and McKenzie, 2001).

A qualitative study of 15 healthcare professionals in Scotland, reported that the "fear of incorrectly labelling patients with asthma may explain underdiagnosis of asthma for some patients" (Akindele et al., 2019). This lack of certainty was suggested as one reason for why some GPs continue to prescribe asthma treatment without a confirmed diagnosis.

The potential benefit of recommending routine lung function testing as part of the diagnostic process is to provide objective evidence for asthma, which will support clinicians to confirm a diagnosis with more certainty. However, none of the available tests are perfect and, as discussed earlier, three of the tests recommended by NICE (NICE, 2017) only demonstrate low to moderate sensitivity at best.

Asthma, by definition, is a condition characterised by variable airflow obstruction (BTS, 2019), and relapsing and remitting signs and symptoms which may not be present during a routine appointment. Even in patients with diagnosed asthma, clinical remission can occur (Vonk et al., 2004, De Marco et al., 2002). In a Canadian study, Aaron and colleagues screened a

random sample of 701 adults with a physician diagnosis of asthma within the past five years (Aaron et al., 2017). Each participant were assessed with a combination of symptoms monitoring, spirometry, and serial methacholine challenges. Asthma medications were tapered off gradually until either the patient had a positive test result or became symptomatic. Current asthma was excluded in 203 patients who had normal test results, no increase in symptoms despite weaning off medications, and after assessment by a respiratory specialist. Out of the 203 patients with current asthma excluded, 24 (12%) had previously had positive lung function tests to confirm asthma. Interestingly, during a year of follow up, 22 (11%) patients went on to have positive bronchial challenge test results, and six resumed asthma medications.

Clinical remission and subsequent relapse is not uncommon, and relapse rates of 12% to 35% have been reported in patients following clinical remission during childhood (Taylor et al., 2005, Sears et al., 2003a). Hence, whilst diagnosing asthma may be relatively straightforward in a patient presenting acutely with the “right” symptoms and positive tests for variable airflow obstruction, excluding asthma is not easy. Normal lung function tests, if these are performed when a patient is well, has mild symptoms, or is in remission, cannot reliably rule out asthma (Kaicker et al., 2014). This is reflected by the low diagnostic sensitivity, but better specificity, of spirometry and eNO reported in the latest NICE guideline (NICE, 2017).

To complicate things further still, different guidelines currently recommend different cut-off values for normal spirometry (Table 10); such that based on the same test, a patient may be classified as having a positive or negative test for airflow obstruction depending on which guidance is being followed. This will hopefully become less of an issue as the gold standard global lung initiative (GLI) equations and lower limits of normal (LLN) are more widely adopted (Quanjer and Weiner, 2014).

Table 10. Cut-offs for Spirometry by Guideline	
Guideline	**Recommended Normal Cut-off for Spirometry in Children**
NICE 2017	FEV_1/FVC > 70% or LLN
GINA 2019	FEV_1/FVC > 90%
BTS 2019	FEV_1/FVC > LLN
NAEPP	FEV_1/FVC > 85%

3.5.2 Monitoring Asthma Using Objective Tests

Earlier in this chapter, I have attempted to summarise the relationship between spirometry/eNO, and asthma severity in terms of current control, and risk of future morbidity. The question remains – do strategies to monitor asthma using objective tests actually confer better clinical outcomes?

Management strategies which aim to monitor and preserve lung function (monitored using spirometry), in addition to controlling symptoms in childhood, would intuitively reduce short and long term asthma morbidity. Indeed, appropriate asthma treatment has been shown to improve lung function.

Two small studies involving children with newly diagnosed asthma have demonstrated improvement in both asthma symptom score and spirometry parameters over 3-6 months following initiation of inhaled steroids (Anandi et al., 2016, Park et al., 2016). Interestingly, symptomatic improvement occurred before improvement in spirometric parameters (Anandi et al., 2016), again demonstrating that children with asthma can be relatively symptom free with abnormal lung function. However, studies comparing conventional symptom based management alone against clinical assessment including spirometry have been less favourable.

A small French study involving 44 children with severe asthma managed at a tertiary centre demonstrated no difference in the number of asthma exacerbations, hospital attendances, lung function, or quality of life over a year in children monitored remotely with daily FEV_1 when compared with

children reviewed in clinic alone (Deschildre et al., 2012). Although it should be noted that this study was underpowered based on the authors own power calculations. The reason for this is unclear from the published article.

The impact of using spirometry in a community setting has been investigated by an Australian group, which randomised 238 children with asthma to either be monitored with or without spirometry by their GPs over a 12 month period (Abramson et al., 2015). No differences were identified in terms of asthma quality of life, exacerbations, activity limitation or nocturnal cough. By contrast an adult study, which included adolescents (14-70 years), found that regular 3-monthly spirometry with medical review was associated with significantly improved asthma control in patients in general practice (Oei et al., 2011). It is worth highlighting that neither study included a standardised algorithm to guide adjustments of asthma treatment based on spirometry data.

Though no studies were identified which adjusted therapy according to FEV_1, a 2007 study, adjusted asthma treatment in 210 children according to either symptoms or degree of airway hyper-responsiveness (AHR) to methacholine (Nuijsink et al., 2007). After two years, although no difference was found in the number of symptom free days between treatment groups, FEV_1 was significantly higher in the AHR group (2.3% predicted). Similarly, in adults, AHR titrated inhaled steroid therapy for asthma has been shown to improve FEV_1 over a 2-year period when compared to standard management based on clinical assessment. Moreover, bronchial biopsies from the AHR group demonstrated a greater reduction in thickness of the sub-epithelial reticular layer and eosinophil counts, implying that improved control has an impact on chronic airway inflammation and remodelling (Sont et al., 1999).

What about eNO?

Multiple studies in children have not demonstrated superiority of eNO directed asthma monitoring, when compared with standard monitoring, in

terms of symptom-free days, lung function, quality of life, exacerbations and SABA use (de Jongste et al., 2009, Fritsch et al., 2006, Peirsman et al., 2014, Petsky et al., 2015, Pike et al., 2013, Szefler et al., 2008, Voorend-van Bergen et al., 2015b). Overall, ICS use appeared to be increased in the eNO directed treatment groups (Peirsman et al., 2014, Petsky et al., 2015, Szefler et al., 2008), but this was not a consistent finding (Pike et al., 2013, Pijnenburg et al., 2005a). Even when children were sub-grouped into the so-called “discordant” phenotype (high inflammation, low symptoms or high symptoms, low inflammation), no difference in clinical outcomes were noted between treatment groups (Voorend-van Bergen et al., 2015a).

However, when the eNO cut-off threshold is adjusted based on an individual’s atopic status, significantly fewer children in the eNO group (6 out of 27) had an asthma exacerbation (requiring oral corticosteroids) compared to controls (15 out of 28, P = 0.021) (Petsky et al., 2015). This Australian study defined elevated eNO as > 10 ppb in children with no positive skin prick test (SPT), > 12 ppb in children with one positive SPT, and > 20 ppb in children with > 2 positive SPT.

A reduction in asthma exacerbations with eNO directed monitoring has been reported in paediatric studies which have defined an “exacerbation” as increased symptoms (cough, wheeze, SABA use) regardless of the need for oral corticosteroids (Peirsman et al., 2014, Verini et al., 2010). In adults, whilst a small reduction in severe exacerbations in patients managed with eNO directed monitoring has been observed, these reductions have not reached statistical significance (Shaw et al., 2007, Smith et al., 2005c).

To summarise, whilst reduced FEV_1 is a potential prognostic indicator for future asthma exacerbations, and asthma treatment can improve both symptom scores and lung function, strategies which include regular spirometry monitoring do not appear to improve clinical outcomes in children. However, a management strategy which includes spirometry will only benefit patients if accompanied by an appropriate spirometry-directed treatment algorithm, which was not specified in previous studies. Similarly, although there is some evidence that regular eNO monitoring may reduce the number

of asthma exacerbations (need for oral corticosteroids, hospitalisation) in adults and children, the evidence is conflicting and there appears to be limited impact on quality of life, symptom control, and lung function as highlighted by a number of recent systematic reviews (Gomersal et al., 2016, Lu et al., 2015, Petsky et al., 2016b, Petsky et al., 2016c).

3.6 Summary

The current literature would suggest that misdiagnosis and mismanagement are common in childhood asthma. Although due to limitations in study designs, the reported figures for over- and under-diagnosis are probably overestimated.

Spirometry and eNO testing are potentially useful tools to provide objective measures of airflow limitation and airway inflammation, and both tests can be used to provide supportive evidence to confirm an asthma diagnosis. Objective tests can be useful but need to be interpreted in context. When performed at the right time, in a patient who presents with the right symptoms, and when interpreted using the right reference values, objective tests can help confirm asthma. Although none of the tests are sensitive, and are less able to exclude a diagnosis, “it is a safe principle that the more practitioners try and fail to identify airflow obstruction, the less likely is a diagnosis of asthma” (Bush and Fleming, 2015).

Measures of exhaled nitric oxide in particular appears to also have a role in identifying patients at risk of asthma attacks, and those more likely to respond to inhaled corticosteroid treatment. Whilst spirometry does not correlate well with current symptoms, and spirometry-directed management appears to have little impact on reducing asthma attack risk, persistently low lung function during childhood has been shown to be related to lower lung function in adults. It remains to be seen however, whether treatment strategies with the aim of normalising lung function during childhood will have any impact on adult lung function trajectories.

The onus placed on objective testing by the latest NICE asthma guideline, and indeed the focus of my MD project, would suggest that the absence of objective tests is the main reason for asthma misdiagnosis and mismanagement, but clearly this is not the case. Provision of objective tests is only one part, albeit an important part, of the solution.

CHAPTER 4: STUDY RATIONALE AND DESIGN

As detailed in chapters two and three, asthma in children is common, frequently misdiagnosed, and often inappropriately managed. Although the literature supporting the use of objective testing (including spirometry, BDR, and eNO) in the context of children's asthma is limited (compared to adults), and their role in diagnosing and monitoring children's asthma is unclear, there is evidence that abnormal lung function and raised eNO levels have both short and longer term implications for respiratory health and asthma related morbidity.

Guideline recommendations promoting the routine use of spirometry in asthma diagnosis and monitoring in children are not new, albeit not stated as explicitly as within the latest NICE guideline. In the US, despite NAEPP recommendations almost a decade ago, less than a quarter of community paediatricians and practitioners report using spirometry routinely to manage asthma in children (Dombkowski et al., 2010).

The discordance between recommended evidence based care and observed clinical practice represents a failure of *knowledge translation*, which can be described as the gulf between "what is known" (and/or recommended) and "what is done" (Davis et al., 2003). This deficiency in implementing a (potentially) beneficial intervention into routine clinical practice was identified in a 2006 NHS research funding review (Cooksey, 2006); and became an area of focus for the National Institute for Health Research through the formation of CLAHRCs (Collaborations for Leadership in Applied Health Research and Care), and promotion of *implementation research* (Rowley, 2014). The classification of translational gaps has evolved over time, but there is now general consensus for a 5 phase (T0-T4) definition (Table 11). The failure of implementation and dissemination of clinical guidelines into practice, explored by this research project, would represent a T3 gap in knowledge translation (Fort et al., 2017).

Table 11. Translational Gap Definitions		
Gap	**Definition**	**Explanation**
T0	Translation to discovery	Involves basic science research to generate new knowledge to meet unmet needs
T1	Translation to humans	Brings ideas from basic research through to human testing
T2	Translation to best practice recommendations	Establishes effectiveness in humans and production of clinical guidelines
T3	Translation to widespread use	Implementation and dissemination of recommendations into common practice
T4	Translation to impact at population level	Explores outcomes and effectiveness of implementation on whole populations

Implementation research is an emerging field in medical science (Wallin, 2009) which asks questions concerning the implementation of an intervention into clinical practice. These may include the initial barriers to implementation, the processes of implementation, and the results following implementation (Peters et al., 2014). The overall aim being to understand what, why, and how interventions work in “real world” settings. Properly conducted implementation research, focused on context, can help implementers foresee and anticipate problems during the implementation process (Peters et al., 2013).

In 2008, the Medical Research Council (MRC) updated their guidance on the development, evaluation and implementation of complex interventions to improve health (Craig et al., 2008). Whilst the original MRC framework (Campbell et al., 2000) advocated a model based on the phases conventionally associated with the evaluation of new drugs (Figure 14), the updated 2008 framework consists of only four phases and recognises that

these may not necessarily follow a linear or cyclical sequence, providing a more flexible model (Figure 15).

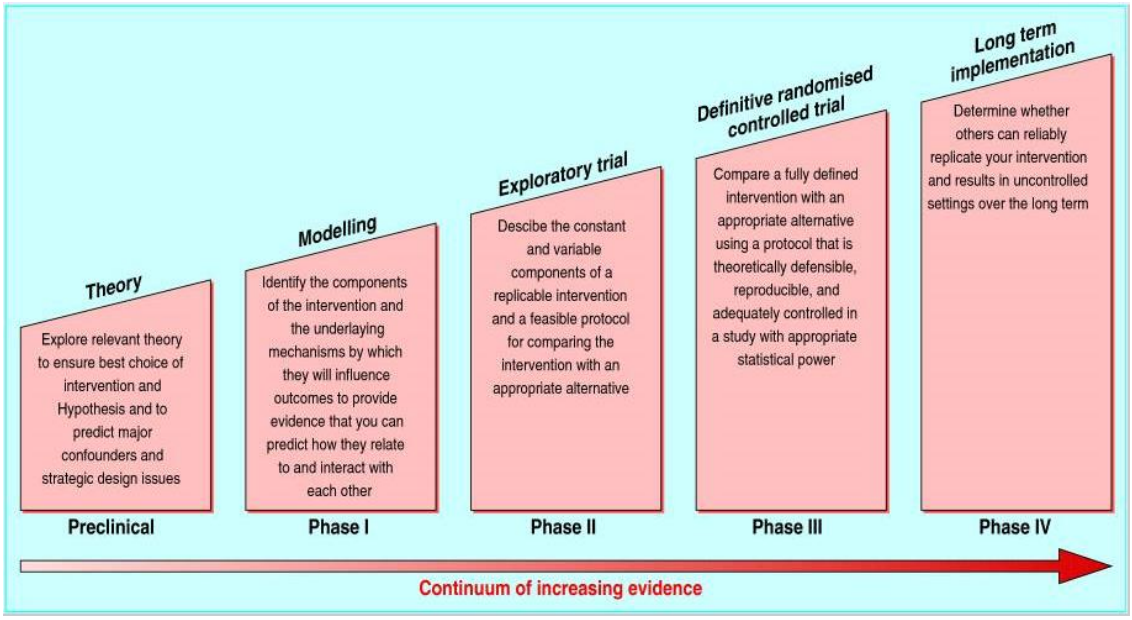


Figure 14. Original MRC Framework (source: Campbell *et al.* 2000)

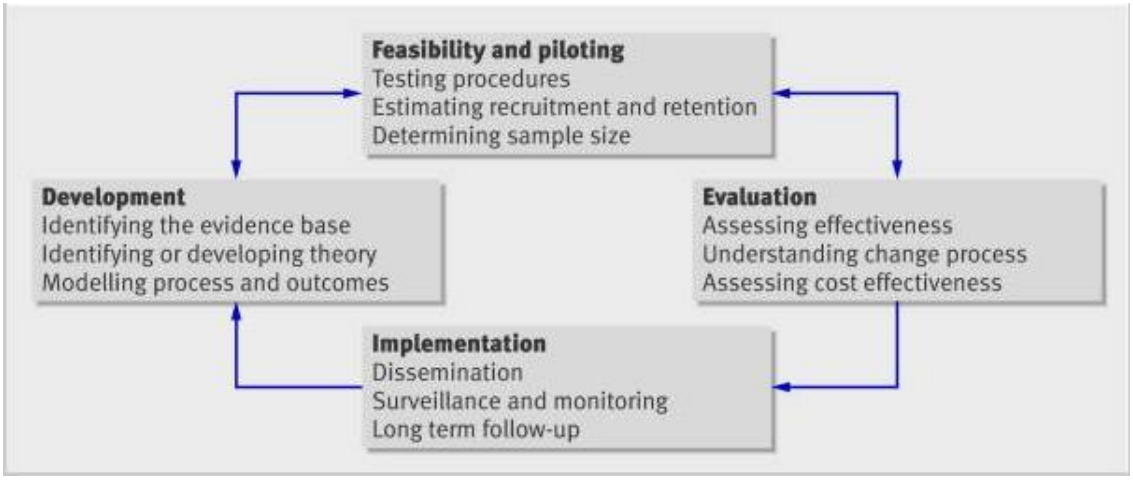


Figure 15. Updated MRC Framework (source: Craig *et al*. 2008)

The development phase requires an intervention's theoretical rationale to be established, whilst the feasibility and piloting phase involves testing of

feasibility in terms of acceptability, compliance, delivery of the intervention, recruitment and retention.

Following development of an intervention, and feasibility has been demonstrated, the intervention should be evaluated for effectiveness. Experimental designs such as randomised controlled trials are preferred to observational designs, but the updated MRC framework recognises that these are not always practicable. Finally, the findings should be disseminated as widely and as accessibly as possible, with further research to monitor the outcomes of implementation. Studies are also needed to address the scale-up of interventions into routine practice.

The MRC complex interventions model provides a structured and iterative framework with which to develop, evaluate, and implement new interventions. It also encourages careful, systematic, background work in order to refine an intervention prior to implementation (Craig and Petticrew, 2013). However, sufficient time and resources are needed to fully apply the principles of the MRC framework, a limitation which has been highlighted in previous studies of its use (Lakshman et al., 2014, Bobrow et al., 2018). A further criticism of the updated MRC framework relates to its applicability to policy-led interventions, which are often ill defined, and does not take into account the gap between “policy as a statement of intent and actual practice” i.e. adoption of recommended practice may only be partial or skewed (Mackenzie et al., 2010).

As I was limited in both time (only allowed two years out of my training programme) and resources (only myself and a research nurse available for the day-to-day work), the MRC framework was not a practicable model on which to base my programme of study. Moreover, the intervention I was aiming to investigate had already been evaluated within published national guidelines (NICE, 2017), and recommended for use nationally.

As discussed earlier, the recommendations made within the NICE asthma guideline would represent a radical change in the way children’s asthma is managed in general practice (GP), and has been met with criticism partly

fuelled by the lack of pragmatic studies using objective testing in children within the “real-world” GP setting.

Obstacles to implementation can be seen as resistors to change, and can be conceptualised using Kurt Lewin’s force-field analysis tool (Lewin, 1943). Previous US and Australian studies of providing spirometry within the community setting have identified concerns including: lack of experience at performing lung function tests, lack of capacity to support additional asthma clinic time and lack of funding for the extra equipment needed. These factors constitute potential resistors to implementation and it is important to identify whether they exist within our community setting also. Force-field analysis theory argues that situations are maintained in equilibrium by a balance of the forces that drive change versus the barriers that resist it. For change to occur, the driving forces must outweigh the resistors. When planning this MD project I therefore envisaged a two-part study; firstly to identify the resistors against change, in terms of implementation related barriers, and secondly the change facilitators relating to the additional clinical information provided by performing objective testing.

Effectiveness-implementation hybrid studies allow for this two-fold objective, by testing the effects of a health intervention on relevant clinical outcomes, whilst observing and gathering information on implementation (Peters et al., 2013). Hybrid designs represent a continuum between pure effectiveness research and pure implementation research (Bernet et al., 2013); however, three main types have been described which differ based on the emphasis placed on either testing the intervention, or the implementation (Curran et al., 2012). Each type describes two aims *a priori* – one to test intervention effectiveness, and one to evaluate implementation strategy (Table 12) (Bernet et al., 2013).

Table 12. Types of Hybrid Study Designs			
Study Design	**Type 1**	**Type 2**	**Type 3**
Research Aim	Primary aim: determine effectiveness of an intervention Secondary aim: better understand context for implementation	Primary aim: determine effectiveness of an intervention Co-Primary aim: determine feasibility and/or (potential) impact of an implementation strategy	Primary aim: evaluate implementation strategy Secondary aim: assess clinical outcomes associated with implementation

Type 1 designs focus primarily on the effectiveness of an intervention whilst exploring the barriers and necessary resources for implementation. A type 2 hybrid study has a dual focus on both clinical and implementation outcomes, which allows for the simultaneous testing of an implementation strategy during an effectiveness trial. Lastly, type 3 hybrid studies focus primarily on implementation outcomes (i.e. data from an implementation strategy) whilst also collecting data on clinical outcomes related to implementation. A type 3 hybrid study is in essence an implementation study coupled with an evaluation of patient outcomes. The secondary clinical outcomes are examined observationally, without patient randomisation or a control group. This type of design is most appropriate when there is a strong call for implementation despite a limited evidence base (which is the case for objective testing for children in primary care), and works best when clinical outcomes can be assessed passively from medical records (Landes et al., 2019).

One of the key advantages of a hybrid study design is in its recognition that both implementation and clinical outcomes are intrinsically linked; and

arguably, by exploring these aspects of an intervention simultaneously, the speed of translation of research findings into routine adoption can be improved (Curran et al., 2012). Importantly, this trial design would allow me to explore both the barriers and potential benefits of providing objective testing for children in primary care, in a time and resource efficient manner within the constraints of my limited funding and approved time out of clinical training.

Using the principles of a type 3 hybrid study design, CHAMPIONS is a pragmatic prospective observational study designed primarily to evaluate the barriers (including training and capacity requirements) to implement spirometry, reversibility, and eNO testing for children in general practice, whilst exploring the additional clinical utility these tests have on the way in which asthma is diagnosed and monitored in primary care.

Proctor *et al.* proposes eight conceptually distinct implementation related outcome measures based on a narrative review of the existing literature (table) (Proctor et al., 2011). The authors aimed to provide clarity of language in the field of implementation research; arguing that a standardised taxonomy of implementation outcomes can help to frame more focused research questions (Table 13).

Table 13. Implementation Outcome Variables		
Outcome	**Definition**	**Related Terms**
Acceptability	The perception amongst stakeholders that an intervention is agreeable	Comfort, credibility, relative advantage
Adoption	The intention, decision, or action to employ a new intervention	Uptake, utilisation, intention to try
Appropriateness	The perceived fit or relevance of an intervention in a particular setting	Relevance, perceived usefulness
Feasibility	The extent to which an intervention can be carried out in a particular setting	Practicality, actual fit, utility
Fidelity	The degree to which an intervention was implemented as planned	Adherence, integrity, delivery as intended
Cost	The incremental cost of the implementation strategy	Marginal cost, total cost
Coverage	The degree to which the population that is eligible to benefit, actually receives the intervention	Reach, access, effective coverage
Sustainability	The extent to which an intervention is maintained	Maintenance, durability

Table. Implementation Outcome Variables. Source: (Proctor et al., 2011)

Using the above framework as a guide, I agreed on a set of research questions with my supervisors (chapter 5), and designed the methodology (chapter 6) around these, in order to explore the outcomes described in more detail below.

4.1 Implementation related outcomes

Acceptability measures the perception amongst stakeholders that an intervention is agreeable. For objective testing, it is important for

acceptability to be measured from the perspectives of clinical staff, families, and the children themselves. If the tests are not palatable to any of these stakeholders, then they will potentially either not be offered by staff, or not be accepted by families.

Adoption provides a measure of the initial intention, or perceived "need", to adopt a new innovation or procedure into practice, and can be measured from the perspective of the provider or organisation (Proctor et al., 2011). Whilst *appropriateness* measures the perceived "fit" of an intervention to address a particular issue. Although appropriateness is conceptually similar to acceptability, and the terms are often used inconsistently (Proctor et al., 2011), they represent distinct, but equally important, implementation related outcomes. An intervention can be appropriate, in terms of clinical utility, but not acceptable to the patients or staff i.e. too difficult or too much time required to carry out.

With failure rates of change programmes reportedly as high as 70% (Balogun and Hailey, 2004), identification of perceived barriers and the motivation or "readiness" for change is important. Weiner (Weiner, 2009) treats organisational readiness as a shared psychological state in which members feel committed to implementing change and feel confident in their collective abilities to do so. He describes organisational readiness as both a multi-level (individual, group, departmental, organisational) and multi-faceted (commitment and change efficacy) construct.

Motivation for change can further be conceptualised using the capability, opportunity, motivation, and behaviour (COM-B) model. COM-B theorises that any given behaviour is a result of the interaction between capability, opportunity, and motivation (Table 14). A new behaviour therefore requires the change of one or more of these components (Michie et al., 2011) to take place. The COM-B model can therefore be used to map the perceived barriers against adoption of objective testing identified from this study.

Table 14. Components of COM-B Model	
Component	**Description**
Physical Capability	Skills or ability to perform a task
Psychological Capability	Knowledge or understanding
Physical Opportunity	Environmental factors – time, location, resources
Social Opportunity	Cultural norms, social cues
Reflective Motivation	Beliefs about capabilities, benefit
Autonomic Motivation	Emotions, incentives, rewards

A qualitative approach was initially considered to address the outcome measures – adoption, appropriateness, and acceptability. The aim of qualitative research is to understand the social reality or perceptions of individuals, groups, or organisations; using a variety of methods which allow more open ended responses, including focus groups and interviews. Using a descriptive and narrative style, qualitative methodology allows for perspectives to be explored in more detail, and for responses to be analysed without destroying complexity and context (Ochieng, 2009). However, the time required for data collection, analysis and interpretation are lengthy.

After discussion with my supervisors, it was agreed that a qualitative approach would be difficult to fit into the available timeframe for this project, particularly after factoring for time required to obtain ethics and R+D approval. I also took advice from two of our GP collaborators, who felt that uptake for interview and focus groups from GP staff may be poor due to clinical pressures and the time needed for these meetings to take place.

I therefore decided to collect information on acceptability, appropriateness, and adoption using questionnaires. These have the advantage of being easy to administer, require less time to complete, and can be administered remotely at the convenience of the respondents (Schmitz, 2012). Survey data is also arguably more reliable as they allow data to be collected from larger population samples using questions phrased in the exact same way for each person. However, this in itself also poses some limitations to survey

methodology due to the inflexibility of questions, which do not allow room for complexity or non-standard responses. I have tried to account for this limitation to an extent by including free text responses within the questionnaires to allow more open-ended responses to the questions.

Feasibility is described as the extent to which an intervention can be successfully performed within a target setting. For instance, spirometry and eNO may be both acceptable and appropriate within secondary care, but not feasible within primary care due to training and resource requirements, and poor cooperation from young children. I plan to measure these by recording the length of training required for primary care staff to be able to perform and interpret spirometry and eNO testing, the time needed to carry out these tests, and the proportion of children able to successfully perform both tests.

Cost relates to the cost impact of implementing a new intervention. Due to the complexity and skills required to calculate cost, we collaborated closely with a health economist to investigate this outcome. The cost analysis is planned to be conducted separately by the health economist using data acquired from my work following completion of the study and is not discussed in detail within this thesis. However, the analyses will broadly consist of four main components: 1) the clinical staff's time and associated costs to provide and receive the education and training, 2) the total clinical staff's time and costs to perform and interpret the two tests as part of an asthma review, 3) change in health care utilisation, and its' associated costs, six months before and following the asthma review, and 4) change in asthma related quality of life at the time of baseline asthma review and at six months follow-up.

The time and resources available for me to conduct this study, would not have allowed sufficient opportunity to also include coverage, and sustainability, whilst the design itself (with the research team present at every clinic) would not have allowed evaluation of fidelity.

4.2 Clinical Related Outcomes

In this study, I planned to explore several clinically relevant outcomes related to the implementation of objective testing. Firstly, to quantify the prevalence of abnormal lung function and eNO in children managed within the community setting, and exploring how these objective measures relate to reported clinical control and unplanned healthcare attendances. Secondly, to determine whether objective testing would allow asthma to be confirmed in children not currently on the practice asthma register but who have had symptoms in the previous year. Finally, to observe whether clinical control and/or number of unplanned healthcare attendances change following an asthma review which has included objective testing. These outcomes were chosen to determine whether abnormal lung function and eNO are common amongst children with asthma or suspected asthma in primary care, whether objective tests provide any additional information during an asthma review over and above a symptoms based assessment alone, and whether they can help primary care staff to confirm an asthma diagnosis in children.
In addition to addressing the outcome measures described above, we plan to use our data to inform the design of a future trial in the GP setting. This is envisaged to be a larger randomised controlled trial comparing current paediatric asthma care in the community, with asthma care which is directed by spirometry and eNO. The aim being to investigate the clinical impact of a spirometry and/or eNO targeted asthma care algorithm in children. The proposed design of this study will be described further in the final chapter of this thesis.

CHAPTER 5: AIMS AND OBJECTIVES

5.1 Research Questions (RQ)

Relating to Implementation Outcomes:

1. What are the perceived barriers to implementation of spirometry and eNO testing for children in general practice? (Adoption and Appropriateness)
2. Are objective tests in children acceptable to staff, families, and children in primary care? (Acceptability)
3. How much training and additional clinic time is needed for general practices to provide these tests? (Feasibility)
4. What proportion of children, from the age of five years, are able to perform spirometry and eNO testing in primary care? (Feasibility)

Relating to Clinical Outcomes:

5. What is the prevalence of abnormal spirometry, eNO, and poor asthma control in children with either suspected or an existing diagnosis of asthma managed in primary care?
6. What is the proportion of children in whom a symptoms-based assessment alone would have failed to identify poor lung function and airway inflammation?
7. What proportion of children with suspected asthma (not on the practice register but receiving asthma medications) could have asthma confirmed with objective testing?
8. Are there observable changes in current asthma control and number of unplanned healthcare attendances in children following a review, which includes objective testing?

5.2 Aims

The main aims of this study were to evaluate relevant implementation and clinical outcomes related to the delivery of spirometry and eNO testing for children aged 5-16 years in primary care.

The secondary aim was to gather implementation data to inform the future design of a larger randomised controlled trial to investigate the impact of childhood asthma management in primary care using a spirometry and eNO directed treatment algorithm.

5.3 Outcome Measures

Implementation outcomes

To quantify the:

- Proportion of general practice staff who found providing spirometry and eNO testing for children acceptable
- Proportion of children and parents who found spirometry and eNO testing acceptable
- Length of training required for GP staff to independently perform/interpret spirometry and eNO in children
- Time needed (per child) to perform paediatric spirometry and eNO testing in general practice
- Proportion of children in whom usable spirometry and eNO data can be obtained

Clinical outcomes

To quantify the:

- Prevalence of abnormal lung function (by spirometry and eNO)
- Proportion of children not on their GP asthma register, but who have been prescribed asthma medications in the past year, in whom a

diagnosis of asthma could be confirmed using spirometry and eNO testing

- Relationship between reported asthma control (assessed by asthma control tests) and objective test results
- Change in number of unplanned healthcare attendances and asthma control scores at 6 months follow up following an asthma review which included objective tests

CHAPTER 6: METHODS

6.1 Outline of study

CHAMPIONS was a prospective observational cohort study designed to evaluate the resources required to implement routine spirometry and exhaled nitric oxide testing for children in primary care, and to explore their clinical utility in diagnosing and monitoring children's asthma. The study involved 10 general practices in Leicestershire and Northamptonshire with a combined patient population of over 100,000 people, and ~1200 children eligible to take part. Recruitment took place over 15 months between June 2016 and September 2017. See Figure 16 for A GANTT chart of study events.

The study outline was as follows:

1. Potential general practice sites were identified through the clinical research network (CRN), and searching Public Health England's National GP profiles database to identify practices of differing sizes and demographics.
2. Study information was sent to practices and a face to face meeting was organised with sites which expressed an interest to participate.
3. The practice manager and clinical staff at each participating practice (who were directly involved with performing routine asthma reviews in children) were sent anonymised "readiness for change" questionnaires to explore their opinions and attitudes towards providing spirometry and eNO testing for children in general practice.
4. A paediatric spirometry and eNO training package was developed; adapted from an existing training package used to deliver adult spirometry training within Leicestershire.
5. Spirometry and eNO training was provided for clinical staff at each practice who were directly involved with performing routine asthma reviews in children.

6. Children meeting the inclusion criteria (see below) were invited to attend for asthma review (performed by practice staff) and consent was sought to take part in this study.
7. Spirometry and eNO testing were attempted in all children, and data were collected from children in whom consent was obtained including: spirometry and eNO test results, time to perform tests, current asthma control assessed by questionnaires, and current asthma medications.
8. Feedback was sought from practice staff, parent and child following each review.
9. Follow up data were collected via postal questionnaires and by review of patient electronic records 6 months following the initial review.

Figure 16. GANTT Chart to Show Study Timeline

Study Task	Time in Months							
	-3	-6	-9	-12	-15	-18	-21	-24
Identified Participating Practices								
Site Survey and Change Readiness Questionnaires Sent								
Developed training package								
Delivered training to healthcare workers performing the tests								
Identified patients under investigation/review for asthma								
Performed asthma reviews								
Collected health outcome data								
Data analysis								
Dissemination and publication of study results								

6.2 Approvals

Ethics approval was sought from the NHS research ethics committee. Application was submitted via the integrated research application system (IRAS) and received on 23rd March 2016. Responses to the committee's

initial comments were further submitted on 5th April 2016 and a favourable ethical opinion was confirmed on 8th April 2016 by the East Midlands - Nottingham 1 Research Ethics Committee. REC reference: 16/EM/0162 (see appendix).

We also sought R+D approval from the Leicester City clinical commissioning group and the Nene and Corby clinical commissioning group in order to perform this study within primary care. Assurances were received for us to commence our study on 11th April 2016 and 26th April 2016 respectively.

Research sponsorship was provided by the University of Leicester, and a green light approval letter was issued on 12th April 2016: UoL0566 (see appendix).

We applied for adoption of this study onto the National Institute for Health Research's (NIHR) Clinical Research Network portfolio and was successfully added on the 12th May 2016: CPMS 30922.

6.3 Funding

Financial support for the study equipment, consumables and reimbursement for general practice time was provided by Circassia Pharmaceuticals. Funding for a full time research nurse was provided by the Midlands Asthma and Allergy Research Association (MAARA). Salary for the project fellow (David Lo) was provided by Health Education East Midlands. None of the funding bodies were involved with the design of the study, data analysis, or data interpretation for this study.

6.4 Primary Care Sites

Potential general practice sites were chosen based on their size and patient demographics. This information is publically available online (Public Health England, 2017). Identification of potential practices was also facilitated by the Clinical Research Network – East Midlands (CRN-EM). We sought to include practices of different sizes, and which served populations of different

ethnic and socioeconomic profiles. Practices were contacted directly by the project fellow via phone or email, in addition to being sent a standardised invitation letter and information sheet (see appendix). In total, 17 general practices were contacted and 10 expressed an initial interest to participate.

Face-to-face meetings with the practice manager(s) and clinical staff were arranged with all 10 interested practices to provide a short presentation explaining the project and to answer any queries. All 10 practices agreed to participate following these meetings, and were asked to sign a research agreement with the study sponsor (University of Leicester).

Site survey questionnaires (see appendix) were completed for each practice by the project fellow which included information about each practice's patient population and current asthma review set up.

6.5 Study Participants

Children fulfilling the inclusion criteria below were invited for an asthma review at each practice. The inclusion criteria were designed to identify children who either a) were already diagnosed with asthma or b) did not have an existing asthma diagnosis but who had received asthma medications in the previous 12 months (suspected asthma).

Children were identified from the participating practice's electronic register (SystmOne) using search criteria matching the inclusion criteria below. Searches were performed by, and invitations sent by the practices themselves.

A priori, we proposed pragmatically to introduce the intervention (implementation of spirometry and eNO testing) to a minimum of 3 general practices and to attempt lung function testing in a minimum of 500 children based on the expected capacity of the project fellow and research nurse. This was a conservative target only, and we planned to recruit more than three general practices in order to demonstrate feasibility in practices of differing patient and staffing numbers. Once 10 practices had been recruited, it was agreed between myself and my supervisors that we would not

physically be able to manage any more practices within the time frame and resources available to us.

6.5.1 Inclusion Criteria

Male or female, aged 5-16 years who:

1. Were on the practice asthma register or
2. Had been prescribed inhaled corticosteroids within the last 12 months, including beclometasone, fluticasone and budesonide. Searches were also conducted specifically for 'brands' that are commonly prescribed and included 'clenil', 'seretide', 'symbicort', and 'qvar' or
3. Had been prescribed ≥ 2 Salbutamol MDI's in the last 12 months or
4. Had received oral corticosteroids for acute wheeze/cough/breathlessness in the last 12 months
5. Were able and willing, in the opinion of the investigator, to give informed consent

6.5.2 Exclusion Criteria

1. Children and young people < 5 years and > 16 years
2. Unable or unwilling, in the opinion of the Investigator, to give informed consent

6.6 Readiness for Change Questionnaire (Adoption and Appropriateness)

Implementation of spirometry and eNO testing for children in primary care represents a change to current practice. Few organisational change initiatives are very successful, with some failing completely (Kotter, 1995). A lack of understanding of an organisation’s readiness to accept the proposed change prior to implementation is a causative factor (Pellettiere, 2006).

Organisational readiness for change has been described as a multi-level, multi-faceted construct and varies depending on how much organisational members' value the proposed change (Weiner, 2009).

A readiness for change questionnaire (RfCQ) was designed and sent to GPs, practice nurses, HCAs and practice managers at each participating site (see appendix). The purpose of the RfCQ was to address the adoption and appropriateness outcome measures by exploring perceived barriers against implementation and describing general practice staff attitudes towards the need for a change to current practice (is there a problem with asthma misdiagnosis and mismanagement?) and whether the proposed objective tests are appropriate?

We had initially considered using a qualitative approach, such as focus groups or face-to-face interviews, to address this outcome measure. However, as discussed in chapter 4, the time and resources available for this project would not have made a qualitative methodology practicable, particularly in light of the other outcomes we were hoping to address within the project timeframe. I discussed my concerns with my supervisors and project collaborators, who agreed that a questionnaire based method would be a more time efficient method to explore perceived barriers, accepting that there are limitations intrinsic to a survey based design; these are discussed later in chapter 9.

There are three key domains assessed by a RfCQ – attitudes, conditions, and resources (Learning Network on Capacity Development, 2017). These domains relate to the perceived capability and the need for change to occur. An RfCQ should include a consideration of individual capability, resource availability, demand for change, and the perceived fit of the proposed intervention/solution to the problem (Weiner, 2009). With this in mind, I designed the RfCQ to include questions which explore – staff attitude towards the role of spirometry and eNO testing in childhood asthma (attitudes), their perceptions towards the need for a change to current practice (condition), and the resources available to deliver the tests (resources) (Learning Network on Capacity Development, 2017). Responses

were collected using a 5-point Likert scale in addition to allowing for free text input.

The first versions of the RfCQ were Microsoft Word based and written with input from Dr. Damian Roland (an honorary associate professor with research interests in educational interventions). It was discussed that an electronic version may facilitate accessibility and encourage a better response rate for the RfCQ. Once we were happy with the wording of the questionnaire, I transcribed the paper version into an electronic web-based questionnaire, which was accessible via a web link.

Links to the RfCQ were then sent to three general practitioners for comment in order to establish face validity (DeVon et al., 2007, Collingridge, 2014). One GP was a clinical academic and Professor of primary care medicine, one a partner and asthma lead at her own practice, and one was a newly qualified GP with an interest in medical education. Face validity refers to the degree to which the respondents judge the questionnaire items to be valid and indicates whether the questionnaire appears to be appropriate to the research question. The purpose is for experts with appropriate expertise to evaluate the appearance of the questionnaire in terms of its readability, feasibility, consistency of style and formatting, and the clarity of the language used. It is the easiest form of validation but also the weakest form as it is based less on the technical components of the questionnaire items, but rather on whether the items appear to be measuring a construct that is meaningful to respondents. Although this is the weakest way to establish the validity of a questionnaire, face validity may motivate respondents to answer more truthfully. Thus, face validity is a form of usability rather than reliability.

The RfCQ was then piloted amongst members of our research group as a final check to ensure that the questionnaire content was appropriate and comprehensible, and that the online platform hosting the questionnaire was intuitive and not confusing.

The final agreed version of the RfCQ was delivered electronically via the “typeform” online platform (https://www.typeform.com/) which allowed

responders to complete the questionnaire in their own time and for responses to be returned anonymously.

Web links were emailed to practice managers at each participating practice, asking them to complete the questionnaire themselves, and to forward to all GPs, nurses, HCAs, and managers within their practice. The same standardised email request was used for all practices involved. All responses were anonymous and collated automatically using the typeform online platform.

6.7 Education and Training (Feasibility)

Each participating practice identified appropriate clinical staff to be trained to perform and/or interpret spirometry and eNO tests in children. These were staff members who would be expected to perform asthma reviews and/or lung function testing in children independently following training i.e. GPs, practice nurses (PNs), nurse practitioners (NPs) and health care assistants (HCAs).

Leicestershire Partnership Trust (LPT) already provide adult spirometry training to general practices within Leicestershire, and a training programme is in place. They do not currently provide training for paediatric spirometry.

The current adult training package is delivered to individual/multiple PN/HCAs during a 2-hour face-to-face training session and consists of a PowerPoint presentation on performance and interpretation of spirometry followed by hands on training with a spirometer. The trainee is then asked to observe the LPT trainer perform at least 10 spirometry tests in patients before performing supervised spirometry themselves. Training is complete once set competencies have been achieved through direct observation by the trainer, self-assessment by the trainee and mutual discussion. In LPT's experience, competency is usually reached following 20-40 supervised procedures.

The paediatric training package delivered as part of the CHAMPIONS study was modelled directly on the existing adult spirometry training package, with

the addition of eNO. Based on GP feedback during initial meetings, we decided to provide 3 levels of training depending on the job role of prospective trainees:

1. Perform spirometry and eNO testing but not to interpret
2. Interpret spirometry and eNO test results but not to perform
3. Perform and interpret spirometry and eNO tests

Prior to training, a training needs assessment was performed for each trainee to document prior experience and to determine training needs.

The LPT Respiratory Specialist Nurse Lead (Karen Moore), who leads on adult training, was directly involved with the development of the CHAMPIONS training programme. I was given access to all training materials used in the adult spirometry training package, and adapted these for use for paediatric spirometry – including the face-to-face presentation, and competencies list. Although I had to include eNO learning objectives within the paediatric training package, this was achievable within the same two hour face-to-face training timeframe as, unlike in the adult training package, we did not need to cover COPD.

Similar to the adult spirometry training currently provided in Leicestershire, GP staff completing this training would not be automatically ARTP accredited. However, the aim was for them to achieve the necessary level of competencies to be able to apply for ARTP accreditation following completion of the CHAMPIONS training package. The training package and competencies list were therefore reviewed, commented on, amended, and agreed with the senior academic and clinical respiratory physiologists within our team.

The face-to-face training was practiced on junior doctors and nurses working within our base hospital, and amended based on immediate verbal feedback received on language, content, and design. Further feedback was received following delivery of training at each practice. Additional training materials

were developed in response to this feedback, including handouts and crib-sheets to facilitate learning and retention of information. The final agreed CHAMPIONS training package consisted of 2 parts plus handouts, and was delivered by the project fellow and research nurse:

Part 1: Two-hour face-to-face teaching

This session addressed the theoretical and practical aspects of spirometry and eNO testing in children. It was delivered in small teaching groups (often as few as 1-2 people), and included a short PowerPoint presentation, demonstrations, practice, and teaching material handouts. Topics covered included: indications for testing, set up and calibration of equipment, test procedure (including incentive spirometry), recognition of acceptable spirometric traces, and interpretation of data.

We included an update on the proposed new NICE guidelines with an emphasis on the proposed changes to current practice. Additionally we discussed the proposed diagnostic algorithm for children under investigation for asthma and the objective tests underpinning a diagnosis of asthma in children.

Part 2: Practical training

The second part of training was delivered alongside the asthma review clinics. Trainees were asked to observe the trainer perform at least five spirometry and eNO tests in children. This number was reduced if the trainee already had experience with performing adult spirometry. Subsequently, trainees were directly supervised to perform and/or interpret spirometry and eNO tests. Supervision continued for at least 10 tests or until assessed as competent by both the trainer and trainee themselves (see appendix for competency forms).

Handouts

The contents of the training pack included:

1. Copy of spirometry presentation
2. Quick reference sheet
3. Patient pre-test check list (for parents)
4. Pre-test check list (for health professionals)
5. Spirometry procedure
6. BTS and NICE diagnostic algorithms
7. BTS clinical clues to alternative diagnosis in wheezy children
8. BTS clinical clues to alternative diagnosis in adults (12+)
9. BTS factors to consider in an initial structured clinical assessment
10. BTS summary of asthma management for adults (12+)
11. BTS summary of asthma management for children
12. BTS categorisation of inhaled corticosteroids by dose – children
13. Commonly used asthma inhalers poster
14. Spirometry crib sheet
15. Asthma action plan blank template
16. Peak flow reference values
17. Peak flow diary blank template
18. Paediatric spirometry competencies (interpret/perform) for CHAMPIONS study
19. Paediatric spirometry log for CHAMPIONS study

Training Data

A log book was maintained which recorded attendance at the face-to-face training, and the number of observed tests performed and/or interpreted by trainees until competencies were achieved. The total time required to achieve the pre-defined competencies in spirometry and eNO testing could then be calculated for each trainee.

6.8 Clinic Set Up

Children identified from the practice databases were invited to attend a designated children's asthma review clinic led by a member of the practice staff being trained to interpret spirometry and eNO testing. Two rooms were available at each clinic. Room one was for the research team to seek consent, collect patient data, and administer asthma control questionnaires (Table 15). Spirometry and eNO testing were also performed in room one, either by the GP, nurse or HCA being trained to perform the tests (trainee 1). The child and parent then moved to room two for their "usual" asthma review carried out by the practice staff member being trained to interpret spirometry and eNO (trainee 2). If the trainee is being trained to both perform and interpret lung function tests, then trainee 1 and 2 may be the same person (Figure 17).

Each patient was allocated 20 minutes in room one, followed by 20 minutes in room two, such that each appointment was 40 minutes long per patient. Twenty minutes for a review was chosen based on input from our GP collaborators as being reflective of the amount of time allocated for a standard asthma review.

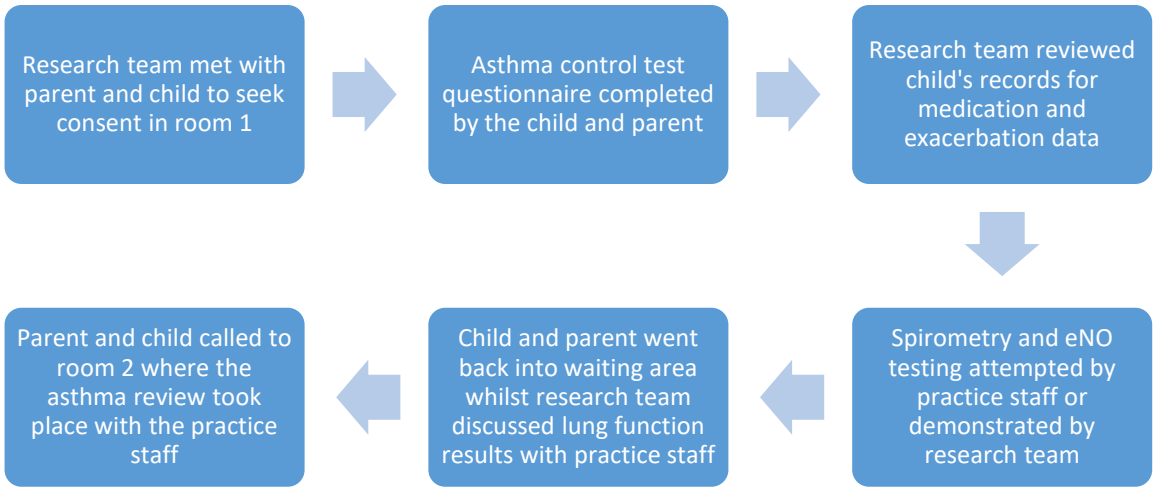


Figure 17. Flow Chart to show order of events

Table 15. Example Clinic Structure			
Room 1 – Study Team +/- HCA		Room 2 – Practice Nurse/GP	
Time	For Consent, data collection, study questionnaires and lung function	Time	Asthma Review with lung function interpretation only
1340	Patient A	1400	Patient A
1400	Patient B	1420	Patient B
		1440	10 minute catch up
1430	Patient C	1450	Patient C
1450	Patient D	1510	Patient D
		1530	20 minute break/catch up if needed
1530	Patient E	1550	Patient E
1550	Patient F	1610	Patient F
		1630	10 minute catch up
1620	Patient G	1640	Patient G
1640	Patient H	1700	Patient H
		1720	Finish

6.9 Study Procedures

6.9.1 Informed Consent

Patient information sheets (PIS) were posted out with the invitation letters to attend clinic (see appendix). On the day of the clinic, a member of the research team met with families in a separate room prior to their review. Potential participants were allowed time to consider the information, and the opportunity to question the study team before deciding whether to participate in the study.

In children and young people aged 5-15 years, we sought written consent from the parents, and verbal assent from the child. In participants aged 16 years, we sought written consent from the young person themselves.

We sought consent to: 1) access the child's electronic records in order to obtain information including recent exacerbations and medications

prescribed, 2) record answers to asthma control questionnaires onto the case report form (CRF), 3) time how long it took to perform each lung function test and 4) ask their GPs to contact them in 3-6 months' time by post to complete repeat asthma control questionnaires. The consent forms were approved by ethics committee (see appendix). The original signed form was retained at the study site within the Site File (SF). A copy of the signed consent form was given to participants and a copy scanned onto the participant's medical records.

6.9.2 Asthma Control Tests

Standardised asthma control tests were used to assess asthma control in our cohort. Participating children were asked to complete either the asthma control test (ACT) (Nathan et al., 2004), for children ≥ 12 years, or the childhood asthma control test (CACT) (Liu et al., 2007), for children aged 4 to 11 years, with support from their parents. The ACT consists of five questions relating to the previous four weeks. Total score range is from 5-25. The CACT consists of seven questions relating to the previous four weeks, of which four are answered by the child and three by the parents. The total score can range from 0-27. Both the ACT and CACT are validated to test asthma control, with better control indicated by higher values (NICE, 2017). A score of ≤ 19 denotes uncontrolled asthma in both questionnaires.

6.9.3 Spirometry

Spirometry was performed using a portable spirometer (Microlab8 Spirometer, CareFusion UK Ltd) by practice staff either directly supervised by a member of the study team during training, or independently once competent to do so.

Forced expiratory manoeuvres were performed according to American Thoracic Society/European Respiratory Society standards (Miller et al., 2005). Children were coached to perform a forced expiratory manoeuvre at least three times with a maximum of eight attempts. Incentive spirometry

was used in all children younger than seven years, whereby visual aids were provided on the spirometer screen.

Within manoeuvre acceptability was assessed by inspection of the flow-volume curve after each blow. We sought to achieve three adequate tests where the difference between the largest and next largest FEV_1 and FVC were within 5% of each other. Achieving such repeatability can be difficult in younger children, so test results were not rejected solely on the basis of its poor repeatability, as recommended in current guidance:

“No spirogram or test result should be rejected solely on the basis of its poor repeatability. The repeatability of results should be considered at the time of interpretation. The use of data from manoeuvres with poor repeatability or failure to meet the end-of-test requirements is left to the discretion of the interpreter.”(Miller et al., 2005)

The values for absolute forced expiratory volume in 1 second (FEV_1) in litres, FEV_1 as a percentage of predicted (FEV_1%), forced vital capacity (FVC) in litres, peak expiratory flow rate (PEFR) in litres per minute and the ratio of FEV_1 to FVC were recorded. The best FEV_1, FVC, and PEFR (even if from different manoeuvres) were recorded, and used to calculate the FEV_1/FVC. Predicted values were based on global lung initiative (GLI) reference equations (Quanjer et al., 2012) and provided automatically by the spirometer. The GLI reference equations (GLI-2012) were chosen as they represent the first global, all-age equations for spirometry available. Reference equations were derived for healthy individuals aged 3–95 years from four distinct ethnic groups: Caucasians (n = 57395), Black (n = 3545), North East Asians (n = 4992), and South East Asians (n = 8255) (Quanjer et al., 2012). Table 16 shows the populations which each of the GLI-2012 ethnic groups are known to be representative.

Table 16. GLI-2012 Ethnic Groups	
Group	**Country/Region Represented**
Caucasian	Europe, Israel, Australia, USA, Canada, Mexican Americans, Brazil, Chile, Mexico, Uruguay, Venezuela, Algeria, Tunisia
Black	African American
South East Asian	Thailand, Taiwan and China (including Hong Kong) south of the Huaihe River and Qinling Mountains
North East Asian	Korea and China north of the Huaihe River and Qinling Mountains

Source: (ers-education, 2017)

As there are significant populations missing from GLI-2012, including people from the Indian sub-continent, GLI-2012 also provides a fifth set of equations – "Other". This group encompasses a combination of data from the four groups above, and which may be applied as a first approximation to individuals not represented by one of the four groups or who are of mixed ethnicity (ers-education, 2017). The predicted values for children of South Asian ethnicity participating in this study came from the "other" GLI-2012 reference category.

The practice clinical staff were trained to assess the flow-volume loop and each spirometric value in turn.

For GP staff training purposes, a normal spirogram was defined as having both FEV_1 and FVC ≥ 80% predicted and FEV_1/FVC ≥ 80%. Although we recognise that the GLI lower limit of normal (LLN) is the gold standard for interpreting spirometry results, a fixed cut-off was chosen to define obstruction for pragmatic reasons, as it was felt that GP staff were already familiar with using fixed cut-offs when interpreting adult spirometry. Moreover, the current adult spirometry training offered within Leicestershire primary care refers to fixed cut-offs also, so we harmonised our training to reflect that. The 80% threshold was chosen as it most closely mirrors the GLI LLN across the 5-16 years age group (Quanjer et al., 2012).

Where FEV_1 or FVC was less than 80% predicted, or FEV_1/FVC was less than 80% reversibility testing was performed: spirometry repeated 15 minutes after administering salbutamol 400 micrograms (4 puffs) given via spacer. An increase in absolute FEV_1 (L) of ≥ 12% was taken to represent a positive bronchodilator response test (positive BDR).

Usable spirometry data was defined as recorded values from at least two acceptable manoeuvres as per ERS/ATS criteria.

6.9.4 Exhaled Nitric Oxide Testing

Exhaled nitric oxide (eNO) measurement was attempted in all children following spirometry. Children were asked to inhale ambient air through a nitrogen oxide scrubber to total lung capacity, and then exhale at a constant flow rate of 50 mL/sec for 10 seconds at a pressure of 10-20 cmH_2O (American Thoracic and European Respiratory, 2005). Testing was performed using a hand held eNO analyser (NIOX Vero; Circassia). The result of the eNO concentration in exhaled breath was available within two minutes and was expressed in parts per billion (ppb). Generic cut-off values for eNO are difficult to define due to individual patient factors including – age, height, gender, smoking, history of atopy, and nitrate intake. We chose a positive cut-off value of 35ppb to represent evidence of active inflammation as suggested by the 2011 American Thoracic Society eNO guideline (Dweik et al., 2011), and which is in line with the proposed eNO cut-off for children recommended by the current NICE asthma guideline(NICE, 2017).

The length of time (minutes) required to perform both spirometry and eNO from the start of verbal instructions until either results were obtained, or abandonment of the attempt was recorded. This data was collected to inform our feasibility implementation outcome measure.

6.10 Additional Data Collected

Demographics

The gender, age, ethnicity, primary language and country of birth were recorded by the research team in the case report form (CRF) following written consent at the asthma review. We also documented whether they have had previous lung function testing, and whether they were under hospital follow up. In children already on the asthma register, we recorded the age of diagnosis, and whether they had had a routine asthma review in the previous 12 months.

Current Treatment and Control

All prescription “asthma” medications (bronchodilators, inhaled corticosteroids, leukotriene receptor antagonists etc.) were recorded on the CRF and participants were assigned to a corresponding asthma treatment step as per 2014 BTS/SIGN asthma guidelines.

The number of prescriptions that the patient should have collected (based on their treatment regimen) was calculated and compared against the number of prescriptions issued over the preceding six months. This data was used as a surrogate objective marker for treatment adherence.

We also documented the number of unplanned healthcare attendances (UHA) in the preceding 6 months. A UHA was defined as any attendance to the GP, hospital, or walk-in-centre with acute respiratory symptoms managed with asthma medications as documented within GP records, and within electronically filed discharge letters.

Physical Examination

Height in centimetres and weight in kilograms of participating children were recorded.

6.11 Feedback (Acceptability)

From Practice Staff

For each child reviewed, the practice nurse or doctor performing the review was asked to complete a review outcome form consisting of the following questions:

- Is the history suggestive of asthma?
- Do you think your plan would have been different if spirometry and eNO data was not available?
- Did you find the tests useful in helping with your diagnosis/management plan?

From Children and Parents

Feedback from parents was obtained using a modified friends and family test (NHS, 2014) using the question “how likely are you to recommend these breathing tests to friends and family if their children needed an asthma review at this practice?”

The Friends and Family Test (FFT) was introduced in the NHS in 2012 to help patients identify the best-performing providers. Answers are recorded on a 5-point scale from “extremely likely” to “extremely unlikely”, and this may be followed by an open-ended question asking the reasons for that response.

We chose to use the FTT as it is a format already familiar to patients and is quick to complete.

In children, we simply posed the question “would you be happy to try these breathing tests again?” Response options were: yes, no, or don’t mind.

6.12 Follow up

We only planned one face-to-face contact with each study participant throughout the study. Having taken appropriate consent, we reviewed each participant's electronic records six months following the initial asthma review to record the number of unplanned healthcare attendances since the initial review. In patients who agreed, we also sent out follow up postal questionnaires with a repeat ACT/CACT questionnaire.

6.13 Discontinuation/Withdrawal of Participants from Study Treatment

Each participant had the right to withdraw from the study at any time. They were provided the contact details of the study team, who they were asked to contact should they wish to withdraw consent.

6.14 Source Data

Source documents were defined as original documents, data, and records from which participants' CRF data were obtained. These included: GP electronic records, completed asthma control test questionnaires (ACT and CACT), and lung function print outs. CRF entries were also considered as source data when the CRF was the site of the original recording (e.g., there was no other written or electronic record of the data). In this study, the CRF was used as the source document for time taken to perform spirometry and eNO only.

All documents were stored safely in confidential conditions – a locked filing cabinet within the research office, which was also locked when unoccupied. On all study-specific documents, other than the signed consent, the participant was referred to by the study participant number/code, not by name.

6.15 Data Handling and Record Keeping

Consent forms and spirometry tracings were scanned into practice computer systems. Patient data recorded on paper CRFs were then entered onto the Redcap online database in fully anonymised fashion in accordance with information governance guidelines developed in consultation with the National Research Ethics Service, the Ethics and Confidentiality Committee.

The participants were identified only by a study specific participant's number. The participant's name and any other identifying details were not entered onto any study electronic database.

6.16 Research Governance

The research team members working on this trial all received GCP (Good Clinical Practice) training. Annual progress forms were completed and submitted to the study sponsor (University of Leicester). The study was also formally monitored by the sponsor on the 21st October 2016, and no further action was required.

6.17 Data Analysis

Readiness for Change

Responses to questions on the readiness for change questionnaire were either in the form of ordinal data (derived from a 5-point Likert scale) or free text open responses. The distribution frequency of Likert response options to each question were presented visually as stacked bar charts. Additionally, the proportion of positive ("agree or strongly agree"), negative ("disagree or strongly disagree"), and neutral ("neither agree nor disagree") responses were calculated as percentages.

Free text data, regarding opinions and barriers to implementation derived from the readiness for change questionnaires, was presented in report form.

Using inductive analysis methodology (Thomas, 2016), the free text data responses were analysed for recurring themes, and coded according to frequently used words and phrases.

Capacity Data

Training times and test times were presented as descriptive data. The mean (SD) number of hours required for training were presented for all staff, then divided by staff group and training requirements. Proportion of successful tests in children were divided by age group and presented visually on a line graph.

Statistical Analysis

For comparison of baseline characteristics, children were grouped according to whether they had an existing diagnosis of asthma or not at the point of recruitment. Continuous variables were compared using unpaired t-tests for parametric data, and Kruskal-Wallis tests for non-parametric data. Chi-squared tests were used to compare count data.

For lung function data, children were firstly analysed according to their diagnosis status, and symptom control status as binary variables (i.e. diagnosed versus not diagnosed, and controlled versus uncontrolled). Secondly, we sought to identify whether there were any significant correlations between different lung function parameters with asthma control test scores. Pearson's r correlation was used for parametric variables and Spearman's rank for ordinal or non-parametric data. The above analyses were also repeated after converting spirometry derived parameters into z-scores using GLI data.

Paired t-tests or paired Wilcoxon signed rank tests were used to assess the change in asthma control test scores and number of UHAs (over previous six months) in children at follow up (six months after the initial review).

Unpaired t-tests or Kruskal-Wallis tests were used to compare the difference in mean number of UHAs and mean asthma control test scores at six month follow up.

All statistical tests were performed at the alpha = 5% level.

Statistical analysis were performed using IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY: IBM Corp) and GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com).

Impact on Diagnosis and Feedback Data

Impact on diagnosis was assessed using the proposed NICE algorithm, by describing the number of children who would fall under each diagnostic category ("asthma confirmed", "asthma suspected", "refer to specialist", or "consider alternative diagnosis") according to the available objective test results if the NICE guideline was implemented.

Patient feedback was presented as descriptive data of the proportion of responses falling under each feedback category (from strongly recommend to strongly not recommend).

CHAPTER 7: RESULTS – IMPLEMENTATION

This chapter will present the data addressing the implementation related research questions outlined in chapter five. Specifically the perceived barriers towards implementation, the length of training and additional clinic time required to provide spirometry and eNO, the feasibility of these tests in children as young as five years old, and the acceptability of these tests for staff and families.

7.1 Practices

Ten practices participated in the CHAMPIONS study. Practices were selected to capture populations with different ethnic and socioeconomic demographics (Table 17), and a mixture of urban and suburban locations (Figure 18). In total, the ten practices served a patient population of almost 120,000 people, ranging from ~3500 to 48000 registered patients. Geographically, five of the practices were located in inner city Leicester (residents ~330 000), two were in village locations (residents 5000-6000), and three were in surrounding towns (residents 50 000 to 60 000).

The most socially deprived populations were served by the five inner city practices (D, G, H, I, J) as indicated by their lower deprivation deciles of one to four. The two village practices (A, F) served the most affluent populations (deprivation index of ten), whilst the three practices located in towns (B, C, E) had deprivation indices of between four and seven.

Practices located in rural and suburban locations served predominantly white populations with percentage of non-white registered patients ranging from 2.6% to 18.5%. Inner-city practices had much larger proportions of non-white registered patients, ranging from 16.7% to 65.5%. Extrapolating the proportion of non-white registered patients at each practice to the total number of registered patients at all ten practices combined, gives a total non-white population of 19 456 out of 119 970 patients (16.2%) across all ten sites.

Compared to nationally, our average practice size was larger and had a slightly higher proportion of people under the age of 18 years. We also had a larger proportion of registered patients who were ethnically non-white, which reflects the local demographic. Our average practice size was skewed by practice B, which is considerably larger than typical GP surgeries. Excluding practice B, our average practice size was 7975 registered patients, which is in line with the national average. The mean proportion of patients recorded on the asthma register and the median deprivation index of our participating practices were similar to the national average.

Table 17. Demographic of Participating Practices

Site	Number of registered patients	% of practice population under 18	% of practice population on asthma register (adults and children)	Deprivation Index 1 (most deprived) - 10 (least deprived)	% Non-white
A	10 288	20.1%	6.2%	10	2.6%
B	48 196	21.8%	5.4%	4	3.8%
C	10 273	22.7%	8.3%	6	6.9%
D	3 519	18.5%	3.5%	4	40.8%
E	8 043	17.7%	6.1%	7	18.5%
F	6 956	17.6%	6.4%	10	3.9%
G	10 522	29.0%	6.8%	1	16.7%
H	5 229	32.4%	3.6%	1	19.3%
I	4 083	28.0%	6.1%	2	65.5%
J	12 861	26.2%	6.0%	3	62.3%
Study Average	11997	23.4%	5.8%	4 (Median)	24.0%
England Average (2017/18)	8035	20.5%	5.9%	5 (Median)	14.0%

Source: Data from Public Health England

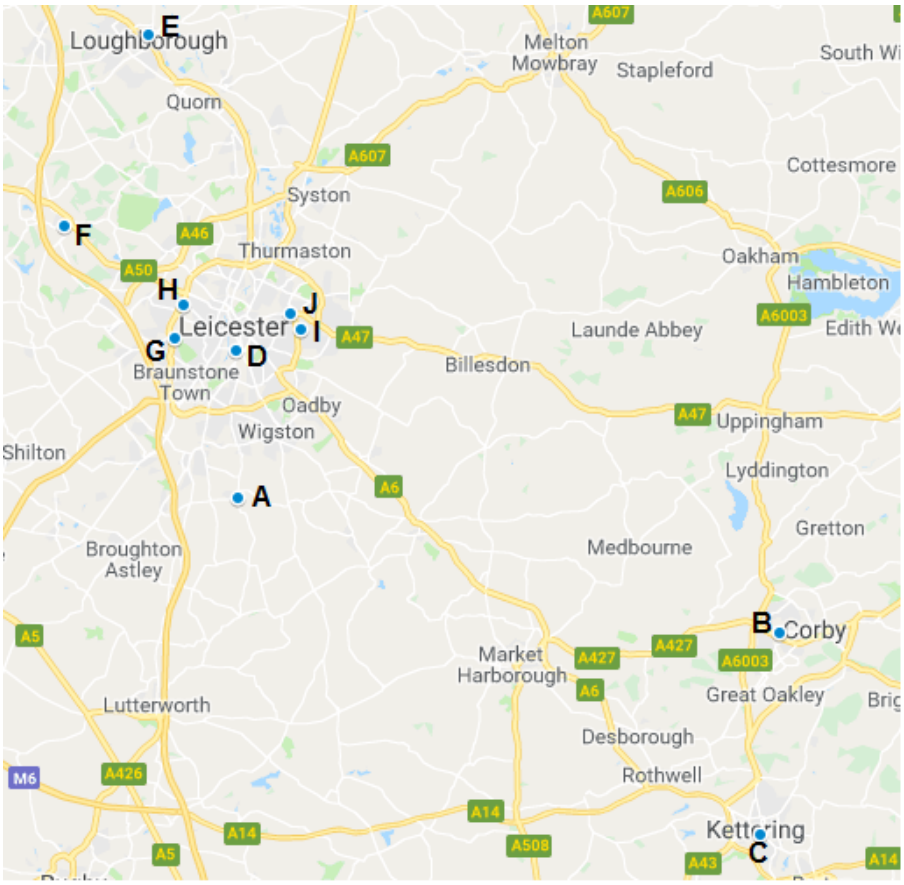


Figure 18. Location of Participating Practices

7.2 Readiness for Change Questionnaire (Adoption and Appropriateness)

In order to assess the implementation outcomes of adoption and appropriateness, we sought to explore the perceived barriers, willingness to adopt, and appropriateness of providing spirometry and eNO testing in primary care amongst GP staff. Electronic readiness for change questionnaires were sent to each practice manager, to be circulated amongst their practice staff, prior to training. We received responses from 62 GP staff members across all 10 practices, representing a mixture of GPs, nurses, HCAs and managers (Table 18). The majority of respondents were clinical staff, 40% GPs, 27% PNs and 18% HCAs. The remaining 15% were practice managers. The number of responders from each practice

corresponded to the practice sizes; with the largest practice returning the most responses (18), and the smallest practices the fewest (3 per practice). It was not possible to calculate the response rate as the questionnaires were sent out by the practice managers themselves, and the number of recipients was not recorded.

Table 18. Number of Responders by Practice and Staff Group

Practice	GPs	Nurses	HCAs	Managers	Total
A	4	2	1	1	8
B	9	4	3	2	18
C	1	2	1	1	5
D	2	1	0	0	3
E	3	1	1	1	6
F	1	1	2	0	4
G	2	3	0	1	6
H	1	1	0	1	3
I	1	0	1	1	3
J	1	2	2	1	6
Total	25	17	11	9	62

The proportion of different responses (5 = strongly agree, 4 = agree, 3 = neither agree nor disagree, 2 = disagree, 1 = strongly disagree) to questions are shown as 100% stacked bar charts below, grouped by question category.

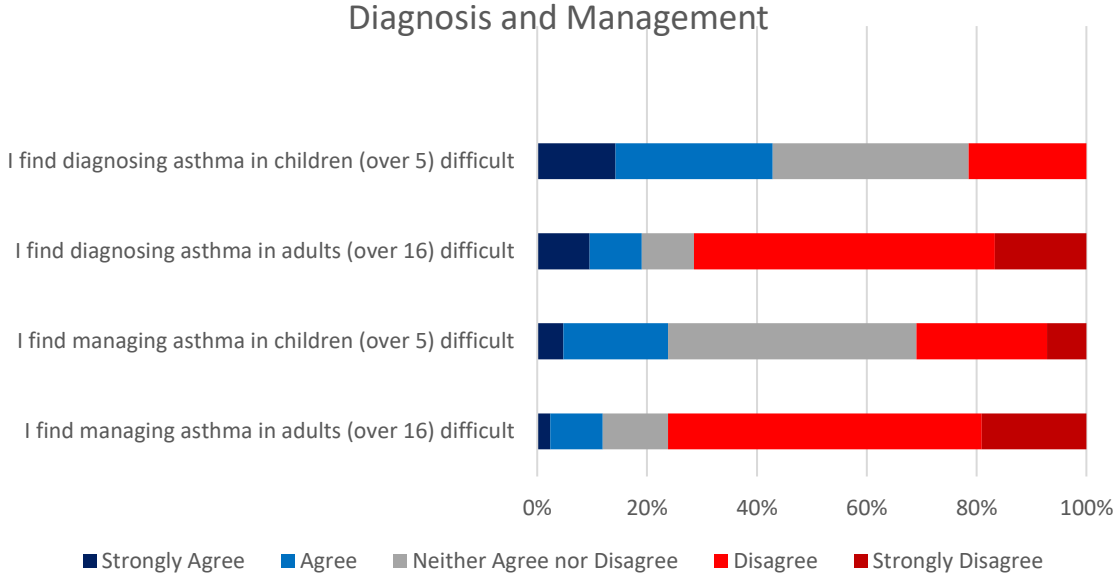
Opinions towards asthma diagnosis in children and adults (GPs and PNs only, n = 42)

Overall, a greater proportion of GPs and PNs found asthma diagnosis and management difficult in children compared to in adults.

Almost half (43%) of the surveyed GPs and PNs reportedly found diagnosing asthma in children difficult, compared to 21% who did not. By contrast, only a fifth (19%) of GPs and PNs found diagnosing asthma in adults difficult, compared to 71% who did not. In terms of managing asthma, the majority of GPs and PNs did not find adult asthma management difficult compared to those who did (76% vs 12%). Whilst, in children 31% of GPs/PNs did not find asthma management difficult, compared to 24% who did (Figure 19).

There were no significant differences in responses between GPs and PNs.

Figure 19. Opinions of GPs and PNs Towards Asthma Diagnosis and Management



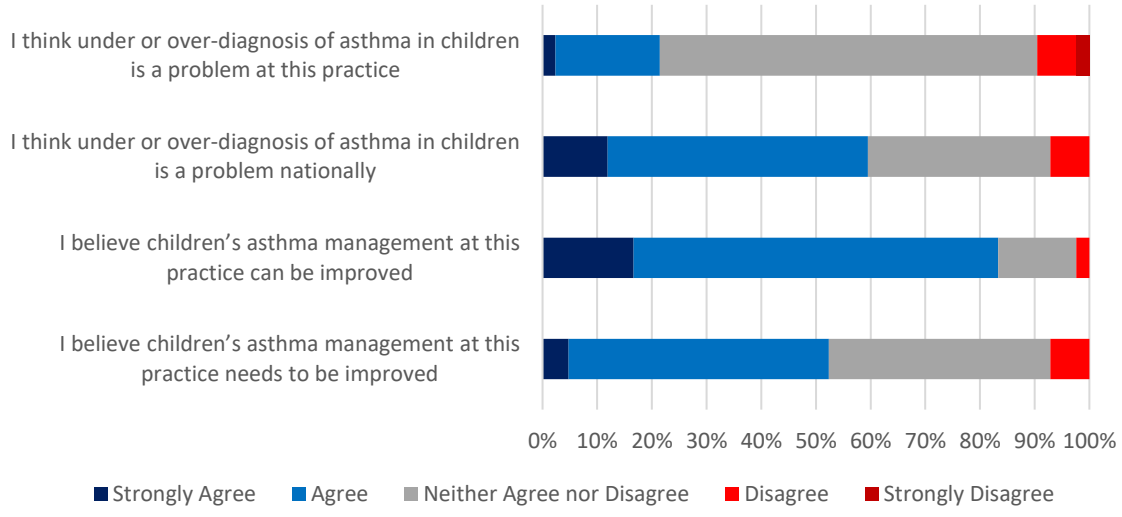
Opinions towards current children's asthma management (GPs and PNs only, n = 42)

60% of GPs and PNs reportedly thought that asthma misdiagnosis in children was a problem nationally, however, only 21% thought it was a problem at their practice; the majority (69%) gave a neutral (neither agree nor disagree) response.

Interestingly, 83% of those surveyed thought that children's asthma management *could* be improved at their own practice; with 52% saying that it *needed* to be improved (Figure 20).

There were no significant differences in responses between GPs and PNs.

Figure 20. Opinions of GPs and PNs Towards Current Children's Asthma Management



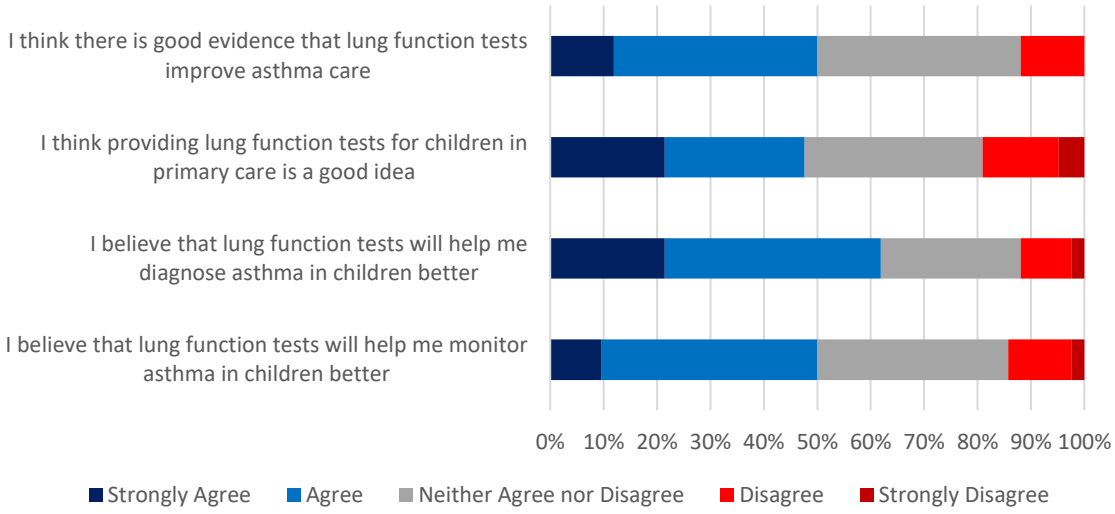
Opinions towards role of spirometry and eNO in primary care (GPs and PNs only, n = 42)

Half of GPs and PNs surveyed felt there was good evidence that spirometry and eNO could improve asthma care, and almost half (48%) felt providing these tests for children in primary care was a good idea.

62% of the GPs/PNs surveyed thought objective tests could help them diagnose asthma in children better, and 50% thought the tests could also help them to monitor asthma in children better. Conversely, 12-19% of those surveyed responded negatively towards the usefulness and need for spirometry and eNO in primary care for children (Figure 21).

There were no significant differences in responses between GPs and PNs.

Figure 21. Opinions of GPs and PNs Towards Spirometry and eNO Testing for Asthma Management in Primary Care

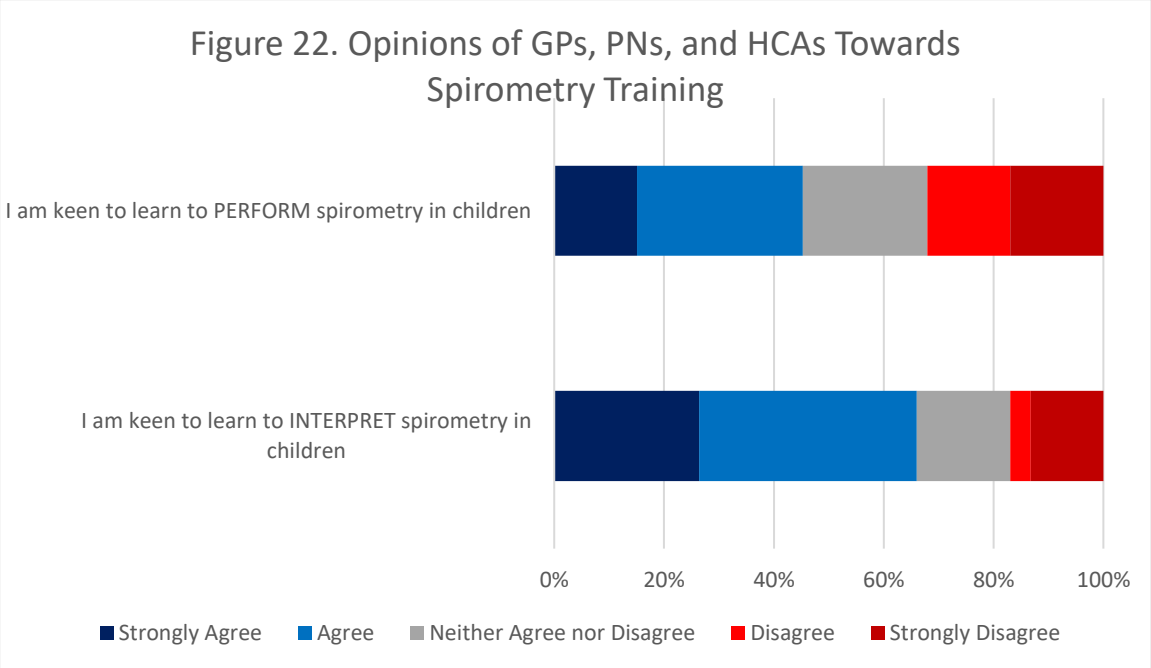


Opinions towards being trained in spirometry (GPs, PNs, and HCAs, n = 53)

Overall, more clinical staff were interested in learning to interpret spirometry (66%) than perform spirometry (45%) in children.

Between staff groups, HCAs were least likely to respond positively towards either performing or interpreting spirometry (27% for both).

48% of GPs and 53% of PNs expressed an interest in performing spirometry; whilst 80% of GPs and 71% of PNs were motivated to learn to interpret spirometry (Figure 22).



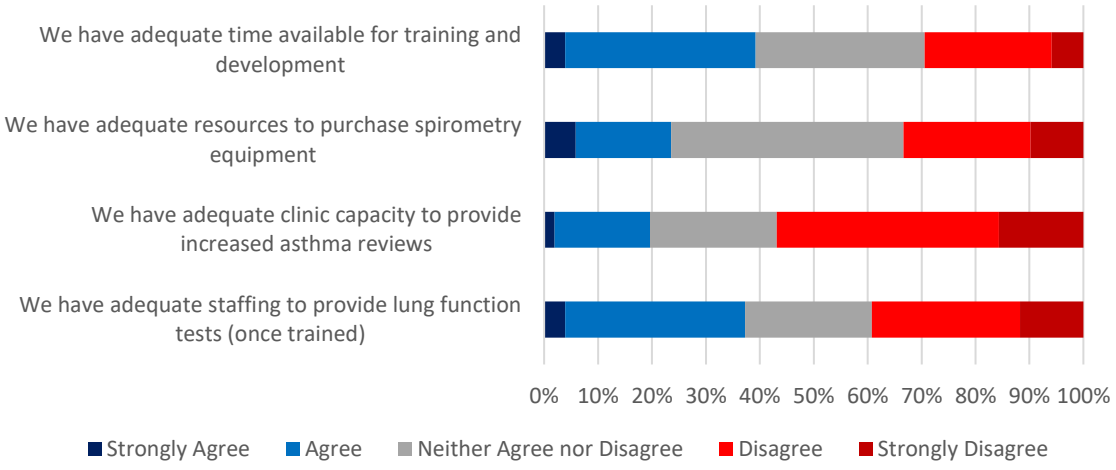
Opinions towards barriers towards spirometry and eNO in primary care (GPs, PNs, and Managers, n = 51)

These questions explored primary care staff perceptions towards four specific barriers against implementation of spirometry and eNO – time to train, clinic capacity, resources to purchase equipment, and staff to perform testing.

Clinic capacity was the barrier which most staff (57%) felt would impede implementation. This was followed by staffing (39%), resources (33%), and time for training (29%).

In contrast, of those surveyed, 39% felt that there was enough time for training, 37% felt there was adequate staffing, 24% adequate resources, and 20% adequate clinic capacity (Figure 23).

Figure 23. Opinions of GPs, PNs, and Practice Managers Towards Barriers to Providing Spirometry and eNO in Primary Care



Free Text Responses

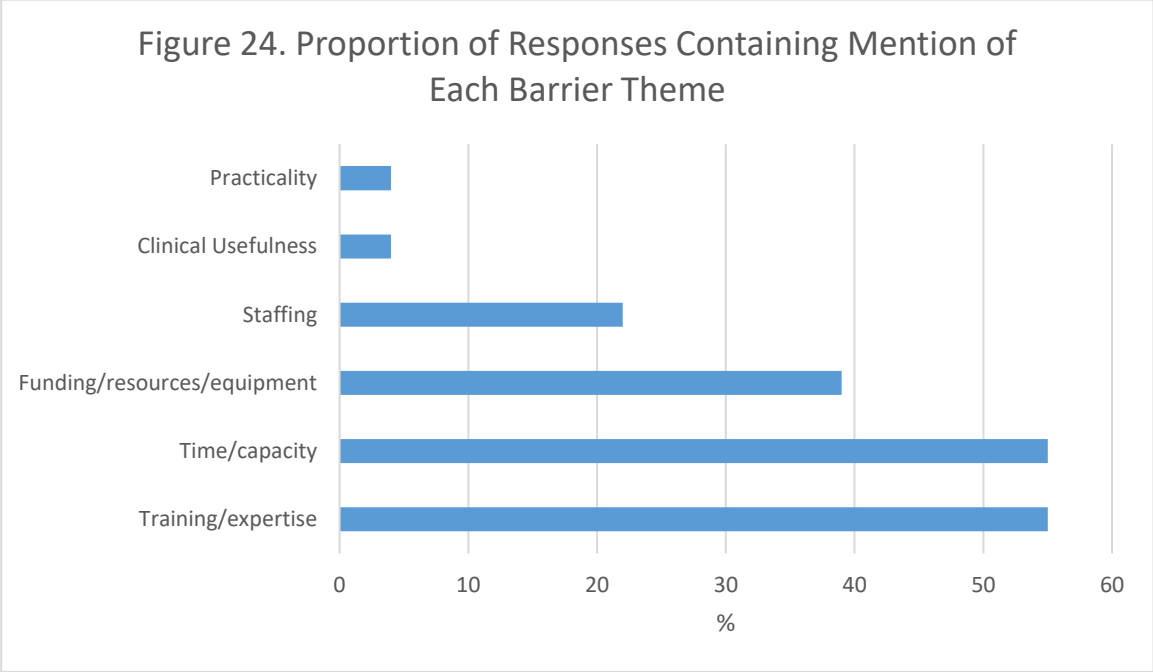
Forty-nine free text responses were received to the question – “In your opinion, what is needed OR what barriers need to be overcome in order for your practice to provide routine lung function testing for children?"

From repeat readings of the individual responses, six themes emerged from the text in relation to perceived barriers from practice staff:

- Training/expertise
- Time/capacity
- Staffing
- Funding/resources/equipment
- Clinical usefulness
- Practicality

Using the principles of content analysis, I analysed the frequency with which the words and themes mentioned above appeared within the free text. Content analysis adopts a quantitative approach towards text analysis, and is a relatively inexpensive way to provide an insight into complex models of human language use by presenting data in a readily understood format. The main disadvantage of quantitative analysis of text data is the potential to oversimplify complex issues, as context can be disregarded; particularly if analysis is treated as a simple word counting exercise (Lovasi, 2019). Hence, I was cautious in my reading of the free text responses to take context into consideration when grouping individual responses into themes.

The proportion of responders which highlighted concerns in relation to each of the six themes identified are shown in Figure 24.



The two most commonly reported barriers related to training needs, and clinic capacity. 55% of GP staff identified lack of previous training and expertise with performing spirometry and eNO testing as barriers to implementation. Specifically, the "practical *performing* of test[s] and *interpretation* of results". They further mentioned the provision of "clear guidance," on "when [tests] should be offered," and ongoing "support after training" as prerequisites for implementation.

Equally mentioned in the returned feedback, by 55% of respondents, was the additional time needed for training, and to perform the tests themselves. GP staff acknowledged that the additional tests would require more time to perform and would "require longer nurse appointments or co-ordination of two or double appointments which can be difficult in practice."

39% of responses highlighted the need for additional funding and resources to purchase equipment, support training, and to increase clinic capacity. One respondent indirectly alluded to the need to financially incentivise lung function testing within primary care – "other clinical responsibilities, which are better funded through incentive schemes, are likely to take priority, unless lung function testing is fully funded."

Moreover, there was a consistency from the responses that providing objective testing would place “significant burden on clinical staff” who were already “overworked;” with 22% of respondents highlighting the need for increased staffing so that objective tests could be provided “not at the loss of other services.”

Finally, 4% of respondents indicated that the ability of children to successfully perform objective testing would be a significant challenge to widespread implementation; and 4% raised the question of whether these tests would be useful within primary care – “[we should] only do this if we are going to make a difference,” and “this service should remain with those expertly trained in this area and who also have the time and resources needed to perform the tests accurately.”

7.3 Training (Feasibility)

Training for eNO and spirometry was delivered to 27 nurses and HCAs across 10 practices (Table 19). No GPs participated in the training as routine asthma reviews were conducted by the practice nurses in all 10 practices we worked with. Twelve people already performed spirometry testing in adults, but none had previously had training to perform spirometry in children. No GP staff had any previous experience with eNO testing.

Table 19. Number of Staff Completing Training by Site			
Practice	**Nurses**	**HCAs**	**Total**
A	2	0	2
B	4	7	11
C	1	0	1
D	1	0	1
E	2	1	3
F	1	2	3
G	1	0	1
H	1	0	1
I	1	1	2
J	1	1	2
Total	15	12	27

Staff members achieved competencies after observing and performing tests (spirometry and eNO) in a median (IQR) number of 24 (20 to 27) children over 5 (4 to 6) clinics.

Each child was allocated 20 minutes for testing, and each member of staff was given 120 minutes of face-to-face training prior to the first clinic session. The mean (SD) time for GP staff to achieve competencies in both spirometry and eNO testing was 10.3 (2.7) hours.

When sub-grouped by training needs, those needing to learn to perform took 9.5 (1.8) hours, to interpret 11.7 (3.4) hours, and to both perform and interpret 9.8 (2.5) hours to train. There were no statistical differences between groups in terms of training times needed.

Staff who previously already performed spirometry in adults took less time on average to train compared to those who did not previously perform spirometry, 9.5 (2.1) vs. 10.9 (2.9) hours, however this did not reach significance ($p = 0.171$).

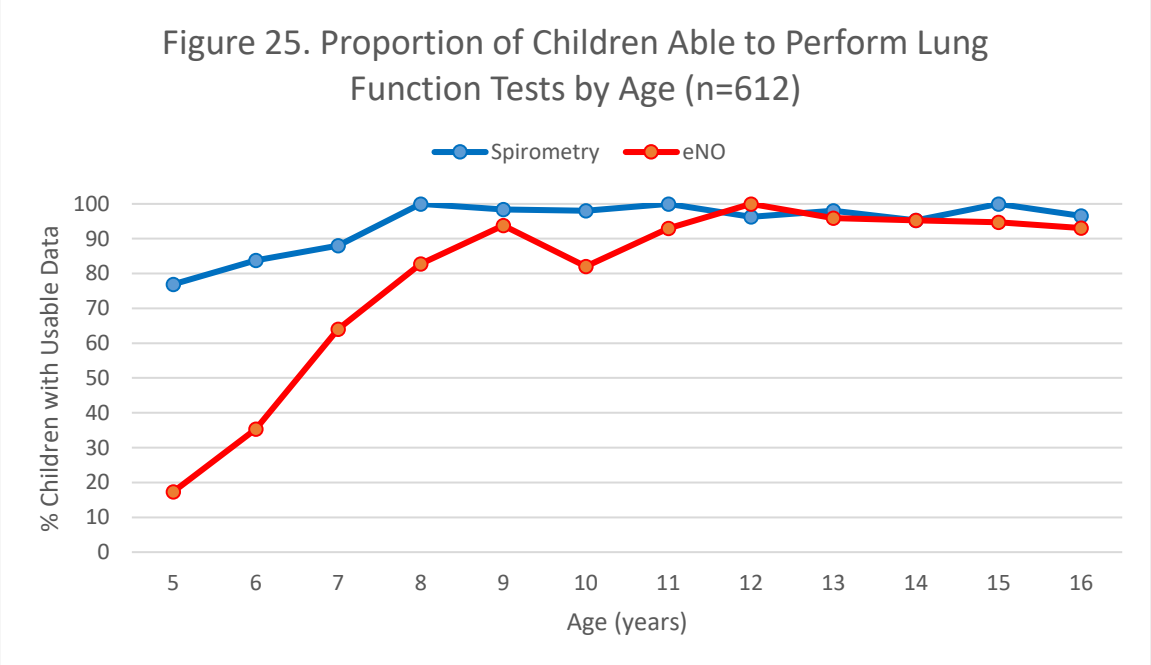
7.4 Lung Function Feasibility

Usable spirometry was obtained from 575 (94.0%) children (Table 20). An eNO result was obtained from 472 (77.1%) children (Table 21). Overall, by age 7 years the majority of children could manage both spirometry and eNO testing (Figure 25). The mean (SD) time to perform tests were 4.3 (1.3) minutes for spirometry, 3.1 (1.0) minutes for reversibility testing, and 2.4 (1.0) minutes for eNO. This did not include the time taken to administer SABA and 15 minute wait for reversibility testing.

Table 20. Number of Children with Usable Spirometry Results by Age

Age	Spirometry Achieved	Spirometry Failed	Total	% Success
5	40	12	52	76.9
6	57	11	68	83.8
7	44	6	50	88.0
8	58	0	58	100.0
9	63	1	64	98.4
10	49	1	50	98.0
11	57	0	57	100.0
12	52	2	54	96.3
13	48	1	49	98.0
14	41	2	43	95.3
15	38	0	38	100.0
16	28	1	29	96.6
Total	575	37	612	94.0

Table 21. Number of Children with Usable eNO Results by Age				
Age	**eNO Achieved**	**eNO Failed**	**Total**	**% Success**
5	9	43	52	17.3
6	24	44	68	35.3
7	32	18	50	64.0
8	48	10	58	82.8
9	60	4	64	93.8
10	41	9	50	82.0
11	53	4	57	93.0
12	54	0	54	100.0
13	47	2	49	95.9
14	41	2	43	95.3
15	36	2	38	94.7
16	27	2	29	93.1
Total	472	140	612	77.1

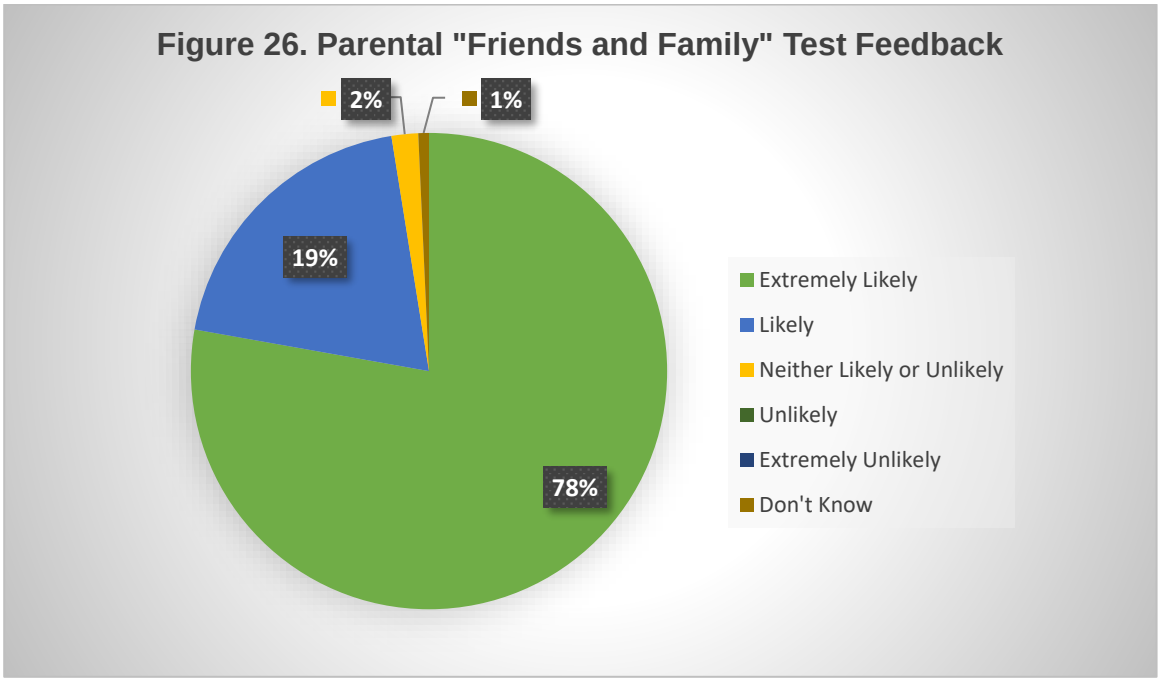


7.5 Feedback from Families (Acceptability)

Feedback forms were completed and returned by 554 (91%) families.

Parents were asked to provide feedback to the question – “How likely are you to recommend these breathing tests to friends and family if their children needed an asthma review at this practice?” 97% of respondents reported a positive experience with lung function testing, saying they were either “extremely likely” or “likely” to recommend the tests to friends and family. 2% of responses were neutral (“neither likely nor unlikely”) and 1% responded “don’t know” (Figure 26).

Children were asked to respond to the question – “Would you be happy to try these breathing tests again?” 87% of children reported that they would be happy to do the tests again, 12% didn’t mind, and 1% would not like to do the tests again (Figure 27).



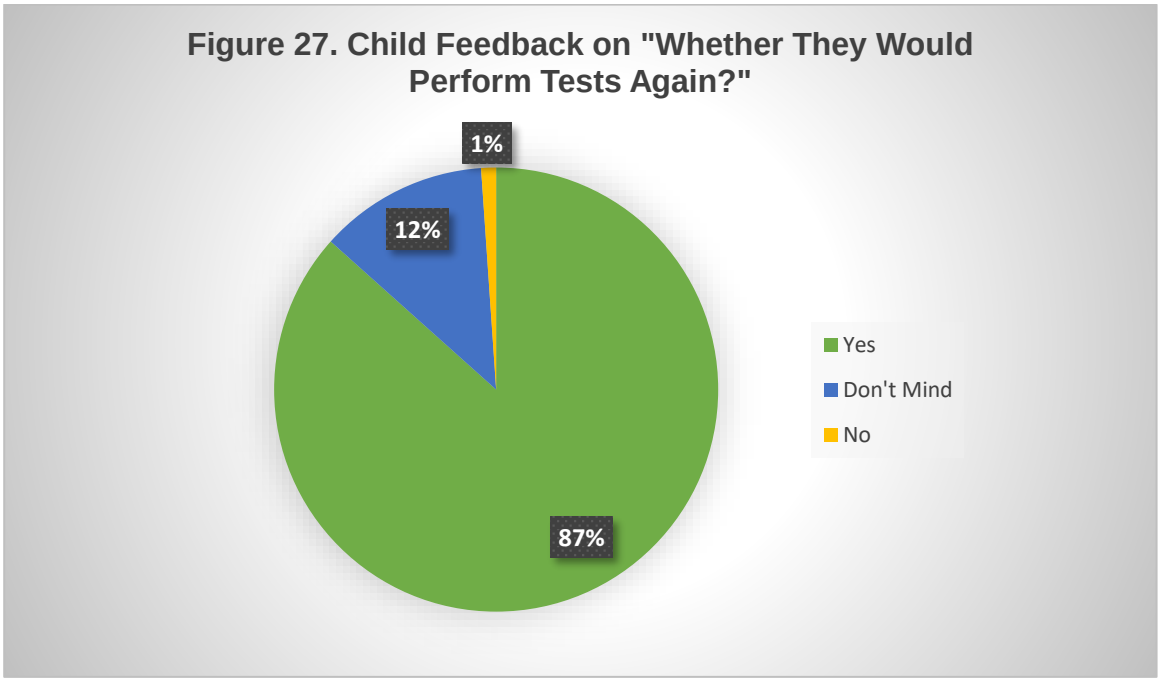


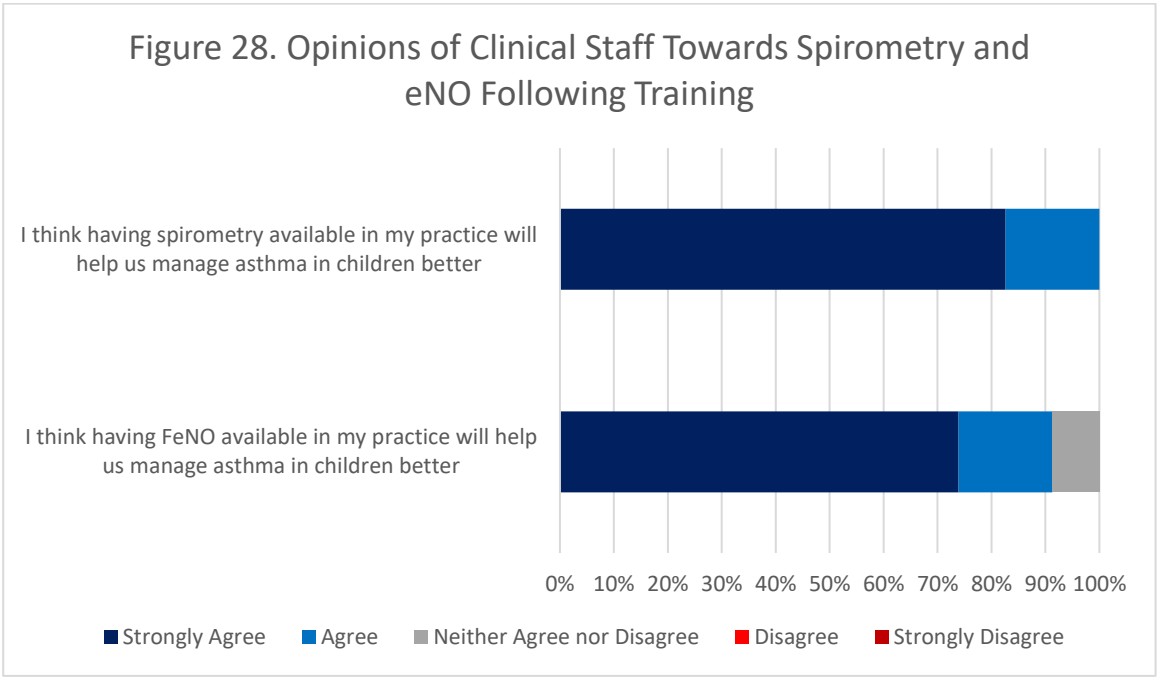
Figure 27. Child Feedback on "Whether They Would Perform Tests Again?"
1%
12%
87%
Yes
Don't Mind
No

Forty-two feedback forms contained free text comments. Two comments were negative and the rest were positive towards spirometry and eNO testing (Table 22).

Table 22. Free Text Feedback from Families
Positive comments (selection)
"A fantastic idea to hold these tests in a GP surgery" "Great tests with positive feedback. Thank you!" "Help to give me a better understanding of my child's asthma and how it changes" "I am very happy to have breathing tests for my daughter, that is great chance to check if she have asthma or not" "I think it is a wonderful idea to have these tests on a regular basis. Very reassuring for both parent and child that their breathing issues are being monitored" "Tests were quick" "This is really fun. Thank you" (child comment) "It only felt like playing a video game, didn't see it being a test in anyway!" (child comment)
Negative comments (all)
"Takes long" "I don't like the sound" (child comment)

7.6 Feedback from Clinical Staff (Acceptability)

Following training and implementation, practice staff who had been trained were asked to feedback anonymously with their opinions towards spirometry and eNO. Twenty three (85%) staff members responded to the online questionnaire. All those who responded, felt that providing spirometry in their practice would help them to manage children's asthma better, and 91% felt that providing eNO would help (Figure 28).



Free text responses were available to the questions – “compared to before training, how has your attitude towards spirometry and eNO testing for children changed and why?”, and “now that you have had your training, do you think it will be possible to continue to provide these tests at your surgery regularly and what is needed in order to do so?”.

Overall practice staff responded very positively towards the use of spirometry and eNO in their practice, specifically saying that they improved their confidence with asthma diagnosis and management in children. Whilst they would be keen to continue providing these tests, the main limitation is lack of available funding and equipment. A selection of responses are shown in Tables 23 and 24.

Table 23. Free Text Responses to "Compared to before training, how has your attitude towards spirometry and eNO testing for children changed and why?" (selection)
"Spirometry and eNO are useful tools for both clinician and patient. History remains of utmost importance but having the results of tests assisted with confidence to change regimes and explaining to patient/parent" "Feel it gives a clearer picture to know how to plan next steps towards better control" "Spirometry enables us to see if asthma is controlled despite parents thinking children are asymptomatic" "Has enhanced diagnosis, given confidence in diagnosis, made me aware of other causes i.e. Rhinitis, insight and training can only improve care" "Have much better understanding of how relates to treatment and whether treatment necessary" "Able to explain better to parents and make better diagnosis"

Table 24. Free Text Responses to "Now that you have had your training, do you think it will be possible to continue to provide these tests at your surgery regularly and what is needed in order to do so?" (selection)
"As long as we have plenty of equipment, there shouldn't be a problem running an asthma clinic for children" "Only the funding/equipment is needed. I believe it would benefit the practice and its patients" "To continue in our practise we would need equipment and time, I believe the possibilities of providing these tests are with our GP partners and in discussion" "I feel that this certainly would be a fantastic opportunity if the was possible. The equipment and funding for this would be the main issue" "Yes it I think it would be possible, spirometry is already in use for adults so we have that capacity, we would need to purchase a eNO monitor" "I'd hope so. We'd need to create a clinic for this. Staff shortage at the moment may prohibit this at the moment"

For each child reviewed, the practice nurse or doctor performing the review was asked to reflect on the impact the objective test results had on their clinical decision making. General practice staff reportedly changed their management plan after seeing the objective test results in 130 out of 542 (24.0%) reviews. Moreover, they reported that spirometry and eNO supported their decision making in 470 out of 508 (92.5%) children.

7.7 Cost of Implementation

As mentioned previously, we planned a health economics (HE) evaluation of the implementation process as part of this project. The HE analysis will be conducted separately by a health economist (Dr. Yaling Yang) based at Oxford University using data collected from this study.

CHAPTER 8: RESULTS - CLINICAL

This chapter will present the data relating to the clinical outcomes of implementing routine spirometry and eNO testing for children managed for asthma in primary care as outlined in chapter five. Specifically to quantify: 1) the prevalence of abnormal spirometry, eNO, and poor asthma control in a cohort of children with either suspected or an existing diagnosis of asthma, 2) the proportion of children in whom a diagnosis of asthma could be confirmed using spirometry and eNO testing, 3) the proportion of children in whom a symptoms-based assessment alone would have failed to identify poor lung function and airway inflammation putting them at risk of asthma attacks, and 4) the change in number of unplanned healthcare attendances and asthma control scores at follow up following an asthma review which included objective tests.

8.1 Electronic Patient Registry Searches

The electronic patient register at each practice was searched to identify children meeting the inclusion criteria as detailed previously. In total, 1097 (71%) were on their GPs asthma register, and 451 (29%) were not, but had received asthma medications in the previous 12 months (Table 25).

The smallest practice (D) had 22 children meeting the inclusion criteria, compared to the largest practice (B) who had 477 children eligible to take part. As a proportion of the total number of registered patients at each practice, the mean percentage of children meeting the inclusion criteria was 1.4% (SD 0.56).

All children identified from the searches were posted an invitation to attend for asthma review in clinics where the research team were present to take consent and train practice staff to perform spirometry and eNO testing.

Table 25. Search Results from Participating Practices				
Practice	**On Asthma Register**	**Not on Asthma Register**	**Eligible Patients as % of All Registered Patients**	**% of Eligible Patients Who Were on Asthma Register**
A	74	88	1.6	45.7
B	330	147	1.0	69.2
C	116	25	1.4	82.3
D	8	14	0.6	36.4
E	70	15	1.1	82.4
F	57	24	1.2	70.4
G	120	36	1.5	76.9
H	30	25	1.1	54.5
I	65	41	2.6	61.3
J	227	36	2.0	86.3
Total	**1097**	**451**	**1.4**	**66.5**

8.2 Baseline Characteristics of Recruited Children

One hundred and forty one clinics were held across all ten practices. Six hundred and fourteen children attended clinics over the course of 14 months (June 2016 to August 2017); 456 (75%) were on the asthma register. Written informed consent was obtained from 613 children. One parent refused consent as they were already seen routinely in hospital and did not want to have further spirometry testing performed in general practice. One parent withdrew consent at a later date without giving a reason, leaving 612 children in total.

The characteristics of recruited children are shown in table 26. Overall, the participation rate was 40% of eligible patients, but ranged from 8% to 59% between practices. Our lowest recruiting practice (as a proportion of those eligible) was practice J, but this was due in part to recruitment at this practice

commencing late into the study and therefore fewer clinics (in relation to the practice size) were set up compared with other practices (Table 27).

Ethnicity data is shown in Table 28. The majority of recruited children were white (n = 480), 448 out of 480 described themselves as white British. The second largest ethnic group were children of Asian descent (n = 82), 50 out of 82 were Asian Indian.

Table 26. Baseline Characteristics of Recruited Children

	On Asthma Register (n = 456)	Not on Asthma Register (n = 156)	P value
Males (%)	247 (54.2)	85 (54.5)	0.945
Mean Age (SEM)	10.3 (0.15)	9.1 (0.26)	**<0.001***
Previous Spirometry Testing (%)	53 (11.7)	5 (3.2)	**0.002***
Mean Number of UHAs per child in Preceding 6 Months (SEM)	0.29 (0.03)	0.37 (0.06)	0.175
Number of children with ≥ 1 UHA in Preceding 6 months (%)	98 (21.5)	42 (26.9)	0.163

* denotes statistically significant difference ($p<0.05$) between sub-groups. UHA = unplanned healthcare attendance.

Table 27. Number of Participants Recruited at each Practice		
Practice	**Number of Children Recruited**	**Proportion of Eligible Children Recruited at Each Practice**
A	67	41.4
B	270	56.6
C	41	29.1
D	13	59.1
E	41	48.2
F	33	40.7
G	58	37.2
H	31	56.4
I	36	34.0
J	22	8.4

Table 28. Ethnicity of Recruited Participants		
Ethnicity	**Number**	**Percentage**
White	480	78.4
Asian	82	13.4
Black	21	3.4
Mixed	20	3.3
Other	9	1.5

8.3 Baseline Asthma Control

An asthma control test (ACT) or Children's Asthma Control Test (CACT) score of 19 or below suggests poor asthma control. Amongst our cohort, 256 children (41.8%) had poor asthma control according to their ACT/CACT test

scores. 197 out of 456 (43.2%) on the asthma register and 59 out of 156 (37.8%) not on the asthma register had ACT/CACT scores ≤19 (p = 0.24).

For all children, the median (IQR) CACT score was 21.0 (17.0 to 24.0) for children aged 5-11 years, and the median ACT score was 20.0 (17.0 to 23.0) for children aged 12-16 years.

In children aged 12-16, the median ACT score was 20.0 (17.0 to 22.0) for children on the asthma register, and 20.5 (16.0 to 24.0) for children who were not (p = 0.41); whilst in children aged 5-11 years, the median CACT score was significantly lower in children on the asthma register compared with those who were not; 20.0 (17.0 to 23.0) vs 21.0 (18.0 to 25.0), p = 0.028 (Figure 29).

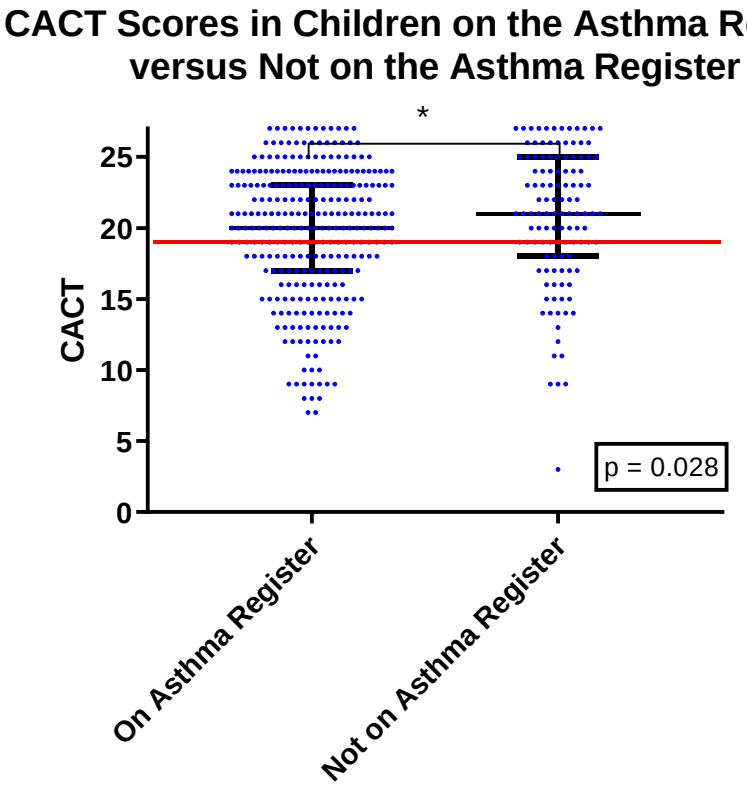


Figure 29. Scatter Graph of Childrens Asthma Control Test (CACT) scores by whether child is on asthma register or not. Median and IQR plotted. Red line denotes cut-off for current asthma control (CACT ≤ 19)

8.4 Spirometry Results

Acceptable spirometry was achieved by 575 (94.0%) children (Table 29).

Table 29. Spirometry Results at Review			
	On Asthma Register (n = 430)	**Not on Asthma Register (n = 145)**	**P value**
Mean FEV_1 % predicted (SEM)	93.29 (0.64)	93.44 (1.05)	**0.904**
Mean FEV_1 Z-Score (SEM)	-0.45 (0.05)	-0.48 (0.09)	**0.797**
Mean FVC % predicted (SEM)	98.36 (0.69)	97.84 (1.00)	**0.694**
Mean FVC Z-Score (SEM)	-0.06 (0.05)	-0.13 (0.08)	**0.462**
Mean FEV_1/FVC (SEM)	83.75 (0.37)	84.29 (0.57)	**0.451**
FEV_1/FVC Z-Score (SEM)	-0.70 (0.05)	-0.66 (0.08)	**0.701**

Using the definition FEV_1 or FEV_1/FVC < LLN, 135 out of 575 (23.5%) children had airflow obstruction. There was no difference in the prevalence of obstructed spirometry between children on the asthma register versus those who were not, 23.7% vs 23.4% (p = 0.95).

For comparison, the numbers of children defined as having airflow obstruction according to different thresholds are presented in Table 30. Compared with using GLI LLN, using a fixed cut-off of FEV_1 < 80% predicted or FEV_1/FVC < 80% misidentified an additional 37 (6%) children as having airflow obstruction, but using the NICE recommended cut-off of FEV_1/FVC < 70% would have missed airflow obstruction in 108 (18%) children.

Table 30. Number of Abnormal Spirometry Results by Definition Used		
Abnormality	**Definition Used**	**Number**
Obstruction	FEV_1 % predicted < 80 OR FEV_1/FVC < 80%	172 (29.9%)
	FEV_1 OR FEV_1/FVC < LLN	135 (23.5%)
	FEV_1/FVC < 70%	27 (4.7%)
Restriction	Isolated FVC predicted < 80%	5 (0.9%)
	Isolated FVC < LLN	4 (0.7%)

8.5 Bronchodilator Reversibility

Bronchodilator reversibility to salbutamol was tested in all children with FEV_1 < 80% predicted or FEV_1/FVC < 80% on baseline spirometry. Of the 172 children (29.9% of the total studied) meeting this criterion, 56 (32.6%) demonstrated an increase in FEV_1 (L) of ≥ 12% post bronchodilation. There was no difference in the proportion of children demonstrating at least 12% BDR between those on the asthma register and those who were not, 32% vs 28% (p = 0.63).

The proportion of children demonstrating positive BDR was dependent on the definition of obstruction used (Table 31). The proposed NICE definition for airflow obstruction yielded the highest proportion of positive BDR tests, but was likely to underestimate children with abnormal lung function.

Table 31. Number of Children Demonstrating Bronchodilator Reversibility by Definition Used		
Definition of Obstruction Used	**% Reversible**	**Number (%)**
FEV_1 OR FEV_1/FVC < LLN (n = 135)	≥12%	51 (39.8%)
	≥10%	64 (50.0%)
	≥8%	77 (60.2%)
FEV_1 < 80% predicted OR FEV_1/FVC < 80% (n = 172)	≥12%	56 (32.6%)
	≥10%	70 (40.7%)
	≥8%	94 (54.7%)
FEV_1/FVC < 70% (n = 27)	≥12%	18 (66.7%)
	≥10%	20 (74.1%)
	≥8%	23 (85.2%)

8.6 Exhaled Nitric Oxide Levels

Exhaled nitric oxide (eNO) results were obtained from 472 (77%) children. Raised eNO levels (≥ 35ppb) were identified in 171 children (36%) ranging from 36 to 231 ppb. Median (IQR) eNO for our cohort was 23.0 (11.0 to 53.0) ppb.

Children on the asthma register were more likely to have a raised eNO compared to those not on the register; 39.4% (143/363) vs 25.7% (28/109) (p = 0.009). The median (IQR) eNO for children on the asthma register was higher; 25 (12 to 54) vs 16 (9 to 37), p = 0.004 (Figure 30).

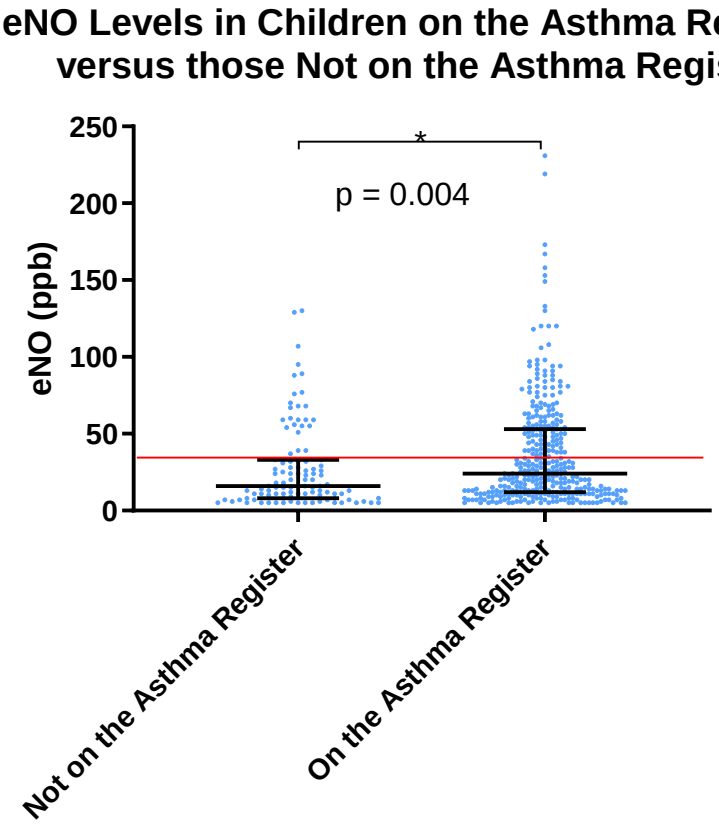


Figure 30. Scatter Graph of Children's Exhaled Nitric Oxide (eNO) levels by whether child is on the asthma register or not. Median and IQR plotted. Red line denotes cut-off for raised eNO (≥ 35 ppb)

8.7 Combined Spirometry and Exhaled Nitric Oxide Results

Four hundred and sixty-five (76.0%) children were able to perform both spirometry and eNO testing (Figure 31). Only half had normal results for both tests, n = 240 (52%).

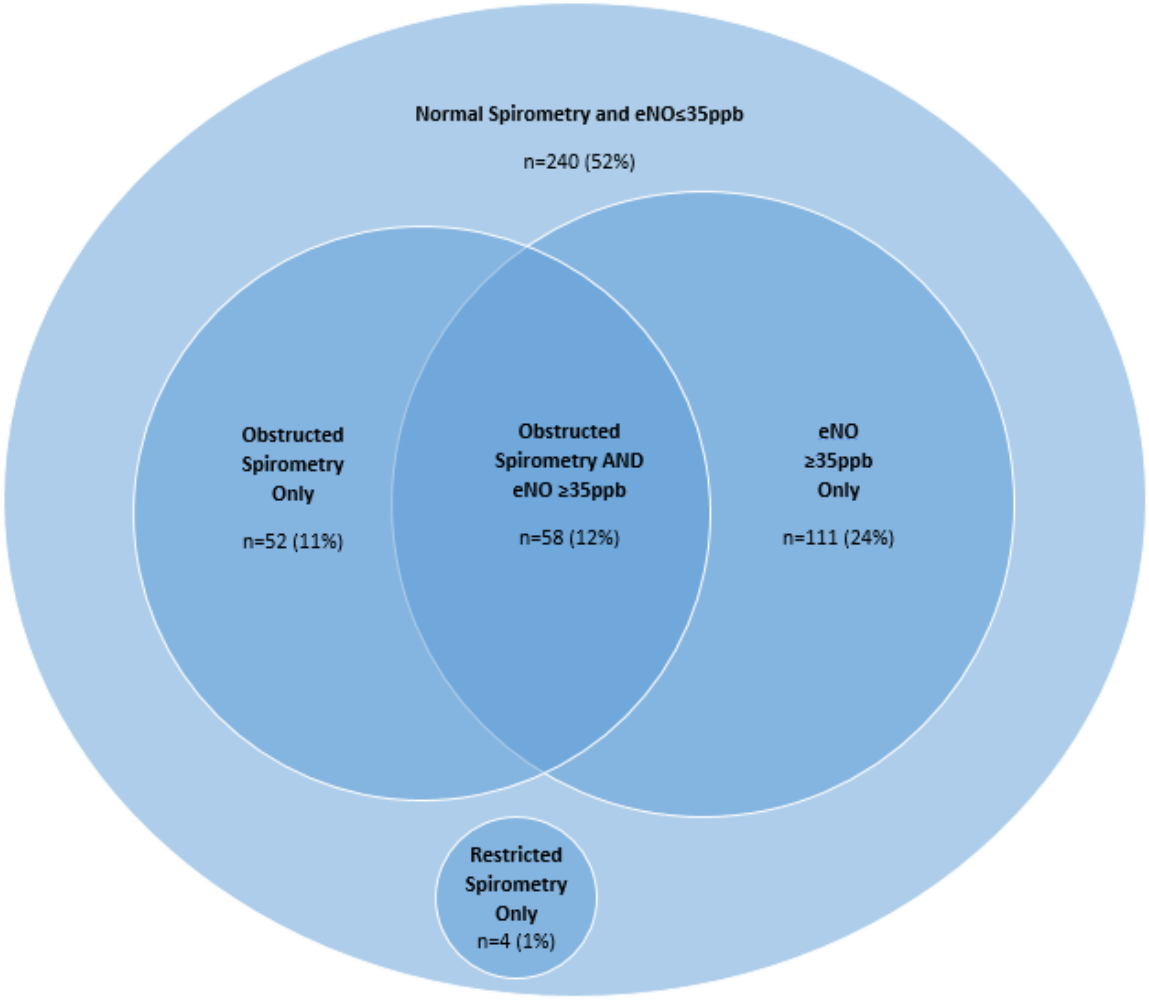


Figure 31. Number (percentage) of children with each combination of eNO and spirometry, based only on children who were able to perform both tests satisfactorily. Obstructed Spirometry defined as FEV_1 or FEV_1/FVC < LLN using GLI reference values. Restricted Spirometry defined as FVC < LLN.

8.8 Asthma Diagnosis

Spirometry and eNO data were available from 109 children who had received asthma medications in the previous year, but who were not on the asthma register. Of these, 12% had obstructed spirometry (GLI LLN) and BDR ≥ 12% to salbutamol and could have asthma confirmed according to NICE guidance. A further 6% had obstructed spirometry and eNO ≥ 35ppb (but BDR < 12%), 11% had obstructed spirometry only, and 13% had raised

eNO only; according to NICE guidance these children would warrant further investigation. Normal spirometry and eNO was found in 58% of children not on the asthma register.

Therefore, we estimated the underdiagnosis rate amongst children not on the asthma register (but on asthma medications) to be at least 12%, but could be as high as 42%.

Overdiagnosis of children on the asthma register is harder to estimate from our cohort, as normal lung function in children may represent the absence of asthma, mild asthma without significant lung function deficit, or current good control.

Spirometry and eNO results were obtained from 358 children already on the asthma register (existing asthma diagnosis).

Twenty-two out of 358 children (6%) reported good current symptom control (CACT/ACT > 19), had no exacerbations (oral steroids or unplanned healthcare attendances) within the previous 6 months, were not on regular inhaled corticosteroids, and had normal spirometry and eNO.

A further 32 children (9%) also met the above criteria but were meant to be on regular inhaled corticosteroids (≤ 400mcg beclomethasone equivalent per day) and had requested < 50% of required prescriptions.

These 54 children were either misdiagnosed or had current well controlled and inactive asthma. Based on these criteria, we estimated that the overdiagnosis rate amongst our cohort of children was potentially as high as 15%. However, 5 out of 54 children (9%) had at least one UHA with respiratory symptoms during the 6 months follow up.

There were also 33 children (9%) who reported good symptom control, had no exacerbations, normal spirometry and eNO, were on regular inhaled corticosteroids and had requested ≥ 50% of required prescriptions. It is possible that some of these children may also have been misdiagnosed with asthma. However, as they were on regular asthma medications, they may also have had current good control, or current inactive asthma. Six out of 33 (18%) had an UHA during follow up.

8.9 Relationship between Spirometry, eNO, Asthma Control Scores and UHAs at baseline

8.9.1 Asthma Control Scores

Children with current uncontrolled asthma (CACT/ACT ≤ 19) were more likely to have obstructed spirometry compared to those with good current control (CACT/ACT > 19); 28.5% vs 20.2% (P = 0.022). Although both FEV_1 Z-scores (r = 0.172; 95% CI 0.037 to 0.302) and FEV_1/FVC Z-scores (r = 0.238; 95% CI 0.105 to 0.362) correlated weakly with ACT scores (children 12-16 years), the correlation coefficients were low, with a wide spread of data. In younger children (5-11 years), whilst there was also a weak trend towards higher values for FEV_1 and FEV_1/FVC with higher CACT scores, these did not reach significance (Figure 32).

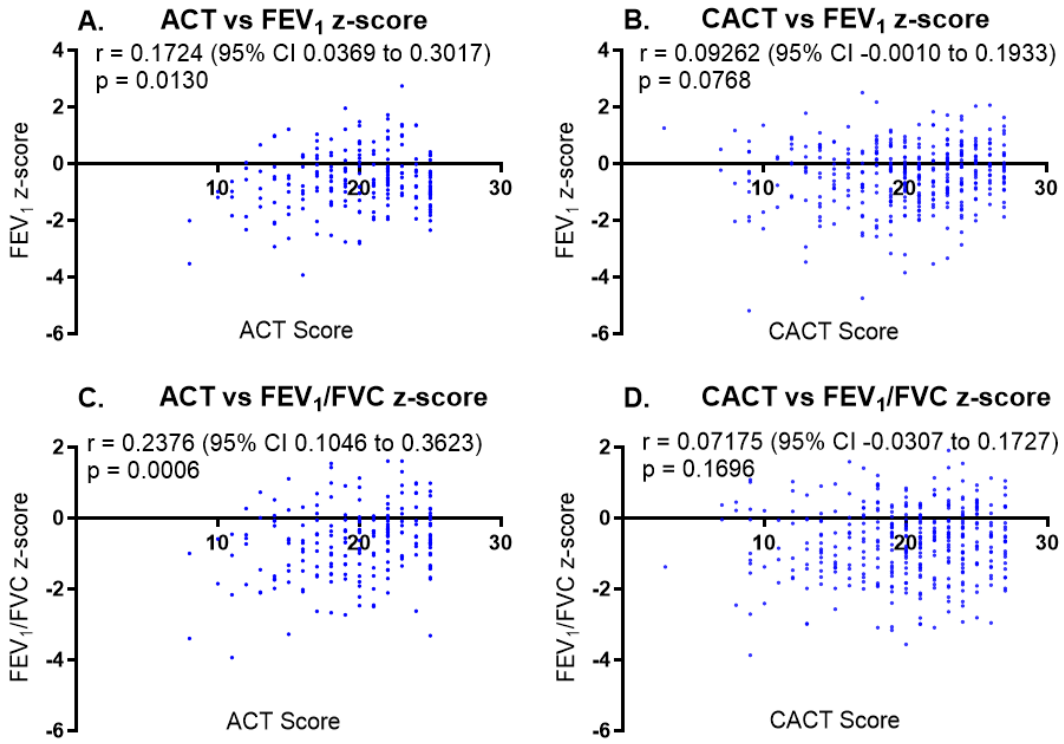


Figure 32 A-D. Scatter plots showing the relationships between spirometric parameters and asthma control as measured using the Asthma Control Test (ACT) for children 12 years and over, and the Children's Asthma Control Test (CACT) for those aged 5 to 11 years. FEV_1 =

forced expiratory volume in once second. FEV_1/FVC = ratio of forced volume expired in one second as a percentage of forced vital capacity (FVC). The correlation coefficient (r), confidence intervals (CI), and p-values are shown.

There was no difference in the prevalence of raised eNO (using a 35ppb cut-off) between those with good or poor current symptom control. Although there was an inverse trend between measured eNO levels and reported symptom control, this did not reach significance.

In children where both spirometry and eNO data were available (Table 32), 46% of children reporting good current control (ACT/CACT score > 19) had at least one objective test abnormality. In contrast, in those reporting poor current control, 93 out of 191 (49%) children had normal spirometry and eNO.

Table 32. Number of Children with Each Combination of Results According to Reported Current Asthma Symptom Control

Poor Control (ACT/CACT ≤ 19) n = 191			
	Obstructed Spirometry	**Normal Spirometry**	**Restricted Spirometry**
eNO ≥ 35	**25 (13%)**	**46 (24%)**	**0**
eNO < 35	**25 (13%)**	**93 (49%)**	**2 (1%)**
Good Control (ACT/CACT > 19) n = 274			
	Obstructed Spirometry	**Normal Spirometry**	**Restricted Spirometry**
eNO ≥ 35	**33 (12%)**	**65 (24%)**	**0**
eNO < 35	**27 (10%)**	**147 (54%)**	**2 (1%)**

Obstructed Spirometry defined as FEV_1 or FEV_1/FVC < LLN using GLI reference values. Normal Spirometry defined as FEV_1 and FEV_1/FVC ≥ LLN. Restricted Spirometry defined as FVC < LLN.

8.9.2 Unplanned Healthcare Attendances

Using multivariable logistic regression analysis, FEV_1/FVC z-score (p = 0.016) and having poor current asthma control (p = 0.002) were found to be independently associated with one or more UHAs in the preceding 6 months. An ACT/CACT score of ≤ 19 was associated with an increased odds ratio of 2.07 (95% CI 1.31 to 3.24) of having had an UHAs in the preceding 6 months; whilst each unit increase in FEV_1/FVC z-score was associated with a lower odds ratio of 0.41 (95% CI 0.20 to 0.85) of having had an UHAs in the preceding 6 months.

FEV_1% predicted (p = 0.861), FEV_1/FVC ratio (p = 0.078), eNO (p = 0.752), and FEV_1 z-score (p = 0.621) were not found to be statistically associated with a recent UHA in the preceding 6 months.

ROC curves were generated for each of the independent variables – ACT, CACT, and FEV_1/FVC z-score. The best cut-off points, using Youden's J statistic (sensitivity + specificity – 1), for identifying a recent UHAs were found to be: ACT ≤ 22, CACT ≤ 21, and FEV_1/FVC z-score ≤ -0.23 (Table 33). Although using these cut-off points would increase sensitivity, this would be at the expense of lowering specificity.

Table 33. Predictive Values of Independent Variables for Recent UHAs

Variable	Cut-off	Sensitivity	Specificity
ACT	≤ 19	0.526	0.674
	≤ 22	0.816	0.446
CACT	≤ 19	0.412	0.700
	≤ 21	0.618	0.552
FEV_1/FVC z-score	≤ -1.64	0.209	0.834
	≤ -0.23	0.775	0.363

8.10 Relationship between Spirometry, eNO, Asthma Control Scores and UHAs at 6 months follow up

8.10.1 Asthma Control Scores

Follow up asthma control tests were returned by 226 (37%) children. Overall, median (IQR) ACT scores improved from 20(17 to 23) to 22(19 to 24), $p = 0.032$, and CACT from 21(19 to 24) to 23(19.5 to 25), $p < 0.0001$ in the six months following review.

Using multivariable logistic regression analysis, only poor asthma control (CACT/ACT ≤ 19) at baseline was associated with poor control at follow up. Having poor symptoms control at baseline was associated with an odds ratio of 3.86 (95% CI 1.83 to 8.10; $p < 0.001$) of having poor symptoms control at follow up.

Neither spirometry nor eNO were found to be statistically associated with poor symptoms control at follow up.

8.10.2 Unplanned Healthcare Attendances

Electronic records were reviewed for 605/612 children six months post asthma review. Seven children had moved GP surgery so their records were no longer accessible. The mean (SEM) number of unplanned healthcare attendances (UHAs) fell from 0.31 (0.03) per child in the six months preceding review to 0.20 (0.02) per child over the six months following review, $p = 0.0004$.

The number of children with at least one UHA also fell from 140 out of 612 (23%) children to 100 out of 605 (16.5%) children at follow up; representing a relative reduction of 28%.

Using multivariable logistic regression analysis, eNO ($p = 0.001$) and a history of ≥ 1 UHA in the 6 months preceding baseline assessments ($p = 0.017$) were found to be independently associated with one or more UHAs during 6 months follow up. Each unit increase in eNO was associated with

an odds ratio of 1.012 (95% CI 1.005 to 1.018), and a preceding history of an UHA at baseline was associated with an odds ratio of 1.994 (95% CI 1.133 to 3.509) of an UHA during follow up.

The best cut-off point for eNO, using Youden's J statistic (sensitivity + specificity – 1), to predict an UHA during follow up was 58 ppb (Table 34).

Table 34. Predictive Value of eNO for UHAs at Follow Up			
Variable	**Cut-off**	**Sensitivity**	**Specificity**
eNO	≤ 35 ppb	0.474	0.659
	≤ 58 ppb	0.355	0.818

FEV_1% predicted (p = 0.135), FEV_1/FVC ratio (p = 0.187), FEV_1 z-score (p = 0.191), FEV_1/FVC z-score (p = 0.159), and poor symptoms control at baseline (p = 0.977) were not found to be statistically associated with UHAs during 6 months follow up.

8.11 Prescriptions

The prescription data from our cohort of children is shown in Table 35 below. Overall, the average daily ICS prescribed, the proportion of children on regular ICS, and the proportion of children on a regular long acting beta agonist (LABA) increased within our cohort from baseline to follow up.

Table 35. Prescription Data at Baseline and Follow Up			
	Baseline (n = 612)	**Follow up (n = 605)**	**P value**
Mean daily ICS dose in mcg (SEM)	190.6 (8.8)	218.2 (8.7)	< 0.001
Number of children on daily ICS (%)	411 (67.2%)	437 (72.2%)	0.006
Number of children on a LABA in addition to ICS (%)	72 (11.8%)	87 (14.4%)	0.018

8.12 Adherence

The adherence rates to regular inhaled ICS were calculated based on the number of prescriptions for inhalers issued over the previous 6 months (from GP records only), expressed as a proportion of the number of inhalers which should have been issued if the patient used their preventer inhaler as directed (Table 36). The proportion of children issued 50% or more of their required inhalers increased from 61.4% at baseline to 73.9% at follow up.

Table 36. Proportion of Children in Each Adherence Rate Category		
Adherence Rate Category	**Baseline**	**Follow Up**
≥ 75%	42.0%	48.2%
50 to 74%	19.4%	25.6%
25 to 49%	17.8%	16.9%
< 25%	20.7%	9.2%
Total	100%	100%

CHAPTER 9: DISCUSSION

Spirometry and fraction of exhaled nitric oxide (eNO) testing are commonly used clinical tools within secondary and tertiary asthma centres. Recent UK guidelines have recommended their use across all care settings, including general practice, in adults and children from five years (NICE, 2017). However, there is currently limited data to inform the implementation of these tests for children within primary care.

We conducted a large prospective observational cohort study to explore outcomes relating to the implementation of spirometry and eNO testing for children with diagnosed or suspected asthma managed within the community; and to obtain information on the extent of lung function deficits and airway inflammation and their relationship with asthma control.

The following sections will highlight the key findings from both parts of my research project, discuss how they fit in with existing literature, what the strengths and limitations were, and suggest ideas for future research.

9.1 Implementation Outcomes

The first part of my project explored implementation outcomes relating to providing spirometry and eNO testing for children in general practice, specifically relating to the outcome measures of: adoption, appropriateness, acceptability, and feasibility described in chapter 4.

9.1.1 Appropriateness and Adoption – Readiness for Change Questionnaire

The implementation outcome measure “appropriateness” measures the perceived fit of an intervention to address a particular issue, whilst “adoption” refers to the perceived need or intention to adopt a new procedure into practice. These two outcome measures are closely related, and were

addressed using the readiness for change questionnaire (RfCQ). Additionally we sought to identify the perceived barriers against adoption from GP staff.

Appropriateness: Only half of those surveyed felt there is good evidence that lung function can improve asthma care, with just over 10% disagreeing. A similar proportion of participants agreed with the statements – “lung function tests will help me diagnose asthma in children better”, and “lung function tests will help me monitor asthma in children better”; although slightly more responded favourably towards using objective testing for diagnosis (~60%) than for monitoring (~50%).

This would suggest that perceived appropriateness may be a significant barrier against widespread adoption of lung function testing in primary care, and reflects the limited evidence base supporting the use of spirometry and eNO for children’s asthma diagnosis and monitoring (see chapter 3). In order for widespread implementation of paediatric spirometry and eNO to take place in primary care, the potential clinical benefits of providing these tests must be firmly established; particularly in terms of their ability to improve asthma outcomes by reducing asthma attack rates and improving symptoms control. The design of such a study is described in more detail later in this chapter.

Adoption: In terms of the perceived need for a new intervention within primary care, twice as many GPs and PNs participating in our study found asthma diagnosis and management difficult in children compared to in adults. This finding is supported by a recent qualitative study exploring the challenges in diagnosing asthma in primary care, which also identified that primary care staff “found it difficult to differentiate between asthma and other closely related conditions at the extremes of age,” acknowledging that the clinical features of asthma can overlap with other conditions such as respiratory viral illnesses in children (Akindele et al., 2019).

In recent years, there have been a number of media headlines claiming that asthma misdiagnosis is common in both children and adults (Knapton, 2016, Roberts, 2015). It was perhaps unsurprisingly therefore that 60% of staff

surveyed in our study thought asthma misdiagnosis is a problem nationally. Interestingly only 21% thought misdiagnosis is a problem within their own practice. This may represent a genuine belief that their local asthma care is better than the national average, or a reluctance to be critical of their own practice. However the majority (83%) did respond that children's asthma management could be improved locally.

Despite this, fewer than half of the survey participants were keen to learn to perform spirometry in children, and only around 60% were interested to learn to interpret results.

This reluctance towards the use of spirometry in general practice poses a significant barrier for routine implementation into UK primary care. Similar issues with the provision and use of spirometry in primary care have been reported in other countries (Blain and Craig, 2009, Finkelstein et al., 2000, Johns et al., 2006).

A recent review article looking at the global trends in the use of spirometry for managing childhood asthma concluded that spirometry is infrequently used for paediatric asthma diagnosis in low income countries. Lack of equipment, lack of proper training, and lack of national asthma guidelines within the context of resource-poor settings were cited as possible barriers to widespread use within developing countries (Ayuk et al., 2017). However, poor uptake of spirometry use in children's asthma management has similarly been reported in high income countries including the US (Finkelstein et al., 2000, Dombkowski et al., 2010), and in adult asthma management in Sweden (Weidinger et al., 2009), and Australia (Barton et al., 2009). Of note, availability of lung function equipment does not appear to correlate with usage. A primary care study in Spain found that although 90% of practices surveyed owned a spirometer, 22% of those spirometers had never been used (Hueto et al., 2006). Likewise in Australia, a study of 247 GPs found that whilst 76% had access to a spirometer, only 12% reported using spirometry routinely to manage asthma (Barton et al., 2009). Despite availability of equipment, and national guidelines recommending the use of

objective testing (NAEPP, 2007), uptake of spirometry within primary care is low even in high-resource settings.

Our study provides further insight into the perceived barriers against implementation. From the free text responses to our survey, lack of time and clinic capacity, and lack of training and expertise in interpreting lung function tests emerged as the most commonly cited reasons against the routine use of spirometry and eNO amongst practices surveyed. These concerns reflect those reported in studies from the US and Australia which have also found that lack of time, training, expertise, and unfamiliarity with interpretation of results to be the main barriers to widespread adoption of spirometry in primary care (Kaminsky et al., 2005, Dombkowski et al., 2010, Walters et al., 2005). In addition, amongst GPs who already own the necessary equipment, lack of funding and adequate reimbursement have been found to limit spirometry usage (Johns et al., 2006, Kaminsky et al., 2005).

Interestingly, although perceived appropriateness of the intervention was identified as a barrier from the Likert scale responses in the survey, appropriateness did not emerge as a major perceived barrier from the free text responses. Similarly, only ~20% of respondents reportedly found asthma management in children difficult, but over 50% felt that management needed to be improved. These contradictory findings highlights a limitation of using survey data to explore complex human perceptions, as they do not allow subtleties and nuances to be explored in more detail due to the rigid response structure (Likert scale). Ideally, the reasoning behind each participant's responses could be explored further using qualitative research methodology, such as focus groups or 1-2-1 interviews if time would have allowed. Particularly it would have been interesting to explore whether, following a programme of training and support to provide these tests in the real world setting, attitudes towards their appropriateness would have changed, or if previously unanticipated barriers would have emerged.

Despite this limitation, data from the RfCQ does provide an insight into the perceptions towards spirometry and eNO testing from a cohort of primary care practices. Suggesting that whilst there is a perceived need for asthma

management to be improved in children, the perceived appropriateness of these tests, willingness to adopt spirometry and eNO into routine practice, and physical challenges (time and resources) will pose significant barriers.

These perceived barriers towards implementation of spirometry and eNO can be mapped using the COM-B model described earlier in chapter 4 (Figure 33).

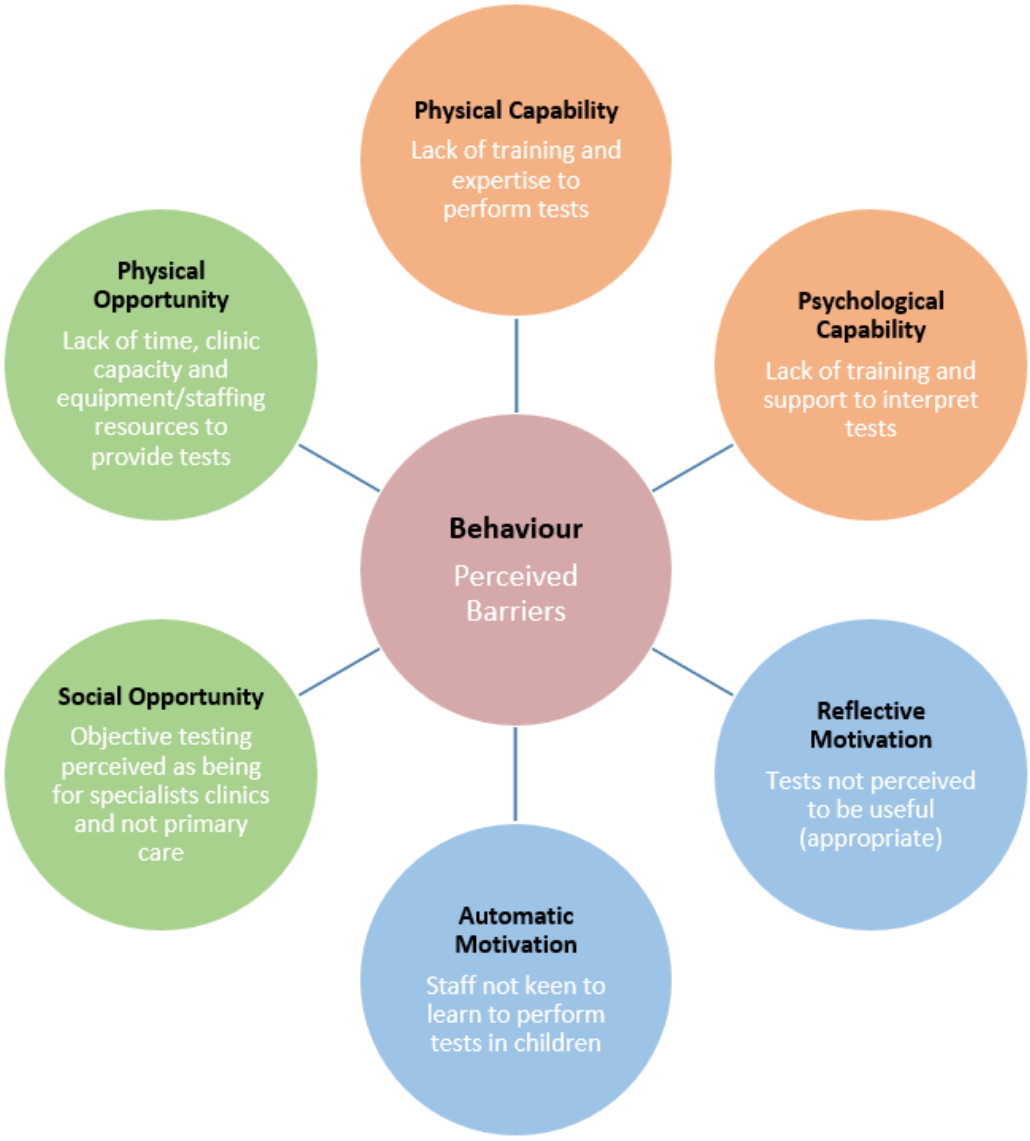


Figure 33. Perceived barriers towards implementation mapped to COM-B framework

A change in behaviour will therefore require the change of one or more of these components (Michie et al., 2011) to take place. This is turn requires evidence to support the clinical usefulness of spirometry and eNO (to improve perceived appropriateness), and data to inform the feasibility and acceptability of these tests to staff and families (to address adoption).

In order for adoption of spirometry and eNO to take place, the training needs of GP staff, and additional clinic time required for testing needs to be quantified. Importantly, the clinical need for these tests must be demonstrated to convince GPs to use them in their routine practice.

9.1.2 Feasibility – Training

In children, I could find no published data on training times needed to reach competency in performing spirometry or eNO. Adult studies have shown that acceptable spirometry can be performed by general practice staff after only four hours of training and six observed procedures (Licskai et al., 2012); and after a 13-hour training course, spirometry usage amongst GPs increased 6-fold (Johansen, 2007). However, the quality of spirometry performed in primary care, even after training, has been shown to be below that performed in pulmonary function laboratories (Akhtar and Wilson, 2005). The reason may be that spirometry is performed less frequently within the primary care setting, and that training is not standardised.

In the UK, training and accreditation in spirometry is being formalised by the Association for Respiratory Technology and Physiology (ARTP). By 2021, all individuals performing or interpreting adult spirometry in the UK must have undergone spirometry certification by ARTP and be recorded on the national register as a qualified practitioner (ARTP, 2019). This is not currently an expected requirement for paediatric spirometry, however, formalised training, accreditation, and registration in paediatric spirometry is available.

At the time of writing, ARTP provide adult spirometry training through their partner provider – The Institute of Clinical Science and Technology (ICS&T). This training consists of eight hours of e-learning and a half day work shop.

Paediatric courses are currently offered in Glasgow, London, and Sheffield consisting of two full days of face-to-face training.

We were able to train 27 members of GP staff (practice nurses and health care assistants) to competently perform and/or interpret paediatric spirometry and eNO in an average of 10 hours per trainee using a training format reflecting the adult training programme currently provided in Leicestershire. Although the training time required by the participants in our study was not dissimilar to the amount of training provided in the ARTP course, our training could have been delivered more efficiently. For instance, the face-to-face training was delivered on a 1-to-1 basis, but could have been provided to a larger audience. However, as the practices were recruited into our study at different time points throughout the year, it was not practicable to provide training sessions to large groups of people in a single session without delaying provision of the tests at each practice during clinical reviews.

In order to scale up training to a wider audience, group training sessions (as currently provided by ARTP) will be required to improve efficiency. Although this will require staff to be freed from clinical duties for up to two days at a time.

Another option will be to deliver part of the training programme as online learning, which is already available for adult spirometry training. This will still require around eight hours of study, but the adult e-learning package is designed to be accessed in shorter 20 minute segments and may be more appealing to busy primary care practitioners.

Sustainability, in terms of maintenance of skills, was not addressed by this study, as we did not have the capacity or funding to revisit our practices to reassess competencies or to continue providing each practice with the necessary equipment once the study had ended. However, this is clearly an important implementation outcome to consider as part of any training programme.

Indeed an Australian study of 18 primary care staff who received 14 hours of spirometry training, found that even five months following the training session adherence to ERS/ATS spirometry standards was poor, but improved with follow up training (Borg et al., 2010). This finding has been reflected in a single-practice UK primary care study which also demonstrated improvement in the quality of adult spirometry testing following a training update (Carr et al., 2011).

In adults, the need for regular training updates has been recognised as part of the proposed ARTP accreditation process. Re-certification of competencies for the performance of diagnostic spirometry, with or without interpretation, will involve an observed assessment of competence plus submission of a comprehensive portfolio every three years (Hill and Morgan, 2016). There is no similar requirement for paediatric spirometry at present.

Widespread implementation of quality assured spirometry appears to be a priority in adults, but less so in children; as evidenced by the roll out of formal accreditation for adult, but not paediatric, spirometry by 2021. Presumably the perceived need for spirometry in adults is viewed to be greater, particularly in the context of COPD diagnosis. Indeed spirometry is specifically listed as a QOF requirement for COPD, but only as an option for asthma (NHSE, 2019).

Our data demonstrates that primary care staff can be trained to perform quality paediatric spirometry and eNO testing in the community within a similar time frame to reported adult training times. However, more efficient and standardised training programmes are needed, including the use of online training tools to provide greater flexibility to primary care staff, and a formal accreditation process for children as in adults. There are currently more options for adult spirometry training than paediatric training, in terms of locations of providers and the method of teaching available. This discrepancy can only be addressed if the perceived need for paediatric objective testing in asthma is established. The feasibility and acceptability of spirometry and eNO testing in children, and the additional clinical information provided by these tests will inform this need, and are discussed next.

9.1.3 Feasibility – of the tests in children

A previous study has demonstrated that quality spirometry can be achieved in children as young as five years (Eigen et al., 2001), however this study was performed within a controlled hospital research setting, and not reflective of the busy general practice environment. In our study, we demonstrated that spirometry data could be obtained from over three-quarters of children from as young as five, and 94% of children between five to sixteen years during real general practice asthma clinics. Despite the majority of children having never performed spirometry and eNO, both tests were achievable in under seven minutes on average. Although additional time was required to administer bronchodilators and test for BDR, we found that it was possible to perform all three tests by allocating twenty minutes to each child for testing alone, prior to their asthma clinical review.

Exhaled nitric oxide testing was unsuccessful in the majority of our cohort under the age of seven years, with only 17% of five year olds producing a result. This reflects the need for a slower controlled exhalation in eNO testing which can be difficult for young children to perform. By eight years, the success rate of eNO testing increases to above 80%. Our finding is consistent with a small UK study which also reported feasibility of eNO testing in general practice in adults and children from eight years onwards (Gruffydd-Jones et al., 2007).

For our study we utilised the 10 second mode for eNO testing in every attempt, this requires a child to exhale at a steady flow rate for 10 seconds before a result can be obtained. The NIOX Vero does offer a six second mode, which may be easier for younger children to achieve. However, at the time of designing our study, we were advised by the manufacturers that the six second mode was not yet validated. Two studies have since been published reporting that eNO measurements obtained using either the six second or 10 second mode are consistent in children up to 10 years of age (Rickard et al., 2019a, Rickard et al., 2019b). This would intuitively improve the feasibility of eNO testing in younger children. It should be noted that the

lead authors for both studies are employees of Circassia pharmaceuticals who manufacture the NIOX Vero.

Both, spirometry and eNO testing are feasible in the majority of children in primary care. Younger children find eNO testing more difficult, but newer machines which require reduced exhalation times should further improve its feasibility.

9.1.4 Acceptability

Spirometry and eNO testing were acceptable to the majority of families. Using the friends and family test, 97% of parents and guardians responded that they were extremely likely or likely to recommend these tests to friends or family, and 87% of children said that they would be happy to perform the tests again.

A previous small UK study, which included 22 adults and 15 children, also found that eNO in primary care was acceptable to patients and staff (Gruffydd-Jones et al., 2007). Similarly, practice staff participating in our study responded positively to the testing, with over 90% of all respondents saying that having spirometry and eNO available in their practice would help them to manage asthma better. This was reflected within their free text comments, which emphasised the perceived usefulness of the tests to aid management decisions. Notably, practice staff performing the asthma reviews felt that spirometry and eNO supported their decision making in 93% of patient consultations, and actively changed their management plan in almost a quarter of consultations.

Following a trial of implementation, perceived appropriateness and willingness to adopt spirometry and eNO into routine practice amongst primary care staff appeared to increase. This would theoretically positively augment the motivation and opportunities components described within the COM-B behaviour model, and promote a change in behaviour favouring adoption of objective testing. However 15% of staff participants did not provide feedback, introducing an element of selective bias to the responses.

Moreover, the implementation methodology utilised within CHAMPIONS provided a lot of direct support to practice staff members throughout the duration of the study, and may have positively influenced perceived acceptability of introducing both tests. As discussed earlier, this would not be an efficient way to implement these tests widely. Additionally, the physical opportunity (Michie et al., 2011) to provide these tests in the long term, afforded by environmental factors including funding and equipment, still existed as barriers to implementation and a change in behaviour.

Paediatric spirometry and eNO testing in primary care are acceptability to families and staff. However, despite their perceived usefulness, the availability of equipment and ongoing funding issues were still seen as major barriers to implementation.

9.1.5 Cost

Data from this study was also used to calculate the support and associated NHS costs needed to implement spirometry and eNO testing for children into the ten participating practices. The cost data is currently being analysed by our health economics collaborator (Dr. Yaling Yang, University of Oxford), who is performing the analysis and drafting the manuscript for publication.

In our study, we only investigated one method of implementation in order to provide proof of concept that providing spirometry and eNO is possible for children managed in primary care. The associated cost calculations for implementing these tests will be based on our training and implementation strategy. More efficient ways of delivering training (as described in section 8.1.2) will need to be explored, in order to reduce the costs associated with wider implementation.

In the Netherlands, primary care practitioners are able to refer patients with suspected respiratory disorders to diagnostic centres for testing. These diagnostic centres offer a range of tests, including spirometry. Patients can be referred to the diagnostic centres for pre- and post-bronchodilator spirometry testing when asthma or COPD is suspected (Schermer et al.,

2016). The advantage of diagnostic centres is to centralise provision and interpretation of spirometry into regional hubs, which ensures maintenance of skills in staff and good reliability of measurements without the need for additional equipment and resources at the practice level. The main drawbacks are additional travel and separate appointments needed for patients, and the need for timely feedback of results to GPs (Schermer et al., 2008).

The most recent NICE asthma guideline also discusses the need for asthma diagnostic hubs in order to achieve economies of scale. If these were to be established for children, the reduced equipment, training, and staffing costs associated with centralisation of testing would need to be balanced against the increased burden of additional travel and time off school or work for patients attending these hubs. Moreover, robust protocols will need to be in place for abnormal results to be fed back to GPs and acted on promptly.

9.2 Clinical Outcomes

The second part of my research project explored the clinical outcomes relating to the implementation of paediatric spirometry and eNO testing into primary care. We reported the prevalence of lung function and eNO abnormalities in our large cohort of children that were either on the GP asthma register or receiving regular asthma medications, their relationship with reported current asthma control and unplanned healthcare attendances (UHA), and the change in asthma control and number of UHAs following a structured clinical review which included objective testing.

9.2.1 Prevalence of Abnormal Spirometry and eNO

Abnormal spirometry was identified in almost one-quarter of our selected cohort of children, regardless of whether or not they were on their GPs asthma register. Comparisons of prevalence of abnormal spirometry with other studies is not straightforward because criteria for abnormality and the reference equations used vary, but our finding is broadly in line with two

previous North American studies involving cohorts of children with asthma. Bacharier and colleagues (Bacharier et al., 2004) identified abnormal FEV_1/FVC in 33% of the 219 children (5-18 years) attending two tertiary care asthma centres for routine evaluation of asthma. Participants were in their "usual state" of asthma control and excluded if they had been seen for an exacerbation or received oral corticosteroids within that last month. In another study of 892 children (5-18 years) who had had asthma diagnosed on clinical history alone as part of a school-based, low income, asthma mobile van program, 24% had abnormal pre bronchodilator spirometry (Galant et al., 2011).

Although some studies have demonstrated an association between low lung function with an increased risk of future asthma attacks (Fuhlbrigge et al., 2001), others have not (Robroeks et al., 2013). A recent systematic review which aimed to identify risk factors for asthma attacks in children (5-12 years) similarly concluded that there is inconclusive evidence to determine whether low lung function is a risk factor for future exacerbations (Buelo et al., 2018).

So why is our finding important? Longitudinal studies of lung function have demonstrated several trajectories from childhood to adulthood, with lower lung function trajectories associated with adverse health outcomes later in life (Agusti and Faner, 2019). Childhood asthma is a potential risk factor for low lung function in adulthood (Sears et al., 2003b, Tai et al., 2014b), which in turn is associated with an increased risk of developing COPD (Bui et al., 2017) and of early cardiopulmonary related mortality (Vasquez et al., 2017). It is unclear whether any intervention can augment abnormal lung function trajectories during growth. However, the increased risk of future poor health should justify the need for spirometry in children, particularly in those with asthma, (Bui et al., 2017) to identify and prompt more proactive monitoring of individuals with low lung function. For eNO, a cut-off level of 35ppb was chosen based on ATS and NICE recommendations (Dweik et al., 2011, NICE, 2017). Baseline eNO levels of greater than 35ppb were identified in 36% of our cohort. This in itself has implications for predicting risk of exacerbations. A cross-sectional study of 12 408 people aged six to 80

years, subjects with eNO ≥ 50ppb had an odds ratio of 2.9 for asthma related emergency department visits compares to subjects with a eNO < 25ppb (Malinovschi et al., 2013). In an adult study involving 341 asthma patients from Belgium, a eNO < 30ppb indicated that "loss of optimal control was unlikely to occur within the next three months" with a negative predictive value of 94% (Michils et al., 2008). Whilst in children, a Korean study of 145 children (8-16 years) with asthma found that a single eNO > 37ppb during serial measurements over 2-years predicted subsequent loss of asthma control over the following year with a sensitivity of 91% (Yang et al., 2015a).

In children able to perform both spirometry and eNO testing, around half had at least one abnormal test result. Of those with at least one abnormality, approximately half had raised eNO alone, one-quarter had obstructed spirometry alone, and one-quarter had abnormal results for both; suggesting a complementary and not mutually exclusive, role for both eNO and spirometry in children's asthma monitoring.

The high prevalence of obstructed spirometry and eNO found in our cohort of children would on face value support the need for objective tests in primary care in order for these abnormalities to be identified. However, in order to augment behaviour (i.e. the intention to adopt spirometry and eNO in primary care), the perceived appropriateness and benefits of testing needs to be justified. The question remains – do they provide any additional useful information to guide clinical decision making, over a traditional history and examination based approach? The next sections discuss the relationship between objective tests, symptoms, and exacerbations observed within our cohort.

9.2.2 Relationship between Spirometry, eNO and current symptom control

We found a statistically significant, but weak relationship between ACT scores with FEV_1 and FEV_1/FVC, and no correlation between CACT scores with either FEV_1 or FEV_1/FVC. There was also no correlation between eNO

with either ACT or CACT scores. Recent studies have similarly reported weak correlations between spirometry and ACT in adults (Papakosta et al., 2011), but not between spirometry or eNO and CACT in younger children (Green et al., 2013). This might reflect a disassociation between a patient's asthma symptoms and their perception of those symptoms (Rietveld and Walter, 2000, Mammen et al., 2017), or a temporal delay between changes in symptoms and lung function (Anandi et al., 2016, Mehta et al., 2009).

The closer relationship we observed between ACT with lung function, compared with CACT with lung function, may further be explained by the CACT questionnaire requiring responses from both the parent and the child. The parent component of the questionnaire refers to the frequency of daytime and nighttime symptoms in the child. As children of this age are normally at school during the day, and sleep in their own rooms at night, this aspect of their control is difficult to estimate. Indeed, it has been reported that parental completed sections of the CACT questionnaire may underestimate symptoms in children (Voorend-van Bergen et al., 2013).

Moreover, the absence of relationship between eNO and patient reported symptoms highlights that spirometry and eNO measure different components of airway physiology. Obstructed spirometry is caused by narrowed airways resulting in turbulent airflow, wheeze, and dyspnoea. It is not too surprising therefore that we observed some relationship between lung function with asthma symptoms, at least in older children. Exhaled nitric oxide on the other hand is a measure of airway inflammation, does not necessarily reflect the degree of airflow limitation, and therefore may or may not result in asthma symptoms. Although eosinophilic airway inflammation, of which eNO is a proposed surrogate marker for, has been shown to reflect risk of future asthma attacks (Gibson et al., 2003).

Importantly, almost half the children in our cohort reporting good current asthma control had at least one objective test abnormality; with 12% having both abnormal spirometry and eNO. This suggests that asthma severity (NAEPP, 2007) and suboptimal control (BTS, 2019) may be under-recognised when clinical evaluation is based on symptoms alone. Indeed, a

Japanese study involving 726 adults and 135 children over 6 years, found that when the severity of asthma was classified based on symptoms alone, 50% of adults and 35% of children classified as having mild symptoms had moderate (FEV_1 predicted 60-79%) to severe (FEV_1 predicted < 60%) airflow limitation (Tomita et al., 2009).

By contrast, 49% of children reporting poor current control had normal tests, suggesting either incorrect asthma diagnosis, or highlighting that children can be symptomatic despite normal lung function. Similarly, a US study involving 201 children found that asthma assessments based on history alone underestimated asthma severity determined by spirometry in 31% of children; whilst assessments using spirometry alone under-recognised poor control in 40% of symptomatic children compared with clinician-determined severity (Cowen et al., 2007). Although this study predates publication of GLI reference values, making direct comparison with our data challenging, it highlights the fact that asthma assessments based on either symptoms, or objective tests in isolation do not provide a full picture of the child with asthma.

Under-recognition of the underlying severity of a child's asthma has potentially severe consequences. Two recent coroners' reports in the UK, both identified failures in the management of two children who died in 2014 and 2015; emphasising the lack of appreciation and recognition of the severity of their condition and the deteriorating nature of their clinical control (Carney, 2015, Radcliffe, 2017). We believe this highlights the need for objective measures of asthma control in addition to the traditional symptoms' based approach.

9.2.3 Relationship between Spirometry, eNO and recent exacerbations

In terms of asthma attacks, around a quarter of our cohort had at least one unplanned healthcare attendance for asthma in the 6 months preceding review regardless of whether they were on the asthma register or not. This is higher than previously reported asthma attack rates in children of 8% to 36%

over a 12-months period (Suruki et al., 2017, Rabe et al., 2000). Likewise the mean number of exacerbations for children aged 5-17 years in the UK has recently been reported as 1.48 exacerbations per 10 person-years (equivalent to 0.074 per child/6 months) (Bloom et al., 2018), compared to 0.31 per child/6 months in our cohort. This difference may be due to the definitions used for what constitutes an exacerbation. In both previous UK studies (Bloom et al., 2018, Suruki et al., 2017), an exacerbation was defined as either worsening of symptoms requiring ED attendance or oral corticosteroids, this criterion may have missed milder exacerbations which either did not require oral steroids or visits to the hospital. Whilst in our study we included any respiratory unplanned healthcare attendance regardless of need for oral steroids, and referred to discharge letters stored as text documents even if they were not coded electronically on SystmOne. The recent Lancet commission on asthma (Pavord et al., 2018) discusses the heterogeneity of asthma attacks at all ages and emphasises that any loss of symptom control should be taken seriously.

Using logistic regression analysis, we found that FEV_1/FVC z-score, and poor current asthma control, but not eNO, were associated with a recent asthma attack in the previous six months. This again supports the notion that lung function is more closely related with current asthma control than eNO.

Interestingly, in adult studies, frequent respiratory exacerbations have been shown to be associated with more rapid lung function decline in patients with asthma (Bai et al., 2007) and COPD (Rennard and Farmer, 2004). Understandably, current asthma guidelines emphasise the importance of assessing both current asthma control, and the risk of future attacks at every review.

9.2.4 Asthma control and exacerbations at follow up

Notably, following an asthma review that included objective tests, we observed a small improvement in ACT/CACT scores during follow up. This is arguably subjective and possibly a result of study (Hawthorne) effect

(McCambridge et al., 2014). Moreover, the improvement in asthma control test scores at follow up were below the published minimally clinically important change in scores for both ACT and CACT of 3-points and 2-points respectively.

However, the mean number of UHAs and the proportion of children having at least one UHA also fell by almost a third. We speculate that this resulted from practice nurses being trained as part of this study to act on both patient reported symptoms and objective evidence from spirometry and eNO, leading to an increased recognition of suboptimal control, under-treatment or poor compliance with preventer medications, and more accurate titration of asthma treatment. Indeed the mean daily ICS dose and proportion of children receiving more than 50% of required prescriptions increased from baseline to follow up. However, previous studies have similarly demonstrated that asthma reviews conducted by trained asthma nurses in primary care can improve patient outcomes and reduce asthma attacks (Cave et al., 2001, Griffiths et al., 2004), even though these studies did not include the use of spirometry or eNO as part of the asthma review.

Previous asthma studies comparing standard symptoms-based monitoring versus monitoring with additional spirometry or eNO have not found significant differences between groups in terms of current symptoms control.

In terms of exacerbations, an Australian trial comparing standard asthma monitoring versus active monitoring with spirometry reported no difference in number of exacerbations (Abramson et al., 2015). It is worth highlighting that this trial did not include a management algorithm to direct treatment of children with abnormal lung function. Intuitively, spirometry-based monitoring would only be effective if abnormal results are acted on appropriately.

There is, however, some evidence that children monitored with eNO may have fewer exacerbations when compared with standard guidelines based monitoring alone. Three systematic reviews have focussed on this question (Lu et al., 2015, Gomersal et al., 2016, Petsky et al., 2016a). The most recent Cochrane review included nine paediatric studies, and reported that significantly fewer children in the eNO directed management group had one

or more asthma exacerbations over the study period when compared with standard management (Petsky et al., 2016a). There were no differences between the groups in terms of change in lung function, asthma control, or eNO over the study period.

Future studies comparing standard asthma care versus a review which includes both spirometry and eNO are required to determine whether there is any impact on asthma symptoms and asthma exacerbations when these two different measures of airway physiology are used in conjunction to inform asthma treatment. This is discussed further later in this chapter.

9.2.5 Risk factors associated with future risk of poor asthma control and exacerbations

Within our cohort of patients, neither lung function nor eNO at baseline were found to be predictors for future poor asthma control. Only poor asthma control at baseline was associated with poor reported control at follow up. This again demonstrates the poor relationship between patient reported symptoms with both lung function and eNO, as observed within our study and described by previous studies (Quaedvlieg et al., 2009).

However, alongside a previous history of an asthma attack, eNO was found to be an independent predictor for an asthma attack during follow up. In a recent systematic review, Buelo *et al.* also identified previous asthma attacks as a significant risk factor for future asthma attacks, with a similar odds ratio (range of odds ratios 2.1 to 4.1) identified in our study (OR 2.0; 95% CI 1.1 to 3.5). They found insufficient evidence to reach a conclusion regarding eNO as a risk factor, but did comment that “lack of evidence does not mean [it is not] a significant factor” (Buelo et al., 2018).

Moreover, our finding that eNO is a risk factor for future asthma attacks is consistent with the conclusions from a recent Cochrane review which concluded that eNO targeted asthma monitoring may reduce the frequency of future asthma attacks (Petsky et al., 2016a).

Taken together, this strengthens the argument that a multifaceted approach towards asthma monitoring, which includes careful history taking and objective testing, is needed to provide a comprehensive picture of a patient's asthma clinical status; in terms of their current control, future risk of attacks, and longer term risk of adverse health outcomes from a more rapid lung function decline.

9.2.6 Asthma Diagnosis

In terms of diagnosis, one-quarter of our cohort were identified based on them receiving asthma medications in the previous year despite not having a coded asthma diagnosis. We believe this may reflect both a hesitance to formally diagnose children with asthma in primary care, and an issue with coding practices i.e. the child is diagnosed but this is not recorded on the practice database. These children would not automatically be recalled for a routine annual asthma review and are at risk of having unrecognised poor symptom control.

Using the NICE asthma diagnosis algorithm, 12% of our cohort without an existing asthma diagnosis had asthma confirmed. Although asthma could not be confirmed in the remaining children with raised eNO and/or obstructed airflow without positive BDR due to lack of PEFR variability data, a further 6% had probable asthma based on two positive tests, demonstrating the potential usefulness of providing objective tests within primary care. We estimated that the underdiagnosis rate amongst our cohort of children to be between 12% and 42%. This range is consistent with previous studies which have reported similarly high estimates of asthma underdiagnosis in children (Annesi-Maesano et al., 2012, Brozek et al., 2013, Oluwole et al., 2017). However, the only previous study to confirm, or exclude, asthma based on spirometry, BDR, and methacholine challenge testing reports an asthma underdiagnosis rate of 10%, which is closer to our lower estimate (Yang et al., 2017).

The NICE asthma guideline feasibility study (NICE 2017) was able to confirm an asthma diagnosis in 24.5% of their cohort, who presented acutely with asthma symptoms. As both lung function and eNO can fluctuate, it is possible that our diagnosis rate was slightly lower, due to our cohort of children being recruited during routine reviews and not when they were presenting acutely unwell.

Although we estimated an overdiagnosis rate of between 6% and 15% in children on the asthma register, this study was not designed to explore overdiagnosis issues. In children with normal eNO and spirometry, when they are asymptomatic, we cannot be certain whether they genuinely do not have asthma or whether they are currently well controlled.

Previous studies which were designed *a* priori to explore misdiagnosis of asthma in children have reported overdiagnosis of asthma in around 50% of children managed within the community (Yang et al., 2017, Looijmans-van den Akker et al., 2016). However, all these studies were subject to limitations, which are discussed in detail in chapter 3.1, and likely overestimated the rate of overdiagnosis. Similar to studies in adults (Aaron et al., 2008, Aaron et al., 2017), a proportion of children from our cohort who were possibly “overdiagnosed”, based on an assessment at a single point in time, had respiratory symptoms during follow up; demonstrating the difficulties in excluding asthma based on a single assessment performed when patients are well. Ideally to “exclude” asthma safely, a period of regular follow up, with repeat objective tests, is necessary following weaning of medications. However, this is not always practicable within already stretched primary care services.

Our findings, and those of previous studies, demonstrate that accurate asthma diagnosis in children is difficult, particularly when it is based on subjective assessments alone. Harder still, is the task of excluding asthma in patients already labelled with asthma. It is difficult to differentiate between patients with misdiagnosed asthma, and those with asthma but no current symptoms and normal airway function when based on a single assessment.

This makes it all the more important to get the diagnosis right in the first place.

Implementation of spirometry and eNO, with training in their interpretation, may help primary care staff to accurately confirm an asthma diagnosis in children presenting with respiratory symptoms. Allowing children with asthma to benefit from more structured and regular asthma reviews, and avoiding inappropriate treatment of children with alternative causes for their respiratory symptoms.

9.3 Strengths and Limitations

9.3.1 Strengths

This study has a number of key strengths. None of the participating general practices were performing spirometry and/or eNO testing in children prior to implementation, and no participating members of practice staff had had previous training in performing these tests in children. Therefore our training and readiness for change questionnaire data is representative and applicable to other general practices who also have no prior experience of these tests in children. All asthma review clinics were performed during normal general practice opening hours, and clinics were set up to reflect usual practice nurse appointment time slots. Therefore both spirometry and eNO tests were performed under routine clinic time pressures. Likewise the majority of our cohort (95%) had never undergone spirometry or eNO testing before. We believe this strengthens the validity of our feasibility and acceptability data.

We also prospectively recruited a large cohort of children from practices representative of different ethno-socioeconomic populations. All children (except two) attending the asthma reviews were recruited. As follow up data was collected primarily from electronic records, only 7 out of 612 (1%) children were lost to follow up because they moved practices; in the remaining children, datasets were complete for baseline and follow up unplanned healthcare attendances, making our data robust. All training for

spirometry and exhaled nitric oxide testing were delivered by the same two study team members (including myself); and every spirogram was reviewed by the same two research team members for acceptability following ATS/ERS recommendations, thus ensuring quality control of lung function data.

9.3.2 Limitations

Our study also had limitations.

First, all participating practices were from the same, albeit diverse, geographical region within the East Midlands, UK. It is likely that only the most motivated practices expressed an interest to participate, resulting in a group of practices that may not be representative.

Second, the readiness for change questionnaires were circulated to practice staff by research/practice managers at each site without involvement of the research team; therefore, I did not have a denominator to quantify the proportion of staff who responded versus those who did not. The responses to my questionnaire are likely to be biased towards staff who have strongly positive or strongly negative views towards objective testing for children in primary care.

Third, we attempted to gain an insight into practice staff perceptions of asthma management and objective testing in children using questionnaire based methodology. This was a pragmatic decision based on the available time and resources available for the study. However, the lack of qualitative work (i.e. focus groups, 1-2-1 interviews) limits our ability to interpret the questionnaire responses in an in depth meaningful way, and to understand the reasoning behind responses.

Fourth, we could not identify an existing validated readiness for change questionnaire to use for this study, so designed and produced our own. The RfCQ was circulated to expert stakeholders during the design process to establish face validity, and piloted amongst the research team, but did not

undergo a more formal process of validation (Tsang et al., 2017). This limits the reliability of our questionnaire findings.

Fifth, although we attempted to conduct a pragmatic study within primary care, the intensity of supervision we were able to offer to practice staff during training is unlikely to be replicable without substantial increases in funding. Therefore the quality of spirometry and eNO data obtained during the conduct of CHAMPIONS may be better than those obtained outside a research setting.

Sixth, the absence of a control arm in our study design meant that interpretation of the apparent fall in UHAs and improvement in asthma control scores observed during follow up difficult. Whilst it is possible that the availability of objective testing provided additional clinical information for practice staff to act upon, optimise asthma management, and resulted in a positive clinical outcome – this is purely speculative. As discussed earlier, an asthma review even in the absence of objective testing, can improve patient outcomes. Regression to the mean is another possible reason for the observed reduction in attacks and improved control after the initial review. A control arm, allowing the comparison of an asthma review that included objective tests versus one that did not, would have allowed us to determine the clinical effectiveness of implementing objective tests into routine reviews and strengthened our study. The absence of a control arm means that a causal relationship between objective tests and improved asthma outcomes cannot be inferred.

Seventh, as attendance for an asthma review was voluntary, it is possible that only children who were more symptomatic were recruited; thus biasing our cohort towards those with poorer control at baseline. Alternatively, the attendance may reflect the level of parental concern, which may reflect factors in addition to symptom control. Without spirometry or eNO data in children who did not attend for comparison, it is possible that the high prevalence of abnormal results seen in our cohort can be partially explained by this selection bias. Moreover, we did not obtain data on UHAs in those patients who did not attend for a review, which may explain why our

observed rate of UHAs was higher than that observed in previous reports. The lack of data available for non-attenders limits the generalisability of our findings.

Eighth, we trained practice staff to interpret spirometry using fixed cut-offs rather than lower limits of normal based on GLI data, despite the latter being the gold standard for interpretation. This was a conscious decision by the study team for pragmatic reasons, as practice staff were already familiar with the use of fixed cut-offs in the context of performing adult spirometry. However, we did analyse our data using both the GLI LLN, and NICE defined obstruction ($FEV_1/FVC < 70\%$) for comparison, and demonstrated that although our *a priori* training definition overestimated airflow obstruction in 37 (6%) children, this was still preferable to using the NICE definition which would have underestimated airflow obstruction in 108 (18%) children. As routine spirometry becomes accepted in general practice, we recommend that fixed cut-offs should be superseded by LLN.

Ninth, despite the GLI-2012 reference equations being the most comprehensive spirometry reference values available for all age groups, there are significant populations missing from GLI-2012, including people from the Indian sub-continent, which represents a significant proportion of our cohort. In our study, we used the GLI “other” category to represent all children from an Indian ethnic background. However, the Indian subcontinent covers a large geographical area, and a single reference category for its entire population is not be appropriate. A recent study suggests that whilst GLI “other” equations approximates for children from North India reasonably well, the GLI “Black” equations may provide a better approximation for children of South-Asian ethnic decent (Lum et al., 2016). As we did not collect data to differentiate between children of North or South Indian descent, all children were categorised using GLI “other”, which may mean that children with borderline lung function were miscategorised as having either normal or abnormal lung function based on ethnicity dependent lower limits of normal.

Tenth, a cut-off of 35 ppb was chosen for eNO in line with existing UK guideline recommendations (NICE, 2017, BTS, 2019) for children and adults. However, eNO is affected by age, with children having lower eNO levels compared to adults (ATS/ERS, 2005). A cut-off of 35 ppb is likely to be too high for children, particularly younger children, to represent active inflammation. Several studies exploring the role of eNO in asthma diagnosis have suggested lower thresholds for a positive eNO test (16 to 25 ppb) in children based on the highest Youden's index (sensitivity+specificity-100) (Sivan et al., 2009, Woo et al., 2012, Grzelewski et al., 2014), however higher specificity is achieved at the expense of sensitivity in these studies. Using a lower cut-off for eNO in our study would have resulted in more children being categorised as having evidence of airway inflammation, but will also increase the number of false positive results amongst our cohort.

Eleventh, asthma is a chronic relapsing condition and this study included clinical assessments at one point in time only. Therefore, our findings and conclusions relate to that one snapshot and may not accurately reflect longitudinal asthma control. Moreover, asthma reviews were carried out "electively", so patients were not attending acutely and would not be expected to have abnormal lung function or eNO. Additionally, many were not steroid naïve, therefore the use of spirometry and eNO to diagnose asthma cannot be reliably commented on using our results. Interestingly, the NICE implementation project were able to confirm asthma in almost 25% of patients who presented to their GP surgeries with active symptoms, despite using a lower fixed cut-off threshold for spirometry which may have underestimated the prevalence of airflow obstruction in children.

Twelfth, we did not set out to control for the effect of seasonality on symptom control and asthma attacks; however, we recruited our patients over a 14-month period across all four seasons, making a seasonal influence on our data unlikely.

Thirteenth, we did not collect data on patient co-morbidities. Conditions, such as rhinitis, may have affected eNO levels even in the absence of

significant lower airway inflammation thus confounding their interpretation in the context of asthma diagnosis and monitoring.

Fourteenth, we based our adherence data on prescription data from the GPs electronic records. This could be unreliable for a number of reasons. For instance, the family may not have collected the medication from pharmacy despite receiving a written prescription. Even if collected, the patients may not have been using the asthma medications regularly. Patients may have been issued medications elsewhere (i.e. walk in centres, hospital, or emergency departments) which is not recorded on their GPs system. Finally, even if used, the inhalers may not have been administered correctly. Although our review of prescription data provided some insight into patient adherence, interpretation of this data needs to be with some degree of scepticism.

Fifteenth, I have not presented data on cost in this thesis, however, health economics data will be analysed and reported by one of the study collaborators separately. We did not address the implementation outcomes of fidelity, sustainability, or coverage in this study. These outcomes are important to inform whether the adoption of these tests are possible on a larger scale. Due to the design of our study, the study team worked very closely with each practice throughout the implementation process, and remained at each site until recruitment was over. There was also no funding to support the ongoing provision of equipment after the study team left, or the time to remain at each practice until all eligible children were tested. It was therefore not possible to explore these three outcome measures in this study.

Sixteenth, Circassia pharmaceuticals, who manufacture the eNO testing machines, partly funded this study. This represents a potential conflict of interest in our study. However, we accepted funding on the basis that Circassia was not involved in the design, data analysis, or data interpretation for this study.

9.4 Conclusions and Implications for Research

9.4.1 Summary of Findings

To our knowledge, this is the first primary care based study in the UK to focus on implementation and clinical outcomes relating to the provision of spirometry and eNO testing for children with asthma in the community.

We set out to investigate the practicalities of providing objective tests in primary care for children, and to explore how the additional clinical information obtained from these tests relate to clinical control and asthma attacks.

The latest NICE asthma guideline has recommended an approach towards asthma diagnosis much more reliant on objective evidence from tests, and which would necessitate both paediatric spirometry and eNO to be widely available within primary care. Unsurprisingly, this guideline generated significant debate amongst GP stakeholders, both in terms of the practicalities and the clinical benefits of providing these tests for children in the community. The co-existence of the SIGN/BTS asthma guideline within the UK, which is less prescriptive about the need for spirometry and eNO, has added to the debate. However, on closer reading of both guidelines, it becomes apparent that they are not so different. Both guidelines recognise that no single symptom, sign, or test is diagnostic of asthma; and that a negative test does not necessarily exclude asthma. SIGN/BTS recommends categorising patients as having a high, intermediate, or low probability of asthma based on a structured clinical review, which allows for patients assessed as having a high probability of asthma to be given a monitored trial of treatment without the need for further testing. However, both guidelines recommend objective testing when the diagnosis is uncertain, in line with other international asthma guidelines including GINA and NAEPP.

So why is there a reluctance to implement objective testing in primary care? Responses to the RfCQ revealed that concerns around expertise, training, capacity and equipment were barriers to implementation. We found that

despite GP staff finding diagnosis and management of asthma more difficult in children than in adults, only around half of those surveyed felt that providing spirometry and eNO in primary care was a good idea. In addition, only half felt the tests would help them diagnose and manage asthma better, and only half were keen to learn to perform or interpret the tests. Unfortunately, we do not have qualitative data from interviews or focus group work to expand on these findings further, but it would seem that perceived appropriateness and perceived physical barriers are important factors. In order for a change in behaviour or attitude towards objective testing to take place, we must be able to demonstrate the appropriateness and practical feasibility of providing these tests in primary care.

Following delivery of our training package, we demonstrated that it is possible for general practice staff to obtain quality spirometry and eNO data from most children aged five to sixteen years in the primary care setting, and that the tests are acceptable to staff and families. The NICE feasibility study similarly demonstrated that it was possible for GPs to provide spirometry and eNO in the community setting. Importantly, the feedback towards spirometry and eNO following training was far more positive. This would suggest that for implementation to be successful, a programme of training and support must be provided in order to augment GP staff attitudes towards spirometry and eNO in a positive way.

In terms of clinical outcomes, we have shown that abnormal lung function is highly prevalent in children managed in primary care, and that a symptoms' based assessment alone is inadequate to identify those children with obstructed airflow or active airway inflammation. This is consistent with previous studies (described earlier in this thesis) which have also observed poor concordance between current symptoms, spirometry, and eNO.

Despite the prevalence of abnormal objective findings, applying the NICE diagnostic algorithm to our cohort of children only allowed confirmation of an asthma diagnosis in 12% of children. We believe this low rate of diagnosis highlights two important issues pertaining to asthma. Firstly, asthma is a variable condition, such that objective measures can be normal when a

patient is well controlled. This means that a single negative test cannot exclude a diagnosis, and timing of testing is very important. The NICE asthma feasibility study performed tests during acute presentations whilst we performed ours at routine asthma reviews; they were able to confirm an asthma diagnosis in 25% of their cohort. We believe this supports the need for spirometry and eNO to be more widely accessible, allowing investigation of patients in primary care close to their initial presentation, and not after several weeks awaiting a specialist appointment. Secondly, applying adult cut-offs for objective tests in children is not appropriate. We demonstrated that using a fixed cut-off for FEV_1/FVC of less than 70%, as suggested by NICE for adults and children, would have under-recognised abnormal spirometry in 18% of our cohort. Similarly, both the recommended 12% cut-off for BDR and 35 ppb cut-off for eNO are based on adult data, and may underestimate abnormalities in children.

In terms of monitoring, existing guidelines have stated the importance of assessing asthma control in terms of current symptoms and the future risk of attacks. In our study, we observed that obstructed spirometry and poor asthma control were associated with a history of UHAs at baseline, whilst raised eNO and a history of UHAs were risk factors for an asthma exacerbation during follow up. Neither spirometry nor eNO were related to current or future poor asthma control; but poor current asthma control was a risk factor for poor asthma control at follow up.

As discussed earlier in this thesis, low lung function trajectories are associated with adverse outcomes in adulthood. The high prevalence of abnormal lung function we observed is therefore concerning, and children with persistent low lung function would warrant closer monitoring and a lower threshold for referral for specialist assessment. Children in our cohort with raised eNO appear to be at a higher risk for asthma attacks, whilst poor asthma control at baseline was a risk factor for poor asthma control at follow up. In principle, monitoring lung function, eNO, and symptoms at asthma reviews should provide a more comprehensive assessment of a patient's asthma, in terms of current control, risk of future attacks, and longer-term risk of poor outcomes. However, it is not clear, from our data or existing

literature, whether asthma management incorporating objective testing confers better clinical outcomes in children with asthma when compared with conventional clinical monitoring alone.

To conclude, we have shown that abnormal lung function and eNO are highly prevalent in children who attend for asthma reviews in primary care, and correlates poorly with patient reported symptom scores. A symptoms-based assessment alone is therefore inadequate, and likely to miss children at increased risk of adverse asthma related outcomes.

9.4.2 Next steps

We observed a fall in the proportion of children experiencing at least one asthma attack during follow up compared to baseline. However, the observational design of our study precludes us from drawing conclusions as to whether the reduction in asthma attacks was due to the implementation of objective tests or not. It could be argued that the clinical review itself, regardless of objective tests being available, resulted in the observed reduction in attacks.

A further clinical trial is needed to determine whether asthma reviews in primary care, which include spirometry and eNO, confer better clinical outcomes for patients compared to standard asthma reviews alone. We propose a two-arm parallel cluster randomised controlled trial (RCT), with practices assigned to either providing “asthma reviews with objective tests” (intervention arm) or “standard asthma reviews” (control arm). Logically, additional information provided by objective testing will only make a difference to patient management if the information is acted upon appropriately. Previous studies investigating the use of spirometry in children with asthma in primary care have not included a standardised management protocol (Abramson et al., 2015) and have reported no difference in outcomes. Therefore, we would also propose the inclusion of a standardised management algorithm, based on information from clinical history and test results, within the intervention arm of the study. To facilitate ease of use, this

could be designed as an electronic algorithm embedded within existing GP systems, allowing users to input data from patient history and tests, with the output being a recommended course of action. The main outcomes of interest would be change in asthma attack rates and change in asthma control scores from baseline to follow up.

The rates of attendance to clinic after invite, prevalence of UHAs at baseline, and recruitment rate found in our study can be used to inform sample size calculations for the proposed trial to ensure adequate power. Similarly, the change in UHAs observed in our study may be useful to guide the choice of minimally clinically significant effect size for the next study.

Even if found to be clinically effective, there may be other barriers besides perceived appropriateness which hinders wider uptake of objective testing for children in primary care. The results from the RfCQ provides an interesting, but superficial, insight into primary care staff attitudes towards children's asthma management and the role of objective testing. However, those findings can help inform the design of a qualitative study to explore areas of staff concern further. In particularly, semi-structured interviews could be conducted pre- and post- our proposed RCT in a subgroup of practices, exploring reasons for the reluctance to train in spirometry and eNO identified from the RfCQ.

Diagnosis is another important issue highlighted in previous studies and our own. Confirmation of asthma using the NICE diagnostic algorithm was relatively low in both this study and in the NICE feasibility study. As discussed earlier, this may be due to several reasons. In our study, we performed asthma reviews electively and not during acute presentations of asthma; meaning children with normal lung function tests may have been asymptomatic and well controlled at the time of testing. The NICE feasibility study involved testing at initial presentation, however, the investigators used cut-offs for abnormal spirometry and eNO derived from adult data which likely underestimated the number of children with obstructed airflow and airway inflammation. Finally, in both studies, children presenting with active symptoms, or who had a history of respiratory symptoms, may not have had

asthma. It would be interesting to investigate the diagnosis rate in children using tests performed during acute presentations, and using age appropriate, gold standard cut-offs. This could be achieved by providing practices involved in our study with equipment to allow continued provision of spirometry and eNO testing; and collecting data on diagnosis rates in children presenting actively with respiratory symptoms suggestive of asthma.

CHAPTER 10: APPENDICES

UNIVERSITY OF LEICESTER

Research & Enterprise Division
University of Leicester
Research Governance Office
Academic Department, Ground Floor
Leicester General Hospital
Gwendolen Road
Leicester, LE5 4PW
Email: uolsponsor@le.ac.uk
Tel: 0116 258 4099/258 4867

12 April 2016

Dr Erol Caillard
Department of Infection, Immunity and Inflammation
Robert Kilpatrick Clinical Sciences Building
Leicester Royal Infirmary
Leicester, LE2 7LX

Dear Dr Erol Gaillard

Ref: 0566
Title: Childhood Asthma Management in Primary Care: Implementation Of Exhaled Nitric Oxide and Spirometry Testing (CHAMPIONS study)
Project Status: Approved
End Date: 01/03/2018
Site: Leicester City CCG, East Leicestershire & Rutland CCG and West Leicestershire CCG.

I am pleased to advise you that following confirmation of a Favourable Opinion from an Ethics Committee, NHS Trust R&D Approval and where relevant regulatory authority agreements have been received, the University are able to confirm sponsorship for the above research at the above sites.

Please note you are required to notify the Sponsor and provide copies of:

- Changes in personnel to the Study
- Changes to the end date
- All substantial amendments and provisional and favourable opinions
- All minor amendments
- All serious adverse events (SAEs) and SUSARS
- Annual progress reports
- Annual MHRA (DSUR) safety reports (if applicable)
- End of study declaration form
- Notifications of significant breaches of Good Clinical Practices (GCP)or Protocol

Please copy the Sponsor into all correspondence and emails by using uolsponsor@le.ac.uk.

Please note it is essential that you notify us as soon as you have recruited your first patient to the study.

I would like to wish you well with your study and if you require further information or guidance please do not hesitate to contact me.

Yours sincerely

Diane M. Delahooke

Dr Diane Delahooke
Acting Research Governance Manager

Childhood **A**sthma **M**anagement in **P**rimary Care: **I**mplementation **O**f **N**itric Oxide and **S**pirometry Testing (**CHAMPIONS** Study)

Chief Investigator: Dr. Erol Gaillard

Dear [GP Practice],

We are writing to invite your practice to be part of this important and exciting asthma project - the **CHAMPIONS** study.

You are probably aware that diagnosis and monitoring of childhood asthma has received a high level of NICE and NHS England attention with widespread media coverage highlighting potential misdiagnoses in children. The 2014 NRAD (National Review of Asthma Deaths) report further emphasised the urgent need for improved asthma services in the UK; having reviewed 195 asthma related deaths (including 18 in children) occurring in 2012 alone.

Getting the diagnosis right, particularly in children, can be difficult. It is even more difficult when objective lung function data is not available to most primary care health professionals, with whom the highest burden of care lies. Recent draft NICE guidance on the diagnosis and monitoring of asthma (https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0640) has recommended that lung function testing for children should be available within primary care.

The aims of this project are to 1) evalute the training and capacity required in primary care, 2) develop and deliver a package of training in lung function testing to staff in participating practices, and 3) investigate the health economic impact of implementation of routine lung function testing in children and how this affects the numbers diagnosed. We would hope that this information can then be used to inform NHS decision makers.

We have attached an information leaflet to this letter summarising the proposed project protocol, but we would value the opportunity to meet with your team in person to discuss the project in more detail and to answer any questions you may have. Please do not hesitate to get in touch with our team to arrange a meeting where we can discuss your participation further.

Thank you for taking the time to consider.

Yours Sincerely,

Dr. Erol Gaillard

Senior Lecturer and Honorary Paediatric Respiratory Consultant

University of Leicester

Information Sheet for Participating Primary Care Practices

Study Title – Childhood **A**sthma **M**anagement in **P**rimary Care: **I**mplementation **O**f **N**itric Oxide and **S**pirometry Testing (CHAMPIONS Study)

Summary – We would like to invite your practice to be a recruitment site for our study which aims to find out the potential barriers and health economic impact of implementing the proposed new NICE guidance on asthma diagnosis and monitoring. As you may already be aware, one of the major changes to standard practice in primary care that NICE recommends is for the routine use of objective lung function tests (spirometry and exhaled nitric oxide testing) for the diagnosis and monitoring of children aged 5-16 years. The complete draft guideline can be found here - (https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0640).

The publication of the finalised guideline has been delayed due to concerns raised about the feasibility of widespread introduction of these tests into primary care. Potential barriers highlighted have included training requirements and local capacity.

What does this study hope to answer? The main objective for this study will be in evaluating the training and capacity requirements of primary care sites in order for them to be able to deliver routine spirometry and exhaled nitric oxide testing for children aged 5-16 years as recommended by the draft NICE guidelines. Secondary objectives relate to studying the impact of providing lung function tests for children in primary care on the processes and outcomes of childhood asthma diagnosis and will include – 1) the number of children in which a diagnosis of asthma can be confirmed using spirometry and exhaled nitric oxide testing, 2) the number of misdiagnoses identified using lung function tests, and 3) the health economic impact of implementation.

How do we plan to do this? We hope to work with multiple GP sites in and around Leicestershire, of differing sizes and patient demographics. At these sites we will be aiming to recruit around 1000 children into our study. Initial meetings will be held at each participating practice during which time the study team will introduce the study and provide an update on the proposed NICE guidance for asthma diagnosis and monitoring. We will then send out short "readiness for change" questionnaires to gather your opinions, concerns and perceived barriers to implementing lung function testing for children into your practice. We will then develop, deliver and refine a package of lung function testing training to appropriate members of staff at your practice i.e. practice nurses and HCAs. Following on from this, we will support the introduction of these tests into the standard asthma review clinics held at each practice to evaluate the success of training, additional support required and to identify any other potential obstacles to their routine use.

To investigate the impact of implementation, we will consent parents for the purposes of accessing their child's electronic records, delivering a health economic questionnaire at the asthma review and sending a follow up postal questionnaire only. There are no other active interventions additional to the asthma review and lung function tests.

What would taking part involve? We will deliver an asthma update session including a summary of the proposed NICE guidance at each participating practice. We will then train practice nurses and HCAs in the performance and interpretation of spirometry and exhaled nitric oxide testing. The implementation team will support the practice in performing the asthma annual review and in the reviews of children 5 years and older under investigation for asthma. We offer to remunerate practice nurse/HCA time for the additional training and the additional tests.

Additionally we will invite GPs, practice managers and other healthcare staff to participate in short questionnaires in order for the study team to identify training and capacity needs and potential barriers to implementation.

Participating GP surgeries need to undertake a database search of their patient register to identify children (5-16) who require an asthma review (i.e. children on the asthma register already and children who have received asthma medications in the past year but who have not been given a diagnosis of asthma). It is anticipated that practices will send out invitations for children to be batch-booked onto an asthma review clinic at the surgery. To this end, participating sites will need to commit designated sessions each week/fortnight for a children's asthma review clinic, and a healthcare assistant/practice nurse to run the clinic and perform the lung function testing.

What will the study team do? In addition to providing the initial training, the study team will support each asthma review clinic for the duration of the study to provide assistance with lung function testing, consent parents and collect health economic and patient medical data.

How long will the study last? The study is funded for 2 years. However we are only planning to have one face-to-face contact with each child at the initial asthma review, followed by a postal questionnaire sent out 3-6 months following this. This means that each practice will be actively involved from the initial meeting until 3-6 months after the last eligible child is reviewed. From our preliminary data we expect around 100 eligible children per 10,000 population; so depending on the size of your practice and the number of children who can be seen at each clinic, this should equate to around 12-16 clinic sessions per 10,000 patient practice.

Will we be reimbursed? The project team have funding to cover the costs of postage, and will provide the equipment for lung function testing for the duration of the study. We also have funding to support nursing/HCA time for the asthma reviews depending on the normal arrangements for asthma reviews at each study site.

What recognition will my practice get? Participating sites will be acknowledged in any publication relating to this study. They will also be one of the first practices to be trained and be able to offer lung function testing to children in the UK.

What will happen to the results of this study? The results will be presented to NHS decision makers, at scientific meetings and published in medical journals and asthma websites. A plain language summary will also be published online which families will be able to access.

Who has reviewed the study? – This study has been approved by a panel of experts from the Nottingham 1 Research Ethics Committee. The committee was satisfied that your

patients' rights will be respected and that they will be given sufficient information on which to make an informed decision.

Where can I get further information? We would be keen to meet with you directly to discuss the study in more detail and to answer any further questions. We are also able to provide you with a more detailed protocol for the study. Please get in touch with a member of the study team using the contact information below.

Thank you very much for taking the time to read this information.

Contact Details

Chief Investigator – Dr. Erol Gaillard (Senior Lecturer and Honorary Consultant Respiratory Paediatrician)

Telephone: (0116) 2523261

Email: eag15@le.ac.uk

Project Fellow – Dr. David Lo (ST8 Specialist Registrar in Paediatric Respiratory Medicine)

Telephone: (0116) 252 5881

Fax: (0116) 252 3282

Email: dkhl1@le.ac.uk

Site Survey

Practice Information

Practice Name			
Address			
Practice Phone Number		**Fax**	
CCG		**IT System**	

Asthma Lead GP		**Asthma Lead Nurse**	
Name		**Name**	
Contact Number		**Contact Number**	
Email		**Email**	
Practice Manager		**Other (Specify):**	
Name		**Name**	
Contact Number		**Contact Number**	
Email		**Email**	

About the Practice

Single or Multiple Site(s)		**If Multi – How many sites?**	
Total Number of Patients Registered			

If multi-sites practice: How many patients are at each site?	**Site Name**	**No. Patients**

Total Number of GPs		**FTE**	
Total Number of PNs		**FTE**	
Total Number of HCAs		**FTE**	

Training

Number of each staff group trained to -				
		GP	**PN**	**HCA**
Independently manage asthma (including adjust treatment) in	**Adults**			
	Children			
Perform spirometry in	**Adults**			
	Children			
Interpret spirometry in	**Adults**			

	Children			

Patient Demographics

% aged 0 to 4 years										
% aged 5 to 14 years										
% aged under 18 years										
Deprivation score (IMD 2015)										
Ethnicity	**White British**		**Asian**		**Black**		**Other Non-White**		**White (Non-British)**	

Respiratory QOF Indicators for Previous Year

	Practice Count	**%**
Asthma: QOF Prevalence (All ages)		
AST002: With Measures of Variability		
AST 003: Review in last 12 months		
AST 004: Smoking recorded in last 12 months		
Emergency Respiratory Admissions (<18)		
Emergency Admission for Asthma, Diabetes or Epilepsy (<18)		
% who would recommend practice		

Current Asthma Review Structure

Children with asthma are seen -	**In designated asthma clinics**		**During routine clinic sessions**		
	With adult asthma patients		**In children only clinics**		
	How often do asthma clinics run?			**NA**	
Routine asthma reviews are done by -	**GPs**		**Practice Nurses**		
Any other comments (i.e. Diagnostic Criteria?) –					
Form Completed by		**Date**			

Readiness and Barriers to Change Questionnaire (22 Questions/10 minutes)

What is your job title? (Please specify also if you are the asthma/respiratory lead)	
What formal asthma training have you had? (i.e. Certificate/Diploma/Degree)	
What formal spirometry training have you had? (Specify adults/children/both)	
Do you routinely utilise spirometry to manage/diagnose asthma? (Circle all that apply)	Yes (Adults) Yes (Children) No

GPs and Practice nurses – please answer ALL sections**, Health care assistants** – please answer section 2 only**, Practice managers** – please answer section 3 only

For each of the questions below, circle the response that best characterises how you feel about the statement -

Section 1

	Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree
1. I find **diagnosing** asthma in children (over 5) difficult	**1**	**2**	**3**	**4**	**5**
2. I find **diagnosing** asthma in adults (over 16) difficult	**1**	**2**	**3**	**4**	**5**
3. I find **managing** asthma in children (over 5) difficult	**1**	**2**	**3**	**4**	**5**
4. I find **managing** asthma in adults (over 16) difficult	**1**	**2**	**3**	**4**	**5**
5. I think there is good **evidence** that lung function tests improve asthma care	**1**	**2**	**3**	**4**	**5**
6. I think providing **lung function** tests for children in **primary care** is a good idea	**1**	**2**	**3**	**4**	**5**
7. I believe that lung function tests will help me **diagnose** asthma in children better	**1**	**2**	**3**	**4**	**5**
8. I believe that lung function tests will help me **monitor** asthma in children better	**1**	**2**	**3**	**4**	**5**

Section 2

9. I am keen to learn to **perform** spirometry in children	**1**	**2**	**3**	**4**	**5**
10. I am keen to learn to **interpret** spirometry in children	**1**	**2**	**3**	**4**	**5**
11. My preferred learning format is **online** training	**1**	**2**	**3**	**4**	**5**
12. My preferred learning format is **face-to-face** training	**1**	**2**	**3**	**4**	**5**

Section 3

	Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree
13. As a practice, we **adapt well** to new ways of working	**1**	**2**	**3**	**4**	**5**
14. As a practice, we have adequate **time** available for **training and development**	**1**	**2**	**3**	**4**	**5**
15. We have adequate **resources** to purchase spirometry equipment	**1**	**2**	**3**	**4**	**5**
16. We have adequate **clinic capacity** to provide increased asthma reviews	**1**	**2**	**3**	**4**	**5**
17. We have adequate **staffing** to provide lung function tests (once trained)	**1**	**2**	**3**	**4**	**5**
18. I think under or over-diagnosis of asthma in children is a problem at **this practice**	**1**	**2**	**3**	**4**	**5**
19. I think under or over-diagnosis of asthma in children is a problem **nationally**	**1**	**2**	**3**	**4**	**5**
20. I believe children's asthma management at this practice **can** be improved	**1**	**2**	**3**	**4**	**5**
21. I believe children's asthma management at this practice **needs** to be improved	**1**	**2**	**3**	**4**	**5**

22. What is needed OR what barriers need to be overcome in order for your practice to provide routine lung function testing for children? (Consider training/capacity/funding etc.)

Training Pack Contents

1. **Copy of spirometry presentation v4.**
2. **Quick reference sheet**
3. **Patient pre-test check list (for parents)**
4. **Pre-test check list (for health professionals)**
5. **Spirometry procedure**
6. **BTS diagnostic algorithm**
7. **BTS clinical clues to alternative diagnosis in wheezy children**
8. **BTS clinical clues to alternative diagnosis in adults (12+)**
9. **BTS factors to consider in an initial structured clinical assessment**
10. **BTS summary of asthma management for adults (12+)**
11. **BTS summary of asthma management for children**
12. **BTS categorisation of inhaled corticosteroids by dose – children**
13. **Commonly used asthma inhalers poster**
14. **Spirometry A5 crib sheet**
15. **Asthma action plan**
16. **Peak flow reference values**
17. **Peak flow diary**
18. **Paediatric spirometry competencies (interpret/peform) for CHAMPIONS study**
19. **Paediatric spirometry log for CHAMPIONS study**

Paediatric Spirometry and eNO Competencies Log (INTERPRET ONLY) for CHAMPIONS study

Competency	Self-Assessed as Competent by Trainee		Assessed as Competent by CHAMPIONS team		Date Achieved
	Signature (Trainee)	Initials	Signature (Trainer)	Initials	
1. Aware of indications and contraindications for performing spirometry • Assisting with diagnosis / monitoring of pulmonary function • Can explain contraindications to trainer					
2. Can identify and explain the terms used in spirometry including: • FVC and FEV_1 • FEV_1/FVC					
3. Aware of how to clean/maintain and calibrate equipment including: • How to set up • How to clean and perform quality assurance checks					
4. Aware of indications for and how to interpret reversibility testing • Aware of indications • Able to calculate degree of reversibility and interpret					
5. Can recognise unacceptable/unusable spirometry traces in children (5-16 years) • Aware of importance of correct patient preparation, instruction and technique					
6. Can recognise normal and abnormal flow loops and lung function values • Including obstructive/restrictive/mixed patterns • Uses GLI reference values and knows impact of height/age/ethnicity					

Competency	Self-Assessed as Competent by Trainee		Assessed as Competent by CHAMPIONS team		Date Achieved
	Signature (Trainee)	Initials	Signature (Trainer)	Initials	
7. Aware of indications and how to interpret eNO tests • Understands utility of eNO as surrogate marker of airway inflammation • Able to interpret eNO levels in context of other tests					
8. Can use spirometry/eNO/reversibility data in context of clinical history • Can utilise test data to assist with asthma diagnosis, monitoring and management • Aware of limitations and seeks advice/makes referrals appropriately					

Trainee – I confirm that I have considered each competency detailed above and feel I have achieved them

Name _____ **Signature** _____ **Role** _____ **Date** _____

Supervisor – I confirm that the trainee has demonstrated competency in each of the domains detailed above during his/her training

Name _____ **Signature** _____ **Role** _____ **Date** _____

Paediatric Spirometry and eNO Competencies Log (PERFORM AND INTERPRET) for CHAMPIONS study

Competency	Self-Assessed as Competent by Trainee		Assessed as Competent by CHAMPIONS team		Date Achieved
	Signature (Trainee)	Initials	Signature (Trainer)	Initials	
1. Aware of indications and contraindications for performing spirometry • Assisting with diagnosis / monitoring of pulmonary function • Can explain contraindications to trainer					
2. Can identify and explain the terms used in spirometry including: • FVC and FEV_1 • FEV_1/FVC					
3. Can clean/maintain and calibrate equipment including: • How to set up • How to clean and perform quality assurance checks					
4. Can demonstrate correct patient preparation, instruction and testing technique • Positions and prepares patient correctly (put's child at ease) • Demonstrates correct technique					
5. Able to obtain technically acceptable spirometry measurements in children (5-16 years) • Can recognise unacceptable/unusable volume traces • Recognises when to stop in uncooperative children					
6. Can perform reversibility testing • Aware of indications • Able to calculate degree of reversibility and interpret					

Competency	Self-Assessed as Competent by Trainee		Assessed as Competent by CHAMPIONS team		Date Achieved
	Signature (Trainee)	Initials	Signature (Trainer)	Initials	
7. Can recognise normal and abnormal flow loops and lung function values • Including obstructive/restrictive/mixed patterns • Uses GLI reference values and knows impact of height/age/ethnicity					
8. Able to obtain technically acceptable eNO measurements in children (5-16 years) • Positions and prepares patient correctly and demonstrates correct technique • Recognises when to stop in uncooperative children					
9. Aware of indications and how to interpret eNO tests • Understands utility of eNO as surrogate marker of airway inflammation • Able to interpret eNO levels in context of other tests					
10. Can use spirometry/eNO/reversibility data in context of clinical history • Can utilise test data to assist with asthma diagnosis, monitoring and management • Aware of limitations and seeks advice/makes referrals appropriately					

Trainee – I confirm that I have considered each competency detailed above and feel I have achieved them

Name _____ **Signature** _____ **Role** _____ **Date** _____

Supervisor – I confirm that the trainee has demonstrated competency in each of the domains detailed above during his/her training

Name _____ **Signature** _____ **Role** _____ **Date** _____

Paediatric Spirometry and eNO Competencies Log (PERFORM ONLY) for CHAMPIONS study

Competency	Self-Assessed as Competent by Trainee		Assessed as Competent by CHAMPIONS team		Date Achieved
	Signature (Trainee)	Initials	Signature (Trainer)	Initials	
1. Aware of indications and contraindications for performing spirometry • Assisting with diagnosis / monitoring of pulmonary function • Can explain contraindications to trainer					
2. Can identify and document the terms used in spirometry including: • FVC and FEV_1 • FEV_1/FVC					
3. Can clean/maintain and calibrate equipment including: • How to set up • How to clean and perform quality assurance checks					
4. Can demonstrate correct patient preparation, instruction and testing technique • Positions and prepares patient correctly (put's child at ease) • Demonstrates correct technique					
5. Able to obtain technically acceptable spirometry measurements in children (5-16 years) • Can recognise unacceptable/unusable volume traces • Recognises when to stop in uncooperative children					
6. Can perform reversibility testing • Aware of indications • Able to calculate degree of reversibility and document					

Competency	Self-Assessed as Competent by Trainee		Assessed as Competent by CHAMPIONS team		Date Achieved
	Signature (Trainee)	Initials	Signature (Trainer)	Initials	
7. Able to obtain technically acceptable eNO measurements in children (5-16 years) • Positions and prepares patient correctly and demonstrates correct technique • Recognises when to stop in uncooperative children					

Trainee – I confirm that I have considered each competency detailed above and feel I have achieved them

Name _____ **Signature** _____ **Role** _____ **Date** _____

Supervisor – I confirm that the trainee has demonstrated competency in each of the domains detailed above during his/her training

Name _____ **Signature** _____ **Role** _____ **Date** _____

Information Sheet for Parents

Study Title – Childhood **A**sthma **M**anagement in **P**rimary Care: **I**mplementation **O**f **N**itric Oxide and **S**pirometry Testing (CHAMPIONS Study)

Summary – Your child has been invited to attend an "asthma review" clinic at the GP surgery because they have had breathing symptoms, with or without wheezing, in the past year. As part of that review, your GP team will perform two simple breathing tests which are not normally available in GP practices, but which are routinely performed in hospitals already. Recently, a UK expert committee has recommended that these tests should be made available to children at their GP surgery. The tests take about 10 minutes, and give more detailed information about the lungs that may help your GP to better manage your child's breathing problems. What we are unsure at present is how much training and extra resources GPs will need to provide this service continually. We would like to ask your permission to gather some extra information from your child's records and to ask you a few questions in order to help the NHS work out: 1) how best to support GPs to provide these breathing tests and 2) what difference they might make to helping with asthma diagnosis in general practice.

What's involved? Your GP practice is one of the first in the UK to offer the breathing tests to children. We are asking your permission to use your child's fully anonymised breathing test results, including the time it takes to perform the tests, to inform NHS decision makers on how best to roll out the tests to all the children with asthma in the UK. We will also ask permission to access your child's records to gather information about your child's asthma medication use, the number of asthma attacks and whether the breathing tests have helped to confirm a diagnosis of asthma in your child. All information we collect will be anonymised, and none of your child's personal data will be taken away from this practice.

What would taking part involve? No additional tests on your child are performed solely for the purposes of the study, but if you are happy on the day we would like to ask you to complete a very short questionnaire, and then another postal questionnaire (which will be posted to you by your GP) 3-6 months following the review.

What are the possible benefits of taking part? There are no direct immediate benefits to your child but it may benefit all children with asthma managed by GPs in the future by helping NHS decision makers decide whether providing breathing tests in GP surgeries is cost effective.

What are the possible disadvantages of taking part? There are no disadvantages with taking part except the additional time it will take you to complete the short questionnaires.

Do I have to give permission? No. It is entirely your choice; your decision will not impact on your child's care. He/she will still have the full asthma review including breathing tests performed by the practice team. You may withdraw your consent at any time during the study by contacting your GP or a member of the study team. We would hope to use any data already collected up to the point of withdrawal of consent unless you instruct us otherwise.

Is my GP aware? Yes your GP has agreed for us to gather this data with your consent.

What will happen to the results of this study? The results will be presented to NHS decision makers, at scientific meetings and published in medical journals and asthma websites. A plain

language summary will also be published online which families will be able to access. Your child will not be identifiable in any report or publication.

What if something goes wrong or I am unhappy with the study team? – There is minimal risk associated with this kind of study but in the extremely unlikely event that something does go wrong and your child is harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Leicester but you may have to pay your legal costs.

Should you wish to complain or have any concerns about the way you have been approached or treated in connection with the study, you should ask to speak to a member of the study team on the number given 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 Patient Information & Liaison Service at pils.complaints.compliments@uhl-tr.nhs.uk. The Firs, c/o Glenfield Hospital, Groby Road, Leicester. LE3 9QP Freephone: 0808 1788337.

Who has reviewed the study? – All research that involves NHS patients, information from NHS medical records or uses NHS premises must be approved by an NHS research ethics committee. This study has been approved by a panel of experts from the Nottingham 1 Research Ethics Committee. Approval means that the committee is satisfied that your rights will be respected and that you will be given sufficient information on which to make an informed decision.

Thank you very much for taking the time to read this information.

A member of the study team will be available at your child's asthma review to answer any questions and to take consent if you agree to participate.

If you have any further questions please contact the following number to speak to or leave a message for a member of the study team

Contact Details

Chief Investigator – Dr. Erol Gaillard (Senior Lecturer and Honorary Consultant Respiratory Paediatrician)
Telephone: (0116) 2523261
Email: eag15@le.ac.uk
Project Fellow – Dr. David Lo (Specialist Registrar in Paediatric Respiratory Medicine)
Telephone: (0116) 252 5881
Fax: (0116) 252 3282
Email: dkhl1@le.ac.uk

This information sheet and a copy of the signed consent is for you to keep

CONSENT FORM

Childhood **A**sthma **M**anagement in **P**rimary Care: **I**mplementation **O**f **N**itric Oxide and **S**pirometry Testing (CHAMPIONS Study)

Chief Investigator: Dr. Erol Gaillard
Participant Identification Number:
Name of child/young person:
Site:

Please initial box

1. I confirm that I have read the information sheet for parents dated 06/04/2016 (version 1.0) for the above study and that I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my child's participation is voluntary and that I am free to withdraw my consent at any time without giving any reason and without my child's medical care or legal rights being affected. ☐

3. I agree for my child's medical records to be accessed by authorised individuals from the research team, the University of Leicester (as the Sponsor), the NHS and the GP practice, where it is relevant to my child's taking part in this research, I authorise these individuals to have access to these records ☐

4. I agree for anonymised data from my child's medical records to be used for analysis as part of this study ☐

5. I agree to take part in a brief health questionnaire today. ☐

6. I agree to be contacted by post in 3-6 months' time from today in order to be invited to complete a further postal questionnaire relating to this study. ☐

7. I agree to take part in this study. ☐

Name of Parent/Guardian and relationship to child	Date	Signature
Name of person taking consent	Date	Signature

REFERENCES

AARON, S. D., VANDEMHEEN, K. L., BOULET, L. P., MCIVOR, R. A., FITZGERALD, J. M., HERNANDEZ, P., LEMIERE, C., SHARMA, S., FIELD, S. K., ALVAREZ, G. G., DALES, R. E., DOUCETTE, S., FERGUSSON, D. & CANADIAN RESPIRATORY CLINICAL RESEARCH, C. 2008. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ,* 179**,** 1121-31.

AARON, S. D., VANDEMHEEN, K. L., FITZGERALD, J. M., AINSLIE, M., GUPTA, S., LEMIERE, C., FIELD, S. K., MCIVOR, R. A., HERNANDEZ, P., MAYERS, I., MULPURU, S., ALVAREZ, G. G., PAKHALE, S., MALLICK, R., BOULET, L. P. & CANADIAN RESPIRATORY RESEARCH, N. 2017. Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma. *JAMA,* 317**,** 269-279.

ABRAMSON, M. J., SCHATTNER, R. L., HOLTON, C., SIMPSON, P., BRIGGS, N., BEILBY, J., NELSON, M. R., WOOD-BAKER, R., THIEN, F., SULAIMAN, N. D., COLLE, E. D., WOLFE, R., CROCKETT, A. J. & MASSIE, R. J. 2015. Spirometry and regular follow-up do not improve quality of life in children or adolescents with asthma: Cluster randomized controlled trials. *Pediatr Pulmonol,* 50**,** 947-54.

ADAMS, R. J., WILSON, D. H., APPLETON, S., TAYLOR, A., DAL GRANDE, E., CHITTLEBOROUGH, C. R. & RUFFIN, R. E. 2003. Underdiagnosed asthma in South Australia. *Thorax,* 58**,** 846-50.

AGUSTI, A. & FANER, R. 2019. Lung function trajectories in health and disease. *Lancet Respir Med,* 7**,** 358-364.

AKHTAR, R. & WILSON, A. 2005. A comparison of spirometry in general practice and a pulmonary function laboratory. *Prim Care Respir J,* 14**,** 215-20.

AKINDELE, A., DAINES, L., CAVERS, D., PINNOCK, H. & SHEIKH, A. 2019. Qualitative study of practices and challenges when making a diagnosis of asthma in primary care. *NPJ Prim Care Respir Med,* 29**,** 27.

ALVING, K., WEITZBERG, E. & LUNDBERG, J. 1993. Increased amount of nitric oxide in exhaled air of asthmatics. *Eur Respir J,* 6**,** 1368-1370.

AMERICAN THORACIC, S. & EUROPEAN RESPIRATORY, S. 2005. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med,* 171**,** 912-30.

ANANDI, S., TULLU, M. S. & LAHIRI, K. 2016. Evaluation of symptoms & spirometry in children treated for asthma. *Indian J Med Res,* 144**,** 124-127.

ANNESI-MAESANO, I., STERLIN, C., CAILLAUD, D., DE BLAY, F., LAVAUD, F., CHARPIN, D. & RAHERISSON, C. 2012. Factors related to under-diagnosis and under-treatment of childhood asthma in metropolitan France. *Multidiscip Respir Med,* 7**,** 24.

ARTP. 2019. *Frequently Asked Questions* [Online]. Association for Respiratory Technology and Physiology. Available: http://www.artp.org.uk/en/spirometry/spiro-faqs.cfm [Accessed 2019].

ATS/ERS 2005. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med,* 171**,** 912-30.

AYUK, A. C., UWAEZUOKE, S. N., NDUKWU, C. I., NDU, I. K., ILOH, K. K. & OKOLI, C. V. 2017. Spirometry in Asthma Care: A Review of the Trends and Challenges in Pediatric Practice. *Clin Med Insights Pediatr,* 11**,** 1179556517720675.

BACHARIER, L. B., STRUNK, R. C., MAUGER, D., WHITE, D., LEMANSKE, R. F., JR. & SORKNESS, C. A. 2004. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med,* 170**,** 426-32.

BACKER, V., HARMSEN, L., LUND, T., PEDERSEN, L., PORSBJERG, C., RASMUSSEN, L., THOMSEN, S. F. & NOLTE, H. 2007. A 3-year longitudinal study of asthma quality of life in undiagnosed and diagnosed asthma patients. *Int J Tuberc Lung Dis,* 11**,** 463-9.

BAI, T. R., VONK, J. M., POSTMA, D. S. & BOEZEN, H. M. 2007. Severe exacerbations predict excess lung function decline in asthma. *Eur Respir J,* 30**,** 452-6.

BALOGUN, J. & HAILEY, V. 2004. *Exploring Strategic Change,* London, Prentice Hall.

BARBATO, A., TURATO, G., BARALDO, S., BAZZAN, E., CALABRESE, F., TURA, M., ZUIN, R., BEGHE, B., MAESTRELLI, P., FABBRI, L. M. & SAETTA, M. 2003. Airway inflammation in childhood asthma. *Am J Respir Crit Care Med,* 168**,** 798-803.

BARRY, L. E., SWEENEY, J., O'NEILL, C., PRICE, D. & HEANEY, L. G. 2017. The cost of systemic corticosteroid-induced morbidity in severe asthma: a health economic analysis. *Respir Res,* 18**,** 129.

BARTON, C., PROUDFOOT, J., AMOROSO, C., RAMSAY, E., HOLTON, C., BUBNER, T., HARRIS, M. & BEILBY, J. 2009. Management of asthma in Australian general practice: care is still not in line with clinical practice guidelines. *Prim Care Respir J.,* 18**,** 100-105.

BECK-RIPP, J., GRIESE, M., ARENZ, S., KORING, C., PASQUALONI, B. & BUFLER, P. 2002. Changes of exhaled nitric oxide during steroid treatment of childhood asthma. *European Respiratory Journal,* 19**,** 1015-1019.

BELGRAVE, D. C. M., GRANELL, R., TURNER, S. W., CURTIN, J. A., BUCHAN, I. E., LE SOUEF, P. N., SIMPSON, A., HENDERSON, A. J. & CUSTOVIC, A. 2018. Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. *The Lancet Respiratory Medicine,* 6**,** 526-534.

BEREND, N., SALOME, C. M. & KING, G. G. 2008. Mechanisms of airway hyperresponsiveness in asthma. *Respirology,* 13**,** 624-31.

BERNET, A. C., WILLENS, D. E. & BAUER, M. S. 2013. Effectiveness-implementation hybrid designs: implications for quality improvement science. *Implementation Science,* 8**,** S2.

BERRY, M. A., SHAW, D. E., GREEN, R. H., BRIGHTLING, C. E., WARDLAW, A. J. & PAVORD, I. D. 2005. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy,* 35**,** 1175-9.

BJERMER, L., ALVING, K., DIAMANT, Z., MAGNUSSEN, H., PAVORD, I., PIACENTINI, G., PRICE, D., ROCHE, N., SASTRE, J., THOMAS, M. & USMANI, O. 2014. Current evidence and future research needs for FeNO measurement in respiratory diseases. *Respir Med,* 108**,** 830-41.

BLAIN, E. & CRAIG, T. 2009. The use of spirometry in a primary care setting. *Int J Gen Med,* 2**,** 183-186.

BLF. 2017. *British Lung Foundation. Asthma Statistics* [Online]. Available: https://statistics.blf.org.uk/asthma [Accessed].

BLOOM, C., NISSEN, F., DOUGLAS, I., SMEETH, L., CULLINAN, P. & QUINT, J. 2018. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax,* 73**,** 313-320.

BOBROW, K., FARMER, A., CISHE, N., NWAGI, N., NAMANE, M., BRENNAN, T. P., SPRINGER, D., TARASSENKO, L. & LEVITT, N. 2018. Using the Medical Research Council framework for development and evaluation of complex interventions in a low resource setting to develop a theory-based treatment support intervention delivered via SMS text message to improve blood pressure control. *BMC Health Serv Res,* 18**,** 33.

BOLTON, C. E., IONESCU, A. A., EDWARDS, P. H., FAULKNER, T. A., EDWARDS, S. M. & SHALE, D. J. 2005. Attaining a correct diagnosis of COPD in general practice. *Respir Med,* 99**,** 493-500.

BONSIGNORE, M. R., PROFITA, M., GAGLIARDO, R., RICCOBONO, L., CHIAPPARA, G., PACE, E. & GJOMARKAJ, M. 2015. Advances in asthma pathophysiology: stepping forward from the Maurizio Vignola experience. *Eur Respir Rev,* 24**,** 30-9.

BORG, B., HARTLEY, M., FISHER, M. & THOMPSON, B. 2010. Spirometry Training Does Not Guarantee Valid Results. *Respir Care,* 55**,** 689-694.

BORLAND, C., COX, Y. & HIGENBOTTAM, T. 1993. Measurement of exhaled nitric oxide in man. *Thorax,* 48**,** 1160-1162.

BRANNAN, J. D. & LOUGHEED, M. D. 2012. Airway hyperresponsiveness in asthma: mechanisms, clinical significance, and treatment. *Front Physiol,* 3**,** 460.

BRIGHTLING, C., BRADDING, P., SYMON, F., HOLGATE, S., WARDLAW, A. & PAVORD, I. 2002. Mast Cell Infiltration of Airway Smooth Muscle in Asthma. *N Engl J Med,* 346**,** 1699-1705.

BROUWER, A. F., VISSER, C. A., DUIVERMAN, E. J., ROORDA, R. J. & BRAND, P. L. 2010. Is home spirometry useful in diagnosing asthma in children with nonspecific respiratory symptoms? *Pediatr Pulmonol,* 45**,** 326-32.

BROZEK, G. M., FARNIK, M., LAWSON, J. & ZEJDA, J. E. 2013. Underdiagnosis of childhood asthma: A comparison of survey estimates to clinical evaluation. *Int J Occup Med Environ Health,* 26**,** 900-9.

BRUSASCO, V., CRIMI, E. & PELLEGRINO, R. 1998. Airway hyperresponsiveness in asthma: not just a matter of airway inflammation. *Thorax,* 53**,** 992-8.

BTS 2019. British Thoracic Society and Scottish Intercollegiate Network Guideline on the Management of Asthma.

BUELO, A., MCLEAN, S., JULIOUS, S., FLORES-KIM, J., BUSH, A., HENDERSON, J., PATON, J. Y., SHEIKH, A., SHIELDS, M. & PINNOCK, H. 2018. At-risk children with asthma (ARC): a systematic review. *Thorax,* 73**,** 813-824.

BUI, D. S., BURGESS, J. A., LOWE, A. J., PERRET, J. L., LODGE, C. J., BUI, M., MORRISON, S., THOMPSON, B. R., THOMAS, P. S., GILES, G. G., GARCIA-AYMERICH, J., JARVIS, D., ABRAMSON, M. J., WALTERS, E. H., MATHESON, M. C. & DHARMAGE, S. C. 2017. Childhood Lung Function Predicts Adult Chronic Obstructive Pulmonary Disease and Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome. *American Journal of Respiratory & Critical Care Medicine,* 196**,** 39-46.

BUI, D. S., LODGE, C. J., BURGESS, J. A., LOWE, A. J., PERRET, J., BUI, M. Q., BOWATTE, G., GURRIN, L., JOHNS, D. P., THOMPSON, B. R., HAMILTON, G. S., FRITH, P. A., JAMES, A. L., THOMAS, P. S., JARVIS, D., SVANES, C., RUSSELL, M., MORRISON, S. C., FEATHER, I., ALLEN, K. J., WOOD-BAKER, R., HOPPER, J., GILES, G. G., ABRAMSON, M. J., WALTERS, E. H., MATHESON, M. C. & DHARMAGE, S. C. 2018. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med,* 6**,** 535-544.

BUSH, A. & FLEMING, L. 2015. Diagnosis and management of asthma in children. *BMJ,* 350**,** h996.

BUSH, A. & FLEMING, L. 2016. Is asthma overdiagnosed? *Arch Dis Child,* 101**,** 688-9.

BUSSE, W., CORREN, J., LANIER, B. Q., MCALARY, M., FOWLER-TAYLOR, A., CIOPPA, G. D., VAN AS, A. & GUPTA, N. 2001. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol,* 108**,** 184-90.

CABRAL, A. L., SOUSA, A. W., MENDES, F. A. & CARVALHO, C. R. 2017. Phenotypes of asthma in low-income children and adolescents: cluster analysis. *J Bras Pneumol,* 43**,** 44-50.

CAI, Y., CARTY, K., HENRY, R. L. & GIBSON, P. G. 1998. Persistence of sputum eosinophilia in children with controlled asthma when compared with healthy children. *Eur Respir J,* 11**,** 848-53.
CAMP 2000. Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med,* 343**,** 1054-1063.
CAMPBELL, M., FITZPATRICK, R., HAINES, A., KINMONTH, A. L., SANDERCOCK, P., SPIEGELHALTER, D. & TYRER, P. 2000. Framework for design and evaluation of complex interventions to improve health. *Bmj,* 321**,** 694-6.
CANE, R. & MCKENZIE, S. 2001. Parents' interpretations of children's respiratory symptoms on video. *Arch Dis Child,* 84**,** 31-34.
CARNEY, T. 2015. Regulation 28 - Report to prevent future deaths. *In:* OFFICE, G. A. S. T. C. S. (ed.).
CAROLAN, B. J. & SUTHERLAND, E. R. 2013. Clinical phenotypes of chronic obstructive pulmonary disease and asthma: recent advances. *J Allergy Clin Immunol,* 131**,** 627-34; quiz 635.
CARR, R., TELFORD, V. & WATERS, G. 2011. Impact of an educational intervention on the quality of spirometry performance in a general practice: an audit. *Prim Care Respir J,* 20**,** 210-3.
CAVE, A., WRIGHT, A., DORRETT, J. & MCERLAIN, M. 2001. Evaluation of a Nurse-run asthma clinic in general practice. *Prim Care Respir J,* 10**,** 65-68.
CHANG, A. B., ROBERTSON, C. F., VAN ASPEREN, P. P., GLASGOW, N. J., MELLIS, C. M., MASTERS, I. B., TEOH, L., TJHUNG, I., MORRIS, P. S., PETSKY, H. L., WILLIS, C. & LANDAU, L. I. 2012. A multicenter study on chronic cough in children : burden and etiologies based on a standardized management pathway. *Chest,* 142**,** 943-950.
CHANG, T. S., LEMANSKE, R. F., JR., MAUGER, D. T., FITZPATRICK, A. M., SORKNESS, C. A., SZEFLER, S. J., GANGNON, R. E., PAGE, C. D., JACKSON, D. J., CHILDHOOD ASTHMA, R. & EDUCATION NETWORK, I. 2014. Childhood asthma clusters and response to therapy in clinical trials. *J Allergy Clin Immunol,* 133**,** 363-9.
CHAPMAN, D. G. & IRVIN, C. G. 2015. Mechanisms of airway hyper-responsiveness in asthma: the past, present and yet to come. *Clin Exp Allergy,* 45**,** 706-19.
CHASTEK, B. K., S; NAGAR, S; ALBERS, F; YANCEY, S; ORTEGA, H; FORSHAG, M; DALAL, A 2016. Economic burden of illness among patients with severe asthma. *Journal of Managed Care & Specialty Pharmacy,* 22.
CHO SH, S. J., CHOI DC, YOON HJ, CHO YJ, MIN KU, LEE GK, SEO JW, KIM YY 1996. Pathological changes according to the severity of asthma. *Clin Exp Allergy,* 26**,** 1210-1219.
CHU, Y. T., CHEN, W. Y., WANG, T. N., TSENG, H. I., WU, J. R. & KO, Y. C. 2009. Extreme BMI predicts higher asthma prevalence and is associated with lung function impairment in school-aged children. *Pediatr Pulmonol,* 44**,** 472-9.
CLOUGH, J. & HOLGATE, S. 1994. Episodes of Respiratory Morbidity in Children with Cough and Wheeze. *Am J Respir Crit Care Med,* 150**,** 48-53.
COLLINGRIDGE, D. 2014. *Validating a Questionnaire* [Online]. SAGE Publishing. Available: https://www.methodspace.com/validating-a-questionnaire/ [Accessed 2019].
COOKSEY, D. 2006. A review of UK health research funding. *In:* HEALTH, D. O. (ed.).
CORNISH, R. P., HENDERSON, J., BOYD, A. W., GRANELL, R., VAN STAA, T. & MACLEOD, J. 2014. Validating childhood asthma in an epidemiological study using linked electronic patient records. *BMJ Open,* 4**,** e005345.
COWEN, M. K., WAKEFIELD, D. B. & CLOUTIER, M. M. 2007. Classifying asthma severity: objective versus subjective measures. *J Asthma,* 44**,** 711-5.
CRAIG, P., DIEPPE, P., MACINTYRE, S., MICHIE, S., NAZARETH, I. & PETTICREW, M. 2008. Developing and evaluating complex interventions: the new Medical Research Council guidance. *Bmj,* 337**,** a1655.

CRAIG, P. & PETTICREW, M. 2013. Developing and evaluating complex interventions: reflections on the 2008 MRC guidance. *Int J Nurs Stud,* 50**,** 585-7.
CURRAN, G. M., BAUER, M., MITTMAN, B., PYNE, J. M. & STETLER, C. 2012. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care,* 50**,** 217-26.
DAL NEGRO, R. W., DISTANTE, C., BONADIMAN, L., TURCO, P. & IANNAZZO, S. 2016. Cost of persistent asthma in Italy. *Multidiscip Respir Med,* 11**,** 44.
DAVIS, D., EVANS, M., JADAD, A., PERRIER, L., RATH, D., RYAN, D., SIBBALD, G., STRAUS, S., RAPPOLT, S., WOWK, M. & ZWARENSTEIN, M. 2003. The case for knowledge translation: shortening the journey from evidence to effect. *British Medical Journal,* 327**,** 33-35.
DE BOT, C. M., MOED, H., BINDELS, P. J., VAN WIJK, R. G., BERGER, M. Y., DE GROOT, H., DE JONGSTE, J. C. & VAN DER WOUDEN, J. C. 2013. Exhaled nitric oxide measures allergy not symptoms in children with allergic rhinitis in primary care: a prospective cross-sectional and longitudinal cohort study. *Prim Care Respir J,* 22**,** 44-50.
DE JONGSTE, J. C., CARRARO, S., HOP, W. C., GROUP, C. S. & BARALDI, E. 2009. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med,* 179**,** 93-7.
DE MARCO, R., LOCATELLI, F., CERVERI, I., BUGIANI, M., MARINONI, A., GIAMMANCO, G. & ITALIAN STUDY ON ASTHMA IN YOUNG ADULTS STUDY, G. 2002. Incidence and remission of asthma: a retrospective study on the natural history of asthma in Italy. *J Allergy Clin Immunol,* 110**,** 228-35.
DEMARCHE, S. F., SCHLEICH, F. N., PAULUS, V. A., HENKET, M. A., VAN HEES, T. J. & LOUIS, R. E. 2017. Asthma Control and Sputum Eosinophils: A Longitudinal Study in Daily Practice. *J Allergy Clin Immunol Pract,* 5**,** 1335-1343.e5.
DESCHILDRE, A., BEGHIN, L., SALLERON, J., ILIESCU, C., THUMERELLE, C., SANTOS, C., HOORELBEKE, A., SCALBERT, M., POUESSEL, G., GNANSOUNOU, M., EDME, J. L. & MATRAN, R. 2012. Home telemonitoring (forced expiratory volume in 1 s) in children with severe asthma does not reduce exacerbations. *Eur Respir J,* 39**,** 290-6.
DEVON, H. A., BLOCK, M. E., MOYLE-WRIGHT, P., ERNST, D. M., HAYDEN, S. J., LAZZARA, D. J., SAVOY, S. M. & KOSTAS-POLSTON, E. 2007. A psychometric toolbox for testing validity and reliability. *J Nurs Scholarsh,* 39**,** 155-64.
DOMBKOWSKI, K. J., HASSAN, F., WASILEVICH, E. A. & CLARK, S. J. 2010. Spirometry use among pediatric primary care physicians. *Pediatrics,* 126**,** 682-7.
DOUWES J, G. P., PEKKANEN J, PEARCE N 2002. Non eosinophilic asthma: importance and possible mechanisms. *Thorax,* 57**,** 643-648.
DUNDAS, I., CHAN, E. Y., BRIDGE, P. D. & MCKENZIE, S. A. 2005. Diagnostic accuracy of bronchodilator responsiveness in wheezy children. *Thorax,* 60**,** 13-6.
DWEIK, R., BOGGS, P., ERZURUM, S., IRVIN, C., LEIGH, M., LUNDBERG, J., OLIN, A., PLUMMER, A. & TAYLOR, D. 2011. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med,* 184**,** 602-615.
EDUCATION FOR HEALTH 2016. Improving the quality of diagnostic spirometry in adults: the National Register of certified professionals and operators. Education for Health.
EHTESHAMI-AFSHAR, S., FITZGERALD, J. M., DOYLE-WATERS, M. M. & SADATSAFAVI, M. 2016. The global economic burden of asthma and chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis,* 20**,** 11-23.
EIGEN, H., BIELER, H., GRANT, D., CHRISTOPH, K., TERRILL, D., HEILMAN, D., AMBROSIUS, W. & RS., T. 2001. Spirometric pulmonary function in healthy preschool children. *Am J Respir Crit Care Med,* 163**,** 619-623.

ELMASRI, M., ROMERO, K. M., GILMAN, R. H., HANSEL, N. N., ROBINSON, C. L., BAUMANN, L. M., CABRERA, L., HAMILTON, R. G., CHECKLEY, W. & INVESTIGATORS, P. S. 2014. Longitudinal assessment of high versus low levels of fractional exhaled nitric oxide among children with asthma and atopy. *Lung,* 192**,** 305-12.

ERS-EDUCATION. 2017. *What reference equations do I apply for non-Caucasians?* [Online]. Available: https://www.ers-education.org/guidelines/global-lung-function-initiative/faq/what-reference-equations-do-i-apply-for-non-caucasians.aspx [Accessed 2019].

FIELDING, S., PIJNENBURG, M., DE JONGSTE, J. C., PIKE, K. C., ROBERTS, G., PETSKY, H., CHANG, A. B., FRITSCH, M., FRISCHER, T., SZEFLER, S., GERGEN, P., VERMEULEN, F., VAEL, R. & TURNER, S. 2019. Change in FEV1 and Feno Measurements as Predictors of Future Asthma Outcomes in Children. *Chest,* 155**,** 331-341.

FINKELSTEIN, J., LOZANO, P., SHULRUFF, R., INUI, T., SOUMERAI, S., NG, M. & WEISS, K. 2000. Self-reported physician practices for children with asthma: are national guidelines followed? *Pediatrics,* 106**,** 886-896.

FISK, M., MCMILLAN, V., BROWN, J., HOLZHAUER-BARRIE, J., KHAN, M. S., BAXTER, N. & ROBERTS, C. M. 2019. Inaccurate diagnosis of COPD: the Welsh National COPD Audit. *Br J Gen Pract,* 69**,** e1-e7.

FITZPATRICK, A. M., TEAGUE, W. G., MEYERS, D. A., PETERS, S. P., LI, X., LI, H., WENZEL, S. E., AUJLA, S., CASTRO, M., BACHARIER, L. B., GASTON, B. M., BLEECKER, E. R., MOORE, W. C., NATIONAL INSTITUTES OF HEALTH/NATIONAL HEART, L. & BLOOD INSTITUTE SEVERE ASTHMA RESEARCH, P. 2011. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol,* 127**,** 382-389 e1-13.

FLEMING, L., TSARTSALI, L., WILSON, N., REGAMEY, N. & BUSH, A. 2013. Longitudinal Relationship between Sputum Eosinophils and Exhaled Nitric Oxide in Children with Asthma. *Am J Respir Crit Care Med,* 188**,** 400-402.

FORT, D. G., HERR, T. M., SHAW, P. L., GUTZMAN, K. E. & STARREN, J. B. 2017. Mapping the evolving definitions of translational research. *J Clin Transl Sci,* 1**,** 60-66.

FRANK P, F. S., MOORHEAD T, HANNAFORD P 1996. Use of a postal questionnaire to estimate the likely underdiagnosis of asthma-like illness in adults. *British Journal of General Practice,* 46**,** 295-297.

FRITSCH, M., UXA, S., HORAK, F., JR., PUTSCHOEGL, B., DEHLINK, E., SZEPFALUSI, Z. & FRISCHER, T. 2006. Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. *Pediatr Pulmonol,* 41**,** 855-62.

FUHLBRIGGE, A. L., KITCH, B. T., PALTIEL, A. D., KUNTZ, K. M., NEUMANN, P. J., DOCKERY, D. W. & WEISS, S. T. 2001. FEV(1) is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol,* 107**,** 61-7.

FUHLBRIGGE, A. L., WEISS, S. T., KUNTZ, K. M., PALTIEL, A. D. & GROUP, C. R. 2006. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. *Pediatrics,* 118**,** e347-55.

GALANT, S., MORPHEW, T., AMARO, S. & LIAO, O. 2007. Value of the Bronchodilator Response in Assessing Controller Naïve Asthmatic Children. *Pediatrics,* 151**,** 457-462.

GALANT, S. P., MORPHEW, T., NEWCOMB, R. L., HIOE, K., GUIJON, O. & LIAO, O. 2011. The relationship of the bronchodilator response phenotype to poor asthma control in children with normal spirometry. *J Pediatr,* 158**,** 953-959 e1.

GAN 2014. Global Asthma Network Asthma Report.

GAUTHIER, M., RAY, A. & WENZEL, S. E. 2015. Evolving Concepts of Asthma. *Am J Respir Crit Care Med,* 192**,** 660-8.

GEMOU-ENGESAETH V, K. A., BUSH A, CORRIGAN CJ 1994. Activated peripheral blood CD4 and CD8 T lymphocytes in child asthma: correlation with eosinophilia and disease severity. *Pediatric Allergy and Immunology,* 5**,** 170-177.

GIBSON, P. G., SIMPSON, J. L., HANKIN, R., POWELL, H. & HENRY, R. L. 2003. Relationship between induced sputum eosinophils and the clinical pattern of childhood asthma. *Thorax,* 58**,** 116-21.

GINA 2019. Global Initiative for Asthma Pocket guide for asthma management and prevention for adults and children older than 5 years.

GOMERSAL, T., HARNAN, S., ESSAT, M., TAPPENDEN, P., WONG, R., LAWSON, R., PAVORD, I. & EVERARD, M. L. 2016. A systematic review of fractional exhaled nitric oxide in the routine management of childhood asthma. *Pediatr Pulmonol,* 51**,** 316-28.

GONZALEZ-GARCIA, M., CABALLERO, A., JARAMILLO, C., MALDONADO, D. & TORRES-DUQUE, C. A. 2015. Prevalence, risk factors and underdiagnosis of asthma and wheezing in adults 40 years and older: A population-based study. *J Asthma,* 52**,** 823-30.

GREEN, R. H., BRIGHTLING, C. E., MCKENNA, S., HARGADON, B., PARKER, D., BRADDING, P., WARDLAW, A. J. & PAVORD, I. D. 2002. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *The Lancet,* 360**,** 1715-1721.

GREEN, R. J., KLEIN, M., BECKER, P., HALKAS, A., LEWIS, H., KITCHIN, O., MOODLEY, T. & MASEKELA, R. 2013. Disagreement among common measures of asthma control in children. *Chest,* 143**,** 117-122.

GREIVER, M., LANG, C., HUNCHUCK, J. & ROTHSCHILD, K. 2002. Improving the diagnosis of asthma in a primary care practice. *Canadian Family Physician,* 58**,** 773.

GRIFFITHS, C., FEDER, G., WEDZICHA, J., FOSTER, G., LIVINGSTONE, A. & SINGH MARLOWE, G. 1999. Feasibility of spirometry and reversibility testing for the identification of patients with chronic obstructive pulmonary disease on asthma registers in general practice. *Respir Med,* 93**,** 903-908.

GRIFFITHS, C., FOSTER, G., BARNES, N., ELDRIDGE, S., TATE, H., BEGUM, S., WIGGINS, M., DAWSON, C., LIVINGSTONE, A. E., CHAMBERS, M., COATS, T., HARRIS, R. & FEDER, G. S. 2004. Specialist nurse intervention to reduce unscheduled asthma care in a deprived multiethnic area: the east London randomised controlled trial for high risk asthma (ELECTRA). *BMJ,* 328**,** 144.

GRUFFYDD-JONES, K., WARD, S., STONHAM, C., MACFARLANE, T. V. & THOMAS, M. 2007. The use of exhaled nitric oxide monitoring in primary care asthma clinics: a pilot study. *Prim Care Respir J,* 16**,** 349-56.

GRZELEWSKI, T., WITKOWSKI, K., MAKANDJOUOLA, E., GRZELEWSKA, A., MAJAK, P., JERZYNSKA, J., JANAS, A., STELMACH, R., STELMACH, W. & STELMACH, I. 2014. Diagnostic value of lung function parameters and FeNO for asthma in schoolchildren in large, real-life population. *Pediatric pulmonology,* 49**,** 632-640.

GUPTA, A., IKEDA, M., GENG, B., AZMI, J., PRICE, R. G., BRADFORD, E. S., YANCEY, S. W. & STEINFELD, J. 2019. Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. *J Allergy Clin Immunol*.

HALLBERG, J., ANDERSON, M., WICKMAN, M. & SVARTENGREN, M. 2010. Factors in infancy and childhood related to reduced lung function in asthmatic children: a birth cohort study (BAMSE). *Pediatr Pulmonol,* 45**,** 341-8.

HALTERMAN, J., YOOS, H., KACZOROWSKI, J., MCCONNOCHIE, K., HOLZHAUER, R., CONN, K., LAUVER, S. & SZILAGYI, P. 2002. Providers underestimate symtom severity among urban children with asthma. *Arch Pediatr Adolesc Med.,* 156**,** 141-146.

HEFFLER, E., CRIMI, C., MANCUSO, S., CAMPISI, R., PUGGIONI, F., BRUSSINO, L. & CRIMI, N. 2018. Misdiagnosis of asthma and COPD and underuse of spirometry in primary care unselected patients. *Respir Med,* 142**,** 48-52.

HEFFLER, E., PIZZIMENTI, S., GUIDA, G., BUCCA, C. & ROLLA, G. 2015. Prevalence of over-/misdiagnosis of asthma in patients referred to an allergy clinic. *J Asthma,* 52**,** 931-4.
HEWITT, R. S., MODRICH, C. M., COWAN, J. O., HERBISON, G. P. & TAYLOR, D. R. 2009. Outcomes using exhaled nitric oxide measurements as an adjunct to primary care asthma management. *Prim Care Respir J,* 18**,** 320-7.
HILL, S. & MORGAN, M. 2016. Improving the quality of diagnostic spirometry in adults: the National Register of certified professionals and operators. *In:* ENGLAND, N. (ed.).
HOLT, E. W., TAN, J. & HOSGOOD, H. D. 2006. The impact of spirometry on pediatric asthma diagnosis and treatment. *J Asthma,* 43**,** 489-93.
HONKOOP, P. J., LOIJMANS, R. J., TERMEER, E. H., SNOECK-STROBAND, J. B., VAN DEN HOUT, W. B., BAKKER, M. J., ASSENDELFT, W. J., TER RIET, G., STERK, P. J., SCHERMER, T. R., SONT, J. K. & ASTHMA CONTROL COST-UTILITY RANDOMIZED TRIAL EVALUATION STUDY, G. 2015. Symptom- and fraction of exhaled nitric oxide-driven strategies for asthma control: A cluster-randomized trial in primary care. *J Allergy Clin Immunol,* 135**,** 682-8 e11.
HUETO, J., CEBOLLERO, P., PASCAL, I., CASCANTE, J., EGUÍA, V., TERUEL, F. & CARPINTERO, M. 2006. Spirometry in primary care in Navarre, Spain. *Arch Bronconeumol,* 42**,** 326-331.
HUTCHINSON, J. 1846. On the capacity of the lungs and on the respiratory functions *Med Chir Trans,* 29**,** 137–252.
IFC 1998. Nitrogen Oxides. *In:* HANDBOOK, P. P. A. A. (ed.). World Bank Group.
JAIN, V. V., ALLISON, D. R., ANDREWS, S., MEJIA, J., MILLS, P. K. & PETERSON, M. W. 2015. Misdiagnosis Among Frequent Exacerbators of Clinically Diagnosed Asthma and COPD in Absence of Confirmation of Airflow Obstruction. *Lung,* 193**,** 505-12.
JAMES, A. L., PALMER, L. J., KICIC, E., MAXWELL, P. S., LAGAN, S. E., RYAN, G. F. & MUSK, A. W. 2005. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. *Am J Respir Crit Care Med,* 171**,** 109-14.
JENKINS, M., HOPPER, J., BOWES, G., CARLIN, J., FLANDER, L. & GILES, G. 1994. Factors in childhood as predictors of asthma in adult life. *BMJ,* 309**,** 90-93.
JOHANSEN, S. 2007. Spirometry in primary care in a region of Northern Norway - before and after a brief training course. *Prim Care Respir J,* 16**,** 112-4.
JOHNS, D., BURTON, D., WALTERS, J. & WOOD-BAKER, R. 2006. National survey of spirometer ownership and usage in general practice in Australia. *Respirology,* 11**,** 292-298.
JONES, K. 1995. The role of measuring forced expiratory volume in one second in determining therapeutic changes made in an asthma clinic in general practice. *Respiratory Medicine,* 89**,** 171-174.
JUST, J., SAINT-PIERRE, P., GOUVIS-ECHRAGHI, R., LAOUDI, Y., ROUFAI, L., MOMAS, I. & ANNESI MAESANO, I. 2014. Childhood allergic asthma is not a single phenotype. *J Pediatr,* 164**,** 815-20.
KAICKER, J., DANG, W. & D'URZO, A. 2014. The challenge of objective confirmation of asthma diagnosis in primary care. *NPJ Prim Care Respir Med,* 24**,** 14032.
KAMINSKY, D., MARCY, T., BACHAND, M. & IRVIN, C. 2005. Knowledge and use of office spirometry for the detection of chronic obstructive pulmonary disease by primary care physicians. *Respir Care,* 50**,** 1639-1648.
KERSTJENS, H., BRAND, P., QUANJER, P., VAN DER BRUGGEN-BOGAARTS, B., KOËTER, G. & POSTMA, D. 1993. Variability of bronchodilator response and effects of inhaled corticosteroid treatment in obstructive airways disease. Dutch CNSLD Study Group. *Thorax,* 48**,** 722-729.
KIRBY JG, H. F., GLEICH GJ, O'BYRNE PM 1987. Bronchoalveolar cell profiles of asthmatic and nonasthmatic subjects.pdf>. *Am Rev Respir Dis,* 136**,** 379-383.

KITCH, B., PALTIE, L. A., KUNTZ, K., DOCKERY, D., SCHOUTEN, J., WEISS, S. & FUHLBRIGGE, A. 2004. A single measure of FEV1 is associated with risk of asthma attacks in long-term follow-up. *Chest,* 126**,** 1875-1882.

KNAPTON, S. 2016. Half a million children with asthma may not actually have condition *The Telegraph*.

KOTTER, J. 1995. Leading change - why transformation efforts fail. *Harvard Business Review*.

LAKSHMAN, R., GRIFFIN, S., HARDEMAN, W., SCHIFF, A., KINMONTH, A. L. & ONG, K. K. 2014. Using the Medical Research Council framework for the development and evaluation of complex interventions in a theory-based infant feeding intervention to prevent childhood obesity: the baby milk intervention and trial. *J Obes,* 2014**,** 646504.

LANDES, S. J., MCBAIN, S. A. & CURRAN, G. M. 2019. An introduction to effectiveness-implementation hybrid designs. *Psychiatry Res,* 280**,** 112513.

LANE, C., KNIGHT, D., BURGESS, S., FRANKLIN, P., HORAK, F., LEGG, J., MOELLER, A. & STICK, S. 2004. Epithelial inducible nitric oxide synthase activity is the major determinant of nitric oxide concentration in exhaled breath. *Thorax,* 59**,** 757-60.

LANGE, P., SCHARLING, H., ULRIK, C. S. & VESTBO, J. 2006. Inhaled corticosteroids and decline of lung function in community residents with asthma. *Thorax,* 61**,** 100-4.

LEARNING NETWORK ON CAPACITY DEVELOPMENT. 2017. *How to assess change readiness* [Online]. Available: http://www.lencd.org/learning/how-assess-change-readiness [Accessed].

LEE, W. Y., SUH, D. I., SONG, D. J., BAEK, H. S., SHIN, M., YOO, Y., KWON, J. W., JANG, G. C., YANG, H. J., LEE, E., SEO, J. H., WOO, S. I., KIM, H. Y., SHIN, Y. H., LEE, J. S., YOON, J., JUNG, S., HAN, M., EOM, E., YU, J., KIM, W. K., LIM, D. H., KIM, J. T., CHANG, W. S., LEE, J. K. & KIM, H. S. 2019. Asthma control test reflects not only lung function but also airway inflammation in children with stable asthma. *J Asthma***,** 1-6.

LEE, Y. K., YANG, S., PARK, J., KIM, H. & HAHN, Y. S. 2015. House dust mite-specific immunoglobulin E and longitudinal exhaled nitric oxide measurements in children with atopic asthma. *Korean J Pediatr,* 58**,** 89-95.

LEI BURTON, D., LEMAY, K. S., SAINI, B., SMITH, L., BOSNIC-ANTICEVICH, S., SOUTHWELL, P., COOKE, J., EMMERTON, L., STEWART, K., KRASS, I., REDDEL, H. & ARMOUR, C. 2015. The reliability and utility of spirometry performed on people with asthma in community pharmacies. *J Asthma,* 52**,** 913-9.

LEVY, M. L. 2016. Is spirometry essential in diagnosing asthma? No. *British Journal of General Practice,* 66**,** 485.

LEVY, M. L., QUANJER, P. H., BOOKER, R., COOPER, B. G., HOLMES, S., SMALL, I. & GENERAL PRACTICE AIRWAYS, G. 2009. Diagnostic spirometry in primary care: Proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society recommendations: a General Practice Airways Group (GPIAG)1 document, in association with the Association for Respiratory Technology & Physiology (ARTP)2 and Education for Health3 1 www.gpiag.org 2 www.artp.org 3 www.educationforhealth.org.uk. *Prim Care Respir J,* 18**,** 130-47.

LEWIN, K. 1943. Defining the 'Field at a Given Time'. *Psychological Review* 50**,** 292-310.

LICSKAI, C., SANDS, T., PAOLATTO, L., NICOLETTI, I. & FERRONE, M. 2012. Spirometry in primary care: An analysis of spirometry test quality in a regional primary care asthma program. *Can Respir J,* 19**,** 249-254.

LINDENSMITH, J., MORRISON, D., DEVEAU, C. & HERNANDEZ, P. 2004. Overdiagnosis of asthma in the community. *Can Respir J,* 11**,** 111-116.

LIU, A. H., ZEIGER, R., SORKNESS, C., MAHR, T., OSTROM, N., BURGESS, S., ROSENZWEIG, J. C. & MANJUNATH, R. 2007. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol,* 119**,** 817-25.

LOO, S. L. & WARK, P. A. 2016. Recent advances in understanding and managing asthma. *F1000Res,* 5.

LOOIJMANS-VAN DEN AKKER, I., VAN LUIJN, K. & VERHEIJ, T. 2016. Overdiagnosis of asthma in children in primary care: a retrospective analysis. *Br J Gen Pract,* 66**,** e152-7.

LOTVALL, J., AKDIS, C. A., BACHARIER, L. B., BJERMER, L., CASALE, T. B., CUSTOVIC, A., LEMANSKE, R. F., JR., WARDLAW, A. J., WENZEL, S. E. & GREENBERGER, P. A. 2011. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol,* 127**,** 355-60.

LOVASI, G. 2019. *Content Analysis* [Online]. Columbia University Mailman School of Public Health Available: https://www.mailman.columbia.edu/research/population-health-methods/content-analysis [Accessed 2019].

LU, M., WU, B., CHE, D., QIAO, R. & GU, H. 2015. FeNO and asthma treatment in children: a systematic review and meta-analysis. *Medicine (Baltimore),* 94**,** e347.

LUM, S., BOUNTZIOUKA, V., QUANJER, P., SONNAPPA, S., WADE, A., BEARDSMORE, C., CHHABRA, S. K., CHUDASAMA, R. K., COOK, D. G., HARDING, S., KUEHNI, C. E., PRASAD, K. V., WHINCUP, P. H., LEE, S. & STOCKS, J. 2016. Challenges in Collating Spirometry Reference Data for South-Asian Children: An Observational Study. *PLoS One,* 11**,** e0154336.

LUSUARDI, M., DE BENEDETTO, F., PAGGIARO, P., SANGUINETTI, C., BRAZZOLA, G., FERRI, P. & DONNER, C. 2006. A randomized controlled trial on office spirometry in asthma and COPD in standard general practice: data from spirometry in Asthma and COPD: a comparative evaluation Italian study. *Chest,* 129**,** 844-852.

MACKENZIE, M., O'DONNELL, C., HALLIDAY, E., SRIDHARAN, S. & PLATT, S. 2010. Do health improvement programmes fit with MRC guidance on evaluating complex interventions? *Bmj,* 340**,** c185.

MAGNONI, M. S., CAMINATI, M., SENNA, G., ARPINELLI, F., RIZZI, A., DAMA, A. R., SCHIAPPOLI, M., BETTONCELLI, G. & CARAMORI, G. 2015. Asthma under/misdiagnosis in primary care setting: an observational community-based study in Italy. *Clin Mol Allergy,* 13**,** 26.

MALINOVSCHI, A., FONSECA, J. A., JACINTO, T., ALVING, K. & JANSON, C. 2013. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. *J Allergy Clin Immunol,* 132**,** 821-7 e1-5.

MAMMEN, J. R., RHEE, H., NORTON, S. A. & BUTZ, A. M. 2017. Perceptions and experiences underlying self-management and reporting of symptoms in teens with asthma. *J Asthma,* 54**,** 143-152.

MATSUNAGA, K., ICHIKAWA, T., OKA, A., MORISHITA, Y., KANAI, K., HIRAMATSU, M., AKAMATSU, H., KAWABATA, H., KIKUCHI, T., AKAMATSU, K., HIRANO, T., KOU, Y., NAKANISHI, M., MINAKATA, Y. & YAMAMOTO, N. 2014. Changes in forced expiratory volume in 1 second over time in patients with controlled asthma at baseline. *Respir Med,* 108**,** 976-82.

MCCAMBRIDGE, J., WITTON, J. & ELBOURNE, D. R. 2014. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J Clin Epidemiol,* 67**,** 267-77.

MCEVOY, C. T. & SPINDEL, E. R. 2017. Pulmonary Effects of Maternal Smoking on the Fetus and Child: Effects on Lung Development, Respiratory Morbidities, and Life Long Lung Health. *Paediatr Respir Rev,* 21**,** 27-33.

MCNICHOLL, D., STEVENSON, M., MCGARVEY, L. & HEANEY, L. 2012. The Utility of Fractional Exhaled Nitric Oxide Suppression in the Identification of Nonadherence in Difficult Asthma. *American Journal of Respiratory and Critical Care Medicine,* 186**,** 1102-1108.

MEHTA, V., STOKES, J., BERRO, A., ROMERO, F. & CASALE, T. 2009. Time-dependent effects of inhaled corticosteroids on lung function, bronchial hyperresponsiveness, and airway inflammation in asthma. *Ann Allergy Asthma Immunol,* 103**,** 31-37.

MELBYE, H., DRIVENES, E., DALBAK, L. G., LEINAN, T., HOEGH-HENRICHSEN, S. & OSTREM, A. 2011. Asthma, chronic obstructive pulmonary disease, or both? Diagnostic labeling and spirometry in primary care patients aged 40 years or more. *Int J Chron Obstruct Pulmon Dis,* 6**,** 597-603.

METTING, E. I., RIEMERSMA, R. A., KOCKS, J. H., PIERSMA-WICHERS, M. G., SANDERMAN, R. & VAN DER MOLEN, T. 2015. Feasibility and effectiveness of an asthma/COPD service for primary care: a cross-sectional baseline description and longitudinal results. *NPJ Prim Care Respir Med,* 25**,** 14101.

MICHIE, S., VAN STRALEN, M. M. & WEST, R. 2011. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci,* 6**,** 42.

MICHILS, A., BALDASSARRE, S. & VAN MUYLEM, A. 2008. Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. *Eur Respir J,* 31**,** 539-46.

MILLER, M. R., HANKINSON, J., BRUSASCO, V., BURGOS, F., CASABURI, R., COATES, A., CRAPO, R., ENRIGHT, P., VAN DER GRINTEN, C. P., GUSTAFSSON, P., JENSEN, R., JOHNSON, D. C., MACINTYRE, N., MCKAY, R., NAVAJAS, D., PEDERSEN, O. F., PELLEGRINO, R., VIEGI, G., WANGER, J. & FORCE, A. E. T. 2005. Standardisation of spirometry. *Eur Respir J,* 26**,** 319-38.

MUKHERJEE, M., STODDART, A., GUPTA, R. P., NWARU, B. I., FARR, A., HEAVEN, M., FITZSIMMONS, D., BANDYOPADHYAY, A., AFTAB, C., SIMPSON, C. R., LYONS, R. A., FISCHBACHER, C., DIBBEN, C., SHIELDS, M. D., PHILLIPS, C. J., STRACHAN, D. P., DAVIES, G. A., MCKINSTRY, B. & SHEIKH, A. 2016. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med,* 14**,** 113.

NAEPP 2007. National Asthma Education and Prevention Programme. Guidelines for the diagnosis and management of asthma.

NASH, S. 2015. *BMA wholly rejects NICE recommendations on asthma in scathing response* [Online]. Available: http://www.pulsetoday.co.uk/clinical/respiratory-/bma-wholly-rejects-nice-recommendations-on-asthma-in-scathing-response/20010520.article#.VavfrYsijdk [Accessed].

NATHAN, R. A., SORKNESS, C. A., KOSINSKI, M., SCHATZ, M., LI, J. T., MARCUS, P., MURRAY, J. J. & PENDERGRAFT, T. B. 2004. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol,* 113**,** 59-65.

NELSON, B., SEARS, S., WOODS, J., LING, C., HUNT, J., CLAPPER, L. & GASTON, B. 1997. Expired nitric oxide as a marker for childhood asthma. *Journal of Pediatrics,* 130**,** 423-427.

NELSON, K. A., LEE, P., TRINKAUS, K. & STRUNK, R. C. 2011. Exhaled nitric oxide levels during treatment of pediatric acute asthma exacerbations and association with the need for hospitalization. *Pediatr Emerg Care,* 27**,** 249-55.

NEWBY, C., AGBETILE, J., HARGADON, B., MONTEIRO, W., GREEN, R., PAVORD, I., BRIGHTLING, C. & SIDDIQUI, S. 2014. Lung function decline and variable airway inflammatory pattern: longitudinal analysis of severe asthma. *J Allergy Clin Immunol,* 134**,** 287-94.

NGUYEN, H. V., NADKARNI, N. V., SANKARI, U., MITAL, S., LYE, W. K. & TAN, N. C. 2017. Association between asthma control and asthma cost: Results from a longitudinal study in a primary care setting. *Respirology,* 22**,** 454-459.

NHLBI. 2014. *What Is Asthma?* [Online]. Available: https://www.nhlbi.nih.gov/health/health-topics/topics/asthma/ [Accessed 11/07/2017 2017].

NHS, E. 2014. The Friends and Family Test. *In:* 01787, P. G. R. N. (ed.).

NHSE 2019. 2019/20 General Medical Services (GMS) contract Quality and Outcomes Framework (QOF) *In:* ENGLAND, N. (ed.).
NICE 2013. Asthma (including children and young people): diagnosis and monitoring: Stakeholder workshop.
NICE. 2017. *The National Institute for Health and Care Excellence (NICE). Guideline for Asthma: diagnosis, monitoring and chronic asthma management.* [Online]. Available: https://www.nice.org.uk/guidance/ng80 [Accessed 2019].
NICE 2019. Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath (DG12).
NUIJSINK, M., HOP, W. C., STERK, P. J., DUIVERMAN, E. J. & DE JONGSTE, J. C. 2007. Long-term asthma treatment guided by airway hyperresponsiveness in children: a randomised controlled trial. *Eur Respir J,* 30**,** 457-66.
O'DOWD, L. C., FIFE, D., TENHAVE, T. & PANETTIERI, R. A. 2003. Attitudes of physicians toward objective measures of airway function in asthma. *The American Journal of Medicine,* 114**,** 391-396.
OCHIENG, P. 2009. An analysis of the strengths and limitations of qualitative and quantitative research paradigms. *Problems of Education in the 21st Century* 13**,** 13-18.
OEI, S. M., THIEN, F. C., SCHATTNER, R. L., SULAIMAN, N. D., BIRCH, K., SIMPSON, P., DEL COLLE, E. A., ARONI, R. A., WOLFE, R. & ABRAMSON, M. J. 2011. Effect of spirometry and medical review on asthma control in patients in general practice: a randomized controlled trial. *Respirology,* 16**,** 803-10.
OLIN, J. T. & WECHSLER, M. E. 2014. Asthma: pathogenesis and novel drugs for treatment. *BMJ,* 349**,** g5517.
OLUWOLE, O., ARINOLA, G. O., HUO, D. & OLOPADE, C. O. 2017. Household biomass fuel use, asthma symptoms severity, and asthma underdiagnosis in rural schoolchildren in Nigeria: a cross-sectional observational study. *BMC Pulm Med,* 17**,** 3.
PAKHALE, S., SUMNER, A., COYLE, D., VANDEMHEEN, K. & AARON, S. 2011. (Correcting) misdiagnoses of asthma: a cost effectiveness analysis. *BMC Pulm Med,* 11**,** 27.
PAPAKOSTA, D., LATSIOS, D., MANIKA, K., PORPODIS, K., KONTAKIOTI, E. & GIOULEKAS, D. 2011. Asthma control test is correlated to FEV1 and nitric oxide in Greek asthmatic patients: influence of treatment. *J Asthma,* 48**,** 901-6.
PARK, G. M., HAN, H. W., KIM, J. Y., LEE, E., CHO, H. J., YOON, J., HONG, S. J., YANG, S. I., YANG, H. J. & YU, J. 2016. Association of symptom control with changes in lung function, bronchial hyperresponsiveness, and exhaled nitric oxide after inhaled corticosteroid treatment in children with asthma. *Allergol Int,* 65**,** 439-443.
PAVORD, I. D. 2009. Asthma control, airway responsiveness and airway inflammation. *Clin Exp Allergy,* 39**,** 1780-2.
PAVORD, I. D., BEASLEY, R., AGUSTI, A., ANDERSON, G. P., BEL, E., BRUSSELLE, G., CULLINAN, P., CUSTOVIC, A., DUCHARME, F. M., FAHY, J. V., FREY, U., GIBSON, P., HEANEY, L. G., HOLT, P. G., HUMBERT, M., LLOYD, C. M., MARKS, G., MARTINEZ, F. D., SLY, P. D., VON MUTIUS, E., WENZEL, S., ZAR, H. J. & BUSH, A. 2018. After asthma: redefining airways diseases. *The Lancet,* 391**,** 350-400.
PAYNE, D., ADCOCK, I., WILSON, N., OATES, T., SCALLAN, M. & BUSH, A. 2001. Relationship between Exhaled Nitric Oxide and Mucosal Eosinophilic Inflammation in Children with Difficult Asthma, after Treatment with Oral Prednisolone. *Am J Respir Crit Care Med,* 164**,** 1376-1381.
PEARCE, N., AIT-KHALED, N., BEASLEY, R., MALLOL, J., KEIL, U., MITCHELL, E., ROBERTSON, C. & GROUP, I. P. T. S. 2007. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax,* 62**,** 758-66.

PEIRSMAN, E. J., CARVELLI, T. J., HAGE, P. Y., HANSSENS, L. S., PATTYN, L., RAES, M. M., SAUER, K. A., VERMEULEN, F. & DESAGER, K. N. 2014. Exhaled nitric oxide in childhood allergic asthma management: a randomised controlled trial. *Pediatr Pulmonol,* 49**,** 624-31.

PELLEGRINO, R., VIEGI, G., BRUSASCO, V., CRAPO, R. O., BURGOS, F., CASABURI, R., COATES, A., VAN DER GRINTEN, C. P., GUSTAFSSON, P., HANKINSON, J., JENSEN, R., JOHNSON, D. C., MACINTYRE, N., MCKAY, R., MILLER, M. R., NAVAJAS, D., PEDERSEN, O. F. & WANGER, J. 2005. Interpretative strategies for lung function tests. *Eur Respir J,* 26**,** 948-68.

PELLETTIERE, V. 2006. Organization Self-Assessment to Determine the Readiness and Risk for a Planned Change. *Organization Development Journal,* 24**,** 38-43.

PERNIS, A. B. & ROTHMAN, P. B. 2002. JAK-STAT signaling in asthma. *Journal of Clinical Investigation,* 109**,** 1279-1283.

PETERS, D., TRAN, N. & ADAM, T. 2013. Implementation Research in Health: A Practical Guide. *In:* ORGANISATION, W. H. (ed.).

PETERS, D. H., ADAM, T., ALONGE, O., AGYEPONG, I. A. & TRAN, N. 2014. Republished research: Implementation research: what it is and how to do it. *British Journal of Sports Medicine,* 48**,** 731-736.

PETSKY, H., KEW, K. & CHANG, A. 2016a. Exhaled nitric oxide levels to guide treatment for children with asthma. John Wiley & Sons, Ltd.

PETSKY, H. L., KEW, K. M. & CHANG, A. B. 2016b. Exhaled nitric oxide levels to guide treatment for children with asthma. *Cochrane Database Syst Rev,* 11**,** CD011439.

PETSKY, H. L., KEW, K. M., TURNER, C. & CHANG, A. B. 2016c. Exhaled nitric oxide levels to guide treatment for adults with asthma. *Cochrane Database Syst Rev,* 9**,** CD011440.

PETSKY, H. L., LI, A. M., AU, C. T., KYNASTON, J. A., TURNER, C. & CHANG, A. B. 2015. Management based on exhaled nitric oxide levels adjusted for atopy reduces asthma exacerbations in children: A dual centre randomized controlled trial. *Pediatr Pulmonol,* 50**,** 535-43.

PIACENTINI, G., BODINI, A., COSTELLA, S., VICENTINI, L., MAZZI, P., SPERANDIO, S. & BONER, A. 1999. Exhaled nitric oxide and sputum eosinophil markers of inflammation in asthmatic children. *Eur Respir J,* 13**,** 1386-1390.

PIACENTINI, G. L., PERONI, D. G., BODINI, A., BONAFIGLIA, E., RIGOTTI, E., BARALDI, E., LIU, A. H. & BONER, A. L. 2009. Childhood Asthma Control Test and airway inflammation evaluation in asthmatic children. *Allergy,* 64**,** 1753-7.

PIJNENBURG, M. W., BAKKER, E. M., HOP, W. C. & DE JONGSTE, J. C. 2005a. Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial. *Am J Respir Crit Care Med,* 172**,** 831-6.

PIJNENBURG, M. W., HOFHUIS, W., HOP, W. C. & DE JONGSTE, J. C. 2005b. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax,* 60**,** 215-8.

PIKE, K., SELBY, A., PRICE, S., WARNER, J., CONNETT, G., LEGG, J., LUCAS, J. S., PETERS, S., BUCKLEY, H., MAGIER, K., FOOTE, K., DREW, K., MORRIS, R., LANCASTER, N. & ROBERTS, G. 2013. Exhaled nitric oxide monitoring does not reduce exacerbation frequency or inhaled corticosteroid dose in paediatric asthma: a randomised controlled trial. *Clin Respir J,* 7**,** 204-13.

POELS, P., OLDE HARTMAN, T. & SCHERMER, T. 2006. Qualitative studies to explore barriers to spirometry use: a breath of fresh air? *Respir Care,* 51**,** 768.

PORSBJERG, C. M., GIBSON, P. G., PRETTO, J. J., SALOME, C. M., BROWN, N. J., BEREND, N. & KING, G. G. 2013. Relationship between airway pathophysiology and airway inflammation in older asthmatics. *Respirology,* 18**,** 1128-34.

PRADO, C. M., MARTINS, M. A. & TIBERIO, I. F. 2011. Nitric oxide in asthma physiopathology. *ISRN Allergy,* 2011**,** 832560.

PRICE, C. 2015. *NICE: GPs should use FeNO and 'twitchiness' tests to confirm asthma diagnosis* [Online]. Available: http://www.pulsetoday.co.uk/clinical/respiratory-/nice-gps-should-use-feno-and-twitchiness-tests-to-confirm-asthma-diagnosis/20009051.article#.VaY3_vlViko [Accessed].
PRICE, C. 2017. *NICE chiefs forced to re-consult on asthma diagnosis plans* [Online]. Available: http://www.pulsetoday.co.uk/clinical/more-clinical-areas/respiratory-/nice-chiefs-forced-to-re-consult-on-asthma-diagnosis-plans/20034091.article [Accessed].
PROCTOR, E., SILMERE, H., RAGHAVAN, R., HOVMAND, P., AARONS, G., BUNGER, A., GRIFFEY, R. & HENSLEY, M. 2011. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Adm Policy Ment Health,* 38**,** 65-76.
PUBLIC HEALTH ENGLAND. 2017. *National General Practice Profiles* [Online]. Available: http://fingertips.phe.org.uk/profile/general-practice/data [Accessed].
QUAEDVLIEG, V., SELE, J., HENKET, M. & LOUIS, R. 2009. Association between asthma control and bronchial hyperresponsiveness and airways inflammation: a cross-sectional study in daily practice. *Clin Exp Allergy,* 39**,** 1822-9.
QUANJER, P. H., STANOJEVIC, S., COLE, T. J., BAUR, X., HALL, G. L., CULVER, B. H., ENRIGHT, P. L., HANKINSON, J. L., IP, M. S., ZHENG, J., STOCKS, J. & INITIATIVE, E. R. S. G. L. F. 2012. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J,* 40**,** 1324-43.
QUANJER, P. H. & WEINER, D. J. 2014. Interpretative consequences of adopting the Global Lungs 2012 reference equations for spirometry for children and adolescents. *Pediatr Pulmonol,* 49**,** 118-25.
RABE, K., VERMEIRE, P., SORIANO, J. & MAIER, W. 2000. Clinical management of asthma in 1999: the asthma insights and reality in Europe (AIRE) study. *Eur Respir J,* 16**,** 802-807.
RADCLIFFE, S. 2017. Regulation 28: Report to prevent future deaths. *In:* COURT, W. C. S. (ed.). London.
RAHERISON, C., ABOUELFATH, A., LE GROS, V., TAYTARD, A. & MOLIMARD, M. 2006. Underdiagnosis of nocturnal symptoms in asthma in general practice. *J Asthma,* 43**,** 199-202.
RCP. 2014a. *National Review of Asthma Deaths* [Online]. Available: https://www.rcplondon.ac.uk/projects/national-review-asthma-deaths [Accessed].
RCP 2014b. Why Asthma Still Kills? The National Review of Asthma Deaths.
RENNARD, S. I. & FARMER, S. G. 2004. Exacerbations and progression of disease in asthma and chronic obstructive pulmonary disease. *Proc Am Thorac Soc,* 1**,** 88-92.
RICKARD, K., JAIN, N. & MACDONALD-BERKO, M. 2019a. Measurement of FeNO with a portable, electrochemical analyzer using a 6-second exhalation time in 7-10-year-old children with asthma: comparison to a 10-second exhalation. *J Asthma,* 56**,** 1282-1287.
RICKARD, K., MACDONALD-BERKO, M., ANOLIK, R., JAIN, N., LA FORCE, C. & WASSERMAN, R. L. 2019b. Measurement of exhaled nitric oxide in young children. *Ann Allergy Asthma Immunol,* 122**,** 343-345.
RIETVELD, S. & WALTER, E. 2000. Perceptions of Asthma by Adolescents at Home. *Chest,* 117**,** 434-439.
RINGSBERG, K. C., BJARNEMAN, P., LARSSON, R., WALLSTROM, E. & LOWHAGEN, O. 2014. Diagnosis of asthma in primary health care: a pilot study. *J Allergy (Cairo),* 2014**,** 898965.
ROBERTS, M. 2015. Asthma diagnosis 'may be wrong' in one million UK adults. *BBC News*.
ROBERTS, N., SMITH, S. & PARTRIDGE, M. 2011. Why is spirometry underused in the diagnosis of the breathless patient: a qualitative study. *BMC Pulm Med,* 11**,** 1-6.
ROBINSON, F. 2015. Fractional Exhaled Nitric Oxide testing. *In:* UPDATE, P. C. R. (ed.).

ROBROEKS, C. M., VAN BERKEL, J. J., JOBSIS, Q., VAN SCHOOTEN, F. J., DALLINGA, J. W., WOUTERS, E. F. & DOMPELING, E. 2013. Exhaled volatile organic compounds predict exacerbations of childhood asthma in a 1-year prospective study. *European Respiratory Journal,* 42**,** 98-106.

ROORDA, R., GERRITSEN, J., VAN AALDEREN, W., SCHOUTEN, J., VELTMAN, J., WEISS, S. & KNOL, K. 1994. Follow-up of asthma from childhood to adulthood: influence of potential childhood risk factors on the outcome of pulmonary function and bronchial responsiveness in adulthood. *J Allergy Clin Immunol,* 93**,** 575-584.

ROWLEY, E. 2014. NIHR CLAHRC EM Implementation and Knowledge Translation documentation. *In:* RESEARCH, N. I. F. H. (ed.).

SACHS-OLSEN, C., LODRUP CARLSEN, K. C., MOWINCKEL, P., HALAND, G., DEVULAPALLI, C. S., MUNTHE-KAAS, M. C. & CARLSEN, K. H. 2010. Diagnostic value of exhaled nitric oxide in childhood asthma and allergy. *Pediatr Allergy Immunol,* 21**,** e213-21.

SADATSAFAVI, M., ROUSSEAU, R., CHEN, W., ZHANG, W., LYND, L. & FITZGERALD, J. M. 2014. The preventable burden of productivity loss due to suboptimal asthma control: a population-based study. *Chest,* 145**,** 787-793.

SAGLANI, S., PAYNE, D. N., ZHU, J., WANG, Z., NICHOLSON, A. G., BUSH, A. & JEFFERY, P. K. 2007. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med,* 176**,** 858-64.

SCHERMER, T., VAN WEEL, C., BARTEN, F., BUFFELS, J., CHAVANNES, N., KARDAS, P., OSTREM, A., SCHNEIDER, A. & YAMAN, H. 2008. Prevention and management of chronic obstructive pulmonary disease (COPD) in primary care: position paper of the European Forum for Primary Care. *Qual Prim Care,* 16**,** 363-77.

SCHERMER, T. R., ROBBERTS, B., CROCKETT, A. J., THOONEN, B. P., LUCAS, A., GROOTENS, J., SMEELE, I. J., THAMRIN, C. & REDDEL, H. K. 2016. Should the diagnosis of COPD be based on a single spirometry test? *NPJ Prim Care Respir Med,* 26**,** 16059.

SCHIFANO, E. D., HOLLENBACH, J. P. & CLOUTIER, M. M. 2014. Mismatch between asthma symptoms and spirometry: implications for managing asthma in children. *J Pediatr,* 165**,** 997-1002.

SCHMITZ, A. 2012. *Principles of Sociological Inquiry: Qualitative and Quantitative Methods*, Saylor Academy.

SCHNEIDER, A., GINDNER, L., TILEMANN, L., SCHERMER, T., DINANT, G.-J., MEYER, F. & SZECSENYI, J. 2009a. Diagnostic accuracy of spirometry in primary care. *BMC Pulmonary Medicine,* 9.

SCHNEIDER, A., TILEMANN, L., SCHERMER, T., GINDNER, L., LAUX, G., SZECSENYI, J. & MEYER, F. J. 2009b. Diagnosing asthma in general practice with portable exhaled nitric oxide measurement--results of a prospective diagnostic study: FENO < or = 16 ppb better than FENO < or =12 ppb to rule out mild and moderate to severe asthma [added]. *Respir Res,* 10**,** 15.

SCOTT, S., CURRIE, J., ALBERT, P., CALVERLEY, P. & WILDING, J. P. H. 2012. Risk of misdiagnosis, health-related quality of life, and BMI in patients who are overweight with doctor-diagnosed asthma. *Chest,* 141**,** 616-624.

SEARS, M., GREENE, J., WILLAN, A., WIECEK, E., TAYLOR, D., FLANNERY, E., COWAN, J., HERBISON, G., SILVA, P. & POULTON, R. 2003a. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med,* 349**,** 1414-1422.

SEARS, M. R., GREENE, J. M., WILLAN, A. R., WIECEK, E. M., TAYLOR, D. R., FLANNERY, E. M., COWAN, J. O., HERBISON, G. P., SILVA, P. A. & POULTON, R. 2003b. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med,* 349**,** 1414-22.

SHAW, D. E., BERRY, M. A., THOMAS, M., GREEN, R. H., BRIGHTLING, C. E., WARDLAW, A. J. & PAVORD, I. D. 2007. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. *Am J Respir Crit Care Med,* 176**,** 231-7.

SIERSTED, H., BOLDSEN, J., HANSEN, H., MOSTGAARD, G. & HYLDEBRANDT, N. 1998. Population based study of risk factors for underdiagnosis of asthma in adolescence: Odense schoolchild study. *BMJ,* 316**,** 651-657.

SIVAN, Y., GADISH, T., FIREMAN, E. & SOFERMAN, R. 2009. The use of exhaled nitric oxide in the diagnosis of asthma in school children. *J Pediatr,* 155**,** 211-216.

SMITH, A., COWAN, J., BRASSETT, K., HERBISON, G. & TAYLOR, D. 2005a. Use of Exhaled Nitric Oxide Measurements to Guide Treatment in Chronic Asthma. *N Engl J Med,* 352**,** 2163-2173.

SMITH, A. D., COWAN, J. O., BRASSETT, K. P., FILSELL, S., MCLACHLAN, C., MONTI-SHEEHAN, G., PETER HERBISON, G. & ROBIN TAYLOR, D. 2005b. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med,* 172**,** 453-9.

SMITH, A. D., COWAN, J. O., BRASSETT, K. P., HERBISON, G. P. & TAYLOR, D. R. 2005c. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med,* 352**,** 2163-73.

SONT, J., WILLEMS, L., BEL, E., VAN KRIEKEN, J., VANDENBROUCKE, J. & STERK, P. 1999. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med,* 159**,** 1043-1051.

SOTO-RAMOS, M., CASTRO-RODRIGUEZ, J. A., HINOJOS-GALLARDO, L. C., HERNANDEZ-SALDANA, R., CISNEROS-CASTOLO, M. & CARRILLO-RODRIGUEZ, V. 2013. Fractional exhaled nitric oxide has a good correlation with asthma control and lung function in latino children with asthma. *J Asthma,* 50**,** 590-4.

SPEIGHT ANP, L. D., HEY EN 1983. Underdiagnosis and undertreatment of asthma in childhood. *British Medical Journal,* 286**,** 1253-1256.

SPOSATO, B. 2016. Predicted Values for Spirometry may Underestimate Long-Standing Asthma Severity. *Open Respir Med J,* 10**,** 70-78.

SULLIVAN, P. W., GHUSHCHYAN, V. H., CAMPBELL, J. D., GLOBE, G., BENDER, B. & MAGID, D. J. 2017. Measuring the cost of poor asthma control and exacerbations. *J Asthma,* 54**,** 24-31.

SURUKI, R. Y., DAUGHERTY, J. B., BOUDIAF, N. & ALBERS, F. C. 2017. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulm Med,* 17**,** 74.

SZEFLER, S. J., MITCHELL, H., SORKNESS, C. A., GERGEN, P. J., O'CONNOR, G. T., MORGAN, W. J., KATTAN, M., PONGRACIC, J. A., TEACH, S. J., BLOOMBERG, G. R., EGGLESTON, P. A., GRUCHALLA, R. S., KERCSMAR, C. M., LIU, A. H., WILDFIRE, J. J., CURRY, M. D. & BUSSE, W. W. 2008. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *The Lancet,* 372**,** 1065-1072.

TAI, A., TRAN, H., ROBERTS, M., CLARKE, N., GIBSON, A. M., VIDMAR, S., WILSON, J. & ROBERTSON, C. F. 2014a. Outcomes of childhood asthma to the age of 50 years. *J Allergy Clin Immunol,* 133**,** 1572-8.e3.

TAI, A., TRAN, H., ROBERTS, M., CLARKE, N., WILSON, J. & ROBERTSON, C. F. 2014b. The association between childhood asthma and adult chronic obstructive pulmonary disease. *Thorax,* 69**,** 805-10.

TAN, W. C., VOLLMER, W. M., LAMPRECHT, B., MANNINO, D. M., JITHOO, A., NIZANKOWSKA-MOGILNICKA, E., MEJZA, F., GISLASON, T., BURNEY, P. G., BUIST, A. S. & GROUP, B. C. R. 2012. Worldwide patterns of bronchodilator responsiveness: results from the Burden of Obstructive Lung Disease study. *Thorax,* 67**,** 718-26.

TANG, S., XIE, Y., YUAN, C., SUN, X. & CUI, Y. 2016. Fractional Exhaled Nitric Oxide for the Diagnosis of Childhood Asthma: a Systematic Review and Meta-analysis. *Clin Rev Allergy Immunol*.

TANTISIRA, K. G., FUHLBRIGGE, A. L., TONASCIA, J., VAN NATTA, M., ZEIGER, R. S., STRUNK, R. C., SZEFLER, S. J., WEISS, S. T. & CHILDHOOD ASTHMA MANAGEMENT PROGRAM RESEARCH, G. 2006. Bronchodilation and bronchoconstriction: predictors of future lung function in childhood asthma. *J Allergy Clin Immunol,* 117**,** 1264-71.

TAYLOR, D., COWAN, J., GREENE, J., WILLAN, A. & SEARS, M. 2005. Asthma in remission: can relapse in early adulthood be predicted at 18 years of age? *Chest,* 127**,** 845-850.

THOMAS, B., RUTMAN, A., HIRST, R. A., HALDAR, P., WARDLAW, A. J., BANKART, J., BRIGHTLING, C. E. & O'CALLAGHAN, C. 2010. Ciliary dysfunction and ultrastructural abnormalities are features of severe asthma. *J Allergy Clin Immunol,* 126**,** 722-729 e2.

THOMAS, D. R. 2016. A General Inductive Approach for Analyzing Qualitative Evaluation Data. *American Journal of Evaluation,* 27**,** 237-246.

TILLIE-LEBLOND, I., MONTANI, D., CRESTANI, B., DE BLIC, J., HUMBERT, M., TUNON-DE-LARA, M., MAGNAN, A., ROCHE, N., OSTINELLI, J. & CHANEZ, P. 2009. Relation between inflammation and symptoms in asthma. *Allergy,* 64**,** 354-67.

TOMITA, K., HANAKI, K., HASEGAWA, Y., WATANABE, M., SANO, H., IGISHI, T., BURIOKA, N., HITSUDA, Y., HORIMUKAI, K., FUKUTANI, K., SUGIMOTO, Y., YAMAMOTO, M., KATO, K., IKEDA, T., KONISHI, T., TOKUYASU, H., KAWASAKI, Y., YAJIMA, H., SEJIMA, H., ISOBE, T., TAKABATAKE, T., SHIMIZU, E. & THE SAN-IN ASTHMA RESEARCH, G. 2009. Underrecognition of the Severity of Asthma and Undertreatment of Asthma in a Rural Area of Japan. *Journal of Asthma,* 42**,** 689-696.

TSANG, S., ROYSE, C. F. & TERKAWI, A. S. 2017. Guidelines for developing, translating, and validating a questionnaire in perioperative and pain medicine. *Saudi journal of anaesthesia,* 11**,** S80-S89.

TSE, S. M., GOLD, D. R., SORDILLO, J. E., HOFFMAN, E. B., GILLMAN, M. W., RIFAS-SHIMAN, S. L., FUHLBRIGGE, A. L., TANTISIRA, K. G., WEISS, S. T. & LITONJUA, A. A. 2013. Diagnostic accuracy of the bronchodilator response in children. *J Allergy Clin Immunol,* 132**,** 554-559 e5.

TURKTAS, H. B., S; MALHAN, S 2014. The Direct Cost of Asthma in Turkey. *Value Health,* 17**,** A593.

TURNER, S. 2015. Exhaled nitric oxide and the management of childhood asthma--yet another promising biomarker "has been" or a misunderstood gem. *Paediatr Respir Rev,* 16**,** 88-96.

VAN GENT, R., VAN ESSEN-ZANDVLIET, L. E., ROVERS, M. M., KIMPEN, J. L., DE MEER, G. & VAN DER ENT, C. K. 2007. Poor perception of dyspnoea in children with undiagnosed asthma. *Eur Respir J,* 30**,** 887-91.

VAN HUISSTEDE, A., CASTRO CABEZAS, M., VAN DE GEIJN, G. J., MANNAERTS, G. H., NJO, T. L., TAUBE, C., HIEMSTRA, P. S. & BRAUNSTAHL, G. J. 2013. Underdiagnosis and overdiagnosis of asthma in the morbidly obese. *Respir Med,* 107**,** 1356-64.

VAN SCHAYCK, C., VAN DER HEIJDEN, F., VAN DEN BOOM, G., TIRIMANNA, P. & VAN HERWAARDEN, C. 2000. Underdiagnosis of asthma: is the doctor or the patient to blame? The DIMCA project. *Thorax,* 55**,** 562-565.

VANKER, A., GIE, R. P. & ZAR, H. J. 2017. The association between environmental tobacco smoke exposure and childhood respiratory disease: a review. *Expert Rev Respir Med,* 11**,** 661-673.

VASQUEZ, M. M., ZHOU, M., HU, C., MARTINEZ, F. D. & GUERRA, S. 2017. Low Lung Function in Young Adult Life Is Associated with Early Mortality. *Am J Respir Crit Care Med,* 195**,** 1399-1401.

VENNERS, S. A., WANG, X., CHEN, C., WANG, B., NI, J., JIN, Y., YANG, J., FANG, Z., WEISS, S. T. & XU, X. 2001. Exposure-response relationship between paternal smoking and children's pulmonary function. *Am J Respir Crit Care Med,* 164**,** 973-6.

VERINI, M., CONSILVIO, N. P., DI PILLO, S., CINGOLANI, A., SPAGNUOLO, C., RAPINO, D., SCAPARROTTA, A. & CHIARELLI, F. 2010. FeNO as a Marker of Airways Inflammation: The Possible Implications in Childhood Asthma Management. *J Allergy (Cairo),* 2010.

VILOZNI, D., HAKIM, F., LIVNAT, G., OFEK, M., BAR-YOSEPH, R. & BENTUR, L. 2016. Assessment of Airway Bronchodilation by Spirometry Compared to Airway Obstruction in Young Children with Asthma. *Can Respir J,* 2016**,** 5394876.

VONK, J. M., POSTMA, D. S., BOEZEN, H. M., GROL, M. H., SCHOUTEN, J. P., KOETER, G. H. & GERRITSEN, J. 2004. Childhood factors associated with asthma remission after 30 year follow up. *Thorax,* 59**,** 925-9.

VOOREND-VAN BERGEN, S., BRACKEL, H., CAUDRI, D., DE JONGSTE, J. & PIJNENBURG, M. 2013. Assessment of asthma control by children and parents. *Eur Respir J,* 41**,** 233-4.

VOOREND-VAN BERGEN, S., VAESSEN-VERBERNE, A., LANDSTRA, A., BRACKEL, H., VAN DEN BERG, N., MERKUS, P., DE JONGSTE, J. & PIJNENBURG, M. 2015a. Fractional Exhaled Nitric Oxide Monitoring Does Not Improve Asthma Management in Children with Concordant and Discordant Asthma Phenotypes. *Am J Respir Crit Care Med,* 192**,** 1016-1018.

VOOREND-VAN BERGEN, S., VAESSEN-VERBERNE, A. A., BRACKEL, H. J., LANDSTRA, A. M., VAN DEN BERG, N. J., HOP, W. C., DE JONGSTE, J. C., MERKUS, P. J. & PIJNENBURG, M. W. 2015b. Monitoring strategies in children with asthma: a randomised controlled trial. *Thorax,* 70**,** 543-50.

WAIBEL, V., ULMER, H. & HORAK, E. 2012. Assessing asthma control: symptom scores, GINA levels of asthma control, lung function, and exhaled nitric oxide. *Pediatr Pulmonol,* 47**,** 113-8.

WALFORD, H. H. & DOHERTY, T. A. 2013. STAT6 and lung inflammation. *JAKSTAT,* 2**,** e25301.

WALLIN, L. 2009. Knowledge translation and implementation research in nursing. *Int J Nurs Stud,* 46**,** 576-87.

WALTERS, J., HANSEN, E., MUDGE, P., JOHNS, D., WALTERS, E. & WOOD-BAKER, R. 2005. Barriers to the use of spirometry in general practice. *Aust Fam Physician,* 34**,** 201-203.

WARKE, T., FITCH, P., BROWN, V., TAYLOR, R., LYONS, J., ENNIS, M. & SHIELDS, M. 2002. Exhaled nitric oxide correlates with airway eosinophils in childhood asthma. *Thorax,* 57**,** 383-387.

WEIDINGER, P., NILSSON, J. & LINDBLAD, U. 2009. Adherence to diagnostic guidelines and quality indicators in asthma and COPD in Swedish primary care. *Pharmacoepidemiology and drug safety,* 18**,** 393-400.

WEINER, B. J. 2009. A theory of organizational readiness for change. *Implement Sci,* 4**,** 67.

WENZEL, S., FORD, L., PEARLMAN, D., SPECTOR, S., SHER, L., SKOBIERANDA, F., WANG, L., KIRKESSELI, S., ROCKLIN, R., BOCK, B., HAMILTON, J., MING, J. E., RADIN, A., STAHL, N., YANCOPOULOS, G. D., GRAHAM, N. & PIROZZI, G. 2013. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med,* 368**,** 2455-66.

WENZEL, S. E. 2006. Asthma: defining of the persistent adult phenotypes. *The Lancet,* 368**,** 804-813.

WHITE, J., PATON, J. Y., NIVEN, R. & PINNOCK, H. 2018. Guidelines for the diagnosis and management of asthma: A look at the key differences between BTS/SIGN and NICE. *Thorax,* 73**,** 293-297.

WHO 2017. World Health Organisation. Asthma: Definition.

WOLFENDEN, L., DIETTE, G., KRISHNAN, J., SKINNER, E., STEINWACHS, D. & WU, A. 2003. Lower physician estimate of underlying asthma severity leads to undertreatment. *Arch Intern Med,* 163**,** 231-236.

WOO, S. I., LEE, J. H., KIM, H., KANG, J. W., SUN, Y. H. & HAHN, Y. S. 2012. Utility of fractional exhaled nitric oxide (F(E)NO) measurements in diagnosing asthma. *Respir Med,* 106**,** 1103-9.

WOODRUFF, P. G., MODREK, B., CHOY, D. F., JIA, G., ABBAS, A. R., ELLWANGER, A., KOTH, L. L., ARRON, J. R. & FAHY, J. V. 2009. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med,* 180**,** 388-95.

WWW.ASTHMA.ORG.UK. 2017. *Asthma UK. Asthma Facts and Statistics* [Online]. Available: https://www.asthma.org.uk/about/media/facts-and-statistics/ [Accessed 11/07/2017].

YANG, C. L., SIMONS, E., FOTY, R. G., SUBBARAO, P., TO, T. & DELL, S. D. 2017. Misdiagnosis of asthma in schoolchildren. *Pediatr Pulmonol,* 52**,** 293-302.

YANG, S., PARK, J., LEE, Y. K., KIM, H. & HAHN, Y.-S. 2015a. Association of longitudinal fractional exhaled nitric oxide measurements with asthma control in atopic children. *Respiratory medicine,* 109**,** 572-9.

YANG, S., PARK, J., LEE, Y. K., KIM, H. & HAHN, Y. S. 2015b. Association of longitudinal fractional exhaled nitric oxide measurements with asthma control in atopic children. *Respir Med,* 109**,** 572-9.

ZACHARASIEWICZ, A., WILSON, N., LEX, C., ERIN, E. M., LI, A. M., HANSEL, T., KHAN, M. & BUSH, A. 2005. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med,* 171**,** 1077-82.

ZANNETOS, S., ZACHARIADOU, T., ZACHARIADES, A., GEORGIOU, A. & TALIAS, M. A. 2017. The economic burden of adult asthma in Cyprus; a prevalence-based cost of illness study. *BMC Public Health,* 17**,** 262.