STUDY PROTOCOL

Full Study Title: Childhood Asthma Management in Primary Care: Implementation Of Exhaled Nitric Oxide and Spirometry Testing (CHAMPIONS study)

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Chief Investigator:	Dr. Erol Gaillard
Investigators:	Prof. Andrew Wilson Dr. David Lo
Sponsor:	University of Leicester
Funders:	1. Midlands Asthma and Allergy Association 2. Aerocrine 3. Health Care East Midlands
Signatures:	

Confidentiality Statement

Authors

List here all authors / collaborators that have assisted with the writing of the protocol

Dr. Erol Gaillard

Professor Andrew Wilson

Dr. David Lo

Dr. Caroline Beardsmore

Dr. Damian Roland

Dr. Yaling Yang

Dr. Matthew Richardson

Ms Karen Moore

Mr. Robert Kirk

Dr. Brigitte Gaillard

Signature Page

Chief Investigator Name: Dr. Erol Gaillard _____

Chief Investigator signature: _____

Date: _____

Sponsor Representative Name: __Wendy Gamble_____

Sponsor Representative signature: _____

Date: _____

(In cases of Multi-centre studies, this must be replicated for each site)

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	3.0	25/5/2016	David Lo	

2. SYNOPSIS

Study Title	**Ch**ildhood **A**sthma **M**anagement in **P**rimary Care: **I**mplementation **O**f Exhaled **N**itric Oxide and **S**pirometry Testing (CHAMPIONS study)
Trial Design	Implementation study
Trial Participants	Children aged 5-16 years
Planned Sample Size	1000
Follow-up duration	Postal questionnaire at 3-6 months
Planned Trial Period	2 years
Primary Objective	The main objective for this study will be to evaluate the training and capacity requirements of primary care sites in order for them to be able to deliver routine spirometry and FeNO testing for children aged 5-16 years as recommended by draft NICE guidelines.
Secondary Objectives	The secondary outcomes measured relate to the impact of implementing the new NICE guidelines on the processes and outcomes of childhood asthma care and will include: 1.The number of children in which a diagnosis of asthma can be confirmed using spirometry and FeNO testing 2.The number of misdiagnoses identified using lung function tests 3.The impact of implementation to health economics

3. ABBREVIATIONS

ACT	Asthma Control Test
AE	Adverse event
AR	Adverse reaction
CCG	Clinical Commissioning Group
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRN	Clinical Research Network
CRO	Contract Research Organisation
CT	Clinical Trials
EC	Ethics Committee (see REC)
FeNO	Fractional Exhaled Nitric Oxide
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
HCA	Health Care Assistant
ICF	Informed Consent Form
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NRES	National Research Ethics Service
PI	Principal Investigator
PIL/S	Participant/ Patient Information Leaflet/Sheet
PN	Practice Nurse
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

4. BACKGROUND AND RATIONALE

In the UK the latest figures indicate that a total of 4.1 million people receive treatment for asthma (1). Of these approximately 1.1 million are children over the age of 5 years, which is the equivalent of one in ten children in the UK (2).

Despite the common nature of asthma there is no gold standard test available to diagnose the condition. The diagnosis is generally based on a thorough clinical history taken by an experienced clinician. Studies in adult populations however suggest that many are misdiagnosed including over and under-diagnosis of asthma (3-6). Over-diagnosis may affect up to 30% of adults diagnosed with asthma (3) and can result in inappropriate and unnecessary use of asthma medications and increased healthcare costs. Under-diagnosis often results in poor control and reduced quality of life.

Under-diagnosis and under-treatment of childhood asthma in primary care have been reported from several European countries (7-8) including the UK (9). The International Study of Asthma and Allergies in Childhood (ISAAC) for example reported that one-third of children aged 12 to 14 years in Great Britain with frequent night time wheezing had no diagnosis of asthma (9). Getting the diagnosis right in children is important because children have the highest asthma hospital admission rates for any age-group with asthma and under-diagnosis is associated with poor asthma control. Moreover, inappropriate treatment of children who do not have asthma with asthma medications can lead to unnecessary side-effects including a decreased growth velocity resulting from long-term inhaled corticosteroid use.

A recent draft NICE guideline (10) for asthma diagnosis and monitoring, originally due for publication in July 2015, recommends the use of objective tests including spirometry and FeNO testing to diagnose asthma in all patients 5 years and older under investigation for asthma. Recent BTS/SIGN asthma guidelines published in October 2014 also state that spirometry is superior to peak flow measurements, currently the most widely used lung function test in primary care in the management of asthma (11).

Proposed NICE asthma diagnostic algorithm: For children aged 5 to 16 years and adults with symptoms of asthma the draft guideline recommends spirometry testing for diagnosis and where obstructive spirometry is present bronchodilator reversibility should be considered. FeNO, an inflammatory marker in exhaled breath linked with asthma, should be considered where spirometry is normal and where obstructive spirometry does not reverse with bronchodilators. The proposed NICE guidance for diagnosis of asthma is summarised below.

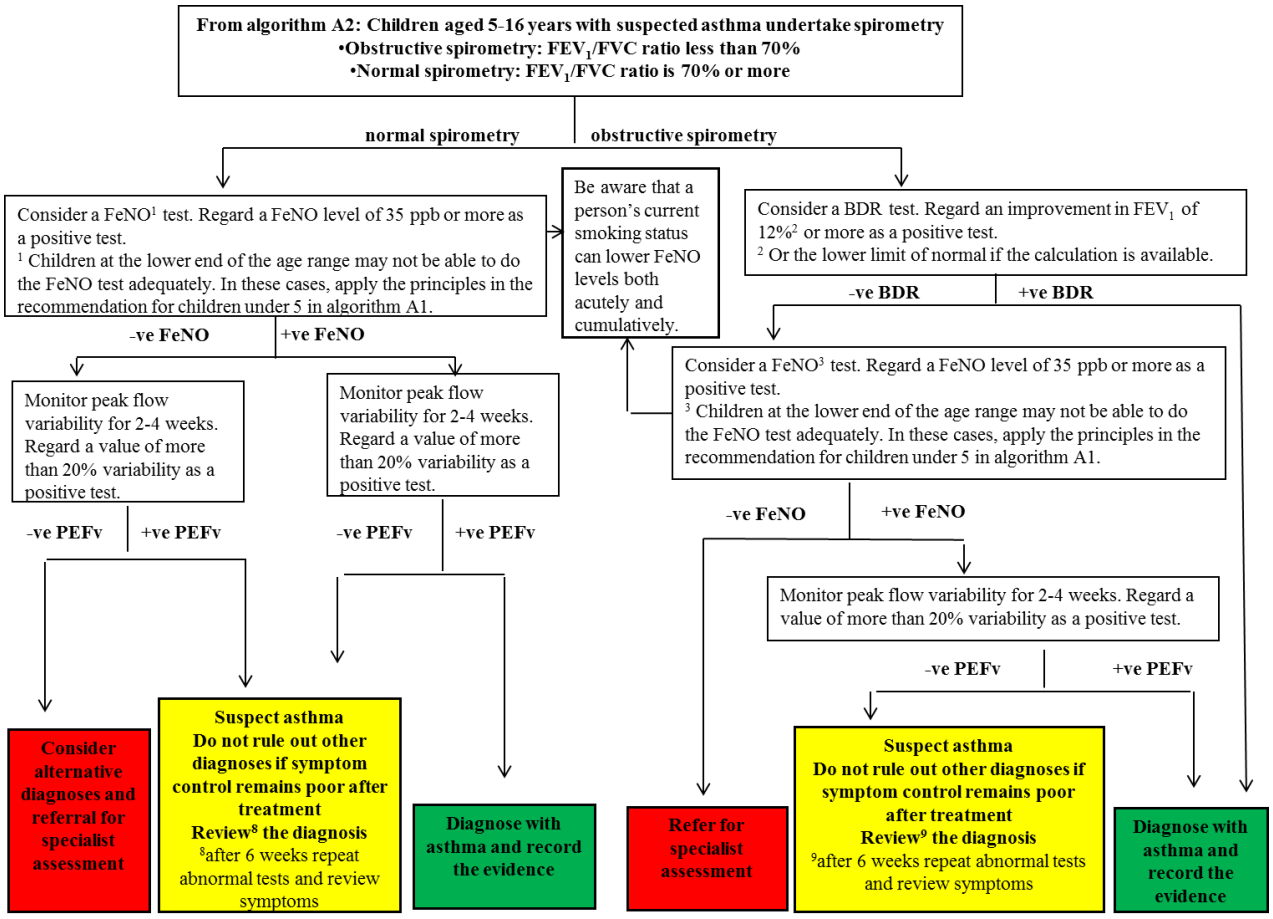
Diagnostic criteria for asthma in children aged 5-16 years:

- Clinical symptoms compatible with the diagnosis

- Objective tests including
  - Obstructive spirometry
  - Reversibility following short acting beta-2-agonists (≥12% increase in FEV_1)
  - Raised FeNO (≥35ppb)
  - Peak flow variability (>20%)

No single positive test is diagnostic for asthma

Draft NICE diagnostic algorithm for children aged 5-16 years with suspected asthma



Asthma monitoring: Spirometry should be done in adults with asthma and considered in children at every asthma review.

Spirometry: Spirometry is available in primary care and performed in adults with COPD where it is already part of the Quality Outcome Framework (QOF). NICE and BTS/SIGN state that spirometry is preferable to measurement of peak expiratory flow because it allows clearer identification of airflow obstruction, and the results are less dependent on effort.

Spirometry is however only rarely performed in children in primary care. Children benefit from visual incentive spirometry which requires a special spirometer usually not available in GP

practices. Interpretation of spirometry in children also requires a slightly different approach. Consequently, practice nurses/health care assistants (PN/HCA) usually have no experience in performing and interpreting spirometry in children, but could be trained to do so. The amount of training required and how best to deliver it are currently not known and addressing these knowledge gaps is one of the main implementation research questions.

FeNO testing: The draft NICE asthma guideline recommends that FeNO testing should be considered in children with symptoms and under investigation for asthma who have normal spirometry and those with obstructive spirometry but no bronchodilator reversibility. FeNO testing in the diagnosis of asthma has been the topic of a separate NICE review published in April 2014, recommending FeNO testing as an option to diagnose asthma in children and adults with an intermediate probability of asthma in combination with other diagnostic options (12) There will be limited training requirements to perform the test and NICE have provided clear-cut guidelines for interpretation of the results.

Preliminary data/focus group meeting results:

Primary care practice focus group meeting: In preliminary work leading up to this protocol we conducted a focus group meeting with GPs, PN/HCAs and managers to explore attitudes, feasibility and potential barriers to implementation which have informed our implementation study proposal. Generally practice health care workers attitude towards spirometry and FeNO testing was favourable but training and capacity issues were raised as a major barrier to implementation.

One major finding from the focus group meetings was that the number of children aged 5-16 years on the asthma register appeared to be much lower than what would be predicted from epidemiological data. This data was gathered to understand how many children would need spirometry as part of their asthma review. Further inquiry of the practice database revealed that the number of children prescribed regular inhaled corticosteroids was more than double the number on the practice asthma register and when children were added who had been prescribed at least two short acting beta-2 agonist inhalers in the previous 12 months the total number of children rose to approximately 4-times the number on the asthma register and very close to the 10% of children predicted by epidemiological data.

These findings resulted from a small sample of children and may not be generalizable. Nonetheless, practice GPs felt that the ‘cleaning up’ of the asthma register by establishing the diagnosis or misdiagnosis of asthma would be a positive effect resulting from the objective tests recommended by NICE.

CCGs and commissioning: In two meetings with Samantha Little, the principal commissioner of children’s services and CCG GP leads there was clear support for the proposed study to inform implementation of the NICE guideline into Leicestershire GP practices. This was identified as a priority funding area for discussion in the next financial year.

Leicestershire Partnership Trust Respiratory Specialist Nurse Lead: The implementation study was discussed with Ms Karen Moore, lead respiratory nurse in the Leicestershire Partnership Trust (LPT). The LPT respiratory nurse team helped implement and continues to support the implementation of spirometry testing for patients with COPD in Leicestershire primary care practices. Ms Moore's experience with implementation informed the study protocol and advised on how best to start addressing the training needs and barriers to implementation and joined the study team.

The current training package is usually delivered to individual PN/HCAs during a 2-hour training session preceding a joint COPD clinic and consists of a PowerPoint presentation on performance and interpretation of spirometry followed by hands on training. Depending on the level of experience of the PN/HCA the spirometry testing of patients in the clinic will be either supervised or supported where necessary or, where the PN/HCA is naïve to spirometry, she/he will observe at least 10 patients before performing supervised spirometry. Nurses are referred to 'A Guide to Performing Quality Assured Diagnostic Spirometry' (13) for further information on spirometry testing. The guide is supported by the NHS, Asthma UK, Primary Care Respiratory Society UK, BTS, the Association for Respiratory Technology & Physiology and others but its emphasis is on the testing in adults with COPD. Additionally, in order to obtain LPT accreditation the PN/HCA has to send in 10 spirometry tracings of which 8 have to comply with Association for Respiratory Technology & Physiology standards and be correctly interpreted. Group sessions for several practices located in close proximity are offered up to four times per year and one to one sessions are offered as appropriate with GPs who interpret the spirometry.

Rationale

The use of the lung function tests in children is already routinely done in hospitals, has been shown to be safe in children and is now being recommended (at least in draft guidance) by NICE. As such, our research question is not whether we should use spirometry and FeNO testing in primary care, indeed they are not viewed as research interventions in this study; the question is – how can this be achieved?

Therefore the primary rationale for this study is to identify the training needs and capacity requirements of primary care practices in order for objective lung function testing to be made available for all children with suspected or confirmed asthma cared for in the non-hospital setting.

5. OBJECTIVES

5.1 Primary Objectives

The main objective for this study will be to evaluate the training and capacity requirements of primary care sites in order for them to be able to deliver routine spirometry and FeNO testing for children with suspected or presumed asthma.

5.2 Secondary Objectives

The secondary objectives relate to investigating the impact of implementing the new NICE guidelines on the processes and outcomes of childhood asthma care and will include:

1. The number of children in which a diagnosis of asthma can be confirmed using spirometry and FeNO testing
2. The number of misdiagnoses identified using lung function tests
3. The impact of implementation to health economics

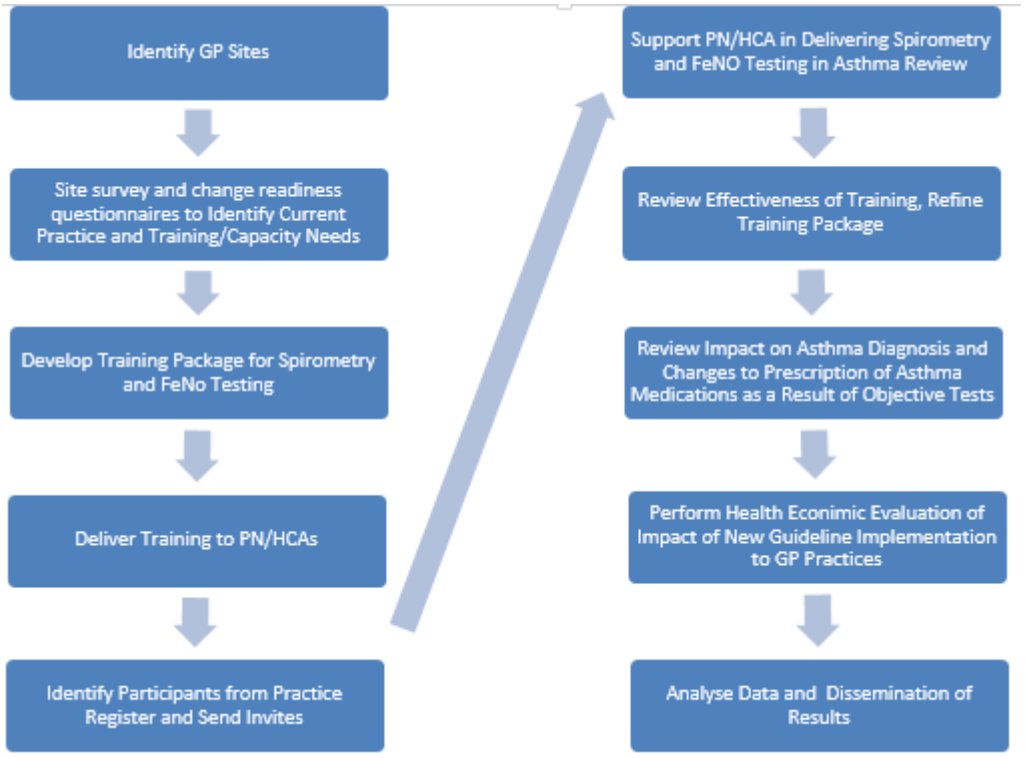
6. STUDY DESIGN SUMMARY

6.1 Summary of Trial Design

This study will employ both qualitative and quantitative measures in order to evaluate the resources required to implement routine lung function testing for children in primary care; and to investigate the impact this would have on diagnosis in children with suspected or presumed asthma. In total we hope to recruit between 3-6 GP sites across Leicestershire and Northamptonshire for the study, which would represent a patient population of ~120,000-150,000 people, representing 1500-2000 children potentially eligible to take part in the study based on our preliminary data. Primary care sites will be approached by the study team with assistance from the CCG R+D manager for Leicester (Debbie Wall) and the CRN locality manager for East Midlands (Debbie Jeffrey). We aim to recruit sites of differing sizes and with different patient demographics.

Site survey questionnaires will be completed for each site by the study team to gather information about the individual practice's patient population and current asthma review set up. Readiness for change questionnaires will be used to investigate staff opinions, concerns and perceived barriers to implementation. These will be sent out to GPs, practice nurses, HCAs and practice managers at each participating site. The study team will develop and refine a package of training and support which will be based on an existing training programme for primary care practitioners to perform spirometry on adult patients with COPD in Leicestershire primary care practices. We will evaluate the success of the training by supporting and monitoring the primary care practitioners utilising these tests in primary care asthma review clinics. The length of training required in order for different staff groups to be able to perform spirometry and FeNO testing independently will be documented.

To investigate the impact of implementing lung function testing for children into primary care, we will consent children onto the study for the purposes of accessing their electronic records (see below for details) and a follow up postal questionnaire only. All children between the ages of 5-16 years inclusive who meet the inclusion criteria (see below) and who are registered patients at the study sites are eligible for recruitment onto the study; we aim to recruit 1000 children based on a 50-70% response rate. We anticipate that the study will last 2 years from beginning to end, which will include time for data analysis and publication of results. This is an outline of the proposed study plan -



Please see Appendix for Gantt chart detailing anticipated duration of study periods.

The study interventions are described in detail below:

Firstly, the study team will meet with interested GP practices to present an overview of the study. The participating practice teams are then expected to complete readiness for change questionnaires and assist the study team in completing the site survey questionnaires in order for the study team to identify training and capacity needs and potential barriers to implementation. Secondly, designated staff (PNs/HCAs) at each practice are expected to complete a package of training aimed at helping them achieve competencies to be able to deliver lung function testing to children independently.

The GPs will then be asked to perform searches of their electronic records to identify children who require or who would benefit from an asthma review based on the inclusion criteria detailed below. The GP practices will then send out clinic appointment letters to these children inviting them to book into an asthma review clinic. The letters from the GPs will make the families aware that they will also be invited to take part in the CHAMPIONS study in addition to their routine review and lung function tests. A patient information sheet will be included with the letters which the GPs send out.

On the day of the clinic, a member of the study team will introduce themselves to the parent and child prior to the appointment in order to give further information about the study, answer questions and to take written consent from those families who wish to participate. It will be made clear that they are welcome to the asthma review and lung function tests whether they choose to consent to the study or not.

For consented patients, the onlyadditional study interventions are 1) the initial health economics questionnaires (CHU9D and PAQLQ), 2) the follow up postal health economics and asthma quality control questionnaires, and 3) allowing us access to their medical records to collect data as detailed below.

Data analysis will be performed using statistical methods described below.

We intend for the results derived from this study to be presented 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. No identifiable data of any child will be included in any report or publication.

6.2 Primary and Secondary Endpoints

The primary end point to this study will be when designated healthcare staff at each participating GP practice are able to independently and competently perform and interpret objective lung function tests; and have done so on all the children with suspected/presumed asthma on their patient register who have agreed to attend an asthma review clinic.

The secondary endpoint is when we have developed and refined a training and support package for primary care staff in the use of spirometry and FeNO testing in children; that is both acceptable to end-users and sustainable by the team delivering the training.

7. STUDY PARTICIPANTS

7.1 Overall Description of Study Participants

Children with asthma or who have suspected asthma managed in primary care.

7.2 Inclusion Criteria

Male or Female, aged 5-16 years who are:

1. On the practice asthma register or
2. Are prescribed regular (on repeat prescription) inhaled corticosteroids including beclometasone, fluticasone and budesonide and also search specifically for 'brands' that are commonly prescribed to include 'clenil', 'seretide', 'symbicort', and 'qvar' or
3. Have been prescribed ≥ 2 Salbutamol MDI's in the last 12 months or
4. Had a documented exacerbation of asthma in the last 12 months
5. Able and willing, in the opinion of the Investigator, to give informed consent

7.3 Exclusion Criteria

1. Children who are unable to perform lung function tests for any reason
2. Children and young people <5 years and >16 years
3. Unable or unwilling, in the opinion of the Investigator, to give informed consent

8. STUDY PROCEDURES

8.1 Informed Consent

Children aged 5 to 16 years who fulfil the inclusion criteria will be identified from electronic searches performed by the practice staff for the purposes of inviting them for an asthma review. We will provide the practices with patient information sheets (PIS) to post out with the invitation letters sent out by the GPs themselves. The PIS will detail no less than: the exact nature of the study and that the parent is free to withdraw the participant from the study at any time for any reason without prejudice to future care, and that there is no obligation to give consent for access to their child's records in the first place. Even if the parent does not consent to the study, their child is still welcome to the full asthma review including lung function tests as these are part of recommended standard care.

On the day of the clinic, a member of the research team will talk to the family prior to their appointment and explain the study and to answer any questions. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the study team to decide whether they will participate in the study.

It will be made clear that none of the tests performed in the asthma clinic, except the short health economic questionnaires, are part of the research and should be viewed as best practice. We are only seeking consent to: 1) access their child's electronic records in order to obtain information including recent exacerbations and medications prescribed, 2) record answers to a health economic questionnaires onto the CRF, 3) time how long it takes to perform each lung function test and 4) ask their GPs to contact them in 3-6 months' time by post to complete a follow up health economic questionnaire and ACT. Written consent will then be taken from the parents should they agree to participate.

The person who obtains the consent will be suitably qualified and experienced, and have been authorised to do so by the Chief Investigator as detailed on the Delegation of Authority and Signature log for the study. The original signed form will be retained at the study site within Investigator Site File (ISF). A copy of the signed Informed Consent will be given to participants and a copy retained in the participant medical notes. Anyone not medically qualified will undergo UHL consent training.

8.2 Screening and Eligibility Assessment

Children who clinically warrant an asthma review, which are also our potential participants, will be identified by the direct care team from participating GP sites. The direct care team will search their practice electronic database for children who meet the inclusion criteria using age limits "5 to 16 years," and to include children who are either on the asthma register or based on asthma medications prescribed as detailed in the inclusion criteria above.

Once identified, the direct care team will send by post the standardised PIS along with the asthma review invitation letters to families. The invitation letter will invite families to phone the GP practice to book onto an asthma review clinic. We anticipate that there will be a minimum of 1 week between the time families receive PIS and the next available asthma review clinic.

<u>Demographics</u>

The date of birth, gender, race, primary language and country of birth will be recorded by the research team in the CRF following written consent at the asthma review.

Medical History
Details of length of asthma diagnosis or duration of "asthma" symptoms will be recorded at time of asthma review by study team following written consent along with concomitant medication and any physical examination (detailed below).

Concomitant Medication
All prescription "asthma" medications (bronchodilators, inhaled steroids, leukotriene receptor antagonists etc.) will be recorded on CRFs and assigned to a corresponding asthma treatment step as detailed in BTS/SIGN asthma guidelines. We will also record number of days of oral steroids prescribed in the preceding 6 months.

Physical Examination
Height and weight of participating children will be recorded.

8.3 Baseline Assessments

Health Care Workers' Training Needs

The study team will gather information using site survey and readiness for change questionnaires at each participating practice. It is expected that practice GPs, nurses, HCAs and managers will complete these questionnaires.
The study team will seek the views particularly, but not exclusively, of the healthcare workers performing the objective tests (spirometry and FeNO) on the delivery and content of the training package and the training time available to those performing the tests.

Assessments Performed as Part of Recommended Standard Asthma Review

Asthma control test: We will use validated asthma control tests for children 4 to 11 years (7 questions) (17) and children 12 years and older (5 questions).

Check inhaler technique: Inhaler technique will be checked by the PN/HCA following training if required. An instruction sheet with written information and pictures will be given to the family.

Check prescription record: We will check and document the electronic prescribing record and dispensing record where available for asthma medication in the previous 6 months including the number of reliever and preventer inhalers. As part of the asthma review the practice PN/HCA will also check the prescription records and inform the GP if they have concerns regarding: suboptimal asthma control; where reliever and preventer medication use are unbalanced for example in cases where preventer prescribing is low and reliever prescriptions are high; and where there are concerns regarding adherence (i.e. fewer than expected number of inhalers dispensed).

Any child presenting to the review visit unwell or with poor lung function (FEV1 <75% predicted) will be referred to the practice GP for assessment.

Written personalised asthma action plan: All children will be given a written personalised asthma action plan. Where children already have an action plan this will be reviewed.

Spirometry and FeNO testing: Children will be asked to perform spirometry and a FeNO measurement where indicated.

Incentive spirometry: Forced expiratory manoeuvres will be performed according to American Thoracic Society/European Respiratory Society standards (15,16). Children will be invited to perform a forced expiratory manoeuvre at least three times with a maximum of eight attempts. Where readings are within 5% of each other the recorded value is the best of these three readings. Achieving such reproducibility can be difficult in younger children and we will then use the best effort as the recorded values. Incentive spirometry will be used in all children, whereby visual aids are provided on the spirometer screen like for example a series of candles have to be blown out encouraging the child to breathe out hard for longer. This technique is very successful, even in young children. The PN/HCA will assess the forced expiratory volume in 1 second (FEV1) and the FEV1/FVC ratio. Where the FEV1/FVC ratio is lower than the GLI threshold or where FEV1 is <80% predicted they will perform reversibility testing using Salbutamol 400 micrograms (4 puffs) given via spacer and repeat the forced expiratory manoeuvre after 15 minutes. Any change in FEV1 of ≥12% will be taken as demonstrating reversible airway narrowing and this in conjunction with the clinical history will be taken as diagnostic for the presence of asthma. The data and the lung function trace will be recorded on the practice electronic patient records and the GP informed.

FeNO measurements: Will be taken in all children five years and older using a NIOX MINO (Aerocrine, Sweden), which is a hand-held device with a mouthpiece. The result of the FeNO concentration in exhaled breath is available immediately in parts per billion (ppb) and we will use the cut-off value of 35ppb and above as diagnostic for asthma as per NICE guideline.

8.4 Randomisation and Codebreaking

There is no randomisation of participants in this study.

8.5 Subsequent Assessments

We will have only one face to face contact with each study participant throughout the study. Having taken appropriate consent, we will review each participants electronic record 3-6 months following the initial asthma review to record any changes in prescription patterns, additional primary care review for exacerbations or hospital attendances. In patients who have agreed, we will also send out a follow up postal health economic questionnaire and asthma control test 3-6 months following the review.

8.6 Definition of End of Trial

The end of trial is when the last participant has attended his/her asthma review clinic and we have reviewed his/her records 3-6 months following this date.

8.7 Discontinuation/Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time and may withdraw consent for their patient records to be accessed by informing the study team directly or via their GP.

8.8 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, GP electronic records (from which medical history and previous and concurrent medication may be summarised into the CRF) and hospital correspondence.

CRF entries will be considered source data if the CRF is the site of the original

recording (e.g., there is no other written or electronic record of data). In this study the CRF will be used as the source document for time taken to perform spirometry and FeNO and health economic questionnaire answers only.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

9. TREATMENT OF TRIAL PARTICIPANTS

9.1 Description of Study Treatment

Educational sessions for Primary Care Staff

We will provide 2 levels of education:

Level 1: This will be conducted by the implementation team as part of the initial meeting with the GPs, PN/HCAs and managers/administrators. These will be update sessions on the latest draft asthma guidelines issued by NICE and BTS/SIGN with an emphasis on proposed changes to current practice. We will discuss in more detail the diagnostic algorithm for children under investigation for asthma and the objective tests underpinning a diagnosis of asthma in children. An understanding of objective tests includes (i) an appreciation that tests need to be technically acceptable to be useful, and (ii) reference values appropriate for the individual are essential for correct interpretation. Equipment needs (incentive spirometry) and NIOX MINO or VERO for FeNO testing will be discussed, as will the training package to be offered by the implementation team.

Level 2: The implementation team will provide formal face-to-face teaching and additional online training material to practice health care workers on performing spirometry and FeNO. In order to maximise the impact of the asthma reviews the initial training intervention will need to be focused, but flexible to the differing learning requirements of the health care professionals involved.

The training session will address practical aspects and clinical interpretation of spirometry in children. We plan to work in small teaching groups (possibly as few as 1-2 people) which will itself lead to mixed teaching methods, including a short PowerPoint presentation (delivered on a laptop), videoclips, demonstrations, opportunities for practical experience with others acting as the subject, and interpretation of results from an available bank of anonymised data/traces.

The training session will cover: **a)** essential physiological principles underlying spirometry **b)** Setting up and calibrating spirometers (directed towards the type of spirometer to be used in that particular practice setting) **c)** how to encourage children of different ages to perform spirometry, including the use of incentive spirometry **d)** how to recognise when sufficient technically acceptable data have been collected for reporting (or when the child is not capable of performing spirometry)and **e)** interpretation of data.

Participants will be shown how to interpret the data first by examining the graphical recordings, ('pattern recognition'), and then by comparing measured outputs (FEV1, FVC, and FEV1/FVC) with predicted values appropriate for the sex, age and height of the child. This approach aims to identify any individual who may have a condition other than asthma (e.g. fixed obstruction), and then quantify the extent of any deficit in lung function. Where measurements are available before and after a bronchodilator the extent of any change in lung function is a measure of bronchial responsiveness.

In addition to training in spirometry, participants will be trained in the performance and interpretation of exhaled nitric oxide testing in children. While this requires careful instructions to be provided to the child so that s/he exhales steadily into the machine, there is minimal requirement for training in interpretation, since this is a straightforward single-number output.

We will also discuss asthma control tests, asthma action plans and inhaler technique but we are aware that many PN/HCAs will be familiar with asthma action plans and the checking of inhaler technique already. PN/HCAs will be able to retain copies of the teaching materials for private learning or revision, and are encouraged to contact the implementation team at any time if they have questions or want further training.

We will supervise the PN/HCAs performing at least 10 paediatric lung function tests or until they are assessed as competent by both the study team and themselves. This will be continually assessed and feed-back given to the PN/HCA. This approach has been employed successfully by the Respiratory Specialist Nurse Team for the Leicestershire Partnership NHS Trust. We will also point nurses towards accredited courses for further training.

A virtually-delivered quality improvement programme designed to improve primary care management for children with asthma has shown increased spirometry quality and improved assessment of asthma severity levels (14).

Success of the intervention will be defined as every participating surgery having a team which can regularly and competently provide objective lung function tests to children 5-16 years old.

Capacity Requirements

We will assess additional capacity needs by timing how long each lung function test takes to perform in addition to the routine asthma review at each surgery. We will also be able to evaluate the number of patients who can be reliably reviewed and tested per session, thus elucidating how many sessions a typical GP practice would have to support in order to provide regular lung function testing to children. This information would further inform the costs required to sustain new NICE recommended practice.

Health Economic Analysis

This will take the form of a questionnaire delivered to parents at the time of the asthma review and a further postal questionnaire 3-6 months following the review. Analysis of this data will be supported by a health economist.

Assessment of Impact of Implementation to Processes of Care

Following the initial review appointment, we will access the electronic records of consented participants. We will seek information on changes to prescribed asthma medications (bronchodilators, oral steroids and inhaled steroids), exacerbations since review, hospital admissions/attendances since review and whether their originally diagnoses had changed as a result of the availability of objective tests.

With parental consent, we will also send out a repeat ACT by post 3-6 months following the initial review.

9.2 Storage of Study Equipment or Related apparatus

There is no specific equipment used for this study. The spirometer and FeNO analysers are not study equipment (they are part of recommended routine care) and will be stored in locked University of Leicester or participating GP premises when not in use.

9.3 Compliance with Study Treatment

There are no compliance issues with this study plan

10. SAFETY REPORTING

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE or adverse experience is:
Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the the study, whether or not considered related to the study.

10.1.2 Adverse Reaction (AR)

All untoward and unintended responses related to the study.
All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study qualify as adverse reactions.

10.1.3 Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.1.4 Serious Adverse Event or Serious Adverse Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.1.5 Expected Serious Adverse Events/Reactions

There are no active interventions involved with this study. As such we do not expect any adverse events directly related to the study.

10.1.6 Suspected Unexpected Serious Adverse Reactions

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information.

10.2 Reporting Procedures for All Adverse Events

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study, will be recorded on the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment (see section 7.7). A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

The relationship of AEs to the study will be assessed by a medically qualified investigator.

Note: Due to the nature of the study it is not the intention to be recording or reporting AEs or SAEs

10.3 Reporting Procedures for Serious Adverse Events

All SAEs, except those expected ones defined in section 10.1.5 that do not require immediate reporting (see 10.1.5), must be reported to the Sponsor within one working day of discovery or notification of the event. The Sponsor will perform an initial check of the information and ensure that it is reviewed at the next R&D Management meeting. All SAE information must be recorded on an SAE form and sent to the Sponsor using the appropriate reporting form and the contact details on there. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form which must be sent to the Sponsor using the appropriate reporting form and the contact details on there.

The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

In addition to the expedited reporting above, the CI shall submit once a year throughout the study or on request an Annual Report to the Ethics Committee which lists all SAEs / SUSARs that have occurred during the preceeding 12 months.

Note: Due to the nature of the study it is not the intention to be recording or reporting AEs or SAEs

11. STATISTICS

11.1 Description of Statistical Methods

The qualitative data regarding opnions and barriers to implementation derived from change questionnaires conducted with the participating GP practices will be presented in report form. Appropriate non-parametric tests such as Kruskal-Wallis, Wilcoxon paired signed and Friedmans 2-Way ANOVA will be used to assess data; including the changes in number of children diagnosed with asthma, the number of misdiagnoses and alterations in prescribing (number of salbutamol inhalers/steroid courses) as a result of implementation of objective lung function tests. Paired t-tests or paired Wilcoxon signed rank tests will be used to assess the change in asthma control test scores, number of school days missed and number of carer work days missed.

A generalized linear mixed model with logit link function will also be used to compare the proportion of children with a personalised asthma plan and other secondary outcomes. The models will include important covariates such as age, gender and ethnicity, and the clustering effect of GP clinic will be accounted for. The effect of GP clinic will also be assessed by fitting a mixed effects model, GP clinic will be fitted as a random effect, covariates such as age, gender and ethnicity will be fitted as fixed effects.

All statistical analysis will be performed using R 3.2.0 (http://www.r-project.org/) and SPSS v22.

11.2 The Number of Participants

We plan to recruit 1000 children into the study. This number has been derived from the expected number of children in the participating practices who would meet the inclusion criteria based on epidemiological data and preliminary searches. It also takes into consideration the capacity of the study team, the study length and anticipated recruitment rates of 50-70%.

11.3 The Level of Statistical Significance

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

11.4 Criteria for the Termination of the Trial.

Once we have accessed the records of the final child to be recruited and they have returned the follow up questionnaire.

11.5 Procedure for Accounting for Missing, Unused, and Spurious Data.

A table listing all key variables with percentage of missing data will be reported and where possible the reason for missing data will be reported. Within the multivariate regression framework missing data will be imputed using multiple imputation. To avoid bias, where it can be reasonably established that data is not missing at random, covariates will not be imputed, a complete case analysis will be used. Outcome variables missing not at random will not be imputed, sensitivity analysis will be performed and an assessment of the models made based on the missing at random assumption. Spurious data will be reported and where possible correct values will be inserted, if it is not possible to supply correct values, value will be deleted.

11.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviations from the original statistical analysis plan will be detailed in the final report.

11.7 Inclusion in Analysis

We plan to include data from all participants in the analysis.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

13. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14. CODES OF PRACTICE AND REGULATIONS

14.1 Ethics

Annual review follow-up of children aged 5 to 16 years on the practice asthma register are expected as part of QOF. All aspects of the proposed review are recommended by national guidelines. The reviews are expected to be performed by the PN/HCA and will not involve written informed consent. All the data recorded by the research team will be fully anonymised and no patient identifiable data will leave the practice at any stage.

14.2 Sponsor Standard Operating Procedures

All relevant Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines

14.3 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

14.4 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

14.5 Approvals

Once Sponsor authorisation has been confirmed, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

Once Sponsor authorisation has been confirmed, the Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.6 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

15. DATA HANDLING AND RECORD KEEPING

All the data will be entered on the practice computer and the spirometry tracing scanned in. Patient data will be recorded on a Redcap 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 will be identified by a study specific participants number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file.

16. STUDY GOVERNANCE

16.1 Trial Steering Committee (TSC)

A study steering committee will be appointed and meet twice yearly. It is anticipated that Mr Kirk the patient representative will sit on the steering committee. The role of the Trial Steering Committee (TSC) will be to provide the overall supervision of the trial. The TSC will include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC will monitor trial progress and conduct and advise on scientific credibility.

17. FINANCING AND INSURANCE

Insurance

University of Leicester insurance will be in place to cover for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research and also to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research.

NHS indemnity scheme will act as insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research.

Costings
We have funding of £136,465.73p to cover the costs of the study programme (£29,368 from Midlands Asthma and Allergy Research Association and £107,097.73p from Aerocrine). We also have additional funding from Health Education East Midlands for the salary of the fellow which is paid directly to the fellow (David Lo) amounting to £113,483.69 over 2 years. Total funding – **£249,949.42p.**

This will include salaries for one full-time research nurse for 18 months (£63,018.77). We have allocated £15,000 to Dr Yang to perform the health economic analysis.

Further funds are requested for: travel of the implementation team between base and practices (£5,000), the cost of 2 spirometers (£4,000), consumables inc. postage costs (£4000), conference attendance costs (£3,000), MD course fees for project fellow (£4,200), computer equipment (£2900) and estates inc. investigator costs (£15,346.96).

We have also allocated £100 for each asthma review session performed by the PN/HCA, allowing for 200 sessions (3-4 sessions per week for 60 weeks) equates to a total of £20,000. Without this funding the study would not be possible due to lack of capacity.

Justification of costs:
Project fellow: The fellow will coordinate the study working closely with the study PI. David will help liaise with participating practices to organise the teaching and training events and participate in the asthma review clinics and support the research nurse. The project fellow will be responsible for the data collection and management and perform the data analysis with the help and support of the statistician. He will take a strong role in the data dissemination and presentation. David will gain significant skills in the diagnosis and management of childhood asthma generally and in primary care particularly and will build capacity. During the course of this project he will also undertake a MD degree to support his research training.

Research nurse: The research nurse will take a strong role in the coordination of training of PN/HCAs in the performance and interpretation of spirometry to and be involved in the practice teaching. The nurse will take a lead in organising the joint follow-up asthma clinics in participating practices and she/he will be involved in data acquisition and entry into the database.

Spirometers: Purchase of two spirometers from Carefusion with incentive software suitable for children, appropriate size mouthpieces and disposable bacterial filters, maintenance and consumables. Costs include the mandatory yearly maintenance costs.
Additional consumables include petrol money calculated using a standard University template of 45 pence per mile for the project fellow and nurse, costs for stationary and postage.

We will buy PN/HCA time and pay £100 to the practice for each session to cover salary and on-costs as there is no capacity in primary care currently to support implementation of the NICE

guideline. We will also reimburse practices for administrator time to perform the relevant database searches.

18. PUBLICATION POLICY

Authorship

The list of authors should accurately reflect who carried out the research and who wrote the article. All multi-authored papers should include an 'Authors' Contributions' section at the end of the paper.

The list of authors should correspond to the following criteria (based on ICMJE guidelines). Authors must meet all 4 of these conditions:

1. Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;
2. Drafting the article or revising it critically for important intellectual content;
3. Final approval of the version to be published; and
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet these criteria for authorship and, conversely, no-one should be omitted from the list if he/she meets these criteria (18).

Affiliation

All University authors must cite University of Leicester as their institutional research base when recording their affiliation in research articles, conference papers and other publications, irrespective of where the affiliation actually appears in the publication.

Review

Manuscripts will be submitted to peer-review journals and data will be presented in anonymised fashion at relevant national and international conferences.

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20. APPENDIX A: STUDY GANTT CHART

Study Task	Time in Months							
	-3	-6	-9	-12	-15	-18	-21	-24
Identify Participating Practices	■	■						
Site Survey and Change Readiness Questionnaires	■	■						
Develop training package	■	■						
Delivery of training package to healthcare workers performing the test	■	■						
Identification of patients under investigation/review for asthma	■	■	■	■				
Perform asthma reviews		■	■	■	■	■	■	
Review and refine training package		■	■	■	■	■	■	
Collection of health outcome data		■	■	■	■	■	■	
Quantitative and qualitative data analysis							■	■
Dissemination and publication of study results							■	■