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To determine the optimum series of investigations to diagnose asthma

Submission date	Recruitment status	[_] Prospectively registered
20/05/2019	Recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
03/07/2019	Ongoing	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
28/10/2024	Respiratory	

Plain English summary of protocol

Background and study aims
Asthma is one of the commonest lung conditions in the UK. Unfortunately, there is no single test to diagnose asthma. Doctors use a range of different breathing tests. It is unclear which one of these is best. As it can be difficult to diagnose asthma, some people may be given long-term treatment they do not need, whilst others are not given treatment that they do need. We want to improve the way asthma is diagnosed, by understanding how to use the routine breathing tests in a better way. We also hope to develop new breathing tests, which may be better to diagnose asthma. The results of this study will be used to help doctors diagnose asthma and get people on the right treatment as soon as possible.

Who can participate?
Patients:
Those with symptoms that could be due to asthma (such as cough, wheeze, breathlessness or chest tightness), aged between 5 and 69 years old. Those who have other lung conditions, are pregnant or have been heavy smokers for a long time are not able to participate.
Healthy Volunteers:
Those aged between 5 and 69 years with no known or suspected lung problems. Those who are pregnant or have been heavy smokers for a long time are not able to participate

What does the study involve?
Patients:
There are 4 clinic visits in total over 3 months. There are 2 more optional visits with further lung tests between core visit 1 and 3. Each core visit includes a lung health check, a questionnaire, and some detailed breathing tests (some of these are standard care and some will be new tests). Each visit can take 1- 2 hours. There is also a blood test and allergy test. At the first visit participants will be asked to sign a consent form confirming they are happy to proceed with the study. They will receive a copy of the consent form and information sheet to keep. Participants will be given an inhaler to use to help relieve symptoms (this is a standard inhaler used in routine care for people with asthma). After the second visit participants will start using an asthma preventer inhaler (this is a standard treatment for asthma), at visit 3 and 4 it will be assessed if

the breathing tests and symptoms have improved with this preventer treatment. At the end of the study, the participant and their doctor will receive a report with your test results and a treatment plan.

Healthy Volunteers:
There are two visits at the research clinic. At each visit participants will do some routine tests used in asthma diagnosis and also new breathing tests. They will receive a comprehensive assessment of their lung health. This information can be passed onto their GP with their permission for future record.

What are the possible benefits and risks of participating?
All the tests being used are low risk and are either routinely used by doctors or are used in research clinics around the country. The drugs prescribed are commonly used in asthma and other conditions.
Side effects:
Reliever inhaler: Occasionally, people feel shaky or jittery after taking this medication, but this wears off quickly.
Preventer inhaler: Side effects: Occasionally people get a sore throat, hoarse voice or a mouth infection called thrush, this can be avoided by rinsing your mouth with water after taking the medicine.
Breathing tests: all breathing tests are safe and are used routinely by GPs and hospital clinics. Sometimes when you breathe in and out quickly it can make you feel dizzy we perform all lung function measurements with you sitting down.
Mannitol test: this is a safe test and is used in asthma clinics around the world. You might feel short of breath, chest tightness or cough, but these symptoms don't last long. We will give medicine to reverse these symptoms if needed. If you are taking antihistamines we would ask you to stop these for 72 hours before this test.
Blood sample: Occasionally a slight discomfort is felt and bruising can occurs where the blood is taken. Some people can feel faint whilst blood is being withdrawn.
Allergy skin prick test: local skin reaction or very rarely systemic reaction that may require antihistamine or anti-inflammatory medication.
Nose swab: It is very rare, but there is a small chance that a nose bleed can occur.

Where is the study run from?
Manchester University NHS Foundation Trust (Wythenshawe site)

When is the study starting and how long is it expected to run for?
December 2018 to December 2027

Who is funding the study?
1. National Institute for Health Research (NIHR) Biomedical Research Centre (BRC)
2. Asthma UK/Innovate

Who is the main contact?
1. Dr Clare Murray
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Study website
http://www.radica.org.uk

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Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
243658

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 40437, IRAS 243658

Study information

Scientific Title
To determine the optimum series of investigations to diagnose asthma

Acronym
RADicA

Study objectives
To determine the optimum series of investigations to diagnose asthma

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/01/19, North West - Greater Manchester East Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ; +44(0)207 104 8009; nrescommittee.northwest-gmeast@nhs.net), ref: 18/NW/0777, IRAS project ID: 243658
REC reference: 18/NW/0777
Amendment approval date: 14/03/2019

Study design
Observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied

Asthma

Interventions

The Rapid Access Diagnostics for Asthma (RADicA) study will aim to determine the optimum diagnostic pathway for asthma and to determine the optimum series of investigations to predict "steroid-responsive airways disease" based on conventional tests of large airway function and novel tests of small airway function. The study will be a prospective cohort study. Participants with symptoms of asthma (i.e., cough, wheeze, chest tightness and/or breathlessness), not currently taking inhaled corticosteroid treatment will be recruited through primary and secondary care sources. Participants will undergo 4 core visits (2 before and 2 following standard asthma treatment), 1 telephone/text/email contact and up to 2 optional visits.

At Core Visit 1, following written informed consent (and assent where applicable), the participant will be thoroughly evaluated (structured clinical history and examination) following a proforma. Participants in whom asthma is deemed low probability AND in whom an alternative diagnosis is suspected (e.g. pneumonia) would be withdrawn from the study and would be evaluated further in collaboration with their GP or if appropriate due to clinical urgency and/or severity direct referral to a general respiratory clinic would be arranged. All other participants will continue in the study. Those continuing will complete the following tests:

1. Skin prick test (if the patient is on antihistamines, this test will be deferred to a future visit and medication withheld as indicated)
2. Blood test(offered to all participants - can be completed at any baseline visit. However as these are not safety bloods, if declined the participant can still continue in the study)
3. Pregnancy test - if applicable
4. Nasopharyngeal swabs
5. FeNO
6. VOCs
7. IOS (pre-salbutamol)
8. PExA (pre-salbutamol)
9. MBW (pre-salbutamol)
10. Spirometry (pre-salbutamol)
11. Administration of inhaled salbutamol for bronchodilator reversibility testing
12. IOS (post-salbutamol)
13. Spirometry (post- salbutamol)

Following the visit all patients in the study will be issued with an inhaled short acting bronchodilator to use as required in case they become symptomatic between visits. Participants will receive an electronic peak flow and be asked to record twice-daily PEF measurements for 2-weeks.

All participants will attend Core Visit 2. This visit will occur between core visit 1 and entering the treatment period phase providing there is a gap of ≥24hrs from completing bronchodilator reversibility challenge (done in core visit 1), and/or ≥48hrs between methacholine challenge visit (optional visit 1) and/or bronchoscopy visit (optional visit 2). The procedures conducted at core visit 2 are:

1. Symptoms (ACQ)
2. Collection of PEF measurements (if not completed 2 weeks this can be collected at next visit)
3. IOS (pre-mannitol)
4. PExA (pre-mannitol)
5. MBW (pre-mannitol)
6. Spirometry (pre-mannitol)
7. Mannitol provocation challenge

8. IOS (post-mannitol)
9. Sputum will be collected where expectoration is voluntarily achieved at any point during the visit, note we would most likely expect sputum during/following the mannitol challenge
10. Participants will be instructed to commence their treatment with a standard steroid inhaler once they have completed their last baseline visit (baseline visits include: core visit 1, core visit 2, optional visit 1, optional visit 2) and 2weeks PEF monitoring.

There will be two optional visits offered to eligible participants, these visits can occur at any point between core visit 1 and starting treatment phase, providing there is a gap of ≥24hrs from completing bronchodilator reversibility challenge (done in core visit 1), or ≥48hrs between challenge tests and/or bronchoscopy.
Optional visit 1: Methacholine challenge. The running order for the procedures conducted at this visit is as follows:
1. Symptoms (ACQ)
2. IOS (pre-methacholine)
3. Spirometry (pre-methacholine)
4. Methacholine provocation challenge
5. IOS (post-methacholine)
Optional visit 2: Broncoscopy visit (offered on upto 20 adult participants). The running order for the procedures conducted at this visit is as follows:
1. Consent
2. Broncoscopy

At the end of the baseline visits and on completion of 2 weeks of PEF monitoring, participants will start the treatment phase with a standard first line asthma treatment (a steroid inhaler 'Flixotide accuhaler' will be prescribed in all patients to be used morning and evening. Also a reliever inhaler 'Ventolin accuhaler' will be prescribed to be used as required for symptom control).
Core visit 3 will occur 1-2 weeks after participant is commenced on steroid inhaler. It is an early response visit. The procedures conducted at this visit are:
1. Symptoms (ACQ)
2. Clinical examination
3. Check adherence
4. Blood test (in adults, also offered in children ≥12yrs. However as these are not safety bloods, if declined the participant can still continue in the study)
5. FeNO
6. VOCs
7. IOS
8. PExA
9. MBW
10. Spirometry
11. Participants will receive a repeat supply of inhalers

Core visit 4 will occur 6-8weeks after participant is first commenced on steroid inhaler. The procedures conducted at this visit are:
1. Symptoms (ACQ)
2. Clinical examination
3. Nasopharyngeal swabs
4. Blood test (in adults, also offered in children ≥12yrs. However as these are not safety bloods, if declined the participant can still continue in the study)
5. FeNO
6. VOCs

7. PExA
8. MBW
9. IOS (pre Mannitol provocation)
10. Spirometry (pre Mannitol provocation)
11. Mannitol provocation
12. IOS (post Mannitol provocation)
13. Spirometry (post Mannitol provocation)
14. GP letter

In addition to the study described we will also recruit age and gender matched healthy controls who will attend 2 visits. This will enable data collection for 'normal' ranges in some of the novel lung function tests where data is lacking. At visit 1, healthy volunteers will be asked to conduct the following:
1. Informed consent
2. Demographics/Clinical history
3. Symptoms
4. Clinical Examination
5. Skin prick test (if the patient is on antihistamines, this test will be deferred to visit 2 and medication withheld as indicated)
6. Blood test (offered to all participants - can be completed at any visit. However as these are not safety bloods, if declined the participant can still continue in the study)
7. Pregnancy test - if applicable
8. Nasopharyngeal swabs
9. FeNO
10. VOCs
11. IOS (pre-salbutamol)
12. PExA (pre-salbutamol)
13. MBW (pre-salbutamol)
14. Spirometry (pre-salbutamol)
15. Administration of inhaled salbutamol for bronchodilator reversibility testing
16. IOS (post-salbutamol)
17. Spirometry (post-salbutamol)
At visit 2 (between 1 and 12 weeks later) , healthy volunteers will be asked to conduct the following:
1. Symptoms
2. Clinical examination
3. FeNO
4. VOCs
5. IOS
6. PExA
7. MBW
8. Spirometry

Intervention Type
Other

Primary outcome measure
Large airway function measured using:
1. Spirometry (FEV1, FVC, MEF25-75) at visits 1, 3, 4.
2. BDR (Δ FEV1 or FVC following 400mcg inhaled Salbutamol) at visit 1.
3. FeNO (NO ppb) at visits 1-4.

4. PEFv (variability measured twice daily over 2 weeks)
5. BHRmann (mannitol PD15) at optional visit 1.
6. BHRmeth (Methacholine PD20) at visits 2, 4.
Small airway function measured using:
1. IOS (Rrs5Hz, Rrs20Hz, R5-20, Xrs5Hz, Xrs 20Hz, X5-20) at visits 1-4.
2. MBW (LCI, Scond, Sacin) at visits 1-4.

Secondary outcome measures
1. Asthma symptoms measured using Asthma Control Questionnaire (ACQ-5) at visits 1-4.
2. Experimental biomarkers of small airway inflammation measured using:
2.1 PExA at visits 1-4.
2.2 VOC at visits 1-4.
3. Blood tests including: Blood eosinophil count, cell culture, immune cell count, measures of immune cell activation (Mbd2, CCL17, CCR4)
YKL-40 (CHI3L1), AMCase (CHIA), Chitotriosidase (CHIT1) at visits 1, 3, 4.
4. Sputum eosinophil at visits 2, 4.

Overall study start date
01/04/2017

Completion date
31/12/2027

Eligibility

Key inclusion criteria
1. Males and females >= 5 years and <70 years
2. Clinical suspicion of asthma from GP or referring health care professional
3. One or more symptom in keeping with asthma (i.e., cough, wheeze, chest tightness and breathlessness)
4. Capable of giving informed consent or where under 16 years attends with parent or legal guardian.
5. Participants must be able to communicate well in English

Participant type(s)
Patient

Age group
Mixed

Lower age limit
5 Years

Upper age limit
70 Years

Sex
Both

Target number of participants

Planned Sample Size: 300; UK Sample Size: 300

Total final enrolment
140

Key exclusion criteria
1. Pregnant women
2. Current ICS (used within previous 2 weeks) or oral steroid treatment (within the previous 4 weeks)
3. Former/Current smokers if > 10 pack year smoking history
4. Other relevant comorbidities (e.g., other lung disease; CF, COPD, ILD or bronchiectasis)
5. Recent antibiotic treatment within previous 2 weeks (these participants may be able to enter the study at a later date)

Date of first enrolment
03/12/2018

Date of final enrolment
30/06/2027

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Manchester University NHS Foundation Trust
Cobbett House
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Sponsor information

Organisation
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Government

Funder Name
Asthma UK; Grant Codes: AUK-PG-2018-406

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
01/06/2028

Individual participant data (IPD) sharing plan
The authors will consider all reasonable requests for deidentified data, following approval by the study sponsors. Proposals should be directed to research.sponsor@mft.nhs.uk. To gain access, data requestors will need to sign a data access agreement.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version V2	14/03/2019	03/07/2019	No	No
Protocol file	version 8.1	22/02/2023	12/06/2023	No	No
HRA research summary			26/07/2023	No	No
Results article		05/09/2024	19/09/2024	Yes	No

Results article	Asthma diagnosis: a comparison of established diagnostic guidelines in adults with respiratory symptoms	05/09/2024	20/09/2024	Yes	No
Protocol article		26/10/2024	28/10/2024	Yes	No