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Can we reduce asthma attacks in children using exhaled nitric oxide measurements?

Submission date
10/04/2017

Recruitment status
No longer recruiting

Registration date
12/04/2017

Overall study status
Completed

Last Edited
28/05/2024

Condition category
Respiratory

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Asthma is a long-term condition which affects the airways. When a person is suffering from asthma, the airways are extremely sensitive (hyperresponsive) to both natural chemicals the body produces and irritants outside the body, such as dust or pollen. Coming into contact with these substances can cause an asthma attack (also known as an exacerbation), which involves feelings of tightness in the chest as the airways become inflamed (swollen), causing coughing, wheezing, chest tightness and difficulty breathing. Every year in the UK, 150,000 children see their family doctor for an asthma exacerbation and 25,000 are hospitalised. One third of the £1 billion NHS budget for asthma is spent on provision for unscheduled care of which about one half is for childhood exacerbations. Exacerbations are relatively infrequent and short-lived but their importance to patients is emphasised in the Global Initiative for Asthma whose major goals include “to prevent asthma exacerbations”. Everyone breathes out a gas called nitric oxide. Exhaled nitric oxide can be measured using a special breathing device. People with asthma breathe out more nitric oxide than people without asthma because nitric oxide is produced by the allergic cells which are present in the lungs of people with asthma. These allergic cells build up before an asthma attack. The aim of this study is to find out whether measuring fractional exhaled nitric oxide (FeNO) can guide asthma treatment and help prevent asthma attacks.

Who can participate?
Children aged between 6 and 16 who have been diagnosed with asthma and are currently being treated with inhaled steroids and who have had an asthma attack treated with steroid tablets.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group have their asthma treatment guided by symptoms and breath tests to measure FeNO. Those in the second group are treated according to the symptoms they are having alone. Participants in both groups are followed up after three, six, nine and twelve months in order to find out how many asthma exacerbations they have had and assessments of their quality of life. Participants are also offered additional allergy testing, which involves a blood test and a coughing up spit test. Additionally around 20 children are invited to take part in an interview at the end of the twelve month follow-up to explore attitudes to, and acceptability of the FeNO measurements. Five research nurses are also interviewed about the practicality of FeNO measurements.

What are the possible benefits and risks of participating?
All children will benefit from regular asthma assessments as part of the study. Asthma treatment is currently only guided by symptoms, and so children in the group where asthma treatment is guided by symptoms will continue to get current best asthma treatment. There is a risk that the optional allergy testing will cause itchiness on the participant's arm for a short time. The optional coughing up spit test may make the participant cough and possibly also wheeze, but this will only be conducted following a lung function check.

Where is the study run from?
25 hospitals around the UK

When is the study starting and how long is it expected to run for?
February 2017 to January 2021

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
1. Dr Stephen Turner (scientific)
s.w.turner@abdn.ac.uk
2. Mrs Jess Wood (public)
raaceno@abdn.ac.uk

Study website
https://www.raaceno.co.uk

Contact information

Type(s)
Scientific

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Type(s)
Public

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
34390

Study information

Scientific Title
Reducing Asthma Attacks in Children using Exhaled Nitric Oxide as a biomarker to inform treatment strategy - a randomised trial (RAACENO)

Acronym
RAACENO

Study objectives
Current study hypothesis as of 08/02/2021:

Study aim:
The aim of the study is to compare treatment guided by exhaled nitric oxide and symptoms against treatment guided by symptoms alone (standard care), in children with asthma who are at risk of an asthma attack (ie have had an asthma attack in the previous 12 months), in terms of the presence of any asthma exacerbations over 12 months requiring prescription of OCS.

Hypothesis:
The proportion of children with ≥1 asthma exacerbation will be reduced when asthma treatment guided by FeNO plus symptoms is compared to treatment guided only by symptoms.

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Previous study hypothesis:

Study aim:
The aim of the study is to compare treatment guided by exhaled nitric oxide and symptoms against treatment guided by symptoms alone (standard care), in children with asthma who are at risk of an asthma attack (ie have had an asthma attack in the previous 12 months), in terms of the presence of any asthma exacerbations over 12 months requiring prescription of OCS for 3-7 consecutive days.

Hypothesis:
The proportion of children with ≥1 asthma exacerbation will be reduced when asthma treatment guided by FeNO plus symptoms is compared to treatment guided only by symptoms.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North of Scotland Research Ethics Committee 1, 17/10/2016, ref: 16/NS/0106

Study design
Randomized; Both; Design type: Screening, Diagnosis, Device, Active Monitoring, Qualitative

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Asthma

Interventions
Eligible and consenting participants will be randomised to one of the two groups (treatment decisions based on FeNO plus symptoms [interventional arm] or treatment decisions based on symptoms alone [standard care]) using a 24-hour telephone Interactive Voice Response randomisation application or via a web-based application, both hosted by CHaRT. Random allocation will use a minimisation algorithm (stratification by centre, age (<11 years, ≥11 years) sex and asthma severity as evidenced by BTS/SIGN treatment step (BTS step 2, BTS step 3, BTS step 4) including a random element (20%).

Experimental arm: Asthma treatment decisions will be guided by Fractional Exhaled Nitric Oxide (FeNO) and symptoms. The experimental intervention and subsequent adjustment of treatment steps are applied at recruitment, and at each of the follow-up visits (3, 6, 9 and 12 months).

FeNO guides treatment to either early escalation of anti-inflammatory medication (algorithm 1, elevated FeNO) or early intervention with bronchodilators (algorithm 2, FeNO not elevated).

Control arm: Asthma treatment decisions will be guided by symptoms alone. The control intervention and subsequent adjustment of treatment steps are applied at recruitment, and at each of the follow-up visits (3, 6, 9 and 12 months). Although FeNO will be measured in children in this arm at recruitment and at each of the follow-up visits, the results of the FeNO will not be used in treatment decisions for this arm of the trial. The FeNO will be used as outcome data only. For participants in this group, the FeNO result will not be available to the patient's GP or paediatrician (where appropriate) during the trial period.

In both arms, treatment decisions will be protocolised through the study website. Data required for step up/down decisions are entered into the study website which contains the algorithm for step up/down treatment decisions; this removes subjectivity from the treatment decisions. The trial algorithm applies to participants in both arms of the trial up to 12 month assessment.

Intervention Type
Other

Primary outcome measure
Current primary outcome measure as of 08/02/2021:

Asthma exacerbation (attack) requiring prescription (and/or use of) one or more course of OCS in the 12 months after randomisation (yes/no). Outcomes will be assessed at the 3, 6, 9 and 12 months follow-up visits. In protocol version 3 (31 August 2017) we refined the definition of the primary outcome to reflect a change in treatment, where some exacerbations were being treated with a single dose of oral corticosteroid; and clarified that the primary source of information on exacerbations would be the child and parent or carer; with GP records used only where this information was missing.

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Previous primary outcome measure:

Asthma exacerbation (attack) requiring prescription of OCS for 3-7 consecutive days determined from a patient held diary and verified by GP records where possible in the 12 months after randomisation (yes/no). Outcomes will be assessed at the 3, 6, 9 and 12 months follow-up visits.

Secondary outcome measures
1. Time to first exacerbation is determined from the child/parent or carer and from GP records in the 12 months after randomisation. Outcomes will be assessed at 3, 6, 9 and 12 months post randomisation
2. Number of exacerbations during follow up, based on prescribed oral corticosteroid, is assessed by responses to asthma attacks that have required oral steroid tablets on the follow-up CRF at 3,6,9, and 12 months follow-up determined from the child/parent or carer and from GP records in the 12 months after randomisation
3. Need for unscheduled healthcare assessment during follow up (yes/no) is measured by responses to health service use on the follow-up CRF at 3,6,9 and 12 months follow-up determined from the child/parent or carer and from GP records in the 12 months after randomisation
4. Number of unscheduled health assessments is measured by responses on the follow-up CRF

to health service use at 3,6,9 and 12 months follow-up determined from the child/parent or carer and from GP records in the 12 months after randomisation
5. Asthma control during follow up (i.e. age-appropriate Asthma Control Test score) is assessed by responses to the Asthma Control Test (ACT)/Children's Asthma Control Test (CACT) - questionnaires completed by child/parent or carer at baseline, and at 3, 6, 9 and 12 month follow-up appointments
6. Asthma severity (%FEV1) is measured using spirometry at baseline and at 3, 6, 9 and 12 month follow-up appointments.
7. Fractional exhaled nitric oxide (FeNO) is measured by Niox Vero device at baseline, and 3, 6, 9 and 12 month follow-up appointments
8. Dose of ICS during the 12 months follow up (i.e. daily dose of budesonide equivalent averaged over 3 months) is assessed from current asthma treatment and from adherence to treatment (measured using adherence monitors); this data is collected at 3, 6, 9 and 12 months follow-up
9. Health status is assessed using the Paediatric Asthma Quality of Life Questionnaire (PAQLQ); a questionnaire completed by the child/parent or carer at baseline and 12 months
10. Exploration of experiences and ascertainment of acceptability of the intervention will be collected through participant interviews following 12 month follow-up
11. Health economic evaluation is undertaken using from GP records and participant reported data at baseline, 3, 6, 9 and 12 months follow-up

Overall study start date
01/02/2017

Completion date
31/01/2021

Eligibility

Key inclusion criteria
1. Asthma diagnosed or confirmed by consultant paediatrician (or Read code for asthma if recruited in primary care)
2. Aged 6 years or older and not yet reached the date of their 16th birthday
3. Currently prescribed inhaled corticosteroids (<1000mcg budesonide equivalent per day in those <12 years; <2000 mcg budesonide equivalent per day for older children)
4. At least one patient/parent reported-asthma exacerbation treated with oral corticosteroids in the 12 months prior to recruitment

Participant type(s)
Patient

Age group
Child

Lower age limit
6 Years

Upper age limit
15 Years

Sex

Both

Target number of participants
Planned Sample Size: 502; UK Sample Size: 502

Total final enrolment
515

Key exclusion criteria
1. Unable to provide FeNO measurement at baseline assessment (expected prevalence <5%)
2. Other chronic respiratory conditions which also have exacerbations
3. Current treatment with maintenance oral steroids

Date of first enrolment
01/06/2017

Date of final enrolment
01/08/2019

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Royal Aberdeen Children's Hospital
Westburn Road
Aberdeen
United Kingdom
AB25 2ZG

Study participating centre
Birmingham Children's Hospital
Steelhouse Lane
Birmingham
United Kingdom
B4 6NH

Study participating centre
Bradford Teaching Hospitals NHS Foundation Trust
Children's Services Directorate

Duckworth Lane
Bradford
United Kingdom
BD9 6RJ

Study participating centre
Royal Alexandra Children's Hospital
Eastern Road
Brighton
United Kingdom
BN2 5BE

Study participating centre
Bristol Royal Hospital for Children
Paul O'Gorman Building
Upper Maudlin Street
Bristol
United Kingdom
BS2 8BJ

Study participating centre
Derbyshire Children's Hospital
Royal Derby Hospital
Uttoxeter Road
Derby
United Kingdom
DE22 3NE

Study participating centre
Royal Hospital for Sick Children
NHS Lothian
Royal Hospital for Sick Children
9 Sciennes Road
Edinburgh
United Kingdom
EH9 1LF

Study participating centre
Royal Hospital for Children
NHS Greater Glasgow & Clyde
1345 Govan Road

Glasgow
United Kingdom
G51 4TF

Study participating centre
Royal Brompton Hospital
Sydney Street
Chelsea
London
United Kingdom
SW3 6NP

Study participating centre
University Hospital Crosshouse
Kilmarnock Road
Crosshouse
Kilmarnock
United Kingdom
KA2 0BE

Study participating centre
Leicester Children's Hospital
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Alder Hey Children's Hospital
E Prescot Road
Liverpool
United Kingdom
L14 5AB

Study participating centre
Manchester Royal Infirmary
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Great North Children's Hospital
Victoria Wing
Royal Victoria Infirmary
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Nottingham Children's Hospital
Queen's Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Southampton Children's Hospital
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Royal Stoke Children's Service
Royal Stoke University Hospital
Newcastle Road
Stoke-on-Trent
United Kingdom
ST4 6PQ

Study participating centre
New Cross Hospital
Wolverhampton Road
Heath Town
Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
Tayside Children's Hospital
NHS Tayside
Dundee
United Kingdom
DD1 9SY

Study participating centre
Barnsley Hospital
Gawber Road
Barnsley
United Kingdom
S75 2EP

Study participating centre
Sheffield Children's Hospital
Western Bank
Sheffield
United Kingdom
S10 2TH

Study participating centre
Royal Devon & Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
Derriford Hospital
Derriford Road
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Walsall Manor Hospital
Moat Road
Walsall

United Kingdom
WS2 9PS

Study participating centre
Leeds General Infirmary
Great George Street
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LS1 3EX

Study participating centre
King's College Hospital
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Royal London Hospital
Barts Health NHS Trust
Whitechapel Road
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United Kingdom
E1 1FR

Study participating centre
Wythenshawe Hospital
Southmoor Road
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M23 9LT

Study participating centre
St George Hospital
Blackshaw Road
London
United Kingdom
SW17 0QT

Study participating centre
Royal Shrewsbury Hospital
Mytton Oak Road
Shrewsbury
United Kingdom
SY3 8XQ

Study participating centre
Countess of Chester Hospital
Liverpool Road
Chester
United Kingdom
CH2 1UL

Study participating centre
Harrogate District Hospital
Lancaster Park Road
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HG2 7SX

Study participating centre
Russells Hall Hospital
Pensnett Road
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DY1 2HQ

Study participating centre
Wishaw General Hospital
50 Netherton Street
Wishaw
United Kingdom
ML2 0DP

Study participating centre
Royal Oldham Hospital
Rochdale Road

Oldham
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OL1 2JH

Study participating centre
Royal Preston Hospital
Sharoe Green Lane
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United Kingdom
PR2 9HT

Study participating centre
Ormskirk District General Hospital
Wigan Road
Ormskirk
United Kingdom
L39 2AZ

Study participating centre
Arrowe Park Hospital
Arrowe Park Road
Upton
Wirral
United Kingdom
CH49 5PE

Study participating centre
Hanscombe House Surgery
52A St Andrew Street
Hertford
United Kingdom
SG14 1JA

Study participating centre
Parsonage Surgery
Cavell Drive
Haymeands Lane
Bishops Stortford
United Kingdom
CM23 5JH

Study participating centre
Barrack Lane Medical Centre
1 Barrack Lane
Ipswich
United Kingdom
IP1 3NQ

Study participating centre
Roundwell Medical Centre
25-27 Dr Torrens Way
Costessey
United Kingdom
NR5 0GB

Study participating centre
Ixworth Surgery
Peddars Close
Bury St Edmunds
United Kingdom
IP31 2HD

Study participating centre
Lakenham Surgery
1 Ninham Street
Norwich
United Kingdom
NR1 3JJ

Study participating centre
Castle Partnership
40 Fishergate
Norwich
United Kingdom
NR3 1SE

Sponsor information

Organisation

University of Aberdeen and NHS Grampian

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Foresterhill House Annex
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researchgovernance@abdn.ac.uk

Sponsor type
University/education

ROR
https://ror.org/00ma0mg56

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
A final report of the study findings will be presented to the funder at the end of the study. It is also envisaged that the main results of the trial will be published in a peer-reviewed medical /scientific journal under an open-access agreement. Once the main report has been published, a

lay summary of the findings will be sent in a final RAACENO Newsletter to all those who participated in the trial.

Intention to publish date
31/01/2022

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Steve Turner (s.w.turner@abdn.ac.uk)

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	04/10/2019	07/10/2019	Yes	No
Results article	Qualitative process evaluation	28/01/2022	02/02/2022	Yes	No
Other publications		05/01/2023	07/06/2023	Yes	No
Results article	Cost analysis	01/05/2022	07/06/2023	Yes	No
HRA research summary			28/06/2023	No	No
Other publications		27/05/2024	28/05/2024	Yes	No