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

Submission date	Recruitment status No longer recruiting	[X] Prospectively registered		
10/04/2017		[X] Protocol		
Registration date	Overall study status Completed	Statistical analysis plan		
12/04/2017		[X] Results		
Last Edited	Condition category	[] Individual participant data		
28/05/2024	Respiratory			

#### 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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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.

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.

#### 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 Leeds United Kingdom 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 Whitechapel London United Kingdom E1 1FR

# Study participating centre Wythenshawe Hospital

Southmoor Road Manchester United Kingdom 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 Harrogate United Kingdom HG2 7SX

# Study participating centre Russells Hall Hospital

Pensnett Road Dudley United Kingdom 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 United Kingdom OL1 2JH

# Study participating centre Royal Preston Hospital

Sharoe Green Lane Preston 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 lxworth 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

#### Sponsor details

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Aberdeen
Scotland
United Kingdom
AB25 2ZB
+44 1224 551123
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?
<u>Protocol article</u>	protocol	04/10/2019	07/10/2019	Yes	No
Results article		28/01/2022	02/02/2022	Yes	No
Other publications	Qualitative process evaluation	05/01/2023	07/06/2023	Yes	No
Results article		01/05/2022	07/06/2023	Yes	No
HRA research summary			28/06/2023	No	No
Other publications	Cost analysis	27/05/2024	28/05/2024	Yes	No