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

PROTOCOL

A UK Collaborative Trial funded by the Efficacy and Mechanisms Evaluation (EME)
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Aberdeen | Foresterhill Aberdeen
AB25 2ZB | AB25 2ZB

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Sponsor reference: | 3.034.16

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Telephone: | 01224 438084
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Website: | https://www.raaceno.co.uk/

Funder
Name: | Efficacy and Mechanisms Evaluation
Funder number: | 15-18-14
Funder start date: | 1 February 2017
Funder end date: | 31 January 2021

Other
ISRCTN | 67875351
REC number | 16/NS/0106
IRAS number | 212541
Signature

By signing this document I am confirming that I have read, understood and approve the protocol for the above study

Steve Turner, Chief Investigator

Signature: 

Date: 19 March 2020

Shona Fielding, Statistician

Signature: 

Date: 

19 March 2020
### VERSION HISTORY:

<table>
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<td>• reflect revised start/end date for the study:</td>
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<td>updated on page 2; in table 4; in figure 3;</td>
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<td>and on Gantt chart (appendix 2);</td>
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<td>• refine the inclusion/exclusion criteria;</td>
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<td>• clarify that the primary outcome is patient</td>
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<td>• clarify that at baseline FeNO will be measured</td>
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<td>rather than at the end of this visit, including</td>
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<td>revision to the flow-diagram to show this;</td>
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<td>• clarify that FeNO should be measured before</td>
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<td>spirometry at all appointments;</td>
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<td>• refine the description of the interventions to</td>
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<td>be evaluated (including figures 1 and 2; and</td>
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<td>appendices 3 and 4 containing detailed treatment</td>
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<td>• add more detail about possible cross-over</td>
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<td>• clarify details about the mechanistic studies</td>
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<td>(including removal of appendix 4 because any</td>
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<td>microbiome analysis will no longer be done in</td>
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<td>the Ryan Laboratory in Dundee)</td>
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<td>• Refine the description of the primary outcome.</td>
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<td>Some exacerbations are now treated with a single</td>
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<td>sections 2, 3, 4.1, and 5.1.3).</td>
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<td>To account for participants who have rescue</td>
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<td>medication (oral corticosteroids) at home, we</td>
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<td>have also refined the text to reflect that the</td>
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<td>primary outcome is prescription and/or use of</td>
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<td>oral corticosteroid (summary, sections 2, 3,</td>
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<td>4.1, and 5.1.3). The primary source of</td>
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<td>data about the asthma exacerbations will be the parent/child report; we will also capture primary outcome data from medical records at the end of follow-up (section 4.1 and 5.1.3).</td>
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<td>• Refine the inclusion/exclusion criteria as suggested by the TSC (section 3.2.2); no more than one sibling per family</td>
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<td>• Add additional information about re-screening children who are unable to provide a FeNO measurement at baseline (section 3.2.2)</td>
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<td>• Addition of email as mode of contact for initial approach by research team of eligible participants (section 3.3.1)</td>
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<td>• Removal of mention of a telephone randomisation service as this will not be used in RAACENO (section 3.3.3)</td>
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<td>• Clarification that deviation from the treatment algorithm would not be considered a protocol deviation (section 3.3.3)</td>
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<td>• <strong>4.1 Primary outcome measure.</strong> Removal of sentence: The primary outcome will be determined from GP records unless access to these records is not possible in which case the patient reported data will be used.</td>
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<td>• <strong>5.1.1.</strong> Addition of web-based description for the baseline CRF.</td>
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<td>• <strong>5.1.3 Capture of data from medical records at 12 months.</strong> Amendment to process of capturing primary outcome data at 12 months</td>
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<td>• clarify details about the mechanistic studies processes</td>
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<td>• Amendment to a typographical error in the study milestones - end of recruitment 31 May 2019 to match the gantt chart</td>
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<td>• Clarification around the statistical methods (section 9)</td>
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| 9            | Version 4           | Algorithm, appendix 3 and clarification of what devices do not currently have a compatible smart inhaler device, footnote 3.  
• Clarification that in the FeNO arm at baseline, a recent step-up is within the last 12 months (appendix 4- decision tree for FeNO intervention)  
3.2, 3.2.1: facilitation of recruitment in primary care in the East of England by UK Clinical Research Networks  
3.2.2: revision to the inclusion criteria to reflect the fact that in some paediatric units, respiratory/asthma specialist nurses may diagnose asthma.  
3.3.1: clarification that the usual care team may include embedded research nurses, and that the initial approach to patients may be from the asthma specialist nurse. Inclusion of the use of practices as Participant Identification Centres for the study. Facilitation of recruitment in primary care in the East of England by UK Clinical Research Networks.  
3.3.3: Clarification that for primary care sites, for the purposes of randomisation, will be grouped together into a geographical area  
3.3.5: Use of text message appointment reminders.  
5.1.2: Replacing reference to OPC with primary care.  
5.1.3: Clarification around the process of capture of data from medical records at 12 months.  
5.2. Clarification as to what happens if children have not withheld their bronchodilator and want to participate in the post-bronchodilator sub-study.  
5.4. Addition of use of commercial saliva testing kits; clarification that the saliva testing can be done at any study visit.  
5.5. Clarification that skin prick testing can be done at any study visit; and that if skin prick testing has been done recently, with the consent of the family the results of that skin prick testing can be used for the study rather than repeating the test. | 9 May 2018 |
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<th>Amendment no.</th>
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<td>5.6 Clarification, that where 4% and 5% saline is not available at a recruitment site, saline of other concentrations can be used in line with local routine practice. 6.1. Further clarification that emergency hospitals admissions that do not relate to use of the NIOX VERO or other study assessments will not be considered as an SAE. 8.2. Additional sites.</td>
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| 11           | 5                    | Revision to sections 2, 3 and 7 in relation to the qualitative component  
Revision to section 3.3.2 to clarify re-consent for young people who turn 16 during their 12-month follow-up  
Revision to 5.1.2 to clarify that, during follow-up children complete the version of the Asthma Control test that is appropriate for their age at that time (not their age at baseline) | 8 March 2019 |
| Non-sub_15   | 6                    | Revision to 3.3.5 to clarify that if an in-person clinic follow-up visit cannot be completed, a telephone consultation can be carried out instead  
Revision to 3.37 to clarify how GP would be notified in the event of a telephone consultation  
Revision to 5.1.2 to clarify how treatment decisions will be determined in the event of a telephone consultation  
Revisions to 7.2.1 and 7.2.2 to clarify the consent process if a telephone interview is proposed | 19 March 2020 |
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PROTOCOL SUMMARY

Question addressed
Does the addition of Fractional Exhaled Nitric Oxide (FeNO) monitoring in addition to standard care reduce the number of exacerbations in children with asthma?

Considered for entry
Children aged 6-16 years with a diagnosis of asthma, current use of inhaled corticosteroids, and with an exacerbation in the previous 12 months.

Inclusion/Exclusion criteria

Inclusion criteria:
(ii) asthma diagnosed or confirmed by consultant paediatrician or respiratory/asthma specialist nurse (or Read code for asthma if recruited in primary care)
(iii) aged 6 years or older and not yet reached the date of their 16th birthday
(iv) currently prescribed inhaled corticosteroids: the maximum dose for children aged less than 12 is 1,000 microgram budesonide equivalent per day; the maximum dose for children aged 12 and over is 2,000 microgram budesonide equivalent per day.
(v) patient/parent reported-asthma exacerbation treated with at least one course of oral corticosteroids in the 12 months prior to recruitment.

Exclusion criteria:
(i) unable to provide FeNO measurement at baseline assessment (expected prevalence <5%)
(ii) other chronic respiratory conditions which also have exacerbations
(iii) Current treatment with maintenance oral steroids (we cannot step up treatment further).

Setting
Participants will be recruited in both primary and secondary care settings (predominantly secondary care).

Interventions
1. asthma treatment guided by FeNO plus symptoms
2. asthma treatment guided by symptoms only (Standard care)

Outcome assessment
The primary outcome is asthma exacerbation (attack) requiring prescription and/or use of OCS, over 12 months as recorded by participant/parent or in GP records. Outcomes will be assessed at 3, 6, 9 and 12 months post randomisation

Co-ordination
Local: by local respiratory teams, local research teams

Central: by Trial Office in Aberdeen
(Telephone 01224 438084).

Overall: by the Project Management Group, and overseen by the Trial Steering Committee and the Data Monitoring Committee.
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<td>ACT</td>
<td>Asthma Control Test</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<td>BDR</td>
<td>Bronchodilator response</td>
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<td>BNF</td>
<td>British National Formulary</td>
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<td>BTS/SIGN</td>
<td>British Thoracic Society/Scottish Intercollegiate Guidelines Network</td>
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<td>CACT</td>
<td>Children’s Asthma Control Test</td>
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<td>CEAC</td>
<td>Cost effectiveness acceptability curve</td>
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<td>CHaRT</td>
<td>Centre for Healthcare Randomised Trials</td>
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<td>CI</td>
<td>Chief Investigator</td>
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<td>CRF</td>
<td>Case Report Form</td>
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<td>Data Monitoring Committee</td>
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<td>DNA</td>
<td>DeoxyriboNucleic Acid</td>
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<td>EME</td>
<td>Efficacy and Mechanism Evaluation</td>
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<td>FEF&lt;sub&gt;25-75&lt;/sub&gt;</td>
<td>Forced Expiratory Flow at 25-75% of Forced Vital Capacity</td>
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<td>FeNO</td>
<td>Fractional Exhaled Nitric Oxide</td>
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<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced Exhaled Volume in one second</td>
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<td>FVC</td>
<td>Forced Vital Capacity</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GP</td>
<td>General Practitioner</td>
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<td>HSRU</td>
<td>Health Services Research Unit</td>
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<td>ICS</td>
<td>Inhaled corticosteroids</td>
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<td>ISRCTN</td>
<td>International Standard Randomised Controlled Trial Number</td>
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<td>LABA</td>
<td>Long Acting Beta Agonist</td>
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<td>LTRA</td>
<td>Leukotriene Receptor Antagonist</td>
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<td>National Health Service</td>
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<td>National Health Service Grampian</td>
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<td>National Institute Health Research</td>
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<td>Oral corticosteroids</td>
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<td>OPC</td>
<td>Optimum Patient Care</td>
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<td>Paediatric Asthma Quality of Life Questionnaire</td>
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<td>Principal Investigator</td>
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<td>PIL</td>
<td>Patient Information Leaflet</td>
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<td>PMG</td>
<td>Project Management Group</td>
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<tr>
<td>ppb</td>
<td>Parts per billion</td>
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<td>PSSRU</td>
<td>Personal Social Service Research Unit</td>
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<td>QALY</td>
<td>Quality Adjusted Life Year</td>
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<td>R&amp;D</td>
<td>Research and Development</td>
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<td>RCT</td>
<td>Randomised Controlled Trial</td>
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<td>SABA</td>
<td>Short Acting Beta Agonist</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>Trial Steering Committee</td>
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<td>United Kingdom</td>
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<td>UoA</td>
<td>University of Aberdeen</td>
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TRIAL PERSONNEL

Chief Investigator
1  Dr Steve Turner

Grant Holders
1  Dr Shona Fielding (Lecturer in Medical Statistics)
2  Dr Erol Gaillard (Consultant Paediatric Pulmonologist)
3  Prof Johan de Jongste (Professor of Paediatrics)
4  Dr Heather Morgan (Post-doctoral Qualitative Researcher)
5  Dr Aileen Neilson (Research Fellow in Health Economics)
6  Prof John Norrie (Director of the Centre for Healthcare Randomised Trials)
7  Dr Marielle Pijnenburg (Consultant Paediatric Pulmonologist)
8  Prof David Price (Professor of Primary Care)
9  Prof Mike Thomas (Professor of Primary Care)

Project Management Group (PMG)
This group is comprised of the grant holders along with representatives from the RACCENO trial office team.

Trial Steering Committee (TSC) Members
The membership of this committee comprises of independent members along with the Chief Investigator (Steve Turner) or a nominated delegate. The other RAACENO grant-holders and key members of the trial office (e.g. the trial manager) may attend TSC meetings. The terms of reference of the Trial Steering Committee, the template for reporting and the names and contact details of members of the TSC will be filed in the Trial Master File.

Data Monitoring Committee (DMC) Members
This committee is comprised of independent members and the trial statistician contributes as appropriate. The CI and or a delegate may contribute to the open session of the meetings as appropriate. The terms of reference of the Data Monitoring Committee, the template for reporting and the names and contact details of members of the DMC will be filed in the Trial Master File.

Trial Office Team
1  Chief Investigator
2  CHaRT Director
3  Trial Manager
4  Data Co-ordinator
5  Senior Trial Manager
6  Senior IT Manager
7  Trial statistician
1. INTRODUCTION

1.1 Background
The search for a biomarker to guide asthma treatment has been underway for many years since current methods of assessment have major limitations, e.g. when to use which treatment, when to step down treatment. Fractional exhaled nitric oxide (FeNO) is a surrogate marker for eosinophilic airway inflammation\textsuperscript{1–4} and, since eosinophils are seen in the airways of people with asthma\textsuperscript{5}, not unreasonably it was assumed that FeNO could be used to improve asthma control. The evidence from clinical trials, however, is that the addition of FeNO to usual care does not improve asthma control\textsuperscript{6–8}. Whilst poor current symptomatic asthma control is certainly a risk factor for future exacerbations\textsuperscript{9} it lacks precision, for example only 29% of children with poor asthma control on validated symptom questionnaires will have an asthma exacerbation in the following year and 8% of children with well controlled asthma will have an exacerbation (unpublished data). The confusion between exacerbation and poor symptomatic control is understandable since increased symptoms are an inevitable feature of exacerbation but most episodes of poor control are self-limiting and do not lead to exacerbation. The disconnect between symptomatic asthma control and exacerbation risk is particularly obvious in children where control is generally excellent but interrupted by exacerbations, usually in association with rhinovirus infection. Sputum eosinophilia is known to be a temporary phenomenon in children\textsuperscript{10} and this temporality at least partly explains the poor correlation between FeNO and current and future asthma control\textsuperscript{11–14}, and also the failure of FeNO guided treatment to improve symptomatic asthma control\textsuperscript{6}. In contrast, changes in FeNO concentrations are more clearly seen in the context of exacerbations. For example FeNO rises before an exacerbation\textsuperscript{15} and falls afterwards\textsuperscript{16}. The relationship between FeNO and exacerbation is replicated by the correlation between airway eosinophilia and asthma exacerbation; asthma treatment guided by airway eosinophilia reduces asthma exacerbations in adults\textsuperscript{17} and children\textsuperscript{18} (the latter with borderline significance in a small study). Of note, asthma control was not improved in either of these studies above the control arms, which were guided by a symptom-based strategy\textsuperscript{17,18}. Eosinophilic inflammation is suppressed by treatment with inhaled corticosteroids (ICS) and FeNO increases after unsuccessful reduction\textsuperscript{19} or cessation\textsuperscript{20} of ICS. Together these observations show how airway eosinophilia is an index of exacerbation risk (but not of poor symptomatic asthma control) which can be suppressed with ICS and which is correlated with FeNO.

Our meta-analysis including studies where exacerbations have been a secondary outcome\textsuperscript{21}, has established beyond a statistical doubt that asthma treatment guided by FeNO reduces asthma exacerbations. We analysed data from 1077 children who took part in seven randomised controlled trials and saw a 33% reduction in the number of children having an exacerbation among the 537 randomised to FeNO guided treatment. We also observed how FeNO guided treatment was associated with higher doses of ICS (mean difference 106 microg budesonide equivalent), and this suggested that treatment stratified by FeNO is effective in reducing exacerbations by directing more appropriate ICS therapy. This work demonstrates that driving down FeNO with ICS treatment reduces exacerbation risk and there is now a need for a clinical trial of FeNO guided asthma treatment with exacerbation as the primary outcome.

Until recently, the application of FeNO into clinical practice has been uncertain since the answer to the question “what a significant change in FeNO is?” was unknown. Previous trials adopted
FeNO cut offs based on comparisons between children with and without asthma or simply empirical values, e.g. 20, 30, 40 parts per billion (ppb). Our recent work has demonstrated how FeNO values may rise and fall, independently of asthma, by up to 50% over two and four months intervals\textsuperscript{13}. We also observed how (not unexpectedly) higher absolute FeNO values may rise by a greater absolute value compared to lower absolute FeNO values, e.g. the upper limit of agreement for paired FeNO measurements in a child with an initial FeNO between 21 and 30 ppb is +14ppb and the upper limit is +35ppb for a child whose FeNO is between 31-50ppb\textsuperscript{13}. Based on these observations we will, for the first time in a clinical trial, use percentage change in FeNO to interpret repeated FeNO measurements.

We will deliver a rigorous and adequately powered trial to confirm whether, in a real world cohort and setting, FeNO guided asthma treatment prevents asthma exacerbations - but also some work to understand the mechanism, and to understand who might benefit most. This trial will evaluate the clinical efficacy of our algorithm, and size of effect, of the intervention on asthma exacerbations while describing the relationship between FeNO, sputum eosinophilia, asthma control and exacerbations.

\textbf{1.2 Rationale for the trial}

This is a randomised controlled trial where outcomes are being compared between two clinical management strategies where the only difference is that FeNO is used to guide asthma treatment in the intervention arm. Our study will add to the current understanding of the relationship between FeNO, sputum eosinophilia and asthma exacerbation and also add to the research base for the management of children with asthma symptoms treated with inhaled corticosteroids. This trial is timely given the 2014 Diagnostic Guideline from NICE\textsuperscript{22} which stated that “FeNO measurement is recommended as an option to support asthma management...in people who are symptomatic despite using inhaled corticosteroids” and stated that “The Committee ... accepted there is a need for more evidence on which protocols offer the safest and most optimal asthma management when used in UK clinical practice”. This is reflected in public discussions on Twitter.

The focus of this trial is childhood asthma exacerbations, which are common, potentially life-threatening and are a considerable financial burden to healthcare systems. Annually in the UK 150,000 children see their family doctor for an asthma exacerbation and 25,000 are hospitalised\textsuperscript{23}, and our meta-analysis\textsuperscript{21} suggests that FeNO guided treatment could reduce the number of children with an asthma exacerbation by 33%. One third of the £1 billion NHS budget for asthma is spent on provision for unscheduled care\textsuperscript{24} 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”\textsuperscript{25}. This trial is based on the scientific principle that elevated FeNO is an index of eosinophilic airway inflammation, and eosinophilic inflammation is known to be present during asthma exacerbations. We are not aware of any FeNO trials currently underway and our focus on asthma exacerbations (not day-to-day symptom control) is informed by the previous trials where the focus was on asthma symptom control and not exacerbation.

Our hypothesis is that 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.
The study will have a mechanistic component which will explore the relationship between FeNO, sputum eosinophils and asthma exacerbations. Airway eosinophilia has not previously been studied within a FeNO trial, and the assumption has been that FeNO reflects airway eosinophilia and it is the suppression of airway eosinophilia with inhaled corticosteroids which reduces asthma exacerbation risk; ours will be the first FeNO trial to explore the relationship between FeNO, airway eosinophilia and asthma exacerbations.

Participants will be invited to provide a sample of saliva to allow DNA extraction and storage. Based on our recent work we seek to determine in an observational manner whether children homozygous for the Arg16 allele of the Arg16Gly variant in the gene coding for the beta 2 adrenoceptor are at increased risk for asthma exacerbations if treated with long acting beta agonist compared to increased inhaled steroid dose.

2. **TRIAL AIM AND OBJECTIVES**

The aim of the study is to compare treatment guided by FeNO and symptoms against treatment guided by symptoms alone (standard care), in children with asthma who are at risk of an asthma attack, in terms of the presence of any asthma exacerbations over 12 months requiring prescription and/or use of OCS.

The specific objectives are:

1. To recruit 502 children with physician diagnosed asthma, currently prescribed inhaled corticosteroids, aged 6-16 years with at least one parent/patient reported exacerbation treated with oral corticosteroids during the previous 12 months.
2. For recruited children to complete an assessment including spirometry, asthma control test (ACT) and FeNO at baseline.
3. To randomise children to intervention (treatment guided by FeNO and symptoms) or standard care (treatment guided by symptoms alone).
4. To monitor adherence to inhaled corticosteroid treatment with an electronic logging device.
5. To repeat FeNO and ACT at 3, 6, 9 and 12 months and change asthma treatment according to the trial protocol.
6. On an optional basis, to collect saliva for DNA isolation to allow genetic analysis in a separate study.
7. On an optional basis, for children (approximately 200) to have skin prick reactivity, bronchodilator response and sputum eosinophilia determined for a mechanistic study.
8. To undertake a qualitative process evaluation of approximately 20 children across both arms of the trial and approximately 15 trial staff, to explore experiences and acceptability of the intervention.
9. To undertake an economic evaluation to assess the health care costs (e.g. asthma related hospital admissions and visits to/from relevant health professionals, asthma medications) and other related costs (e.g. parents time of work) and quality of life effects (QALYs) of the intervention compared to routine care.
10. To compare the primary and secondary outcomes between treatment arms.
3. TRIAL DESIGN

This will be a multi-centred randomised trial comparing the efficacy of asthma treatment guided by symptoms and Fractional Exhaled Nitric Oxide (FeNO) with asthma treatment guided by symptoms alone for risk of asthma exacerbation.

FeNO will be measured in both arms, but only used to guide treatment decisions in the experimental arm (asthma treatment guided by symptoms and FeNO). In the control arm (asthma treatment guided by symptoms alone), FeNO will be measured, but the results will not contribute to any treatment decisions. Therefore in the control arm the result will only be recorded once the child has left the room. FeNO is measured in both arms because it is an outcome (as well as part of the intervention).

Participants will be in the trial for 12 months. The primary outcome will be determined up to 12 months. Clinical assessments will take place at recruitment and 3, 6, 9 and 12 months afterwards. The primary outcome will be determined by clinicians who are independent of the trial since the primary outcome (i.e. exacerbation requiring prescription and/or use of oral corticosteroid (OCS)) will not be determined by trial staff and therefore the primary outcome will not be influenced by which arm of the trial the child is randomised to.

Adherence to inhaled corticosteroid treatment will be logged electronically where an smart inhaler is available. The research design also includes an evaluation of healthcare costs (including primary and secondary care contacts and asthma treatment) and this information will be collected at each assessment, supported by a patient held diary, to inform a health economic evaluation; the inclusion of a health economic evaluation is in response to a recent Health Technology Assessment publication\(^8\) which noted that “little or no empirical evidence exists” for economic evaluation of FeNO monitoring.

The qualitative process evaluation using established research techniques will explore experiences and determine the acceptability of the intervention by interviewing ≥20 children across both arms of the trial and ≥15 trial staff until saturation of themes is achieved.

There are no stopping rules or discontinuation criteria, children who fail to respond to treatment will, per protocol, be referred for specialist care but remain in the trial. The flow diagram overleaf summarises the participant’s journey.
3.1 Intervention to be evaluated
In this study, treatment decisions in the experimental arm will be guided by FeNO measurement and symptoms. In the control arm, treatment decisions will be guided by symptoms alone, as per the current British Thoracic Society/Scottish Intercollegiate Guideline Network (BTS/SIGN) national guideline\(^9\).

Experimental intervention
In the experimental arm, asthma treatment will be guided by FeNO and symptoms. Figure 1 describes the experimental intervention and Table 1 describes the treatment steps. 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). Note that:

1. 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). Response to increasing ICS or the addition of long-acting beta agonist (LABA) or leukotriene receptor antagonist (LTRA) is known to be heterogeneous in children\(^27\) and this algorithm uses FeNO to stratify treatment with early escalation of ICS treatment or early addition of LABA and LTRA “add on” therapies, an approach which has been proven in a FeNO trial in pregnant mothers\(^28\).

2. ICS are only increased once in controlled children with elevated FeNO and only if their ICS dose was not increased since their exacerbation and they are adherent.

3. In accordance with the BTS/SIGN guideline\(^9\), poor adherence will be considered (and discussed) before escalating treatment. Elevated FeNO is due to airway inflammation but does not identify the cause of airway inflammation, poor adherence is an important mechanism for persisting airway inflammation, and adherence is therefore part of the algorithm. Adherence is a continuous measure of a complex outcome and a single cut off value to prompt a discussion about adherence is arbitrary but needed (as is also the case for asthma control). Poor adherence will be defined as <70%, an audit of children attending the asthma clinic in Aberdeen found that 48% had collected ≥70% of their inhaled corticosteroid treatment from their GP over 12 months.

4. Interpretation of FeNO on the first visit relies on population norms, rather like lung function or height, but at subsequent visits is interpreted as a percentage change from the previous measurement.

5. Asthma control is defined as ACT score of ≥20. We know from two previous FeNO intervention trials\(^29, 30\) and one observational study\(^31\) that 75% of children with asthma have ACT ≥20 at any one time.
Figure 1 – Simplified schematic of experimental intervention.

Table 1. Treatment steps for the experimental intervention.

<table>
<thead>
<tr>
<th>Step</th>
<th>Algorithm 1</th>
<th>Algorithm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Short acting beta agonist as required only (SABA)</td>
<td>Short acting beta agonist as required only (SABA)</td>
</tr>
<tr>
<td>2</td>
<td>Budesonide (or beclomethasone) 200 µg daily plus SABA</td>
<td>Budesonide (or beclomethasone) 100 µg twice daily plus SABA</td>
</tr>
<tr>
<td>3</td>
<td>Budesonide (or beclomethasone) 400 µg OR fluticasone 200 µg daily plus SABA</td>
<td>Budesonide (or beclomethasone) 400 µg OR fluticasone 200 µg daily plus SABA</td>
</tr>
<tr>
<td>4</td>
<td>Budesonide (or beclomethasone) 800 µg OR fluticasone 500 µg daily plus SABA</td>
<td>Add Long Acting Beta Agonist</td>
</tr>
<tr>
<td>5</td>
<td>Budesonide (or beclomethasone 1600 µg daily or Fluticasone 1000 µg daily plus SABA (only for &gt;=12 year olds). go to step 6 for &lt;12 year olds)</td>
<td>Add Leukotriene Receptor Antagonist</td>
</tr>
<tr>
<td>6</td>
<td>Add LABA in fixed dose combination</td>
<td>Budesonide 800 µg or fluticasone 500 µg daily in fixed dose combination</td>
</tr>
<tr>
<td>7</td>
<td>Add Leukotriene Receptor Antagonist</td>
<td>Budesonide (or beclomethasone 1600 µg daily or Fluticasone 1000 µg daily plus SABA (only for &gt;=12 year olds). Go to step 8 for &lt;12 year olds</td>
</tr>
<tr>
<td>8</td>
<td>Refer for specialist assessment</td>
<td>Refer for specialist assessment</td>
</tr>
</tbody>
</table>

*relative to previous assessment

More details in relation to the treatment steps are provided in Appendix 3; the detailed decision tree is given in Appendix 4.
Control intervention
In the control arm, asthma treatment will be guided by symptoms alone.

Figure 2 describes the algorithm for the control intervention and Table 2 describes the treatment steps, which are in accord with the national guideline⁹. 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).

Figure 2 – Simplified schematic of control intervention

Table 2. Treatment steps for the control intervention

<table>
<thead>
<tr>
<th>Treatment steps</th>
<th>Daily ICS dose µg Budesonide or equivalent</th>
<th>The delivery device used prior to enrolment will be used after enrolment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>No ICS</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>Very low dose ICS</td>
</tr>
<tr>
<td>3</td>
<td>400</td>
<td>Low dose ICS</td>
</tr>
<tr>
<td>4</td>
<td>400</td>
<td>ICS+LABA combination inhaler</td>
</tr>
<tr>
<td>5</td>
<td>400</td>
<td>Add on LTRA‡</td>
</tr>
<tr>
<td>6</td>
<td>800</td>
<td>High dose ICS</td>
</tr>
<tr>
<td>7</td>
<td>1600</td>
<td>High dose ICS</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Refer for specialist opinion</td>
</tr>
</tbody>
</table>
More details in relation to the treatment steps are provided in Appendix 3; the detailed decision tree is shown in Appendix 4.

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. FeNO results will be recorded once the child has left the room. 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. Treatment decisions in both arms will be protocolised (i.e. the relevant data for that treatment decision will be entered into the study website which incorporates the treatment algorithm and will apply this without subjectivity).

**Study exit/plan at 12 month follow up for both intervention and control arms**
The trial algorithm applies to participants in both arms of the trial at the 12 month assessment. The letter to the GP describes the treatment determined at this assessment, ongoing management will thereafter revert to the standard arm in all participants, i.e. current standard practice. This may result in some children formerly in the FeNO arm being on relatively high doses of ICS and not on LABA - this is not inconsistent with the UK BTS/SIGN guideline and is highly consistent with the guidelines in the USA and Netherlands.

### 3.2 Trial population

We will recruit 502 children – approximately 452 in secondary care sites across the UK, and 50 in primary care centres in the East of England through Optimum Patient Care (OPC) or through the UK Clinical Research Networks (CRN).

#### 3.2.1 Selection of participants

Clinical staff in recruiting secondary care centres will identify potentially eligible participants from medical records (both electronic and paper based), and from clinic lists. For recruitment in primary care centres, OPC or other primary care or CRN staff will interrogate primary care records to identify eligible participants. See section 3.3.1 for more details.

#### 3.2.2 Planned inclusion and exclusion criteria

**Inclusion criteria:**

1. asthma diagnosed or confirmed by consultant paediatrician or respiratory/asthma specialist nurse (or Read code for asthma if recruited in primary care)
2. aged 6 years or older and not reached the date of their 16th birthday (generally children below the age of 6 find it difficult to provide FeNO measurements)
3. currently prescribed inhaled corticosteroids in a device that can be fitted with a smartinhaler: the maximum dose for children aged less than 12 is 1,000 microgram budesonide equivalent per day; the maximum dose for children aged 12 and over is 2,000 microgram budesonide equivalent per day.
4. parent/patient reported asthma exacerbation treated with at least one course of oral corticosteroids in the 12 months prior to recruitment.

**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 (we cannot step up treatment further).

**Notes on inclusion and exclusion criteria:**

- There may be children who wish to take part in the study but are currently using an ICS inhaler device that cannot be fitted with a smartinhaler device. If they are subsequently established on an alternative device that can be fitted with a smartinhaler device, they can be re-approached to take part in the study after establishing on a new device (that can be fitted with a smartinhaler) for at least one month.
- No more than one sibling per family can participant in RAACENO at a time, once a sibling has completed 12 month follow-up another sibling could be approached to take part in the study provided they are eligible.
- There may be children who wish to take part in the study but cannot provide a FeNO measurement at baseline. They are not eligible at that appointment, but can be re-screened at a later date. In such cases, eligibility should be re-checked at the subsequent screening. Providing that they met the inclusion criteria “parent/patient reported asthma exacerbation treated with at least one course of oral corticosteroids in the 12 months prior to recruitment” at the time of the initial screen, they can be considered to meet this criteria at a subsequent screen, even if at the rescreen, it is more than 12 months since their last course of oral corticosteroid.
- There is no minimum dosage of ICS for inclusion. There is no minimum time since last dosage of OCS. Use of antihistamines, LABAs and LTRAs are permitted. There are no minimum/maximum FeNO readings. There is no restriction on quality of inhaler technique.

### 3.3 Recruitment and Trial Procedures

#### 3.3.1 Identifying and approaching participants

In secondary care, the local clinical team responsible for patient care will identify eligible children from paper and electronic records. The initial approach will be in person (at a clinic appointment) by a member of the usual care team (which may include embedded research nurses), or by letter/email from the managing clinician or asthma specialist nurse. For those approached in clinic, the parent and child patient information leaflets (PIL) will be handed to the family by a member of the usual clinical team. At this time, the parent will be asked whether they would be happy for a member of the study team to speak to them in the clinic or to contact them by telephone to answer any questions they may have about the study. For those approached by post or email, the parent and child patient information leaflets (PIL) and letters of invitation will be sent to the family by the managing clinician or asthma specialist nurse. A member of the usual care team (which may include embedded research nurses) may contact the parent by telephone around two weeks after the initial approach to answer any questions they have about the study.

Practices can act as Participant Identification Centres for secondary care (or other primary care) sites. NRS Primary Care Network staff, CRN staff or staff employed in the primary care practice will identify eligible children from general practice records. The initial approach will
be by letter, from a GP in the practice. This will be sent with the short PIL. Those interested in taking part in the research will be asked to contact the research team based at the recruitment site. Interested families will then be sent the parent and child patient information leaflets and arrangements made for those who wish to take part to be seen at the recruitment site for a recruitment appointment.

In primary care, the OPC team, or other primary care or CRN staff will identify eligible children from general practice records. The initial approach will be by letter, from a GP in the practice. The parent and child PILs and letters of invitation will be sent to the family or handed to the family by the managing clinician. If approached by OPC, around two weeks afterwards, a member of the OPC team will contact the family to determine whether they are interested in participating. The practices have an agreement with OPC to facilitate this activity.

Alternatively, in both secondary and primary care, the short PIL can be sent/given to the family with the invitation letter. Families who express interest in taking part will be sent the parent and child patient information leaflets before attending a recruitment appointment.

### 3.3.2 Informed consent

For families who are interested in participating in the study, a recruitment appointment will be arranged either in secondary or primary care. At this recruitment appointment, consent will be sought according to Good Clinical Practice (GCP). Written consent will be obtained from parent(s)/carer(s) and (where appropriate) from the participant. If the child does not provide written consent, they will be asked to give verbal assent.

Children who turn 16 during follow-up may wish to re-consent to their continued participation at the next follow-up visit by signing a new consent form. They will be given a participant information leaflet. If they do not wish to do this, the study team will confirm verbally that they are happy to continue taking part in the study.

### 3.3.3 Randomisation and allocation

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 the proven 24-hour web-based randomisation application hosted by CHaRT. Random allocation will use a minimisation algorithm (stratification by centre [for primary care sites this will be by primary care area], 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%). The primary care centres will be collectively considered as one centre for randomisation.

The Principal Investigator (PI) at site, or individual at site with delegated authority, will access the web-based randomisation system. Minimisation characteristics (centre, age, sex, asthma severity) will be entered into the web-based system, which will return the allocation status. After obtaining patient consent, randomisation will happen in the clinic and participants will be informed of their allocated treatment group following randomisation.

Methods to protect against sources of bias will include strict adherence to inclusion and exclusion criteria and minimising loss to follow up by using routinely acquired data (from
primary care records) as the primary outcome (funds are available to cover the cost of practice staff for this data extraction).

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. Furthermore, it will prevent any influence of FeNO results in the control arm on treatment decisions.

In the intervention arm (FeNO plus symptoms), it is not feasible to blind the participant and parent to the FeNO, e.g. in the scenario where a child’s asthma is controlled and treatment stepped down, it will be clear that FeNO has fallen.

In the control arm (symptom only group) the participant and parent will be blinded to the FeNO result. The FeNO result will be recorded after the symptom data has been entered into the study website and any treatment step up/down decisions made (see section 5.3 for more details).

There may be cases where the PI at site (or other delegated individual) feels, in their clinical opinion, that the child should not follow the step on the treatment algorithm. Such cases are not considered to be a protocol deviation, and will be documented within the study case report forms. At the next follow-up the algorithm will be applied from the treatment they are currently taking.

3.3.4 Code break/Emergency unblinding procedures
There is no requirement for emergency unblinding procedures. This is because knowledge of whether a participant is in the control or intervention group would not impact on any management decisions being taken if an adverse event occurs.

3.3.5 Follow-up procedures
Participants will be followed up, in clinic at 3, 6, 9 and 12 months. Ideally the timing of these appointments will be +/- two hours of the previous appointment to minimise any diurnal variation. However, if it is not possible to arrange an appointment +/- two hours of the previous appointment, the appointment should be organised at a time convenient to the participant. Table 3 (below) summarises what outcomes are assessed at baseline, 3, 6, 9, and 12 month assessments. Further details about collection of outcome data are provided in sections 4 and 5.

Table 3: Timing of outcomes to be assessed

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Baseline</th>
<th>3 month</th>
<th>6 month</th>
<th>9 month</th>
<th>12 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeNO</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Smart inhaler data</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Respiratory case-report form (current medication, recent asthma history and exacerbations, inhaler technique etc)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma Control Test</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Paediatric Asthma Quality of Life</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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In advance of study appointments, where families have provided a mobile number, a reminder text can be sent. In the event that an in-person visit cannot be completed, the clinic visit can be completed over the telephone by the local site team or trial office team (see section 5.1.2 for more details).

### 3.3.6 Change of Status/Withdrawal procedures

Participants will remain in the trial unless they choose to withdraw consent or if they are unable to continue for a clinical reason. All changes in status (with the exception of complete withdrawal of consent) will mean the participant is still followed up for all trial outcomes wherever possible. All data collected up to the point of complete withdrawal will be retained and used in the analysis.

If participants withdraw from the intervention or control, they will be encouraged to remain in the trial and be followed up as per trial schedule. Participants who wish to withdraw from study follow-up will be encouraged to allow routine follow-up data from hospital or GP records to be used for trial purposes.

Patients who do not attend for follow-up assessment but for whom any outcome data are available will be included in an intention to treat analysis.

Cross-over within the study (i.e. those in the intervention arm not completing FeNO measurements, or the use of FeNO measurements in someone in the control arm) will not result in withdrawal from the study. Participants will be included in an intention to treat analysis. Cross-over may be temporary (for example if the FeNO machine malfunctions during an appointment and so measurement of FeNO cannot be used to inform treatment decisions for a participant in the FeNO arm at that appointment), or permanent (for example participants in the FeNO arm may decide that they no longer wish to have their treatment informed by FeNO measurements).

### 3.3.7 Subsequent arrangements

The GP will be informed in writing when a participant joins the study; the letter will include any treatment decisions made at the recruitment appointment. They will also be informed of any treatment decisions following the 3, 6 and 9 month follow-up visits. After the 12 month follow-up visit, the GP will be informed of any treatment decision, and also that the participant has completed follow-up within the study. These letters will be signed by the local research team and generated by the study website from information entered during baseline and follow-up.
visits. Letters to GPs will be generated by site staff immediately after the study visit (see section 5.1 for more detail). When issuing the GP letter following a telephone follow-up it will be clearly documented that the visit was carried out by telephone. If there is a change in treatment the family (and GP) will be informed as to how the change should be enacted (see section 5.1.2 for further details).

The local Research Nurse/Recruitment Officer and/or PI will:

i) file a copy of the consent form in the hospital/primary care notes along with information about the study.

ii) file a copy of the GP letter into the hospital/primary care notes.

iii) enter study data regarding the participant into the bespoke study website.

iv) maintain study documentation at site. A copy of the signed consent form will be returned to the Study Office in Aberdeen.

v) provide any relevant follow-up clinical data.

If a participant withdraws from the study during the follow-up period, the local research team will write to the GP informing them of this.

Participants will be contacted by phone, post or email as appropriate. In case of non-attendance at follow-up clinic appointments or non-return of questionnaires, attempts will be made by site staff or staff at the Study Office to trace the participant directly using these means or indirectly by contacting the GP.

4. OUTCOME MEASURES

4.1 Primary outcome measure
The primary outcome, which was identified in our meta-analysis and approved as an exacerbation outcome by the ATS/ERS task force on asthma exacerbations, will be determined from the child/parent or carer and from GP records and is prescription for (and/or use of) ≥1 course of OCS for asthma exacerbations in the 12 months after randomisation (yes/no). The decision to prescribe OCS will be made by clinicians independent of the research team and working in accordance with the national guideline. Some children may have “rescue” packs of OCS at home and use of such rescue packs will also be captured as part of the primary outcome. Primary outcome data will also be captured from medical records at the end of each child’s 12 month follow-up (as described in section 5.1.3). In addition, for those recruited in hospital, hospital records will be checked for any OCS prescription during follow-up.

4.2 Secondary outcome measures
Secondary outcomes include:

- time to first exacerbation;
- number of exacerbations during follow up, based on prescribed oral corticosteroid;
- need for unscheduled healthcare assessment during follow up (yes/no);
- number of unscheduled health assessments;
• asthma control during follow up (i.e. age-appropriate Asthma Control Test score ACT \( \geq 20 \)) as used in our observational study\(^{13} \) and other FeNO studies\(^{29,30} \);
• spirometry during the 12 month follow up (i.e. %FEV\(_1\), a standard objective index of asthma severity);
• FeNO during the 12 month follow up;
• dose of ICS during the 12 months follow up (i.e. daily dose of budesonide equivalent averaged over 3 months);
• Paediatric Asthma Quality of Life Questionnaire (PAQLQ)\(^{34} \) score at 12 months;
• qualitative outcomes from interviews;
• health economic evaluation (derived from GP records and participant reported data).

5. DATA COLLECTION AND PROCESSING

5.1 Measuring outcomes

5.1.1 Baseline
At baseline, the web-based case report form (CRF) will record the participant’s details (age, sex, respiratory information (including current treatment, past history), co-morbidities, family history, socioeconomic status, etc.) plus measurements including FEV\(_1\), height and weight. Information about inhaler technique will also be recorded on the CRF. The CRF will also record the child’s FeNO (for the control group (treatment decisions based on symptoms only) this will be recorded once the assessment is completed and the child has left the assessment room).

The CRF will also be used to record participation (and any results) relating to any of the mechanistic components of the study:
• post-bronchodilator FEV\(_1\) (allowing the bronchodilator response to be derived). If the participant is likely to opt into this component of the study, they will be asked to withhold SABA for 4 hours before their appointment. No other medications will be withheld before the appointment.
• results of the skin prick test will be recorded (available within 15 minutes).
• whether sputum and saliva were obtained.

The mechanistic components of the study will only be available to those recruited in secondary care.

In addition at the recruitment appointment, children and their parent/carer attending the appointment will be asked to complete an asthma questionnaire. For children aged 11 and under, the questionnaire will comprise the CACT and the PAQLQ. For children aged 12 and over, the questionnaire will comprise the ACT and the PAQLQ.

For those in the intervention arm, data from the CACT/ACT and the FeNO results will be entered into the study website and, based on the treatment step up/down algorithm, the study website will determine any change to existing treatment. The study website will generate a summary of any treatment change (or that there is no change) for the family, for the participant’s GP, and, for those recruited in hospital, for the hospital asthma team.
For those in the control arm, data from the CACT/ACT will be entered into the study website and, based on the treatment step up/down algorithm, the study website will determine any change to existing treatment. The study website will generate a summary of any treatment change (or that there is no change) for the family, for the participant’s GP, and, for those recruited in hospital, for the hospital asthma team.

At the recruitment appointment, a SmartInhaler (if available) will be given to participants.

At the end of the recruitment appointment, a diary card will be given to participants. This can be used by participants and their parent(s)/carer(s) to document any asthma exacerbations, asthma related health care and other related resource use. If it is brought back to follow-up appointments, it will act as an aide memoir to recollect outcome data.

5.1.2 Follow-up
At the 3, 6, 9 and 12 month assessments, the web-based CRF will record FEV₁, height, and FeNO (for those in the control group FeNO will be recorded once the assessment is completed and the child has left the assessment room). Adherence (Smartinhaler) data will be downloaded and recorded in the CRF.

Inhaler technique will be checked at each assessment.

Children and their parent/carer attending the appointment will be asked to complete an asthma questionnaire (for children aged 11 and under, the CACT; for children aged 12 and over, the ACT). They will also be asked about any asthma exacerbations, and asthma related health care and other related resource use.

Based on the data captured at each appointment, the treatment may be stepped up or down if indicated by the protocol (see section 3.1). As described above in relation to the baseline appointment, once data has been entered into the study website, the treatment step up/down algorithm will determine any change to existing treatment.

Where the assessment is carried out by telephone, it will not be possible to measure FeNO or download adherence data. Family reported adherence should be captured. The treatment algorithm (for both arms) can be run without FeNO measurements or Smartinhaler data. In the FeNO arm, the symptom-only algorithm will apply. If it is the local site trial team carrying out the telephone assessment, then any change in treatment should be discussed with the PI. If the asthma control test score is less than 20, this should also be discussed with the PI.

If it is the central trial office team carrying out the telephone assessment, then any suggested change in treatment will be flagged up to the site PI and team. Similarly, if the child has an asthma control test score <20 this will be flagged up to the site PI and team if the algorithm does not recommend step up (e.g. if there are concerns about adherence).

The study website will generate a summary of any treatment change (or that there is no change) for the family, for the participant’s GP, and for those recruited in hospital, for the hospital asthma team. The letter generated following the 12 month assessment will include a
recommendation for a hospital review in 3-6 months (or GP review for those recruited in primary care). If the central office team has carried out the telephone assessment it should be agreed with the site who is going to issue the GP letter and ensure the family are informed about any change in treatment.

In addition, at the 12 month assessment, weight will also be measured, and the participant (with the assistance of parent/caregiver for younger children) will be asked to complete the PAQLQ.

Those who do not attend for follow-up at 3, 6 or 9 months will be contacted by telephone and another appointment made. There will be a six week window before and after each assessment date for that assessment to take place. Those who do not attend will be sent a brief questionnaire by post comprising the CACT/ACT and asking about any asthma exacerbations since their last visit. Non-responders will be contacted by telephone.

Those who do not attend for follow-up at 12 months will be contacted by telephone and another appointment made. There will be a six week window before and after the assessment date for that assessment to take place. Those who do not attend will be sent a brief questionnaire by post comprising the PAQLQ, CACT/ACT and asking about any asthma exacerbations since their last visit. Non-responders will be contacted by telephone.

5.1.3 Capture of data from medical records at 12 months
At the end of the 12 month follow-up period, primary outcome data will be captured from medical records. In Scotland we anticipate doing this through data linkage using the Scottish prescribing information service, and this exercise will include all participants recruited in Scotland. For participants in England where record linkage is not possible, for patients who fail to attend for follow-up at 12 months, the research nurse at site or the Trial office will contact the GP practice at which the participant is registered to capture primary outcome data: prescription for ≥1 course of OCS for asthma exacerbation in the 12 months after randomisation (yes/no). The time to first OCS course, number of OCS courses and unscheduled attendances for asthma will also be requested. If we are unable to capture data in Scotland using data linkage we will revert to the process to be used in England.

5.2 Methodology for spirometry
The standard methodology will be used. Apparatus will be calibrated in accordance with manufacturer recommendations. Apparatus may vary between centres. Ideally, the same apparatus will be used for each individual throughout their follow-up. Incentive spirometry will be used where appropriate. The participant will be seated and nose clip used. After a full breath in, the participant will exhale as quickly as possible and for as long as possible. At least three technically acceptable attempts will be made. All FEV₁ and FVC values will be recorded from the three technically acceptable attempts. FEV₁ will be the primary spirometric outcome. Other indices will be FVC, FEF₂₅-₇₅ and FEV₁/FVC ratio.

Those who opt into the optional bronchodilator response component of the study will be asked to withhold their bronchodilator (SABA) for 4 hours before their recruitment appointment. However they can participate even if they have not withheld their bronchodilator prior to their appointment. At the recruitment appointment, the child will be
asked to take their bronchodilator (400 microgram salbutamol or equivalent ideally via spacer device) and repeat the spirometry after 15 minutes using the methods described above.

Those not opting into the bronchodilator response component of the study do not need to withhold their bronchodilator before their recruitment appointment. No other medication needs to be withheld before recruitment or any follow-up appointment.

5.3 **Methodology for FeNO measurement**

The standard methodology will be used. The NIOX VERO will be switched on and a clean mouth piece applied. When the machine indicates it is ready, the participant will breathe in slowly through the mouth piece and then breathe out slowly (as directed by the visual incentive) for 10 seconds (6 seconds if aged under 10 years). Only one technically acceptable measurement is required. Wherever possible, the same apparatus will be used for the same individual and the measurement will take place at the same time (± 2 hours) at each assessment. The apparatus takes 1 minute to produce the result, an acceptable result is indicated by a beep.

FeNO will be measured before spirometry for all participants because FeNO is known to fall slightly (i.e. 6ppb) after spirometry, and so measuring FeNO before spirometry more accurately reflects the value. Furthermore, by consistently measuring FeNO before spirometry throughout the trial, intrasubject comparison of FeNO results will be valid.

For participants in the intervention arm of the trial (FeNO plus symptoms) the result can be seen by researcher, participant and parent. For participants in the symptom only arm, the FeNO measurement will be recorded after any treatment step up/down decisions have been made and the participant has left the room. Once the “beep” is heard, the assessment is complete. The NIOX VERO can be put to one side (out of view of the participant, parent and researcher). The researcher will see and enter the FeNO result into the study website once the participant and parent have left the room.

5.4 **Saliva collection for DNA analysis**

Participants who opt into this optional mechanistic component of the study will have the saliva collection done after completion of questionnaires and FeNO measurement. If commercial saliva testing kits are available at the site, manufacturer’s protocol for collection if saliva will be followed. If commercial saliva testing kits are not available at site, the participant will rinse their mouth for 20 seconds with 10 mls tap water and spit the fluid into a universal container which will be labelled and stored at minus 20 degrees or below. Samples will be sent to Aberdeen on dry ice in batches for storage at minus 80 degrees. When funding is available, samples will be thawed and DNA extracted prior to analysis of genetic variants associated with asthma and allergy outcomes. The primary variant of interest is the arg16gly single nucleotide polymorphism of the gene coding for the beta 2 adrenoceptor. Consent for DNA testing of these samples will be sought at the outset of the study. If the saliva test is not completed at baseline, it can be done at any of the study visits.

5.5 **Skin prick test**

Participants who opt into this optional mechanistic component of the study will have the skin prick test done after completion of questionnaires and FeNO measurement. The method
described by Pepys will be used to determine skin prick reactivity to cat dander, house dust mite, hen’s egg and timothy/mixed grass. Positive (histamine 10 mg/ml) and negative controls (0.9% saline) will be used. A drop of each of the six agents will be placed on the volar surface of the non-dominant forearm. The skin under the drop will be pricked with a lancet. The response to the positive control will be measured as the greatest diameter ten minutes after the skin is broken and any response to the other agents will be measured after 15 minutes. Atopy will be defined as at least one wheal that measured at least 3 mm in longest diameter or, in cases of dermatographism, a wheal greater than the negative control. Itching can be minimised by scratching the skin >5 cm away from the skin prick and/or at the end of testing by application of a damp paper towel.

There is no requirement to withhold antihistamines or skin corticosteroids or other medication prior to skin prick testing.

If the skin prick testing is not done at baseline, it can be done at any of the study visits. If skin prick testing has been carried out as part of routine clinical care in the previous 6 months, results from this test can be entered into the CRF with the consent of the family.

If the allergen agents used routinely at site differ to those described above, then the routine allergens should be used in the study skin prick testing.

5.6 Sputum induction

Participants who opt into this optional mechanistic component of the study will have the sputum collection done after completion of questionnaires and FeNO measurement, and after saliva collection and skin prick test (if done). The participant will be asked not to eat anything for one hour prior to sputum induction and to rinse out their mouth prior to testing. 200 microgram of salbutamol (via MDI/spacer or dry powder device) will be given and FEV₁ determined 15 minutes afterwards. Induction will not be carried out when FEV₁ is <50% of predicted after salbutamol. The participant will inhale 4% saline for 5 minutes via a new nebuliser mouthpiece driven by air from a wall mounted gas supply or portable nebuliser. After this time, the participant will cough. If no sputum is brought up then 5% saline will be inhaled by nebuliser for another 5 minutes and the participant asked to expectorate again. If no sputum is brought up, no further attempt will be made to obtain sputum.

The sample will be processed according to the standard operating procedure in the local laboratory (either NHS or university depending on local expertise). Briefly, the sample will be centrifuged and the cell pellet re-suspended in a standard volume before staining. A slide will be created and 400 non-squamous cells will be counted by a blinded investigator and the percentages averaged to give a final eosinophil count. The slide will be sent to Aberdeen for quality assurance purposes. The remainder of the fluid sample will be a frozen in a minus 20 freezer or below and transported to Aberdeen. The frozen sample will then be stored in Aberdeen. If funding can be secured, microbiome analysis will be carried out in the future. Consent for testing of these samples will be sought at the outset of the study.

Those who agree to participate in this optional mechanistic component of the study will be asked to provide sputum at the recruitment and 3 month study visits. If they are unable to
produce a sputum sample at the recruitment visit, they will not be asked to provide one at the 3 month visit.

Where 4% and 5% saline is not available at a recruitment site, saline of other concentrations can be used in line with local routine practice.

5.7 Data processing
Research nurses at each centre will enter locally collected data into the study website. As the treatment decisions are protocolised via the study website (see section 3.3.3), the data entry will be done in real-time to allow for any treatment step-up/down decisions to be communicated with participants and their families at the clinical appointment.

Staff in the Trial office will work closely with local Research Nurses to ensure the data are as complete and accurate as possible. Follow-up questionnaires to participants unable to attend for follow-up will be sent from and returned to the Trial Office in Aberdeen (or, if sites prefer, sent from and returned to the site team). Data from questionnaires returned to the trial office will be entered into the study website by trial office staff. Extensive range and consistency checks will further enhance the quality of the data.

5.8 Long term follow-up
We plan to seek funding to follow-up participants in the longer term using data from NHS and other government central registries, and GP and hospital notes. We propose to seek informed consent for at the outset of the study.

6. SAFETY

6.1 Definitions
The NIOX VERO is CE certified and known to be safe for use in this age group. Within RAACENO, we will only record any Adverse Events (AEs) and Serious Adverse Events (SAEs) relating to use of the NIOX VERO or other study assessments.

An asthma attack (defined as an increase in asthma symptoms requiring treatment with oral corticosteroids) is the primary outcome and is NOT an AE or SAE.

An adverse event (AE) is any untoward medical event affecting a clinical trial participant. Each initial AE will be considered for severity, causality or expectedness and may be reclassified as a serious event or reaction based on prevailing circumstances.

A serious adverse event (SAE) is any AE that:
- results in death;
- is life threatening (i.e. the subject 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 hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect,
- is otherwise considered medically significant by the investigator.
Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE or SAE. Emergency hospitals admissions that do not relate to use of the NIOX VERO or other study assessments will not be considered as an SAE.

An asthma exacerbation is an outcome for this study and is not an AE or SAE.

**RAACENO specific expected adverse events:**
In this trial the following events are potentially expected:
- Faint following any of the study interventions
- Itch (following skin prick testing)
- Cough/wheeze (following spirometry or sputum collection)

### 6.2 Procedures for detecting, recording, evaluating & reporting AEs, SAEs

#### 6.2.1 Detecting AEs and SAEs
All AEs and SAEs meeting the criteria for recording within RAACENO will be recorded from the time a participant consents to join the trial until the last trial visit. The Investigator will ask about the occurrence of AEs/SAEs at every visit. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence.

#### 6.2.2 Recording AEs and SAEs
Depending on severity, when an SAE occurs, it is the responsibility of the Investigator (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator (or delegate) should then record all relevant information on the SAE form.

Information to be collected includes type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.
6.2.3 Evaluating AEs and SAEs
Seriousness, causality, and expectedness should be evaluated.

Assessment of Seriousness
The Investigator should make an assessment of seriousness, as defined above.

Assessment of Causality (relatedness)
The Investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:
- Related: resulted from administration of any of the research procedures (for this study, use of the NIOX VERO or other study assessments)
- Unrelated: where an event is not considered to be related to any of the research procedures (for this study, use of the NIOX VERO or other study assessments).
Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Expectedness
When assessing expectedness refer to the expected events (Section 6.1).

6.2.4 Reporting AEs and SAEs
Site staff are responsible for notifying the trial office of any AEs and SAEs that require to be recorded in line with the RAACENO protocol. To summarise the information above, AEs and SAEs that require to be reported in RAACENO are those relating to use of the NIOX VERO or other study assessments. An asthma exacerbation is an outcome for this study and is not an AE or SAE. Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE or SAE.

When an SAE form is uploaded onto the trial website, the Trial Manager will be automatically notified. If, in the opinion of the local PI and the CI, the event is confirmed as being serious and related and unexpected, the CI or Trial Manager will notify the sponsor within 24 hours of receiving the signed SAE notification. The sponsor will provide an assessment of the SAE. A Sponsor cannot downgrade an assessment from the PI or CI. Any disparity will be resolved by further discussion between these parties.

The CI or delegate will report any related and unexpected SAEs to the REC within 15 days of the CI becoming aware of it. All related SAEs will be summarised and reported to the Ethics Committee, the Funder and the Trial Steering Committee in their regular progress reports.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.
7. QUALITATIVE INTERVIEWS

7.1 Overview
In a qualitative process evaluation to explore experiences and ascertain acceptability of the intervention, and to solicit in depth feedback on the process of taking part in this trial, children in both the intervention and control arms (n=<20) will be invited to give a qualitative interview with an experienced qualitative researcher. A range of trial staff representing a number of roles and across different sites (n=<15) will also be interviewed to understand the feasibility of intervention delivery from provider perspectives and to access any additional observations made around acceptability/process.

7.2 Data collection

7.2.1 Interviews with children (and their parent(s)/carer(s) where appropriate)
Selection (sampling for diversity of cases) and recruitment will be undertaken by research nurses for children in Aberdeen and a sample from across other sites. Potential participants will be identified by researchers during the course of the study and approached at their 6- or 9- or 12-month assessment to ask whether they would be happy to give an interview following their 9-month (penultimate) or 12-month (final) assessment. Qualitative interviews with individual children who consent will be arranged to take place on sites (face to face) following this final assessment (ideally immediately after the assessment, but at the convenience of the family). Telephone interviews will be offered as an alternative should the face to face arrangement prove inconvenient on the day of the pre-arranged appointment.

Informed consent procedures will be in place for all interviews. This will involve a process of revisiting the study information sheet, the consent already taken (to participate in the study), revisiting willingness to consent to a qualitative interview given at 6- or 9- or 12-month assessment, and answering any questions before interviews are undertaken.

Parent(s)/carer(s) and participants will be asked to sign an additional consent form to this effect. Children aged 16 will be able to give their own consent to be interviewed. Children will be interviewed with parent(s)/carer(s) present where appropriate. Families themselves will be asked to decide. Participation will be voluntary and will not affect treatment or trial participation. For telephone interviews, families will be given the option to provide written informed consent in advance of the interview or to provide verbal agreement at the start of the interview. If the family are happy to provide verbal agreement, the qualitative researcher will clarify that the interview is being recorded and then take verbal agreement to participate by reading each statement on the consent form to the family and giving them opportunity to agree or decline (which will be therefore recorded and transcribed). The record of agreement to take part will be in the transcript (anonymised but date and time of the interview noted).

Interviews will continue until saturation of emerging themes.

7.2.2 Interviews with trial staff
Invitations to trial staff will be made by the study team based on sampling for diversity of roles and a sample will be taken from across sites (between 10-15). Potential participants will be identified during the course of the study and will be invited either at the time of arranging
interviews with children to ask whether they would be happy to give an interview (face to face). For example, qualitative interviews with trial staff could take place at sites during visits on dates when children are being interviewed across the six sites being sampled for children/parent participants in the process evaluation. However, telephone interviews will be offered as an alternative if more convenient.

Informed consent procedures will be in place for all interviews. This will involve a process of providing a study information sheet and answering any questions before interviews are undertaken. Participants will be asked to sign a consent form to this effect. Participation will be voluntary and will not affect employment on the trial. For telephone interviews, at the start the qualitative researcher will clarify that the interview is being recorded and then take verbal agreement to participate by reading each statement on the consent form (which will be therefore recorded and transcribed). The record of agreement to take part will be in the transcript (anonymised but date and time of the interview noted).

The sample will contribute data collected across various time points within the whole course of the study. Interviews will continue until saturation of emerging themes.

7.2.3 Standard Procedures
All interviews will be semi-structured following a topic guide (one for children/parents and one for trial staff, both of which are submitted as appendices to this protocol) and, with consent, will be digitally audio-recorded and will be transcribed verbatim (by study staff or a professional typing company) for subsequent analysis. The interviews will be undertaken by an experienced qualitative researcher (DB, with supervision from HM) who will not have previously met any of the participants (children/parent(s)/carer(s) or trial staff) and who has a current, valid NHS research passport.

7.3 Analysis
A thematic approach will be used to analyse transcripts from the qualitative interviews within and across cases and data management will be assisted by NVivo10 software. Initially, one researcher (DB) will independently look for key themes and categories within and across cases by listening to the participant interviews and reading transcripts of them. These will be checked by a second researcher (HM) and shared with the wider research team. Description and interpretation of themes will contribute to the final report/recommendations.

7.4 Risks/adverse events associated with the qualitative component
We do not anticipate any major risks for participants who take part in qualitative interviews per se as they will be conducted by an experienced qualitative interviewer (DB, who has NHS research passports, which involve criminal record and occupational health assessments). However, we recognise that the sensitive content of an interview might cause distress. We will seek to minimise any adverse effects to children and their parents/carers by respecting their rights not to answer certain questions or by stopping the interview if they wish.

7.5 Confidentiality and anonymity
All participants will be informed of the confidentiality and anonymity procedures in place regarding their data (detailed within the Qualitative Study Information Leaflets), with additional information provided on a verbal basis.
Child participants will be identified using their RAACENO study identification number. This number will be used to identify participants in the qualitative component of the study. Personal identifiable details will only be accessible by the researchers.

Trial staff will be assured of confidentiality and the data they contribute will be anonymised.

Direct quotes may be used in the publication of research findings, but these will not be attributed to named individuals and any identifiable information will be removed.

7.6 Data storage
Qualitative interview data (digitally recorded and transcribed verbatim) will be stored as research data. With participant consent, electronic data will be transferred to the independent transcription service provider using FileZilla encryption software. Research data will be stored securely on password protected audio recording equipment and University/health service partner computers with only members of the direct research team having access. Paper copies will be held in locked tambour units at the University of Aberdeen that only members of the research team have access to. Any contact information or demographic details for a participant will be stored securely and separately from the interview data following the University of Aberdeen Research Governance Guidelines (http://www.abdn.ac.uk/staffnet/governance/research-governance-278.php).

Pseudoanonymised data will be archived according to University of Aberdeen guidelines. Access will only be for research purposes with the consent of the chief investigator, research funders and the research sponsor.

7.7 Withdrawal from qualitative component
Participants will be advised that they do not have to answer any questions and that they can end/leave the interview at any point. Medical care and legal rights will not be affected. Employment rights will not be affected.

8. SAMPLE SIZE, PROPOSED RECRUITMENT RATE AND MILESTONES

8.1 Sample size
We know from an audit of GPs records of children attending the asthma clinic at Royal Aberdeen Children’s Hospital that 55% of children received ≥1 course of OCS in the past year. An exacerbation incidence of 55% is consistent with results from a study of children in secondary care asthma clinics across Scotland\(^1\) however, we anticipate a lower exacerbation rate of 44%\(^2\) since outcomes in clinical trials are often better than in observational studies. Our meta-analysis finds a relative 33% reduction in the proportion with ≥1 exacerbation receiving FeNO-guided treatment\(^3\). Assuming an exacerbation proportion of 44% for the symptom-guided treatment group and 29.5% for the intervention group, we have 90% power with 5% significance (2-sided) if we recruit 238 children per group. Allowing for 5% incomplete follow up we will recruit 502 children (i.e. 251 per group). Our experience from secondary care is that 30% will participate. We will therefore invite at least 1675 children to take part (112 in each centre assuming 15 recruiting centres). For the mechanistic study, we anticipate that ≥20
children will participate and we will obtain paired FeNO and sputum samples in ≥200 of these. We have obtained the raw data from the only study to have measured both FeNO and sputum eosinophils on more than one occasion in children\textsuperscript{36}. Reanalysis of these data from the 45 study participants showed a positive relationship between change in FeNO (parts per billion) and sputum eosinophilia (%) – correlation coefficient 0.901, standard error 0.405, p=0.031. To detect a correlation coefficient 0.3 at 90% power will require 109 individuals. In our trial we anticipate having paired FeNO and sputum eosinophil count on two occasions in 200 children which will have >99% power to detect a correlation coefficient of 0.3. Our sample size is adequately powered to relate changes FeNO to changes in sputum eosinophil count. We anticipate that the mechanistic study will give insight into why FeNO might be less useful in guiding asthma treatment in some individuals (e.g. FeNO and sputum eosinophils are not correlated) and collecting data in 200 children will be crucial to understanding this (no power calculation is possible for this).
### 8.2 Recruitment rates & Milestones

#### Table 4: Study milestones

<table>
<thead>
<tr>
<th>Month</th>
<th>Date</th>
<th>Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>01/02/17</td>
<td>Monthly project management meetings for project staff. Contact and recruit site/centre, HRA and R&amp;D approvals start. Develop site manuals. Arrange first TSC meeting. Finalise web site design. Investigators meeting (1st)</td>
</tr>
<tr>
<td>2</td>
<td>01/03/17</td>
<td>Site contracting starts. Start to arrange site/centre visits and research staff training days.</td>
</tr>
<tr>
<td>3</td>
<td>01/04/17</td>
<td>First Joint TSC and DMC meeting. Hold training event.</td>
</tr>
<tr>
<td>4-5</td>
<td>01/05/17</td>
<td>R&amp;D approvals in place for centres 1-6.</td>
</tr>
<tr>
<td>6</td>
<td>01/07/17</td>
<td>Start Participant recruitment and baseline assessments</td>
</tr>
<tr>
<td>14</td>
<td>01/03/18</td>
<td>Preparation for DMC</td>
</tr>
<tr>
<td>15</td>
<td>01/04/18</td>
<td>DMC Meeting (2nd). All 15 centres set up and recruiting. Preparation for TSC</td>
</tr>
<tr>
<td>16</td>
<td>01/05/18</td>
<td>TSC Meeting (2nd)</td>
</tr>
<tr>
<td>18</td>
<td>01/07/18</td>
<td>Final assessments (12 month visits) Primary Outcome data collection starts</td>
</tr>
<tr>
<td>25</td>
<td>01/02/19</td>
<td>Qualitative interviews start</td>
</tr>
<tr>
<td>26</td>
<td>01/03/18</td>
<td>Preparation for DMC</td>
</tr>
<tr>
<td>27</td>
<td>01/04/19</td>
<td>DMC Meeting (3rd) Preparation for TSC</td>
</tr>
<tr>
<td>28</td>
<td>31/05/19</td>
<td>Participant recruitment and baseline assessments finish</td>
</tr>
<tr>
<td>29</td>
<td>01/06/19</td>
<td>TSC Meeting (3rd)</td>
</tr>
<tr>
<td>34</td>
<td>01/11/19</td>
<td>Qualitative interviews finish</td>
</tr>
<tr>
<td>40</td>
<td>31/05/20</td>
<td>Final assessments (12 month visits) finish</td>
</tr>
<tr>
<td>42</td>
<td>01/07/20</td>
<td>Finish collecting primary outcome data</td>
</tr>
<tr>
<td>43</td>
<td>01/08/20</td>
<td>Data checking and database closure</td>
</tr>
<tr>
<td>44</td>
<td>01/09/20</td>
<td>Data analysis starts. Preparation for final TSC meeting</td>
</tr>
<tr>
<td>46</td>
<td>01/11/20</td>
<td>TSC Meeting (4th), Interpretation of results. Drafting final report and papers. Investigators meeting (2nd)</td>
</tr>
<tr>
<td>48</td>
<td>31/01/21</td>
<td>End of study, submit final report</td>
</tr>
</tbody>
</table>
Additional sites, over and above the 15 originally anticipated, will recruit patients into the study.

A GANTT chart is shown in appendix 2.
9. **STATISTICAL ANALYSIS**

Analysis will be by intention to treat. To determine whether the intervention leads to reduction in
the primary outcome, logistic regression will be used to compare the primary outcome
(yes/no) between treatment groups adjusting for relevant baseline factors known to be strongly
related to exacerbation at 12 months (age, gender, socioeconomic status, asthma severity and
centre). Number of exacerbations will be analysed using Poisson regression adjusting for the
same baseline factors. Time to first exacerbation will be compared between groups using Cox
regression. Secondary outcomes including Asthma Control Test, FeNO, FEV₁, and dose of ICS
will be compared between treatment groups using linear mixed effects models to account for
the correlation between repeated measures, the benefit of this approach is inclusion of all
individuals where there is ≥1 clinical assessment. Unscheduled health care attendance (yes or
no) will be compared between treatment groups using Generalised estimating equations and if
deemed appropriate the number of unscheduled health care attendances will be compared
using Poisson regression. Full details will be described in the statistical analysis plan for the
study. Comparison of quality of life (using the PAQLQ) at the final assessment (12 months)
between treatment groups will be assessed using analysis of covariance, adjusting for
minimisation variables, baseline values and other appropriate baseline predictors. The
influence of any missing data on the robustness of the findings will be examined using sensitivity
analyses incorporating multiple imputation or other relevant strategies under alternative
assumptions. The mechanistic part of the study will describe the correlation between
percentage change in FeNO and sputum eosinophilia over three months and will repeat the
primary outcome analysis described above among the subset concordant for FeNO and sputum
eosinophilia (as previously defined³⁶) since we anticipate FeNO will be most efficacious in
guiding ICS treatment in this subset.

10. **ECONOMIC EVALUATION**

Our primary economic evaluation will be conducted from a UK National Health Services (NHS)
and Personal Social Services perspective; however we will also present data from a wider
societal perspective. Data from the cost perspective of the NHS, the social care perspective and
the participant’s perspective will include costs to participant/parent of time and travel, costs to
carers and family members, purchase of additional medications and costs to society (e.g.
societal losses due to children missing school and their parents missing work – value of lost
productivity/ away from normal activities to care for their child during an exacerbation).

The economic evaluation framework will follow a similar approach to the methods used in the
PLEASANT trial (a large UK trial assessing the impact of a brief postal intervention from the GP
on reducing the main endpoints of unscheduled appointments and exacerbation of asthma in
school aged children associated with return to school after the summer holidays)³⁷. Our study
also assumes that the intervention has no effect on survival and that any QALY gain will be
wholly driven by improvements in quality of life achieved by preventing asthma exacerbations.

The costs and benefits of the two treatment options (asthma treatment guided by symptoms
plus FeNO, asthma treatment guided by symptoms only) will be synthesised using an
incremental (cost-effectiveness) analysis. We will develop a simple decision model to perform
an exploratory analysis, based on observed trial resource use data (translated to a cost-per-
patient using standard sources of NHS unit costs), the exacerbation rate associated with the
study arms, and published estimates/literature evidence on the health-related-quality of life decrement associated with asthma exacerbation that results in an unscheduled medical contact to then estimate QALYs.

We will adopt both a cost-effectiveness approach, assessing health gain in terms of asthma exacerbations prevented, and a cost–utility approach, assessing gains in QALYs. We will model costs and effectiveness over the short term trial (12 months) time horizon. Results will be presented as cost-per exacerbation avoided and cost-per-QALY gained within the trial period. Univariate sensitivity analyses and probabilistic sensitivity analyses will be used to examine the uncertainty in the model, with results displayed using cost-effectiveness planes and cost-effectiveness acceptability curves (if more appropriate).

10.1 Collection of resource use and cost data
We will focus on capturing use of primary and secondary health care and personal costs to participants collected via case report forms at the 3, 6, 9 and 12 month follow-up visits, with questionnaire and telephone follow-up of those not attending scheduled trial assessment.

The diary cards given to participants at recruitment (and at 3, 6 and 9 month follow-up) describes the information that will be collected at the follow-up visits, and gives space for participants and their families to write down information about their asthma, exacerbations, and any treatment. If they bring the diary card to their follow-up appointments, this will act as an aide memoire at the appointment.

Information about specific asthma related health care (eg due to an acute asthma attack or related to non-acute asthma episodes) during the previous 3 months will be collected via case report forms at recruitment and the 3, 6, 9 and 12 month assessment. These will include primary care contacts (e.g. GP, practice or community nurse, other community contacts), secondary care contacts (e.g. hospital outpatient appointments and hospital inpatient admissions) and prescription asthma-related drug medications (e.g. asthma/inhaled corticosteroid (ICS) treatment). Health care use will then be valued by applying unit cost information for the use of specific resources using standard unit costs sources (e.g. Personal Social Service Research Unit (PSSRU)\textsuperscript{38} unit costs, NHS reference costs\textsuperscript{39}, British National Formulary (BNF)\textsuperscript{40}). Total costs will be aggregated across patients to derive an average total cost per patient/trial participant at 12 months for each group (FeNO + symptoms schedule and symptoms schedule only) Non-parametric bootstrapping of observed resource use/cost data will be conducted to address uncertainty. Regression techniques will be used to estimate differences in costs between the two treatment groups from the information collected on resource during the trial. We will undertake a range of sensitivity analyses (such as deterministic sensitivity analysis, various methods for imputation of any missing data, best and worst case scenarios for the intervention cost) to test uncertainty in assumptions we make in our analyses on the overall cost results.

Intervention costs associated with repeated FeNO measurement/ guided treatment/ monitoring in childhood asthma practice include the cost of purchasing the FeNO measurement apparatus and the need for staff to supervise measurements. Staff training and changing asthma treatment per protocol are not barriers to introducing a FeNO guided treatment algorithm. Staff need no training in the clinical application of the device used in the study. A "staff time record
form” will be developed to collect information on the additional time spent, if any, a result of the new service for the management of childhood asthma.

10.2 Participant costs
Direct health care costs and non-health care costs falling on the participant/parent/carer will be incorporated into the participant perspective analysis. These will cover information on time (e.g. costs associated with parents lost days at work), travel costs related to visits to GP, hospital doctor or other health care provider relating to their child’s asthma, and out of pocket patient expenses (including the purchase of over the counter asthma medicines/products) and be collected as part of the trial (via CRFs). These data will enable cost-effectiveness analyses from both an NHS and wider societal perspectives to be undertaken.

10.3 Quality of life
We are not collecting health utility data as part of the trial, but rather we will derive our quality of life weight estimates (for health status valuations used in the model) from the available published evidence (to calculate QALYs related to asthma exacerbations). The Paediatric Asthma Quality of Life Questionnaire is included as a patient-centred outcome and not a health economic outcome. The quality of life of children with asthma is usually similar to children without asthma outwith an exacerbation. Therefore we do not believe the collection of EQ-5D data is absolutely necessary given the assumption made that any gain in QALYs will be wholly driven by improvements in quality of life achieved by preventing asthma exacerbations and wanting to limit the burden of outcome measures on participants.

10.4 Cost effectiveness
We will adopt both a cost-effectiveness approach, assessing health gain in terms of incremental asthma exacerbations prevented, and a cost–utility approach, assessing gains in incremental QALYs. We will model mean incremental costs and effectiveness and cost-effectiveness of a FeNO plus symptom treatment schedule compared to a symptom-only schedule (routine care) over the short term, 12-month trial follow-up period. Therefore no discounting of costs and benefits will be applied. The results of the analysis will be presented as incremental costs, effects and incremental cost-effectiveness ratios (in terms of cost per exacerbation avoided or cost per QALY gained). A range of one- and multi-way deterministic sensitivity analyses (or probabilistic sensitivity analysis if more appropriate) will be conducted to address uncertainty in these estimates and robustness of the results. Cost per QALY data will also be presented in the form of cost-effectiveness acceptability curves (CEAC) to show the probability that different the intervention is cost effective for different values of willingness to pay per additional QALY.

11. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 Trial office in Aberdeen
The Trial Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The Trial Manager in CHaRT at Aberdeen will take responsibility for the day to day transaction of trial activities. The Data co-ordinator will provide clerical support to the trial, including organising all aspects of the postal questionnaires for participants unable to attend the
assessments (mailing, tracking, and entering returned data using the trial web data entry portal).

The RACEENO Trial Office Team will meet formally approximately monthly during the course of the trial to ensure smooth running and trouble-shooting.

We intend to produce regular newsletters for participants and collaborators to inform everyone of progress and maintain enthusiasm.

Any modification to the project shall be approved by the Sponsors and funder before application to REC and R&D unless in the case of immediate safety measures when the Sponsor shall be notified as soon as possible.

11.2 Local organisation in sites
The PI and research nurse(s) in each site are responsible for all aspects of local organisation including identifying potential recruits, consenting and assessing participants. Appropriate members of the local team require current good clinical practice certification. A study-specific Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the study. The local team is also responsible for notifying SAEs to the trial office (see section 6).

11.3 Project Management Group (PMG)
The trial is supervised by its Project management Group (PMG). This consists of the grant holders and representatives from the Trial Office. Observers may be invited to attend at the discretion of the PMG. We will meet/teleconference every 2-3 months on average.

There will be regular teleconferenced “site meetings”, usually chaired by the CI and attended by research nurses from each centre. Fixed items on the agenda for these meetings will include recruitment (numbers and challenges), apparatus/equipment (what will need replacing) and problems arising or solved.

There will be a meeting at the end of the study to share the results with investigators.

11.4 Trial Steering Committee (TSC)
A Trial Steering Committee (TSC), with independent members, will be established to oversee the conduct and progress of the trial. The terms of reference of the TSC, the template for reporting and the names and contact details of members of the TSC will be filed in the Trial Master File.

11.5 Data Monitoring Committee (DMC)
An independent Data Monitoring Committee (DMC) will be established to oversee the safety of subjects in the trial. The terms of reference of the DMC and the names and contact details will be filed in the Trial Master File. The committee will meet regularly to monitor the unblinded trial data and serious adverse events and make recommendations as to any modifications that are required to be made to the protocol or the termination of all or part of the trial.
12. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

12.1 Research Governance
The trial will be run under the auspices of CHaRT. This will aid compliance with Research Governance and the principles of Good Clinical Practice (GCP), and provide centralised trial administration, and database support. CHaRT is a registered Clinical Trials Unit with particular expertise in running multicentre RCTs of complex and surgical interventions.

The CI will ensure, through the TSC, that adequate systems are in place for monitoring the quality of the trial (compliance with appropriate governance) and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the trial. The Sponsor’s Standard Operating Procedures (SOPs) shall be followed.

12.2 Data protection
Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participant’s details will be stored on a secure database under the guidelines of the 1998 Data Protection Act and regular checks and monitoring are in place to ensure compliance. Data are stored securely in accordance with the Act and archived to a secure data storage facility. The CHaRT senior IT manager (in collaboration with the CI) will manage access rights to the data set. Participants will be allocated an individual specific trial number. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

12.3 Sponsorship
The University of Aberdeen and Grampian Health Board (NHS Grampian) are the co-sponsors for the trial.

13. ETHICS AND REGULATORY APPROVALS
The North of Scotland Research Ethics Committee will review this trial. The trial will be conducted according to the principles of Good Clinical Practice provided by Research Governance Guidelines. Annual progress reports and a final report at the conclusion of the trial will be submitted to the Sponsor and the North of Scotland REC within the timelines defined in the regulations.

14. QUALITY ASSURANCE
The trial will be monitored to ensure that it is being conducted as per protocol, adhering to Research Governance, the principles of GCP, and all other appropriate regulations. The approach to, and extent of, monitoring (specifying both central and on-site monitoring) will be specified in a trial monitoring plan which is usually initially determined by a risk assessment, undertaken prior to start of trial. Investigators and their host Trusts will be required to permit trial related monitoring and audits to take place by the Sponsor and/ or regulatory representatives providing direct access to source data and documents as requested.
14.1 Risk assessment
An independent risk assessment has been carried out by the Sponsor. The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate and proportionate to the risk assessment of the study.

15. Finance and Insurance
The trial is funded by a grant awarded by the National Institute for Health Research Efficacy and Mechanisms Evaluation (NIHR EME).

The necessary trial insurance is provided by the University of Aberdeen.

16. End of Trial
The end of follow-up for each participant is defined as the final data capture to answer the research question. The end of the trial is defined as the end of funding.

The end of the trial will be reported to the REC within 90 days, or 15 days if the trial is terminated prematurely. The end of the trial will be reported to the Sponsors within 90 days. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the trial will be provided to the Sponsor and to REC within one year of the end of the trial. An end of trial report should also be issued to the funders at the end of funding.

17. Data Handling, Record Keeping and Archiving
Clinical data will be entered into the database by the local investigator and/or research nurse working in each hospital site, together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial office will be entered there. Staff in the trial office will work closely with local research nurses to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

Responsibilities for archiving are documented in the co-sponsorship agreement. All essential data and documents (electronic and hard copy) shall be retained for a period of at least 10 years after close of trial according to the relevant UoA/NHSG Sponsor and CHaRT archiving SOPs. Electronic data will be archived by CHaRT. The archiving procedures for hard copy documentation held at local sites will be performed as documented in the Sponsor site agreement.
18. SATELLITE STUDIES

It is recognised that the value of the trial may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advance with the Project Management Group, and if appropriate with the Trial Steering Committee. Depending on the nature of the satellite study, the Sponsor may consider this to be a non-substantial or a substantial amendment to the REC approval for the RAACENO study, or to require REC approval as a project in its own right. R&D management approval may also be required. In such situations, the sponsor will be contacted for advice.

19. AUTHORSHIP & PUBLICATION

All RCTs conducted by CHaRT have a commitment to publish the findings of the research. At a minimum this trial will have a results paper published in a peer-reviewed medical/scientific journal. If all grant-holders and research staff fulfil authorship rules, group authorship will be used under the collective title of ‘the RAACENO Trial Group’. If one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to the named individual(s) and the RAACENO Trial Group assuming that the named individual fulfils the authorship criteria as detailed in the ICMJE http://www.icmje.org/recommendations/browse/.

For reports which specifically arise from the trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to the named individual(s) for the RAACENO Trial Group.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the Project Management Group.

Further details on the publication policy can be found in Appendix 1.

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.

The project will have a Twitter account. It is anticipated that this will be used to disseminate study news and milestones (for example the first patient recruited; new sites opening). The account will be public, so available to researchers, participants and anyone else who may come across the account. The research team will not offer clinical advice on individual cases via Twitter and this will be made clear on the Twitter account. The Twitter account will have a link to the RAACENO project website, where we will host our terms of engagement with Twitter. Any information considered vital to the study, or to study participation would be shared with participants through other means (for example by letter), rather than through Twitter – therefore participants who do not use social media would not be disadvantaged.
REFERENCES

Appendix 1. Authorship policy for the RAACENO study

1. DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria in3:

i. Substantial contributions to the conception or design of the work represented by the article OR analysis and interpretation of the data OR both; AND

ii. Drafting the article or revising it for critically important content; AND

iii. Final approval of the version to be published, AND

iv. 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.

2. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals1,2 and are in accordance with the rules of the International Committee of Medical Journal Editors3.

a. Group authorship

Group authorship will be appropriate for some publications, such as main reports. This will apply when the intellectual work underpinning a publication 'has been carried out by a group, and no one person can be identified as having substantially greater responsibility for its contents than others'.1 The authorship will be presented by the collective title - The RAACENO Trial Group - and the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. In most cases, one or more authors will, however, take responsibility for drafting the paper. In such cases the authorship will be presented using the by-line 'Jane Doe and the RAACENO Trial Group'.2 Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the by-line would read 'Jane Doe for the Trial Group').2

b. Individual authorship

Other papers, such as those describing satellite studies, will have individual authorship and must fulfil the criteria detailed in the section ‘DEFINING AUTHORSHIP’ above in order to qualify for authorship.

Contributors who meet fewer than all four of the criteria for authorship listed above should not be listed as authors, but they should be acknowledged. For example, participation solely in the acquisition of funding, collection of data or writing assistance with the article is insufficient by itself to justify authorship.3 Those persons may be acknowledged and their contribution described.
c. **Determining authorship**
   Tentative decisions on authorship should be made as soon as possible\(^1\), ideally during the trial set up phase. These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Trial Steering Committee (TSC).

d. **Ordering of authors**
   The ordering of authors, particularly for publications with individual authorship, is governed by three rules:
   
i. The person who has taken the lead in writing is entitled to be the first author.
   
   ii. Those who have made a major contribution to analysis or writing (i.e. have done more than commenting in detail on successive drafts) are entitled to follow the first author immediately; where there is a clear difference in the size of these contributions, this should be reflected in the order of these authors.
   
   iii. All others who fulfil the four authorship criteria described in Section 1: Defining Authorship should complete the list in alphabetical order of their surnames.

3. **ACKNOWLEDGEMENTS**
   All those who make a contribution to a publication, but who do not fulfil the criteria for authorship, such as interviewers, data processors, secretaries and funding bodies, should be acknowledged by name, usually in an ‘Acknowledgements’ section specifying their contributions.

4. **DISCLAIMERS**
   All papers arising from CHaRT must include the full title of the Unit and the appropriate disclaimer specified by the Chief Scientist Office (CSO): ‘HSRU is funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorates. The author accepts full responsibility for this talk/paper’.

   A disclaimer should also be included to take account of relevant funders, e.g. For studies funded by the NIHR EME programme the disclaimer would be ‘The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health’.

5. **QUALITY ASSURANCE**
   Ensuring quality assurance is essential to the good name of the trial group. For reports of individual projects, internal peer review among members of the Project Management Group is a requirement prior to submission of papers. All reports of work arising from the RAACENO trial including conference abstracts should be peer reviewed by the Project Management Group.

   The internal peer review for reports of work arising from the RAACENO project is mandatory and submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. The Project Management Group will be responsible for
decisions about submission following internal peer review. If individual members of the group are dissatisfied by decisions, the matter may be referred to the TSC.

The Project Management Group undertake to respond to submission of articles for peer review at the Project Management Group Meeting following submission (assuming the report is submitted to the trial secretariat in Aberdeen at least two weeks prior to the meeting).

It is hoped that the adoption and dissemination of this policy will prevent grievances that cannot be resolved by informal discussion. However, anyone with such a grievance should discuss it with the relevant Chief Investigator, TSC, Line Manager or Programme Director as appropriate.

REFERENCES
3. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Developed by members of the ICMJE over the period 2011 to 2013. (www.icmje.org/#authors)
Appendix 2. GANTT chart
### Appendix 3. Treatment step algorithm

<table>
<thead>
<tr>
<th>Baseline inhaled corticosteroid</th>
<th>Bud equiv; L (LABA)</th>
<th>BTS Step</th>
<th>Drug no1</th>
<th>Control - Symptom only (&lt;12 years)</th>
<th>Control - Symptom only (&gt;12 years)</th>
<th>FeNO Algorithm 1 (&lt;12 years)</th>
<th>FeNO Algorithm 1 (&gt;12 years)</th>
<th>FeNO Algorithm 2 (&lt;12 years)</th>
<th>FeNO Algorithm 2 (&gt;12 years)</th>
<th>D/S</th>
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</thead>
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<tr>
<td>SABA only (no inhaled corticosteroid)</td>
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<td>0</td>
<td>1</td>
<td>n/a</td>
<td>1</td>
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<td>1</td>
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<td>1</td>
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<tr>
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<td>200</td>
<td>Step 2</td>
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<td>1</td>
<td>0/4</td>
<td>2</td>
<td>1/2</td>
<td>0</td>
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<td>400</td>
<td>Step 2</td>
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<td>4</td>
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<td>4</td>
<td>0</td>
<td>2</td>
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<td>4/2</td>
<td>0/2</td>
<td>0</td>
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<td>28</td>
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<td>2</td>
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<td>4</td>
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<tr>
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<td>Step 2</td>
<td>8</td>
<td>9</td>
<td>0</td>
<td>2</td>
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<tr>
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<td>1000</td>
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RAACENO trial protocol
ISRCTN 67875351; IRAS 212541
Version 6, 19 March 2020
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Abbreviations:  
mg - microgram  
A – children aged <12 years who are on this medication at baseline would not be eligible for the study.  
n/a – children on SABA only cannot step down further; if the decision tree indicates step down; there will be no change to their treatment step (ie they will remain on SABA only until a step up is indicated by the decision tree)  
RSO – refer specialist opinion. If the decision tree indicates step up; the child will be referred to see the asthma doctor.  
D/S – this column summarises whether the algorithms for symptom only/FeNO 2 and FeNO 1 are the same [S], different [D] or different only in the children aged >=12 years [D(o)]. Refer to general note 6 on next page.

Footnotes:  
1 Drug rows 6 and 7 do not exist on the treatment algorithm. They have been deleted because the drug that was included in these rows is not available. Drug row 57 has been deleted because it duplicated row 45.  
2 BTS step is based on the following. All children on 200-400 bud equivalent ics without LABA OR LTRA are considered to be on BTS step 2. All children on 200-400 bud equivalent plus LABA and/or LTRA are considered to be on BTS step 3. Children aged <12 years on 800-1,000 bud equivalent will be on BTS step 4. Children aged >=12 years on 800-1000 bud equivalent with LABA and/or LTRA are considered to be on BTS step 4. Children aged >=12 years on 2000 bud equivalent will be on BTS step 4 (younger children on this dose would not be eligible).  
3 There is currently not a suitable smartinhaler to fit Flutiform, Twisthaler and Qvar devices. These rows are therefore not currently active on the treatment algorithm. If a suitable smartinhaler becomes available, children on these devices would be eligible for the study, and these rows would become active on the treatment algorithm. The rows that are currently active on the treatment algorithm do NOT direct to rows 16-19 or 30-33.
Rationale for step-up / step down treatments

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<tr>
<td>• Increase ICS to 400 mcg bud equivalent per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Add LABA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Add LTRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increase ICS to 2000 mcg bud equivalent per day</td>
<td></td>
<td></td>
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<tr>
<td>Step down:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reduce ICS to 400 mcg bud equivalent per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Remove LTRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Remove LABA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reduce ICS further</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mcg – microgram

Additional rules:

- When increasing/decreasing ICS, the steps are: 200 bud equivalent per day; 400 bud equivalent per day; 800/1000 bud equivalent per day; 2000 bud equivalent per day. Children who step down from 200 bud equivalent per day will be on SABA only.
- Where possible, delivery device should be maintained. In general, step up with the same inhaler device where possible. If the maximum dose is reached on a dry powder device and step up is still required, switch to MDI/spacer. Therefore, when the maximum (for age) dose of ICS is reached on the Accuhaler device and both LABA and LTRA have been added, the delivery device should be changed to an Evohaler device (with spacer) at the same dose.
- Younger children on Seretide Accuhaler 250 1 dose twice daily plus LTRA will therefore step up to Seretide Evohaler 125/25 MDI/spacer 2 puffs twice daily. Older children on Seretide Accuhaler 500 1 dose twice daily plus LTRA will therefore step up to Seretide Evohaler 250/25 MDI/spacer 2 puffs twice daily.
- Children aged >=12 years who step up from Symbicort Turbohaler 400/12 DPI 1 dose twice daily (800 mcg bud equiv) will step up to Seretide Evohaler 250/25 MDI/spacer 2 puffs twice daily (2000 mcg bud equiv).

General notes:

Note 1. The treatment steps for the symptom only group are based on the BTS guidelines (2014). These guidelines are similar to the updated guidelines in 2016; however the 2016 guidelines have recommendations for which there is not an appropriate inhaler device.

Note 2. If the FeNO responds to the increased ICS and at the next appointment has not increased again by more than 50%, FeNO algorithm 2 will be applied; therefore doses of ICS above 400 bud equivalent would be supplemented with LABA/LTRA before increasing further.

Note 3. The drugs included on the treatment algorithm are based on table 9 of the current BTS guidelines. A number of the drugs listed in the guideline are not included on the algorithm either because (i) they are not licensed for use in children (Fostair, DuoResp Spiromax), (ii) a suitable smart inhaler device is not available (Qvar autohaler, Asmacbe, Budelin Novolizer, Asmanex Twinthaler, Relvar), or (iii) children on these medications would not be eligible for the study (Alvesco Aerosol inhaler (ciclesonide)).

Note 4. If new drugs/devices become available during the study period, these will be considered for inclusion on the treatment algorithm if (i) they are licensed for children; (ii) a suitable smart inhaler device is available; and (iii) they are appropriate given the step up/down rules listed above.

Note 5. There are differences in algorithms for symptom only/FeNO 2 and FeNO 1 at the lower and upper ends of the treatment spectrum. The algorithms for symptom only/FeNO 2 and FeNO 1 are:

**The same when the starting treatment step is:**

- 200 mcg bud equivalent;
- 200 mcg bud equivalent plus LTRA;
- 400 mcg bud equivalent plus LABA and LTRA;
- 800-1000 mcg bud equivalent plus LABA and LTRA;
- 2000 mcg bud equivalent +/- LABA/LTRA.

**Different for children of all ages when the starting treatment step is:**

- 400 mcg bud equivalent;
- 400 mcg bud equivalent plus LABA;
- 400 mcg bud equivalent plus LTRA.

**Different for children >=12 years when the starting treatment step is:**

- 800-1000 mcg bud equivalent;
- 800-1000 mcg bud equivalent plus LABA;
- 800-1000 mcg bud equivalent plus LTRA.
Appendix 4. Decision trees for control and FeNO arms
Decision tree - control intervention

First assessment (baseline)
- Current ACT≥20
  - No change
  - Step up

Second assessment (3 mo)
- Current ACT≥20
  - Baseline ACT≥20
    - Step down
    - No change
  - Baseline ACT<20
    - Step up
    - No change

- Current ACT<20, adherence ≥70%
  - Previous ACT≥20
    - Step up
  - Previous ACT<20
    - No change

- Current ACT<20, adherence <70%
  - Previous ACT≥20
    - Step up
  - Previous ACT<20
    - No change

Third assessment (6 mo)
- Current ACT≥20
  - Previous ACT≥20
    - Step down
    - No change
  - Previous ACT<20
    - Step up
    - No change

- Current ACT<20, adherence ≥70%
  - Previous ACT≥20
    - Step up
  - Previous ACT<20
    - No change

Fourth assessment (9 mo)
- Current ACT≥20
  - Previous ACT≥20
    - Step down
    - No change
  - Previous ACT<20
    - Step up
    - No change

- Current ACT<20, adherence ≥70%
  - Previous ACT≥20
    - Step up
  - Previous ACT<20
    - No change

Fifth assessment (12 mo)
- Current ACT≥20
  - Previous ACT≥20
    - Step down
    - No change
  - Previous ACT<20
    - Step up
    - No change

- Current ACT<20, adherence ≥70%
  - Previous ACT≥20
    - Step up
  - Previous ACT<20
    - No change

- Current ACT<20, adherence <70%
  - Previous ACT≥20
    - Step up
  - Previous ACT<20
    - No change

ACT = Asthma Control Test / Childhood Asthma Control Test. The "current" test is the one completed at this assessment.

1 Step up regardless of whether or not they were stepped up after their last asthma attack (pre baseline).
2 At 3, 6, 9 and 12 months, if the asthma is well controlled (ie current ACT≥20), adherence does not need to be considered in the decision tree. The decision to step down or make no change is based on current and previous ACT only.
3 At the 3 month time-point, when deciding whether or not there was a previous step-up, we are thinking about previous step-up through the red route, (ie poor adherence) at baseline. Any step up through the blue route, ie when adherence was good is not relevant in making this decision. Over the 12 month period, patients can only step up once through the red route.
4 At the 6 month time-point, the previous ACT will be at 3 months. If the participant did not attend for the 3 month visit, the previous ACT will be the baseline ACT.
5 At the 6 month time-point, when deciding whether or not there was a previous step-up, we are thinking about previous step-up through the red route, (ie poor adherence) at baseline OR at 3 months. Any step up through the blue route at 3 months, ie when adherence was good is not relevant in making this decision. Over the 12 month period, patients can only step up once through the red route.
6 At the 9 month time-point, the previous ACT will be at 6 months. If the participant did not attend for the 6 month visit, the previous ACT will be the 3 month ACT. If the participant did not attend for either the 3 or the 6 month visit, the previous ACT will be the baseline ACT.
7 At the 9 month time-point, when deciding whether or not there was a previous step-up, we are thinking about previous step-up through the red route, (ie poor adherence) at baseline OR at 3 months OR at 6 months. Any step up through the blue route at 3 months OR at 6 months, ie when adherence was good is not relevant in making this decision. Over the 12 month period, patients can only step up once through the red route.
8 At the 12 month time-point, the previous ACT will be at 9 months. If the participant did not attend for the 9 month visit, the previous ACT will be the 6 month ACT. If the participant did not attend for either the 6 or the 9 month visit, the previous ACT will be the baseline ACT. If the participant did not attend for either the 3 or the 6 or the 9 month visit, the previous ACT will be the baseline ACT.
9 At the 12 month time-point, when deciding whether or not there was a previous step-up, we are thinking about previous step-up through the red route, (ie poor adherence) at baseline OR at 3 months OR at 6 months OR at 9 months. Any step up through the blue route at 3 months OR at 6 months OR at 9 months, ie when adherence was good is not relevant in making this decision. Over the 12 month period, patients can only step up once through the red route.
FeNO intervention

1. **First assessment (baseline)**

   - ACT<20, FeNO≤20
   - ACT≥20, FeNO≤20
   - ACT<20, FeNO≥20
   - ACT≥20, FeNO≥20

2. **Second assessment (3 mo)**

   - ACT<20, FeNO≤20
   - ACT≥20, FeNO≤20
   - ACT<20, FeNO≥20
   - ACT≥20, FeNO≥20

3. **Third assessment (6 mo)**

   - ACT<20, FeNO≤20
   - ACT≥20, FeNO≤20
   - ACT<20, FeNO≥20
   - ACT≥20, FeNO≥20

4. **Fourth assessment (9 mo)**

   - ACT<20, FeNO≤20
   - ACT≥20, FeNO≤20
   - ACT<20, FeNO≥20
   - ACT≥20, FeNO≥20

5. **Fifth assessment (12 mo)**

   - ACT<20, FeNO≤20
   - ACT≥20, FeNO≤20
   - ACT<20, FeNO≥20
   - ACT≥20, FeNO≥20

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1. At baseline, information about any recent step up is captured in the baseline CRF, question 13B. If the response to 13B is "no" or "unsure" or "missing" then we assume that there has been no recent step up. Recent-last 12 months

2. Children who are asymptomatic and who have elevated FeNO (shown in purple at each visit) can step up more than once on the purple route during the 12 month follow-up period. However, they cannot step up treatment more than once unless they have stepped down after the first step-up. So for example, a child who steps up to the purple route at 3 months and steps down at 6 months could step up again at 9 months through the purple route; but a child who steps up through the purple route at 3 months, and has either no change at 6 months (or a step up through red or blue routes) cannot step up again through the purple route at 9 months.

3. At the 3 month assessment, change in FeNO is calculated in respect to baseline FeNO value.

4. At the each of the 3, 6, 9 and 12 month assessments, "recent" step up is since joining the study (ie a step up since baseline).

5. Children who are poorly adherent can only have one step up through the red route once over the 12 month follow-up period. So for example, any children who are poorly adherent at 6 months and who have previously stepped up through the red route at 3 months will have no change to their treatment step at the 6 month appointment. Similarly, children who are poorly adherent at 9 months and who have previously stepped up through the red route at 3 or 6 months will have no change to their treatment step at the 12 month appointment.

6. At the 6 month assessment, change in FeNO is calculated in respect to 3 month FeNO value. If the participant did not attend at the 6 month assessment, the change is based on the most recent FeNO value (in this case baseline).

7. At the 9 month assessment, change in FeNO is calculated in respect to 6 month FeNO value. If the participant did not attend at the 6 month assessment, the change is based on the most recent FeNO value (in this case baseline or 3 or 6 months, whichever is most recent).

8. At the 12 month assessment, change in FeNO is calculated in respect to 9 month FeNO value. If the participant did not attend at the 9 month assessment, the change is based on the most recent FeNO value (in this case baseline or 3 or 6 months, whichever is most recent).

9. If at the most recent visit, the child has stepped up through the purple route, there will be no change to the treatment step.

10. At consecutive visits, if the participant has ACT>20; FeNO≥35%, adherence≥70%, step, the decision tree should be followed (ie step up, A2); however the PI should be alerted for discussion of alternative diagnosis (eg whooping cough).