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Reducing Asthma Attacks in Children using Exhaled Nitric Oxide as a biomarker to inform treatment strategy – a randomised trial

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Abstract:	Background. The benefit of Fractional Exhaled Nitric Oxide (FeNO) in guiding asthma treatment is uncertain. Our hypothesis was that FeNO plus symptom-guided treatment reduces exacerbations in children with asthma compared to symptom-guided treatment alone. Methods. A multicentre randomised controlled trial recruited 6-15 year olds with asthma treated with inhaled corticosteroids (ICS) with an exacerbation in the previous year. Randomisation was to asthma treatment guided by FeNO plus symptoms (intervention) or by symptoms only (standard care). A web-based algorithm using symptom control, ICS adherence, current treatment and (within the intervention group) FeNO gave treatment recommendations. Participants attended assessments 3, 6, 9 and 12-months post-randomisation. The primary outcome was exacerbation requiring oral corticosteroid over the 12 months post-randomisation. Findings. There were 509 children recruited. At randomisation, the mean (SD) age was 10•1y (2.6), median (IQR) FeNO 21 ppb (10, 48), mean (SD) %FEV 1 90% (18), 56% received ≤400 microg

	budesonide equivalent ICS and 50% had controlled symptoms. The primary outcome occurred in 123/255 (48%) of the intervention group and 129/251 (51%) of the standard care group. The adjusted difference in percentage of participants who received the intervention where the primary outcome occurred exacerbation compared to those receiving standard care was -3•13% (95% CI: -11•9% to 5•6%). In adjusted intention-to-treat analysis, the odds ratio (OR) for primary outcome was 0 •88 [95%CI 0•61 to 1•27]. In 377 of 1771 assessments, the algorithm recommendation was not followed. In complier average causal effect analysis, adjusting for algorithm adherence, the OR for those fully adherent was 0•82 [95% CI 0•48 to 1•41]. There were no differences in secondary outcomes between groups. Interpretation. In this exacerbation-prone population, adding FeNO to symptom-guided treatment did not reduce exacerbations. Funding. This study was funded by the Efficacy and Mechanisms Evaluation programme of the National Institute for Health Research (reference 15-18-14).

Reducing Asthma Attacks in Children using Exhaled Nitric Oxide as a biomarker to inform treatment strategy – a randomised trial

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ABSTRACT

Background. The benefit of Fractional Exhaled Nitric Oxide (FeNO) in guiding asthma treatment is uncertain. Our hypothesis was that FeNO plus symptom-guided treatment reduces exacerbations in children with asthma compared to symptom-guided treatment alone.

Methods. A multicentre randomised controlled trial recruited 6-15 year olds with asthma treated with inhaled corticosteroids (ICS) with an exacerbation in the previous year. Randomisation was to asthma treatment guided by FeNO plus symptoms (intervention) or by symptoms only (standard care). A web-based algorithm using symptom control, ICS adherence, current treatment and (within the intervention group) FeNO gave treatment recommendations. Participants attended assessments 3, 6, 9 and 12-months post-randomisation. The primary outcome was any asthma exacerbation treated with oral corticosteroid over the 12 months after randomisation.

Findings. There were 509 children recruited. At randomisation, the mean (SD) age was 10·1y (2.6), median (IQR) FeNO 21 ppb (10, 48), mean (SD) %FEV_1 90% (18), 56% received ≤400 microg budesonide equivalent ICS and 50% had controlled symptoms. The primary outcome occurred in 123/255 (48%) of the intervention group and 129/251 (51%) of the standard care group. The adjusted difference in percentage of participants who received the intervention where the primary outcome occurred exacerbation compared to those receiving standard care was -3·13% (95% CI: -11·9% to 5·6%). In adjusted intention-to-treat analysis, the odds ratio (OR) for primary outcome was 0·88 [95%CI 0·61 to 1·27]. In 377 of 1771 assessments, the algorithm recommendation was not followed. In complier average causal effect analysis, adjusting for algorithm adherence, the OR for those fully adherent was 0·82 [95% CI 0·48 to 1·41]. There were no differences in secondary outcomes between groups.

Interpretation. In this exacerbation-prone population, adding FeNO to symptom-guided treatment did not reduce exacerbations.

Funding. This study was funded by the Efficacy and Mechanisms Evaluation programme of the National Institute for Health Research (reference 15-18-14).

Key words: Algorithms, Asthma, Child, Clinical Trial, Nitric oxide, Therapeutics

RESEARCH IN CONTEXT

Evidence before this study

Asthma exacerbations in children are frequent, cause morbidity, occasional mortality and place an every-day burden on unscheduled health care in the UK and other countries. Asthma exacerbations can be prevented by appropriate treatment. The benefit of using Fractional Exhaled Nitric Oxide (FeNO), in addition to asthma symptoms, to guide asthma treatment and prevent asthma exacerbations remains uncertain. A 2016 Cochrane review found that in children had reduced odds ratio for asthma exacerbation when their asthma treatment was guided by both FeNO and symptom, compared to symptoms only. UK National asthma guidelines do not recommend FeNO should be used to guide asthma treatment decisions. This study was designed in 2016 and considered the previously mentioned Cochrane review as it's source of evidence. A search in Oct '21 using OVID and applying the terms "child" "nitric oxide" " randomised controlled trial" and "asthma" limited to the years 2016 and onwards yielded one systematic review published in 2020 but no additional new original research.

Added value of this study

This was the first adequately-powered randomised clinical trial designed to determine whether the addition of FeNO to symptom guided treatment reduced asthma exacerbations in children. The population recruited was exacerbation-prone and typical for children seen in the secondary and tertiary care UK setting. There was no significant reduction in odds ratio for exacerbation when participants whose treatment was guided by FeNO plus symptoms was compared to participants with symptom-only guided treatment.

Implications of all the available evidence

We find no evidence that the addition of FeNO to symptom-guided asthma treatment in exacerbation-prone children attending secondary and tertiary care asthma clinics reduces

exacerbations. Neither the Cochrane review nor our study find that the addition of FeNO to symptom-guided asthma treatment improves other asthma outcomes, such as symptoms control or lung function.

INTRODUCTION

Asthma affects 1 million in the UK[1] and 6 million children in the US[2]. There is no cure for asthma, and treatment with preventer medications including inhaled corticosteroids (ICS), long acting beta agonists (LABA) and Leukotriene Receptor Antagonists (LTRA) reduce the risk for asthma exacerbations (also called attacks)[3–5]. Asthma treatment decisions are driven by symptoms, with treatment being stepped up in the context of increasing symptoms and *vice versa*. There is a well-recognised need for objective tests to support treatment decision making where there is clinical uncertainty[6].

Fractional Exhaled Nitric Oxide (FeNO) is an objective test which may have a role in guiding the choice of asthma medication. FeNO is an index of allergic airway inflammation[7], is responsive to asthma treatment[8,9] and is easily measured in clinical practice[10]. Despite almost twenty year's research, there is clinical uncertainty as to the role of FeNO in monitoring asthma; whilst current guidelines do not recommend that FeNO should be used to guide asthma treatment[3–5] a Cochrane review found reduced exacerbations in children when FeNO was added to symptom-guided treatment[11]. A child is admitted to hospital in the UK every 20 minutes[1] for an asthma exacerbation, and many more have exacerbations managed in the community without needing hospitalisation. Asthma exacerbations are common, serious and an intervention which can reduce exacerbations would be highly desirable.

The Reducing Asthma Attacks in Children using Exhaled Nitric Oxide (RAACENO) trial[12] was designed to meet the previously unmet need for a large clinical trial with exacerbation as the primary outcome and which evaluated the efficacy of the addition of FeNO to symptom-

guided treatment in children with asthma against symptom-guided treatment only. Our hypothesis was that the proportion of children with one or more asthma exacerbation over 12 months will be reduced when asthma treatment guided by FeNO plus symptoms is compared to treatment guided by symptoms only.

METHODS

Study design

RAACENO was a phase III multi-centred, parallel, randomised trial which compared algorithm-guided treatment using either symptoms and FeNO ("intervention") or symptoms only ("standard care") for risk of asthma exacerbation. The protocol has been published[12]. Children were recruited from asthma hospital clinics and primary care practices between June 2017 and August 2019. There was no run in period. At the recruitment appointment, consent was taken, data on the child's asthma was collected and randomisation took place. Thereafter, participants were followed up at three-month intervals over one year. At all five assessments, the Asthma Control Test (ACT)[13], or Childhood ACT (CACT) for <12 year olds[14], was completed and spirometry performed. Height and FeNO (NIOX Vero®, Circassia, Oxford, UK) were measured. Adherence to ICS treatment was assessed throughout the period of follow-up using an electronic logging device (Adherium Haile®, Adherium, Auckland, NZ). At each assessment, the following were entered into a web-based algorithm to produce individualised treatment recommendations in both arms of the trial: ACT/CACT score; current treatment; adherence over the last three months (not available at baseline); and FeNO for participants in the intervention arm. The algorithm recommended increase or reduction in treatment or no change. At each visit, the local clinical team could apply the treatment recommended by the algorithm or make an alternative treatment decision in consultation with the family. In some clinical scenarios, the algorithm recommended review by the local

clinical team. At baseline and twelve months, weight and Paediatric Asthma Quality of Life Questionnaire (PAQLQ) score[15] were obtained. At baseline, to characterise participants, there was an option of having bronchodilator response to 400 micrograms salbutamol and skin prick reactivity to common allergens determined. Qualitative and health economic analyses were undertaken and are reported separately. The study was approved by the North of Scotland Research Ethics Committee (16/NS/0106). The trial registered (ISRCTN 67875351).

Participants

Inclusion criteria were: confirmed asthma diagnosis; aged 6-15 years; prescribed ICS inhaler; and at least one asthma exacerbation treated with a course of oral corticosteroids (OCS) in the 12 months prior to recruitment. Exclusion criteria were: being unable to provide FeNO measurement at baseline; co-existent chronic respiratory condition; treatment with maintenance oral steroids; and having a sibling already enrolled in the trial.

Study Setting

35 secondary care and 17 primary care centres in the UK.

Intervention

Participants receiving the intervention had protocolised treatment decisions (based on the 2016 UK guideline[16]) informed by current treatment, ACT/CACT score, adherence plus FeNO. Treatment decisions for participants in the standard care arm were informed by current treatment, ACT/CACT score and adherence. For 63 treatment combinations step up and step down options were agreed for participants in each trial arm. Within the intervention arm, the FeNO result informed different treatment options where available[12] (in the presence of elevated/reduced FeNO, ICS dose was elevated/reduced and in the presence of unchanged FeNO LABA and LTRA treatment was started if not already prescribed). Differences in

treatment options for a participant who was not controlled would depend on what treatment options were available and (for the intervention group) FeNO concentration, e.g. a participant in the intervention arm who was not controlled on low dose ICS could have either ICS dose increased (if their FeNO was elevated) or LABA added (if their FeNO was not elevated) whilst in the standard care arm would have LABA added, but a participant who was not controlled on intermediate dose ICS and LABA and LTRA would only have the option to increase ICS dose regardless of trial arm and (within the intervention arm) their FeNO concentration. As required ICS/LABA (MART) treatment was not an option. At baseline, reduced FeNO was defined as <20 parts per billion (ppb) and elevated FeNO as >35 ppb for <12 year-olds and >50 ppb for older participants[10]. Subsequently reduced and elevated FeNO were defined as >50% fall or rise relative to the previous concentration[17]. An ACT/CACT score of >19 was defined as fully control[1314]. Treatment was stepped up if symptoms were not controlled or (for the intervention arm) if symptoms were controlled but FeNO had risen (limited to one increase for the duration of the trial). Treatment was stepped down in the intervention arm if symptoms were controlled and FeNO had fallen and in the standard care arm if symptoms were controlled on successive assessments. In both trial arms treatment was stepped up on only one assessment where symptoms were uncontrolled and adherence was <70% (thereafter participants were referred to the local clinical team). When symptoms were uncontrolled on two successive occasions in the intervention arm but FeNO was low (suggesting a non-asthmatic cause for symptoms) the participant was referred to the local clinical team. When the participant was not controlled but could be stepped up no further according to current guidelines[16], the participant was referred to the local clinical team. Pulmonary function was measured as an outcome but not used in the algorithm to make medication adjustment decisions. Eosinophils were not measured in this study.

Outcomes

The primary outcome, which was collected at every assessment, was any asthma exacerbation treated with OCS in the 12 months after randomisation. The initial definition was prescription for ≥1 course of 3-7 consecutive days OCS in the 12 months after randomisation (yes/no) but two recruitment centres started using a single dose of dexamethasone to treat asthma exacerbations. To accommodate this change and capture primary outcome, the definition was changed to include any number of days OCS for an asthma exacerbation. When a participant was lost to follow up or withdrew, the primary outcome was determined from primary care records. Secondary outcomes included: time to first exacerbation; number of exacerbations during follow-up; number of unscheduled healthcare assessments during follow up; difference in PAQLQ score at 12 months between trial arms; and changes in ACT/CACT, spirometry ($FEV_{1,}$ % predicted), FeNO and dose of ICS (i.e. daily dose of budesonide equivalent averaged over 3 months) during the 12-month follow-up. All data were collected on a web based case report form which ensured that data had to be in the correct format (e.g. date) and for numerical values within a plausible range. The trial team checked that all data fields were complete and correctly entered, and worked with individual centres to maintain data quality.

Power and Sample size

We assumed a 44% annual exacerbation incidence, a 33% reduction in the primary outcome associated with the intervention[18], 5% incomplete follow-up, 90% power and 5% significance (2-sided). Our intended sample size was 502 participants (continuity corrected chi-squared).

Randomisation (allocation concealment mechanism)

Randomisation was by 24-hour web-based randomisation application using a minimisation algorithm, stratified by centre (primary care sites were considered as one centre), age (<11

years, ≥11 years) sex and asthma severity as evidenced by the 2016 UK guideline (step 2, step 3 or step ≥4)[16] including a random element (20%).

Blinding

Participants knew which arm they were randomised to, as did the clinical and research teams. FeNO was measured in all participants. In the intervention arm, FeNO results were known to participants, parents and the research and clinical team. In the standard care arm, the FeNO result was only available to the research team after the algorithm was executed and the assessment was completed.

Statistical methods

Analysis was by intention-to-treat (ITT), i.e. all participants excluding those excluded post-randomisation were analysed according to the group they were randomised to, and set out in a statistical analysis plan which was agreed before the dataset was locked. All models were adjusted for minimisation covariates: age, sex, asthma treatment step and centre fitted as a random effect (with primary care sites as a single centre). Logistic regression was used for the comparison of primary outcome between treatment groups. Negative binomial regression was used for the total number of primary outcome and unscheduled healthcare attendance. The secondary outcomes of ACT/CACT, FeNO, %FEV_1, and dose of ICS were compared between treatment groups using linear mixed effects models with an unstructured variance-covariance structure and centre fitted as a random effect to incorporate data collected at multiple time points. A treatment by time point interaction was also included. Cox proportional hazards regression was used to determine whether the time to first exacerbation differed between treatment groups. Comparison of PAQLQ at the final assessment between treatment groups was assessed using analysis of covariance. Algorithm compliance was defined as where the treatment decision was followed on ≥3 of the baseline, 3-, 6- and 9-month assessments. A per-protocol analysis compared odds for the primary outcome for

participants where there was compliance with the algorithm. A complier average causal effect (CACE)[19] analysis was undertaken for the primary outcome to account for the effect of compliance with the treatment algorithm. For the primary outcome, pre-specified sub-group analyses were carried out using logistic regression models and using all participants with an interaction term between each subgroup and treatment in a separate model and also for separate subgroups, based on the randomisation stratification variables (age (<11 years, ≥11 years), sex, and asthma treatment step 2, 3 or 4[16]) and obesity[20], eczema[20], skin prick positivity[20] and LTRA treatment[20]. For completeness both unadjusted and adjusted results are presented, with the adjusted results being the primary analysis. Significance was assumed at $p<0.05$ and analyses used Stata version 16.1 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC). In a post hoc analysis we described how algorithm treatment recommendations for participants in the standard care arm would have differed had they been in the intervention arm.

Role of the funding source

The funding source had no involvement in any aspect of the study.

RESULTS

Recruitment

There were 515 participants recruited between June 2017 and August 2019 identified at 42 sites. Sixteen participants were recruited in seven primary care sites. Six participants were recruited but did not meet the inclusion criteria and were excluded after randomisation (two in the FeNO arm, four in the standard arm). These were children aged less than 12 years who were on a dose of ICS higher than the protocol allowed for children of that age.

Primary outcome data were available for 506 (99%) participants and missing for three participants randomised to receive standard care.

Baseline characteristics

The two randomised groups were well balanced in terms of demographic and asthma characteristics at baseline, table one. The mean age of participants was 10·1y (SD 2·6) and 60·5% were male. The median number of courses of OCS in the previous year was three (IQR 1-5). The median number of asthma admissions to hospital in the previous year was one (IQR 0-2). The median daily dose of ICS was 400 micrograms budesonide equivalent (IQR 400,1000), 76% of participants were prescribed LABA, and 59% were prescribed LTRA. Asthma was controlled in 50% of participants (i.e. ACT/CACT score >19). The median FeNO was 21 parts per billion (ppb, IQR 10,48). The mean FEV_1 was 90% predicted (SD 18). The mean bronchodilator response was 9·8% (SD 9·1), n=160. In the 140 tested, 102 (76%) were skin prick positive.

Primary outcome

The primary outcome occurred in 123 of 255 (48·2%) participants randomised to receive the intervention and in 129 out of 251 (51·4%) randomised to receive standard care, the ITT adjusted odds ratio (OR) was 0·88 (95%CI 0·61 to 1·27), table two. The adjusted difference in percentage of participants who received the intervention where the primary outcome occurred compared to those receiving standard care was -3·1% (95% CI: -11·9% to 5·6%). There was no statistically significant difference in the primary outcome for any of the subgroups (see figure S1) or when investigating interactions between the subgroup and treatment arm (table S1).

Secondary outcomes

There was no statistically significant difference between trial arms for any secondary outcome (figure two, tables three and S2-6). The adjusted HR for the time to first

exacerbation was 0·92 (95% CI: 0·71 to 1·18) for participants in the intervention group compared with the standard care group (figure S2 and table three).

Additional analyses

In the intervention group 165 of 255 (64·7%) participants had treatment which was adherent to the algorithm, and the corresponding figure for the standard care arm was 153 out of 251 (61·0%). Table S7 presents the algorithm recommendations at each assessment and table S8 shows the compliance with the algorithm at each assessment. In the per protocol analysis, 84 (50·9%) in the intervention group and 79 (51·6%) in the standard care group had at least one exacerbation (adjusted odds ratio: 0·98 [95% CI: 0·61 to 1·55]), table two. In a CACE analysis, comparing those in the intervention arm where there was compliance with the algorithm with those in the standard care arm, the OR for primary outcome was 0·82 (95% CI: 0·48 to 1·41). At the completion of follow up there were 324/481 (67.4%) participants treated with LTRA and 323/428 (75.5%) treated with LABA and the median ICS dose (p25, p75) was 400 (400, 1000) [n=428].

In the post hoc similarity of interventions analysis 99% (299/300) "review by the local clinical team", 82% (183/227) of "increase treatment" and 70% (208/297) of "reduce treatment" recommendations for individuals in the standard treatment arm would have been the same had they been randomised to the FeNO guided treatment arm. Only 28% (70/253) of "no change" algorithm recommendations for participants in the standard treatment arm would have also been given had the participant been in the FeNO-guided treatment arm. The minimal impact of the COVID pandemic on RAACENO is described in the supplement.

Harms

There were no serious adverse events or deaths. All adverse events reported by 28 participants (15 in the standard care group) were related to trial procedures and expected, e.g. cough after spirometry.

DISCUSSION

The RAACENO trial was designed to determine whether the addition of FeNO to symptom-guided asthma treatment reduced the proportion of children who experience one or more asthma exacerbations. The sample size was met, participants had characteristics typical for children attending hospital asthma clinics in the UK[21] (table S9) and the primary outcome was determined in 99% of participants. Neither the primary nor any secondary outcomes differed between participants in the FeNO-guided treatment and standard treatment trial arms. We conclude that among exacerbation-prone children the addition of FeNO to algorithm-guided treatment does not significantly reduce the proportion who have an asthma attack.

A Cochrane review concluded that the addition of FeNO to symptom-guided treatment was associated with an OR for an exacerbation requiring OCS in children of 0·63 (95% CI: 0·48 to 0·83), compared to symptom-only treatment[11], but this finding was not replicated in RAACENO when the whole population or various subgroups were considered. The many differences in study design between the trials that have used FeNO to guide asthma treatment in children may explain the heterogenous findings for exacerbations between studies. These differences include the chosen primary outcome, sample size, severity, follow up periods, FeNO cut offs and treatment algorithms (see Table S10). Compared to participants in other trials, the RAACENO participants were notable for higher LABA and LTRA use, and lower FeNO concentrations, spirometry and poor symptom control (see Table S11). There is

consistency between the Cochrane review[11] and RAACENO since neither found evidence for other asthma outcomes between children in different trial arms.

There are several potential reasons for the intervention not to have changed outcomes for participants. First, our similarity of interventions analysis found that algorithm recommendations for increasing or reducing treatment for participants in the two arms of the trial were often comparable, reflecting the correlation between FeNO and symptoms and also, since the majority of participants received LTRA and LABA, the only treatment option in either trial arm was to change the ICS dose. Similarity of intervention analyses in three other FeNO trials found that on between 35-50% of assessments the treatment advice would have been the same had participants been allocated to the other study group[22–24]. Our analysis demonstrated that FeNO-guided treatment would have been different for 72% of participants receiving standard care when the algorithm recommendation was "no change", but despite this the addition of FeNO to symptom guided treatment did not affect any outcome.

Second, the typical FeNO concentration was 21ppb (<20 is defined as low[10]) and little further FeNO-guided improvement may have been possible. Third, there were marked improvements in outcomes for participants in the standard care arm which made it difficult to detect differences in secondary outcomes between trial arms. For example the median ACT/CACT scores for participants receiving standard care rose from 18 to 21 (potentially equivalent to a 33% reduced risk for exacerbation[25]) and PAQLQ rose from 5.6 to 6.2 (exceeding the clinically meaningful difference of 0.5).[26] A previous RCT which used FeNO to guide asthma treatment found that the proportion with well controlled asthma symptoms improved from 24% to 71% between screening and randomisation[27], and this consistent with the paradigm that simply standardising management leads to improved symptom control.

A further reason for intervention not being effective in reducing exacerbations is that the algorithm recommendation was not followed in ~25% of cases for participants in both arms of RAACENO. In childhood asthma studies where an algorithm has been applied, the proportion of assessments when the child's physician declines to deliver algorithm recommendations is 5-19%[23,24,27]. The per protocol and CACE analysis found the same magnitude of difference for primary outcome between trial arms compared to the ITT analysis, and this provided evidence that intentional non-adherence did not substantially affect the RAACENO outcome.

A three-month interval between FeNO measurements was chosen since this reflects current hospital asthma clinic practice, but it is possible that a different outcome from RAACENO might have arisen if FeNO measurements were made on more frequent occasions. A previous trial found no benefit of daily FeNO measurements over standard care,[28] and other trials, which have reported that FeNO-guided treatment was associated with reduced exacerbations compared with standard care, had protocols where FeNO was measured at intervals of between six weeks and three months.[22,29] These observations suggest that the three-month interval used in RAACENO did not affect the outcome of the intervention.

The strengths of the study include the large number of study participants, the well organised and executed study design, and the analytical plan. There are number of potential limitations to our study. First, a well-recognised cut off value from a validated symptom score was used to define uncontrolled asthma,[13] but control is a continuum and an algorithm which included more than two categories of control, e.g. controlled, partly controlled and uncontrolled, may have yielded different results. Second, the change in FeNO, which triggered a change in

treatment was based on the best evidence available,[17] but this threshold might not have been correct. A third potential limitation is that adherence to ICS medication may have been over reported, despite the use of electronic logging devices. Participants with unrecognised poor adherence will have raised FeNO[30] but relatively low baseline FeNO concentrations in RAACENO participants suggest that ICS adherence was good.

A fourth limitation is that some as-of-yet-unidentified subgroup(s) of patients with asthma may benefit from FeNO guided treatment; our approach explored several subgroups where FeNO guided treatment is currently thought to be potentially effective in improving asthma outcomes[20] but we found no evidence of any subgroups benefitting from FeNO guided treatment for any outcome studied. Our study had a pragmatic design and did not include a "run in" period during which treatment was optimised and poor adherence was addressed; given that there were no differences in outcomes between trial arms and within subgroups we do not believe that the results would have been different had a run in period been included. Participants in the intervention arm were not blinded to FeNO results. If FeNO was found to improve the outcome then in clinical practice patients would be told their FeNO results and for this reason we did not blind participants in the intervention group. Knowledge of FeNO values might have affected the primary outcome, e.g. by increasing or affirming treatment adherence, but we had an objective index of adherence. Ultimately, there was no difference in any outcome between groups thus suggesting that knowledge of FeNO results in the intervention arm did not affect outcomes. A final limitation is that the skin test reactivity component of the study was optional, and the subgroup whose skin test reactivity was determined as an option was underpowered.

The rationale for using FeNO to guide asthma treatment is that suppressing FeNO with ICS will control airway eosinophilia and result in improved asthma outcomes, but there are

potential problems with this paradigm. For example some individuals have elevated FeNO but do not have elevated airway eosinophils, and FeNO is not suppressed by ICS in all individuals[18]. Earlier work suggests that FeNO guided treatment may improve asthma outcomes limited to those not treated with LTRA[20] and, although we were not able to replicate this finding in our trial, it is possible that LTRA treatment may confound the relationship between FeNO and ICS. A further limitation is that many participants in this trial were already receiving the highest recommended ICS dose, and titrating ICS treatment to FeNO in the context of uncontrolled asthma is not feasible. Titrating ICS treatment on FeNO is attractive but is problematic for reasons stated above, however FeNO might be used to guide non-ICS treatments such as biologicals as well as identifying ICS-responsive, and non-responsive, asthma patients in an initial assessment and follow-up.

In summary, the RAACENO study finds no evidence that the addition of FeNO to symptom-guided asthma treatment leads to reduced exacerbations among exacerbation-prone children. Asthma symptoms remain the only tool for guiding treatment decisions and objective tests to guide asthma treatment need to be identified and validated.

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DECLARATION OF INTERESTS

Circassia provided at no cost the apparatus to allow FeNO measurements to be made in the intervention.

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DATA SHARING

Data are available on reasonable request to Prof Turner (s.w.turner@abdn.ac.uk).

Contributions of authors

ST (Chief Investigator) contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report. SC (trial manager) contributed to the design of the trial and the development of the treatment algorithm, conduct of the trial, was responsible for the day-to-day management of the trial, and contributed to the interpretation of results and writing/editing the report. JW (trial manager) was responsible for the day-to-day management of the trial, and contributed to the interpretation of results and writing/editing

the report. VB (assistant trial manager) was responsible for aspects of the day-to-day management of the trial and contributed to the interpretation of results and writing/editing the report. E-AR contributed to the statistical analysis including the interpretation of results and writing/editing the report. NS was responsible for statistical analysis and contributed to the interpretation of results and writing/editing the report. HM contributed to the conception and design of the qualitative process evaluation, was responsible for the day-to-day management of the qualitative process evaluation and contributed to the interpretation of results and writing/editing the relevant parts of the report. LL contributed to the design of the qualitative process evaluation, was responsible for the day-to-day management of the study, including interviewing participants, and contributed to the interpretation of results and writing/editing the relevant parts of the report. DE contributed to the design of the trial, was responsible for the development and computerisation of the treatment algorithm, and editing the report. CK was responsible for the health economic analysis and contributed to the interpretation of results and writing the report. GS oversaw the health economic analysis and contributed to the interpretation of results and writing/editing the report. SF contributed statistical expertise to the design and conduct of the trial, statistical analysis, and contributed to editing the report. GMacL contributed to the statistical analysis and interpretation of results and writing/editing the report. JN contributed to the conception and design of the trial and writing/editing the report. MF contributed to the development and computerisation of the treatment algorithm and writing/editing the report. EG, JdeJ, MP, MT and DP contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, interpretation of results and writing/editing the report. E-AR and NS accessed and verified the data. All authors were responsible for the decision to submit the manuscript. All authors saw and approved the final text.

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Table one. Baseline characteristics of participants in each trial arm and combined.

		Intervention			Standard care			Combined		
		N			N			N		
Sex, male (N, n, %)		255	156	61·2	254	152	59·8	509	308	60·5
Age, years (N, mean, SD)		255	10·0	2·6	254	10·1	2·5	509	10·1	2·6
BMI groups[a] (N, n, %)	Healthy weight	255	161	63·6	254	151	59·9	209	312	61·8
	Obese		24	9·5		22	8·7		46	9·1
	Overweight		51	20·2		55	21·8		106	21·0
	Thin		17	6·7		24	9·5		41	8·1
White ethnic group (N, n, %)		255	187	73·3	254	198	78·0	509	385	75·6
Age mother left education, years (N, median, p25, p75)		248	18	16, 21	247	18	16, 21	495	18	16, 21
Age of asthma diagnosis, years (N, mean, SD)		253	3·94	2·6	253	3·72	2·5	506	3·83	2·6
Premature birth (before 36 weeks) (N, n, %)		255	43	16·9	254	26	10·2	509	69	13·6
Hospital admission for asthma, last year (N, median, p25, p75)		255	1	0, 2	254	1	0, 2	509	1	0, 2
Number of hospital admissions for asthma, lifetime (N, n, %)	Never	255	30	11·8	254	34	13·4	509	64	12·6
	1-5 times		114	44·7		97	38·2		211	41·5
	>5 times		111	43·5		123	48·4		234	46·0
Number of courses of oral corticosteroid tablets, last year (N, median, p25, p75)		255	3	1, 4	254	3	1, 5	509	3	1, 5

Wheeze only with a cold (N, n, %)		255	100	39·2	253	90	35·6	508	190	37·4
Median daily dose of inhaled corticosteroid (budesonide equivalent; N, p25, p75)		255	400	400,1000	254	400	400,1000	509	400	400,1000
Daily dose of inhaled corticosteroid (budesonide equivalent; N, n, %)	≤ 400 microgram	255	143	56·1	253	143	56·3	508	286	56·2
	401-800 microgram		27	10·6		27	10·6		54	10·6
	>800 microgram		85	33·3		84	33·0		169	33·2
Current LABA use (N, n, %)		255	196	76·9	254	190	74·8	509	386	75·8
Current LTRA use (N, n, %)		255	150	58·8	254	152	59·8	509	302	59·3
Controlled Asthma[b] (N, n, %)		255	132	51·8	254	124	48·8	509	256	50·3
% predicted FEV_1 (N, mean, SD)		234	89·8	17·8	221	89·3	18·2	455	89·6	18·0
FeNO, parts per billion (N, median, p25, p75)		255	20	11, 45	254	22·5	10, 51	509	21	10, 48
Child exposed to smoking (N, n, %)		255	45	17·6	254	49	19·3	509	94	18·5
Eczema diagnosed by a doctor, ever (N, n, %)		255	141	55·3	254	152	59·8	509	293	57·6
Rhinitis, ever (N, n, %)		255	151	59·2	254	153	60·2	509	304	59·7
First degree family history of asthma (N, n, %)		254	165	65·0	254	151	59·4	508	316	62·2

SD=Standard Deviation. BMI=Body Mass Index. LABA=long acting beta agonist. LTRA=Leukotriene Receptor Antagonist. FeNO=Fractional Exhaled Nitric Oxide. [a] Defined using the categories from the International Obesity Task Force (Cole TJ et al BMJ 2000; 320(7244): 1240-3).which categorises individuals as Thin, Healthy Weight, Overweight or Obese by back-extrapolating Body Mass Index (BMI) cut offs for these

weight categories at age 18 years adjusting for age. [b] Controlled asthma control was defined as ACT score of ≥20 in line with commonly used cut-offs for partly/fully controlled asthma

Table two. The odds ratio (OR) for the primary outcome, i.e. asthma exacerbation requiring oral corticosteroids over 12 months post randomisation, between the intervention and standard care arms of the trial. The per protocol analysis included only those compliant with the algorithm, i.e. the algorithm recommended treatment was followed on three or four scheduled visits between baseline and nine months. The complier average casual effect analysis included participants in the FeNO arm where there was algorithm compliance plus all participants in the standard care arm.

Outcome	Intervention	Standard care		Effect size	Lower 95% CI	Upper 95% CI	p-value
Intention to treat analysis	**N=255**	**N=251**					
Number with at least one exacerbation	123	129	unadjusted OR	0·88	0·62	1·25	0·48
Percentage with at least one exacerbation	48·2	51·4	adjusted OR[a]	0·88	0·61	1·27	0·49
Per protocol analysis	**N=165**	**N=153**					
Number with at least one exacerbation	84	79	unadjusted OR	0·97	0·62	1·51	0·90
Percentage with at least one exacerbation	50·9	51·6	adjusted OR[a]	0·98	0·61	1·55	0·92
Complier average causal effect analysis							
			adjusted OR[a]	0·82	0·48	1·41	

[a] adjusted for age, sex, asthma severity and centre

Table three. Comparison between participants in the trial arms of time to first exacerbation, number of exacerbations, number of unscheduled healthcare contacts and the Paediatric Asthma Quality of Life Questionnaire (PAQLQ).

Outcome	Intervention N=255	Standard care N=251		Effect size	Lower 95% CI	Upper 95% CI	p-value
Time to first exacerbation (from randomisation)							
Number with at least one exacerbation	123	129					
Median time to first exacerbation (days)	nr	344	unadjusted HR	0·92	0·72	1·17	0·49
25th percentile (time to first exacerbation (days))	137	112	adjusted HR[a]	0·92	0·71	1·18	0·50
75th percentile (time to first exacerbation (days))	nr	nr					
Number of exacerbations							
Total number of exacerbations	254	255					
Mean number of exacerbations per participant	0·99	1·01					
Median number of exacerbations (p25, p75)	0 (0,2)	1 (0,2)	unadjusted IRR	0·98	0·77	1·26	0·89
			adjusted IRR[a]	0·99	0·82	1·18	0·87
Number of unscheduled healthcare contacts							

Unscheduled healthcare contacts (n, %)	133 (52·2%)	139 (55·4%)	unadjusted OR	0·88	0·62	1·25	0·47
			adjusted OR[a]	0·88	0·65	1·17	0·37
Number of unscheduled healthcare contacts (median, p25, p75)	1 (0,2)	1 (0,3)	unadjusted IRR	0·92	0·70	1·21	0·54
			adjusted IRR[a]	0·91	0·72	1·13	0·39
PAQLQ at 12 months – overall quality of life							
Median score (p25, p75)	6·4 (5·5, 6·9)	6·2 (5·4, 6·8)	Unadjusted	0·092	-0·095	0·279	0·33
			adjusted[a]	0·098	-0·088	0·283	0·30

nr=not reached. HR=hazards ratio. IRR=incidence rate ratio. OR=odds ratio. [a]Adjustment was for age, sex, asthma severity and centre.

Figure one. CONSORT flow diagram

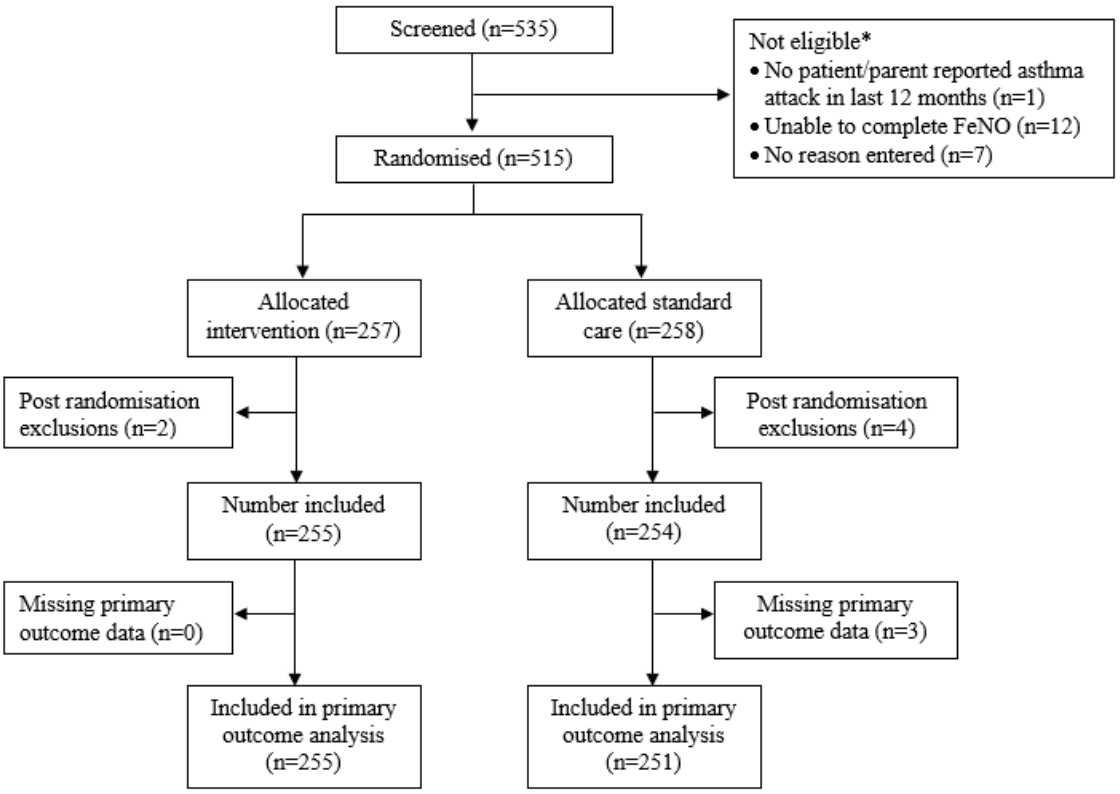
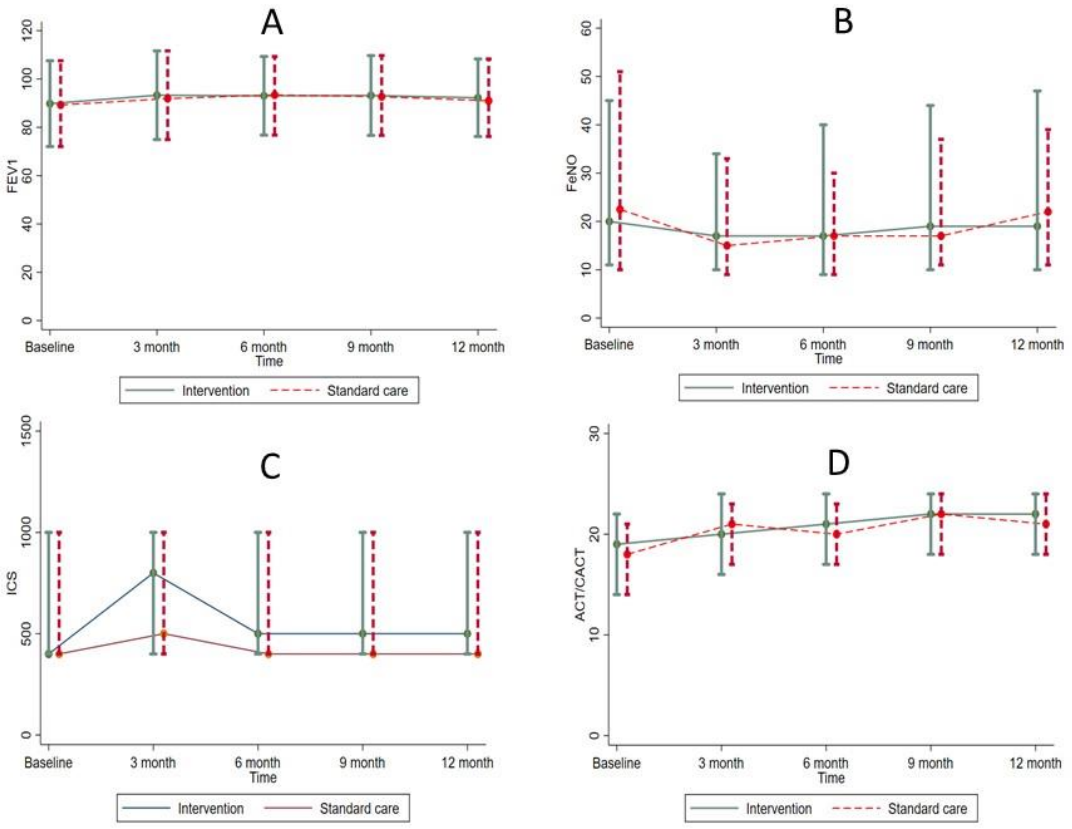


Figure two. Panels showing trends over the period of follow up in: A. Mean percentage predicted forced expiratory volume in 1 second (FEV1, error bars denote SD); B. Median Fractional Exhaled Nitric Oxide (FeNO, parts per billion, error bars denote p25, p75); C. Median daily inhaled corticosteroid dose (budesonide equivalent, microgram, error bars denote p25, p75); D. Median asthma control (ACT=Asthma Control Test, CACT=Children's Asthma Control Test, error bars denote p25, p75).



Reducing Asthma Attacks in Children using Exhaled Nitric Oxide as a biomarker to inform treatment strategy – a randomised trial

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ABSTRACT

Background. The benefit of Fractional Exhaled Nitric Oxide (FeNO) in guiding asthma treatment is uncertain. Our hypothesis was that FeNO plus symptom-guided treatment reduces exacerbations in children with asthma compared to symptom-guided treatment alone.

Methods. A multicentre randomised controlled trial recruited 6-15 year olds with asthma treated with inhaled corticosteroids (ICS) with an exacerbation in the previous year. Randomisation was to asthma treatment guided by FeNO plus symptoms (intervention) or by symptoms only (standard care). A web-based algorithm using symptom control, ICS adherence, current treatment and (within the intervention group) FeNO gave treatment recommendations. Participants attended assessments 3, 6, 9 and 12-months post-randomisation. The primary outcome was any asthma exacerbation treated with oral corticosteroid over the 12 months after randomisation.

Findings. There were 509 children recruited. At randomisation, the mean (SD) age was 10·1y (2.6), median (IQR) FeNO 21 ppb (10, 48), mean (SD) %FEV_1 90% (18), 56% received ≤400 microg budesonide equivalent ICS and 50% had controlled symptoms. The primary outcome occurred in 123/255 (48%) of the intervention group and 129/251 (51%) of the standard care group. The adjusted difference in percentage of participants who received the intervention where the primary outcome occurred exacerbation compared to those receiving standard care was -3·13% (95% CI: -11·9% to 5·6%). In adjusted intention-to-treat analysis, the odds ratio (OR) for primary outcome was 0·88 [95%CI 0·61 to 1·27]. In 377 of 1771 assessments, the algorithm recommendation was not followed. In complier average causal effect analysis, adjusting for algorithm adherence, the OR for those fully adherent was 0·82 [95% CI 0·48 to 1·41]. There were no differences in secondary outcomes between groups.

Interpretation. In this exacerbation-prone population, adding FeNO to symptom-guided treatment did not reduce exacerbations.

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Key words: Algorithms, Asthma, Child, Clinical Trial, Nitric oxide, Therapeutics

RESEARCH IN CONTEXT

Evidence before this study

Asthma exacerbations in children are frequent, cause morbidity, occasional mortality and place an every-day burden on unscheduled health care in the UK and other countries. Asthma exacerbations can be prevented by appropriate treatment. The benefit of using Fractional Exhaled Nitric Oxide (FeNO), in addition to asthma symptoms, to guide asthma treatment and prevent asthma exacerbations remains uncertain. A 2016 Cochrane review found that in children had reduced odds ratio for asthma exacerbation when their asthma treatment was guided by both FeNO and symptom, compared to symptoms only. UK National asthma guidelines do not recommend FeNO should be used to guide asthma treatment decisions. This study was designed in 2016 and considered the previously mentioned Cochrane review as it's source of evidence. A search in Oct '21 using OVID and applying the terms "child" "nitric oxide" " randomised controlled trial" and "asthma" limited to the years 2016 and onwards yielded one systematic review published in 2020 but no additional new original research.

Added value of this study

This was the first adequately-powered randomised clinical trial designed to determine whether the addition of FeNO to symptom guided treatment reduced asthma exacerbations in children. The population recruited was exacerbation-prone and typical for children seen in the secondary and tertiary care UK setting. There was no significant reduction in odds ratio for exacerbation when participants whose treatment was guided by FeNO plus symptoms was compared to participants with symptom-only guided treatment.

Implications of all the available evidence

We find no evidence that the addition of FeNO to symptom-guided asthma treatment in exacerbation-prone children attending secondary and tertiary care asthma clinics reduces

exacerbations. Neither the Cochrane review nor our study find that the addition of FeNO to symptom-guided asthma treatment improves other asthma outcomes, such as symptoms control or lung function.

INTRODUCTION

Asthma affects 1 million in the UK[1] and 6 million children in the US[2]. There is no cure for asthma, and treatment with preventer medications including inhaled corticosteroids (ICS), long acting beta agonists (LABA) and Leukotriene Receptor Antagonists (LTRA) reduce the risk for asthma exacerbations (also called attacks)[3–5]. Asthma treatment decisions are driven by symptoms, with treatment being stepped up in the context of increasing symptoms and *vice versa*. There is a well-recognised need for objective tests to support treatment decision making where there is clinical uncertainty[6].

Fractional Exhaled Nitric Oxide (FeNO) is an objective test which may have a role in guiding the choice of asthma medication. FeNO is an index of allergic airway inflammation[7], is responsive to asthma treatment[8,9] and is easily measured in clinical practice[10]. Despite almost twenty year's research, there is clinical uncertainty as to the role of FeNO in monitoring asthma; whilst current guidelines do not recommend that FeNO should be used to guide asthma treatment[3–5] a Cochrane review found reduced exacerbations in children when FeNO was added to symptom-guided treatment[11]. A child is admitted to hospital in the UK every 20 minutes[1] for an asthma exacerbation, and many more have exacerbations managed in the community without needing hospitalisation. Asthma exacerbations are common, serious and an intervention which can reduce exacerbations would be highly desirable.

The Reducing Asthma Attacks in Children using Exhaled Nitric Oxide (RAACENO) trial[12] was designed to meet the previously unmet need for a large clinical trial with exacerbation as the primary outcome and which evaluated the efficacy of the addition of FeNO to symptom-

guided treatment in children with asthma against symptom-guided treatment only. Our hypothesis was that the proportion of children with one or more asthma exacerbation over 12 months will be reduced when asthma treatment guided by FeNO plus symptoms is compared to treatment guided by symptoms only.

METHODS

Study design

RAACENO was a phase III multi-centred, parallel, randomised trial which compared algorithm-guided treatment using either symptoms and FeNO ("intervention") or symptoms only ("standard care") for risk of asthma exacerbation. The protocol has been published[12]. Children were recruited from asthma hospital clinics and primary care practices between June 2017 and August 2019. There was no run in period. At the recruitment appointment, consent was taken, data on the child's asthma was collected and randomisation took place. Thereafter, participants were followed up at three-month intervals over one year. At all five assessments, the Asthma Control Test (ACT)[13], or Childhood ACT (CACT) for <12 year olds[14], was completed and spirometry performed. Height and FeNO (NIOX Vero®, Circassia, Oxford, UK) were measured. Adherence to ICS treatment was assessed throughout the period of follow-up using an electronic logging device (Adherium Haile®, Adherium, Auckland, NZ). At each assessment, the following were entered into a web-based algorithm to produce individualised treatment recommendations in both arms of the trial: ACT/CACT score; current treatment; adherence over the last three months (not available at baseline); and FeNO for participants in the intervention arm. The algorithm recommended increase or reduction in treatment or no change. At each visit, the local clinical team could apply the treatment recommended by the algorithm or make an alternative treatment decision in consultation with the family. In some clinical scenarios, the algorithm recommended review by the local

clinical team. At baseline and twelve months, weight and Paediatric Asthma Quality of Life Questionnaire (PAQLQ) score[15] were obtained. At baseline, to characterise participants, there was an option of having bronchodilator response to 400 micrograms salbutamol and skin prick reactivity to common allergens determined. Qualitative and health economic analyses were undertaken and are reported separately. The study was approved by the North of Scotland Research Ethics Committee (16/NS/0106). The trial registered (ISRCTN 67875351).

Participants

Inclusion criteria were: confirmed asthma diagnosis; aged 6-15 years; prescribed ICS inhaler; and at least one asthma exacerbation treated with a course of oral corticosteroids (OCS) in the 12 months prior to recruitment. Exclusion criteria were: being unable to provide FeNO measurement at baseline; co-existent chronic respiratory condition; treatment with maintenance oral steroids; and having a sibling already enrolled in the trial.

Study Setting

35 secondary care and 17 primary care centres in the UK.

Intervention

Participants receiving the intervention had protocolised treatment decisions (based on the 2016 UK guideline[16]) informed by current treatment, ACT/CACT score, adherence plus FeNO. Treatment decisions for participants in the standard care arm were informed by current treatment, ACT/CACT score and adherence. For 63 treatment combinations step up and step down options were agreed for participants in each trial arm. Within the intervention arm, the FeNO result informed different treatment options where available[12] (in the presence of elevated/reduced FeNO, ICS dose was elevated/reduced and in the presence of unchanged FeNO LABA and LTRA treatment was started if not already prescribed). Differences in

treatment options for a participant who was not controlled would depend on what treatment options were available and (for the intervention group) FeNO concentration, e.g. a participant in the intervention arm who was not controlled on low dose ICS could have either ICS dose increased (if their FeNO was elevated) or LABA added (if their FeNO was not elevated) whilst in the standard care arm would have LABA added, but a participant who was not controlled on intermediate dose ICS and LABA and LTRA would only have the option to increase ICS dose regardless of trial arm and (within the intervention arm) their FeNO concentration. As required ICS/LABA (MART) treatment was not an option. At baseline, reduced FeNO was defined as <20 parts per billion (ppb) and elevated FeNO as >35 ppb for <12 year-olds and >50 ppb for older participants[10]. Subsequently reduced and elevated FeNO were defined as >50% fall or rise relative to the previous concentration[17]. An ACT/CACT score of >19 was defined as fully control[1314]. Treatment was stepped up if symptoms were not controlled or (for the intervention arm) if symptoms were controlled but FeNO had risen (limited to one increase for the duration of the trial). Treatment was stepped down in the intervention arm if symptoms were controlled and FeNO had fallen and in the standard care arm if symptoms were controlled on successive assessments. In both trial arms treatment was stepped up on only one assessment where symptoms were uncontrolled and adherence was <70% (thereafter participants were referred to the local clinical team). When symptoms were uncontrolled on two successive occasions in the intervention arm but FeNO was low (suggesting a non-asthmatic cause for symptoms) the participant was referred to the local clinical team. When the participant was not controlled but could be stepped up no further according to current guidelines[16], the participant was referred to the local clinical team. Pulmonary function was measured as an outcome but not used in the algorithm to make medication adjustment decisions. Eosinophils were not measured in this study.

Outcomes

The primary outcome, which was collected at every assessment, was any asthma exacerbation treated with OCS in the 12 months after randomisation. The initial definition was prescription for ≥1 course of 3-7 consecutive days OCS in the 12 months after randomisation (yes/no) but two recruitment centres started using a single dose of dexamethasone to treat asthma exacerbations. To accommodate this change and capture primary outcome, the definition was changed to include any number of days OCS for an asthma exacerbation. When a participant was lost to follow up or withdrew, the primary outcome was determined from primary care records. Secondary outcomes included: time to first exacerbation; number of exacerbations during follow-up; number of unscheduled healthcare assessments during follow up; difference in PAQLQ score at 12 months between trial arms; and changes in ACT/CACT, spirometry ($FEV_{1,}$ % predicted), FeNO and dose of ICS (i.e. daily dose of budesonide equivalent averaged over 3 months) during the 12-month follow-up. All data were collected on a web based case report form which ensured that data had to be in the correct format (e.g. date) and for numerical values within a plausible range. The trial team checked that all data fields were complete and correctly entered, and worked with individual centres to maintain data quality.

Power and Sample size

We assumed a 44% annual exacerbation incidence, a 33% reduction in the primary outcome associated with the intervention[18], 5% incomplete follow-up, 90% power and 5% significance (2-sided). Our intended sample size was 502 participants (continuity corrected chi-squared).

Randomisation (allocation concealment mechanism)

Randomisation was by 24-hour web-based randomisation application using a minimisation algorithm, stratified by centre (primary care sites were considered as one centre), age (<11

years, ≥11 years) sex and asthma severity as evidenced by the 2016 UK guideline (step 2, step 3 or step ≥4)[16] including a random element (20%).

Blinding

Participants knew which arm they were randomised to, as did the clinical and research teams. FeNO was measured in all participants. In the intervention arm, FeNO results were known to participants, parents and the research and clinical team. In the standard care arm, the FeNO result was only available to the research team after the algorithm was executed and the assessment was completed.

Statistical methods

Analysis was by intention-to-treat (ITT), i.e. all participants excluding those excluded post-randomisation were analysed according to the group they were randomised to, and set out in a statistical analysis plan which was agreed before the dataset was locked. All models were adjusted for minimisation covariates: age, sex, asthma treatment step and centre fitted as a random effect (with primary care sites as a single centre). Logistic regression was used for the comparison of primary outcome between treatment groups. Negative binomial regression was used for the total number of primary outcome and unscheduled healthcare attendance. The secondary outcomes of ACT/CACT, FeNO, %FEV_1, and dose of ICS were compared between treatment groups using linear mixed effects models with an unstructured variance-covariance structure and centre fitted as a random effect to incorporate data collected at multiple time points. A treatment by time point interaction was also included. Cox proportional hazards regression was used to determine whether the time to first exacerbation differed between treatment groups. Comparison of PAQLQ at the final assessment between treatment groups was assessed using analysis of covariance. Algorithm compliance was defined as where the treatment decision was followed on ≥3 of the baseline, 3-, 6- and 9-month assessments. A per-protocol analysis compared odds for the primary outcome for

participants where there was compliance with the algorithm. A complier average causal effect (CACE)[19] analysis was undertaken for the primary outcome to account for the effect of compliance with the treatment algorithm. For the primary outcome, pre-specified sub-group analyses were carried out using logistic regression models and using all participants with an interaction term between each subgroup and treatment in a separate model and also for separate subgroups, based on the randomisation stratification variables (age (<11 years, ≥11 years), sex, and asthma treatment step 2, 3 or 4[16]) and obesity[20], eczema[20], skin prick positivity[20] and LTRA treatment[20]. For completeness both unadjusted and adjusted results are presented, with the adjusted results being the primary analysis. Significance was assumed at $p<0.05$ and analyses used Stata version 16.1 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC). In a post hoc analysis we described how algorithm treatment recommendations for participants in the standard care arm would have differed had they been in the intervention arm.

Role of the funding source

The funding source had no involvement in any aspect of the study.

RESULTS

Recruitment

There were 515 participants recruited between June 2017 and August 2019 identified at 42 sites. Sixteen participants were recruited in seven primary care sites. Six participants were recruited but did not meet the inclusion criteria and were excluded after randomisation (two in the FeNO arm, four in the standard arm). These were children aged less than 12 years who were on a dose of ICS higher than the protocol allowed for children of that age.

Primary outcome data were available for 506 (99%) participants and missing for three participants randomised to receive standard care.

Baseline characteristics

The two randomised groups were well balanced in terms of demographic and asthma characteristics at baseline, table one. The mean age of participants was 10·1y (SD 2·6) and 60·5% were male. The median number of courses of OCS in the previous year was three (IQR 1-5). The median number of asthma admissions to hospital in the previous year was one (IQR 0-2). The median daily dose of ICS was 400 micrograms budesonide equivalent (IQR 400,1000), 76% of participants were prescribed LABA, and 59% were prescribed LTRA. Asthma was controlled in 50% of participants (i.e. ACT/CACT score >19). The median FeNO was 21 parts per billion (ppb, IQR 10,48). The mean FEV_1 was 90% predicted (SD 18). The mean bronchodilator response was 9·8% (SD 9·1), n=160. In the 140 tested, 102 (76%) were skin prick positive.

Primary outcome

The primary outcome occurred in 123 of 255 (48·2%) participants randomised to receive the intervention and in 129 out of 251 (51·4%) randomised to receive standard care, the ITT adjusted odds ratio (OR) was 0·88 (95%CI 0·61 to 1·27), table two. The adjusted difference in percentage of participants who received the intervention where the primary outcome occurred compared to those receiving standard care was -3·1% (95% CI: -11·9% to 5·6%). There was no statistically significant difference in the primary outcome for any of the subgroups (see figure S1) or when investigating interactions between the subgroup and treatment arm (table S1).

Secondary outcomes

There was no statistically significant difference between trial arms for any secondary outcome (figure two, tables three and S2-6). The adjusted HR for the time to first

exacerbation was 0·92 (95% CI: 0·71 to 1·18) for participants in the intervention group compared with the standard care group (figure S2 and table three).

Additional analyses

In the intervention group 165 of 255 (64·7%) participants had treatment which was adherent to the algorithm, and the corresponding figure for the standard care arm was 153 out of 251 (61·0%). Table S7 presents the algorithm recommendations at each assessment and table S8 shows the compliance with the algorithm at each assessment. In the per protocol analysis, 84 (50·9%) in the intervention group and 79 (51·6%) in the standard care group had at least one exacerbation (adjusted odds ratio: 0·98 [95% CI: 0·61 to 1·55]), table two. In a CACE analysis, comparing those in the intervention arm where there was compliance with the algorithm with those in the standard care arm, the OR for primary outcome was 0·82 (95% CI: 0·48 to 1·41). At the completion of follow up there were 324/481 (67.4%) participants treated with LTRA and 323/428 (75.5%) treated with LABA and the median ICS dose (p25, p75) was 400 (400, 1000) [n=428].

In the post hoc similarity of interventions analysis 99% (299/300) "review by the local clinical team", 82% (183/227) of "increase treatment" and 70% (208/297) of "reduce treatment" recommendations for individuals in the standard treatment arm would have been the same had they been randomised to the FeNO guided treatment arm. Only 28% (70/253) of "no change" algorithm recommendations for participants in the standard treatment arm would have also been given had the participant been in the FeNO-guided treatment arm. The minimal impact of the COVID pandemic on RAACENO is described in the supplement.

Harms

There were no serious adverse events or deaths. All adverse events reported by 28 participants (15 in the standard care group) were related to trial procedures and expected, e.g. cough after spirometry.

DISCUSSION

The RAACENO trial was designed to determine whether the addition of FeNO to symptom-guided asthma treatment reduced the proportion of children who experience one or more asthma exacerbations. The sample size was met, participants had characteristics typical for children attending hospital asthma clinics in the UK[21] (table S9) and the primary outcome was determined in 99% of participants. Neither the primary nor any secondary outcomes differed between participants in the FeNO-guided treatment and standard treatment trial arms. We conclude that among exacerbation-prone children the addition of FeNO to algorithm-guided treatment does not significantly reduce the proportion who have an asthma attack.

A Cochrane review concluded that the addition of FeNO to symptom-guided treatment was associated with an OR for an exacerbation requiring OCS in children of 0·63 (95% CI: 0·48 to 0·83), compared to symptom-only treatment[11], but this finding was not replicated in RAACENO when the whole population or various subgroups were considered. The many differences in study design between the trials that have used FeNO to guide asthma treatment in children may explain the heterogenous findings for exacerbations between studies. These differences include the chosen primary outcome, sample size, severity, follow up periods, FeNO cut offs and treatment algorithms (see Table S10). Compared to participants in other trials, the RAACENO participants were notable for higher LABA and LTRA use, and lower FeNO concentrations, spirometry and poor symptom control (see Table S11). There is

consistency between the Cochrane review[11] and RAACENO since neither found evidence for other asthma outcomes between children in different trial arms.

There are several potential reasons for the intervention not to have changed outcomes for participants. First, our similarity of interventions analysis found that algorithm recommendations for increasing or reducing treatment for participants in the two arms of the trial were often comparable, reflecting the correlation between FeNO and symptoms and also, since the majority of participants received LTRA and LABA, the only treatment option in either trial arm was to change the ICS dose. Similarity of intervention analyses in three other FeNO trials found that on between 35-50% of assessments the treatment advice would have been the same had participants been allocated to the other study group[22–24]. Our analysis demonstrated that FeNO-guided treatment would have been different for 72% of participants receiving standard care when the algorithm recommendation was "no change", but despite this the addition of FeNO to symptom guided treatment did not affect any outcome.

Second, the typical FeNO concentration was 21ppb (<20 is defined as low[10]) and little further FeNO-guided improvement may have been possible. Third, there were marked improvements in outcomes for participants in the standard care arm which made it difficult to detect differences in secondary outcomes between trial arms. For example the median ACT/CACT scores for participants receiving standard care rose from 18 to 21 (potentially equivalent to a 33% reduced risk for exacerbation[25]) and PAQLQ rose from 5.6 to 6.2 (exceeding the clinically meaningful difference of 0.5).[26] A previous RCT which used FeNO to guide asthma treatment found that the proportion with well controlled asthma symptoms improved from 24% to 71% between screening and randomisation[27], and this consistent with the paradigm that simply standardising management leads to improved symptom control.

A further reason for intervention not being effective in reducing exacerbations is that the algorithm recommendation was not followed in ~25% of cases for participants in both arms of RAACENO. In childhood asthma studies where an algorithm has been applied, the proportion of assessments when the child's physician declines to deliver algorithm recommendations is 5-19%[23,24,27]. The per protocol and CACE analysis found the same magnitude of difference for primary outcome between trial arms compared to the ITT analysis, and this provided evidence that intentional non-adherence did not substantially affect the RAACENO outcome.

A three-month interval between FeNO measurements was chosen since this reflects current hospital asthma clinic practice, but it is possible that a different outcome from RAACENO might have arisen if FeNO measurements were made on more frequent occasions. A previous trial found no benefit of daily FeNO measurements over standard care,[28] and other trials, which have reported that FeNO-guided treatment was associated with reduced exacerbations compared with standard care, had protocols where FeNO was measured at intervals of between six weeks and three months.[22,29] These observations suggest that the three-month interval used in RAACENO did not affect the outcome of the intervention.

The strengths of the study include the large number of study participants, the well organised and executed study design, and the analytical plan. There are number of potential limitations to our study. First, a well-recognised cut off value from a validated symptom score was used to define uncontrolled asthma,[13] but control is a continuum and an algorithm which included more than two categories of control, e.g. controlled, partly controlled and uncontrolled, may have yielded different results. Second, the change in FeNO, which triggered a change in

treatment was based on the best evidence available,[17] but this threshold might not have been correct. A third potential limitation is that adherence to ICS medication may have been over reported, despite the use of electronic logging devices. Participants with unrecognised poor adherence will have raised FeNO[30] but relatively low baseline FeNO concentrations in RAACENO participants suggest that ICS adherence was good.

A fourth limitation is that some as-of-yet-unidentified subgroup(s) of patients with asthma may benefit from FeNO guided treatment; our approach explored several subgroups where FeNO guided treatment is currently thought to be potentially effective in improving asthma outcomes[20] but we found no evidence of any subgroups benefitting from FeNO guided treatment for any outcome studied. Our study had a pragmatic design and did not include a "run in" period during which treatment was optimised and poor adherence was addressed; given that there were no differences in outcomes between trial arms and within subgroups we do not believe that the results would have been different had a run in period been included. Participants in the intervention arm were not blinded to FeNO results. If FeNO was found to improve the outcome then in clinical practice patients would be told their FeNO results and for this reason we did not blind participants in the intervention group. Knowledge of FeNO values might have affected the primary outcome, e.g. by increasing or affirming treatment adherence, but we had an objective index of adherence. Ultimately, there was no difference in any outcome between groups thus suggesting that knowledge of FeNO results in the intervention arm did not affect outcomes. A final limitation is that the skin test reactivity component of the study was optional, and the subgroup whose skin test reactivity was determined as an option was underpowered.

The rationale for using FeNO to guide asthma treatment is that suppressing FeNO with ICS will control airway eosinophilia and result in improved asthma outcomes, but there are

potential problems with this paradigm. For example some individuals have elevated FeNO but do not have elevated airway eosinophils, and FeNO is not suppressed by ICS in all individuals[18]. Earlier work suggests that FeNO guided treatment may improve asthma outcomes limited to those not treated with LTRA[20] and, although we were not able to replicate this finding in our trial, it is possible that LTRA treatment may confound the relationship between FeNO and ICS. A further limitation is that many participants in this trial were already receiving the highest recommended ICS dose, and titrating ICS treatment to FeNO in the context of uncontrolled asthma is not feasible. Titrating ICS treatment on FeNO is attractive but is problematic for reasons stated above, however FeNO might be used to guide non-ICS treatments such as biologicals as well as identifying ICS-responsive, and non-responsive, asthma patients in an initial assessment and follow-up.

In summary, the RAACENO study finds no evidence that the addition of FeNO to symptom-guided asthma treatment leads to reduced exacerbations among exacerbation-prone children. Asthma symptoms remain the only tool for guiding treatment decisions and objective tests to guide asthma treatment need to be identified and validated.

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DECLARATION OF INTERESTS

Circassia provided at no cost the apparatus to allow FeNO measurements to be made in the intervention.

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DATA SHARING

Data are available on reasonable request to Prof Turner (s.w.turner@abdn.ac.uk).

Contributions of authors

ST (Chief Investigator) contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report. SC (trial manager) contributed to the design of the trial and the development of the treatment algorithm, conduct of the trial, was responsible for the day-to-day management of the trial, and contributed to the interpretation of results and writing/editing the report. JW (trial manager) was responsible for the day-to-day

management of the trial, and contributed to the interpretation of results and writing/editing the report. VB (assistant trial manager) was responsible for aspects of the day-to-day management of the trial and contributed to the interpretation of results and writing/editing the report. E-AR contributed to the statistical analysis including the interpretation of results and writing/editing the report. NS was responsible for statistical analysis and contributed to the interpretation of results and writing/editing the report. HM contributed to the conception and design of the qualitative process evaluation, was responsible for the day-to-day management of the qualitative process evaluation and contributed to the interpretation of results and writing/editing the relevant parts of the report. LL contributed to the design of the qualitative process evaluation, was responsible for the day-to-day management of the study, including interviewing participants, and contributed to the interpretation of results and writing/editing the relevant parts of the report. DE contributed to the design of the trial, was responsible for the development and computerisation of the treatment algorithm, and editing the report. CK was responsible for the health economic analysis and contributed to the interpretation of results and writing the report. GS oversaw the health economic analysis and contributed to the interpretation of results and writing/editing the report. SF contributed statistical expertise to the design and conduct of the trial, statistical analysis, and contributed to editing the report. GMacL contributed to the statistical analysis and interpretation of results and writing/editing the report. JN contributed to the conception and design of the trial and writing/editing the report. MF contributed to the development and computerisation of the treatment algorithm and writing/editing the report. EG, JdeJ, MP, MT and DP contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, interpretation of results and writing/editing the report. E-AR and NS accessed and verified the data. All authors were responsible for the decision to submit the manuscript. All authors saw and approved the final text.

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Table one. Baseline characteristics of participants in each trial arm and combined.

		Intervention			Standard care			Combined		
		N			N			N		
Sex, male (N, n, %)		255	156	61·2	254	152	59·8	509	308	60·5
Age, years (N, mean, SD)		255	10·0	2·6	254	10·1	2·5	509	10·1	2·6
BMI groups[a] (N, n, %)	Healthy weight	255	161	63·6	254	151	59·9	209	312	61·8
	Obese		24	9·5		22	8·7		46	9·1
	Overweight		51	20·2		55	21·8		106	21·0
	Thin		17	6·7		24	9·5		41	8·1
White ethnic group (N, n, %)		255	187	73·3	254	198	78·0	509	385	75·6
Age mother left education, years (N, median, p25, p75)		248	18	16, 21	247	18	16, 21	495	18	16, 21
Age of asthma diagnosis, years (N, mean, SD)		253	3·94	2·6	253	3·72	2·5	506	3·83	2·6
Premature birth (before 36 weeks) (N, n, %)		255	43	16·9	254	26	10·2	509	69	13·6
Hospital admission for asthma, last year (N, median, p25, p75)		255	1	0, 2	254	1	0, 2	509	1	0, 2
Number of hospital admissions for asthma, lifetime (N, n, %)	Never	255	30	11·8	254	34	13·4	509	64	12·6
	1-5 times		114	44·7		97	38·2		211	41·5
	>5 times		111	43·5		123	48·4		234	46·0
Number of courses of oral corticosteroid tablets, last year (N, median, p25, p75)		255	3	1, 4	254	3	1, 5	509	3	1, 5

Wheeze only with a cold (N, n, %)		255	100	39·2	253	90	35·6	508	190	37·4
Median daily dose of inhaled corticosteroid (budesonide equivalent; N, p25, p75)		255	400	400,1000	254	400	400,1000	509	400	400,1000
Daily dose of inhaled corticosteroid (budesonide equivalent; N, n, %)	≤ 400 microgram	255	143	56·1	253	143	56·3	508	286	56·2
	401-800 microgram		27	10·6		27	10·6		54	10·6
	>800 microgram		85	33·3		84	33·0		169	33·2
Current LABA use (N, n, %)		255	196	76·9	254	190	74·8	509	386	75·8
Current LTRA use (N, n, %)		255	150	58·8	254	152	59·8	509	302	59·3
Controlled Asthma[b] (N, n, %)		255	132	51·8	254	124	48·8	509	256	50·3
% predicted FEV_1 (N, mean, SD)		234	89·8	17·8	221	89·3	18·2	455	89·6	18·0
FeNO, parts per billion (N, median, p25, p75)		255	20	11, 45	254	22·5	10, 51	509	21	10, 48
Child exposed to smoking (N, n, %)		255	45	17·6	254	49	19·3	509	94	18·5
Eczema diagnosed by a doctor, ever (N, n, %)		255	141	55·3	254	152	59·8	509	293	57·6
Rhinitis, ever (N, n, %)		255	151	59·2	254	153	60·2	509	304	59·7
First degree family history of asthma (N, n, %)		254	165	65·0	254	151	59·4	508	316	62·2

SD=Standard Deviation. BMI=Body Mass Index. LABA=long acting beta agonist. LTRA=Leukotriene Receptor Antagonist. FeNO=Fractional Exhaled Nitric Oxide. [a] Defined using the categories from the International Obesity Task Force (Cole TJ et al BMJ 2000; 320(7244): 1240-3).which categorises individuals as Thin, Healthy Weight, Overweight or Obese by back-extrapolating Body Mass Index (BMI) cut offs for these

weight categories at age 18 years adjusting for age. [b] Controlled asthma control was defined as ACT score of ≥20 in line with commonly used cut-offs for partly/fully controlled asthma

Table two. The odds ratio (OR) for the primary outcome, i.e. asthma exacerbation requiring oral corticosteroids over 12 months post randomisation, between the intervention and standard care arms of the trial. The per protocol analysis included only those compliant with the algorithm, i.e. the algorithm recommended treatment was followed on three or four scheduled visits between baseline and nine months. The complier average casual effect analysis included participants in the FeNO arm where there was algorithm compliance plus all participants in the standard care arm.

Outcome	Intervention	Standard care		Effect size	Lower 95% CI	Upper 95% CI	p-value
Intention to treat analysis	**N=255**	**N=251**					
Number with at least one exacerbation	123	129	unadjusted OR	0·88	0·62	1·25	0·48
Percentage with at least one exacerbation	48·2	51·4	adjusted OR[a]	0·88	0·61	1·27	0·49
Per protocol analysis	**N=165**	**N=153**					
Number with at least one exacerbation	84	79	unadjusted OR	0·97	0·62	1·51	0·90
Percentage with at least one exacerbation	50·9	51·6	adjusted OR[a]	0·98	0·61	1·55	0·92
Complier average causal effect analysis							
			adjusted OR[a]	0·82	0·48	1·41	

[a] adjusted for age, sex, asthma severity and centre

Table three. Comparison between participants in the trial arms of time to first exacerbation, number of exacerbations, number of unscheduled healthcare contacts and the Paediatric Asthma Quality of Life Questionnaire (PAQLQ).

Outcome	Intervention N=255	Standard care N=251		Effect size	Lower 95% CI	Upper 95% CI	p-value
Time to first exacerbation (from randomisation)							
Number with at least one exacerbation	123	129					
Median time to first exacerbation (days)	nr	344	unadjusted HR	0·92	0·72	1·17	0·49
25th percentile (time to first exacerbation (days))	137	112	adjusted HR[a]	0·92	0·71	1·18	0·50
75th percentile (time to first exacerbation (days))	nr	nr					
Number of exacerbations							
Total number of exacerbations	254	255					
Mean number of exacerbations per participant	0·99	1·01					
Median number of exacerbations (p25, p75)	0 (0,2)	1 (0,2)	unadjusted IRR	0·98	0·77	1·26	0·89
			adjusted IRR[a]	0·99	0·82	1·18	0·87
Number of unscheduled healthcare contacts							

Unscheduled healthcare contacts (n, %)	133 (52·2%)	139 (55·4%)	unadjusted OR	0·88	0·62	1·25	0·47
			adjusted OR[a]	0·88	0·65	1·17	0·37
Number of unscheduled healthcare contacts (median, p25, p75)	1 (0,2)	1 (0,3)	unadjusted IRR	0·92	0·70	1·21	0·54
			adjusted IRR[a]	0·91	0·72	1·13	0·39
PAQLQ at 12 months – overall quality of life							
Median score (p25, p75)	6·4 (5·5, 6·9)	6·2 (5·4, 6·8)	Unadjusted	0·092	-0·095	0·279	0·33
			adjusted[a]	0·098	-0·088	0·283	0·30

nr=not reached. HR=hazards ratio. IRR=incidence rate ratio. OR=odds ratio. [a]Adjustment was for age, sex, asthma severity and centre.

Figure one. CONSORT flow diagram

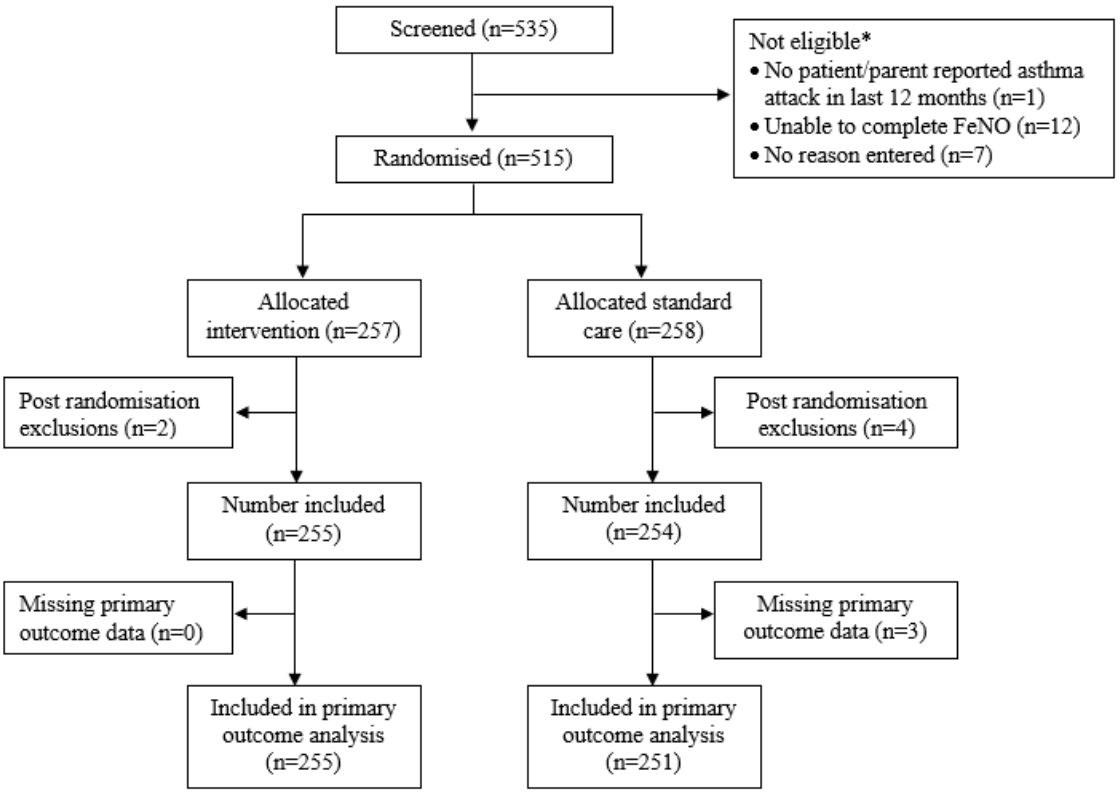


Figure two. Panels showing trends over the period of follow up in: A. Mean percentage predicted forced expiratory volume in 1 second (FEV1, error bars denote SD); B. Median Fractional Exhaled Nitric Oxide (FeNO, parts per billion, error bars denote p25, p75); C. Median daily inhaled corticosteroid dose (budesonide equivalent, microgram, error bars denote p25, p75); D. Median asthma control (ACT=Asthma Control Test, CACT=Children's Asthma Control Test, error bars denote p25, p75).

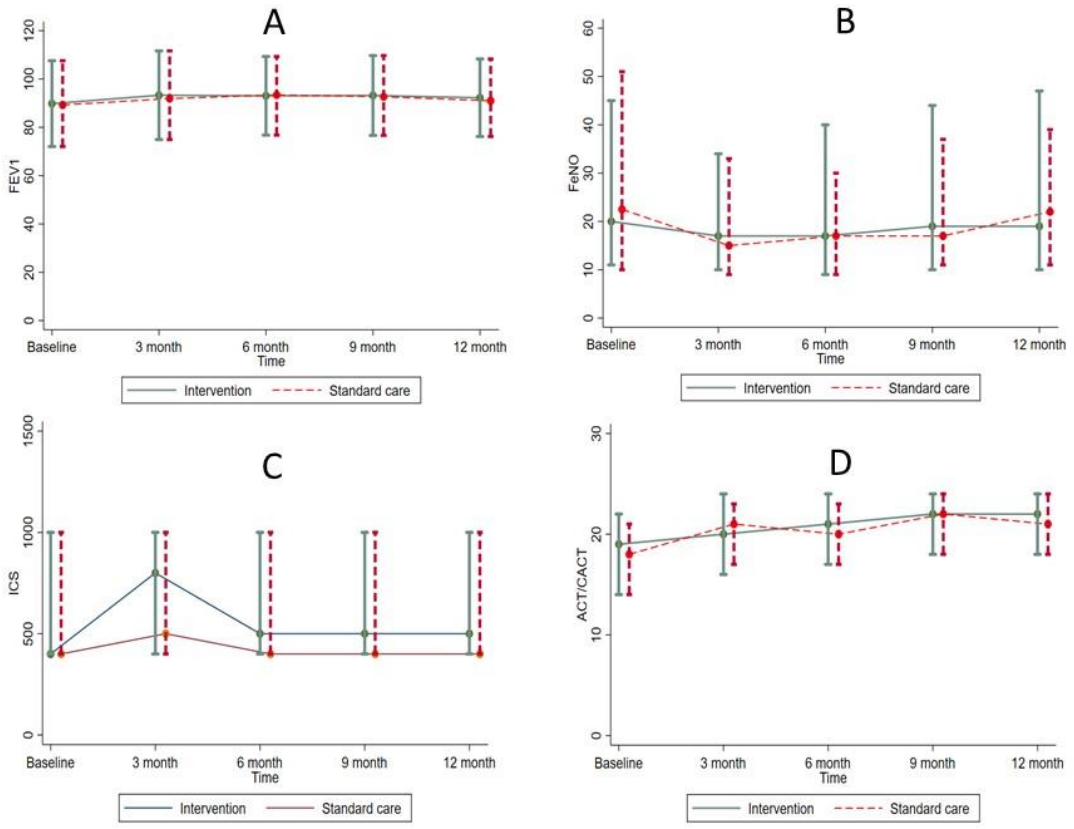


Figure one

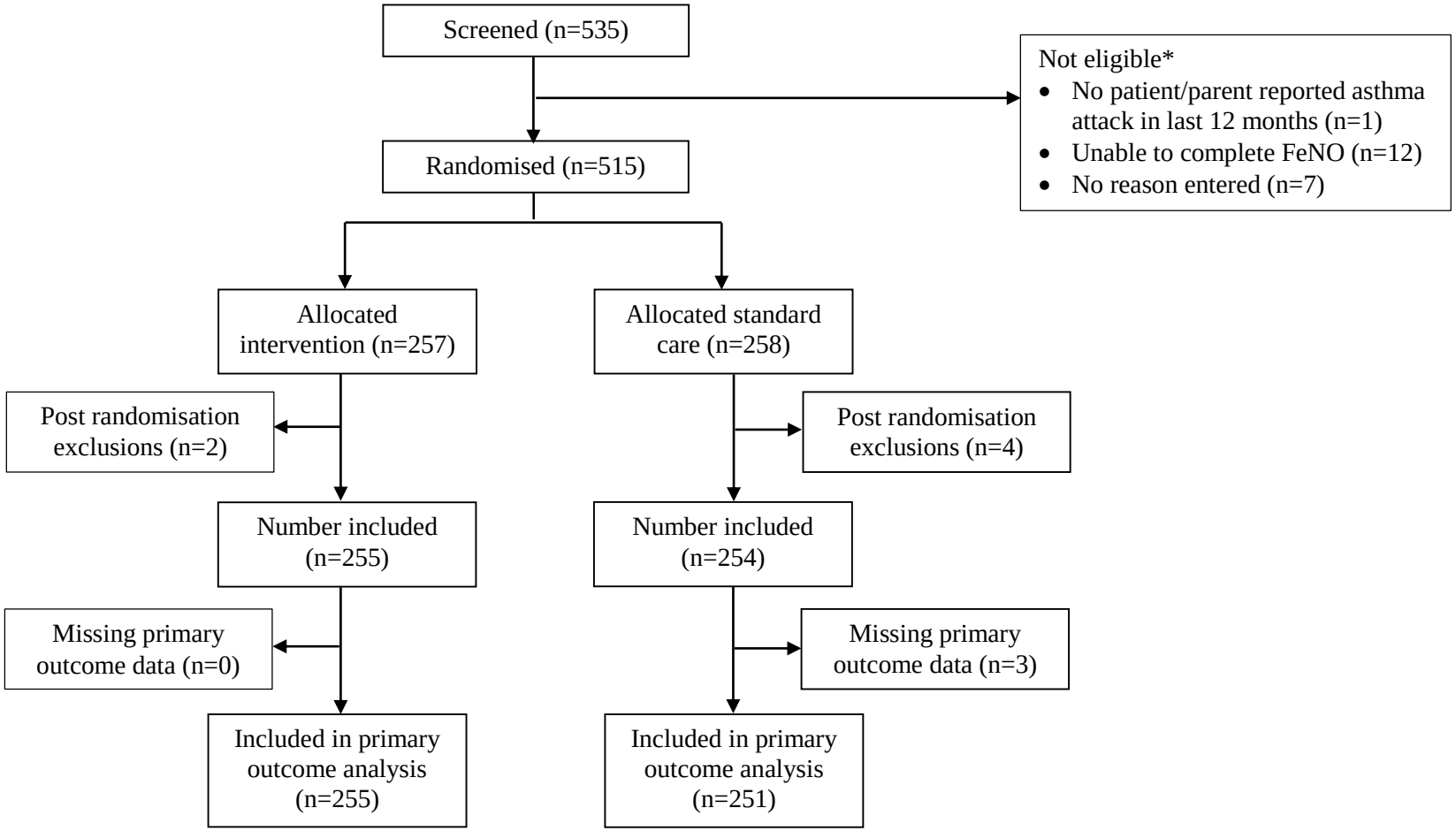
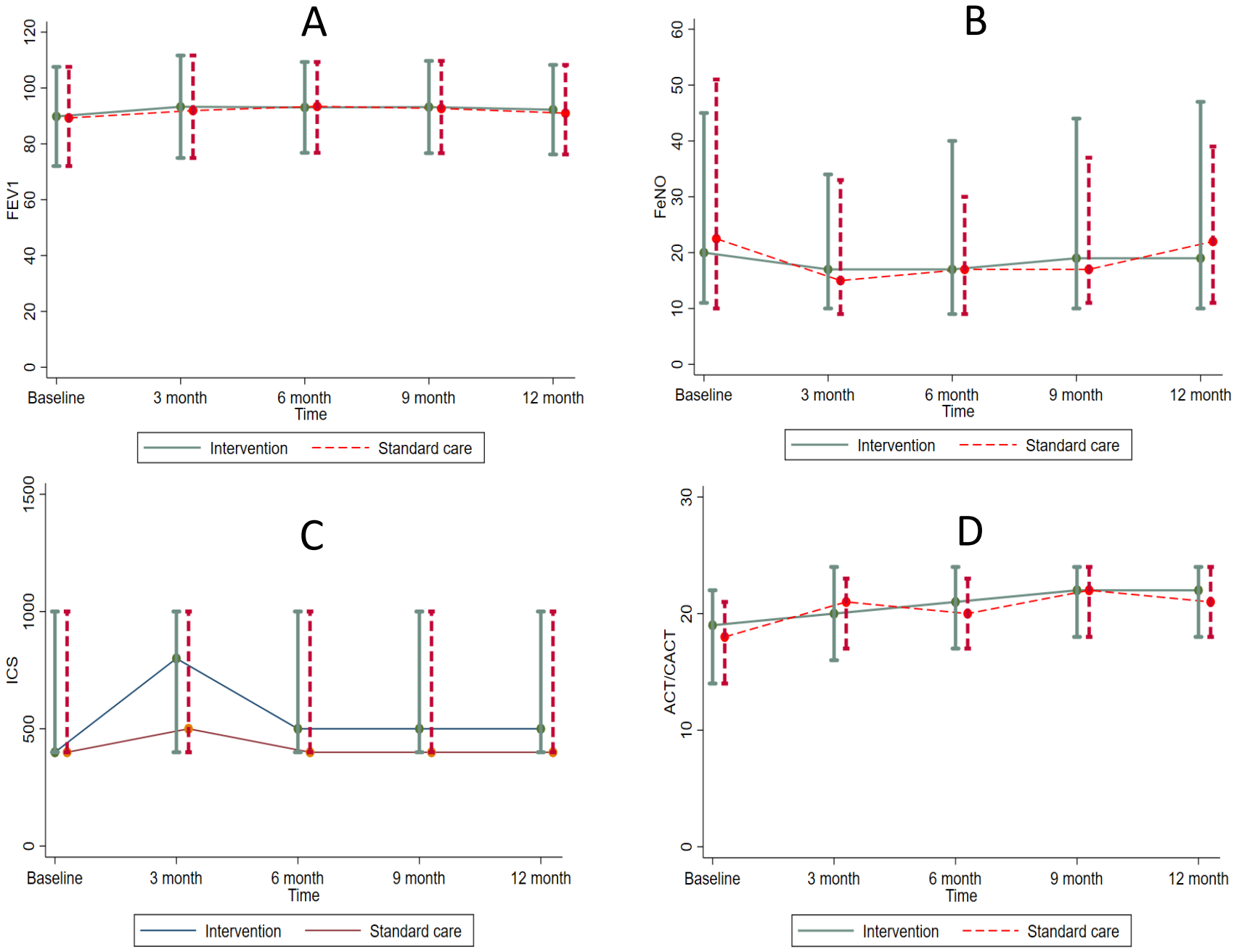

Screened (n=535)
Not eligible*
No patient/parent reported asthma attack in last 12 months (n=1)
Unable to complete FeNO (n=12)
No reason entered (n=7)
Randomised (n=515)
Allocated intervention (n=257)
Allocated standard care (n=258)
Post randomisation exclusions (n=2)
Post randomisation exclusions (n=4)
Number included (n=255)
Number included (n=254)
Missing primary outcome data (n=0)
Missing primary outcome data (n=3)
Included in primary outcome analysis (n=255)
Included in primary outcome analysis (n=251)

Figure two


A
FEV1
0
20
40
60
80
100
120
Baseline
3 month
6 month
9 month
12 month
Time
Intervention
Standard care
B
FeNO
0
10
20
30
40
50
60
Baseline
3 month
6 month
9 month
12 month
Time
Intervention
Standard care
C
ICS
0
500
1000
1500
Baseline
3 month
6 month
9 month
12 month
Time
Intervention
Standard care
D
ACT/CACT
0
10
20
30
Baseline
3 month
6 month
9 month
12 month
Time
Intervention
Standard care

SUPPLEMENTARY MATERIAL

Impact of COVID-19

The impact of COVID-19 was that follow-up visits scheduled on or after 20 March 2020 could not be carried out face-to-face and had to be re-arranged to a telephone follow-up. All the 6 month follow-up visits had been completed before 20 March 2020. Thirteen children in the intervention arm completed a 9 month visit by telephone after 20 March 2020; because FeNO could not be measured at this follow-up, these children received the treatment recommendation for the standard care arm. Twelve children in the standard care arm completed a 9 month visit by telephone after 20 March 2020; they received the recommendation for the standard care arm (as they would have done if the visit had been face-to-face).

The follow period for RAACENO ended in August 2020, which was five months after the first lockdown of the COVID-19 pandemic. Due to COVID-19 restrictions there were 25 participants who missed their nine-month RAACENO assessment. Twelve of these individuals were in the standard care arm and received a treatment recommendation from algorithm albeit delivered over the telephone. There were 13 individuals in the FeNO-guided treatment arm who could not have FeNO measured, and these individuals had treatment recommendations as if they were in the standard care treatment arm. An additional challenge presented by the COVID-19 pandemic to RAACENO was that face-to-face qualitative interviews could not take place, however with the support of sponsor we were able to swiftly move to remote interviews and recruited the pre-specified number of participants. Asthma exacerbations reduced during lockdown and afterwards[1] but, since this period occurred late in the RAACENO time-course, COVID-19 did not substantially affect the RAACENO outcome – and would have affected both arms equally. In summary COVID did not make a meaningful impact on any aspect of the RAACENO trial.

Table S1. Results of subgroup analyses which included an interaction term between the factor of interest and the intervention received (i.e. standard care or FeNO guided care).

Subgroup factors	Intervention			Standard care			Adjusted OR[a]	Upper 95% CI	Lower 95% CI	p-value	p-value for interaction
	N	n	%	N	n	%					
Treatment at baseline											0·15
Includes LTRA	150	83	55·3	151	86	57·0	0·95	0·56	1·60	0·842	
Does not include LTRA	105	40	38·1	100	43	43·0	0·81	0·46	1·44	0·476	
Age at baseline											0·63
<11 years	146	72	49·3	139	70	50·3	0·95	0·62	1·46	0·823	
11+ years	109	51	46·8	112	59	52·7	0·79	0·42	1·49	0·469	
Sex											0·95
Male	156	78	50·0	150	82	54·7	0·86	0·57	1·29	0·457	
Female	99	45	45·4	101	47	46·5	0·86	0·49	1·52	0·607	
Wheeze only with cold											0·21
Yes	100	41	41·0	88	44	50·0	0·67	0·38	1·20	0·179	
No	155	82	52·9	162	84	51·9	1·03	0·69	1·56	0·872	
Obesity											0·25
Obese	24	16	66·7	22	11	50·0	1·91	0·53	6·86	0·324	
Non-obese	229	106	46·3	227	117	51·5	0·81	0·56	1·18	0·278	
Eczema in the last year											0·66
Yes	91	46	50·65	90	44	48·9	1·03	0·59	1·81	0·913	
No	164	77	47·0	161	85	52·8	0·79	0·50	1·25	0·315	
Asthma Severity[c]											0·56
BTS Step 2	39	14	35·9	37	9	24·3	1·41	0·45	4·37	0·553	
BTS Step 3	109	50	45·9	108	58	53·7	0·74	0·39	1·43	0·376	
BTS Step 4	107	59	55·1	106	62	58·5	0·86	0·53	1·40	0·552	

The analyses adjusted for age, sex, asthma severity and centre. LTRA=Leukotriene Receptor Antagonist

Table S2. Median Paediatric Asthma Quality of Life Questionnaire (PAQLQ) scores for symptoms, limitations and emotional domains for participants in the intervention and standard care arms of RAACENO.

Outcome	Intervention N=215	Standard N=199		Mean difference	Lower 95% CI	Upper 95% CI	p-value
PAQLQ at 12 months – symptoms domain							
Median	6·33	6·11	unadjusted	0·162	-0·050	0·374	0·14
p25, p75	5·33, 6·89	5·22, 6·67	adjusted[a]	0·169	-0·042	0·379	0·12
PAQLQ at 12 months – limitations domain							
Median	6·20	6·20	unadjusted	-0·012	-0·216	0·192	0·91
p25, p75	5·20, 6·80	5·20, 6·80	adjusted[a]	-0·007	-0·209	0·196	0·95
PAQLQ at 12 months – emotional domain							
Median	6·63	6·63	unadjusted	0·074	-0·116	0·264	0·45
p25, p75	5·75, 7·00	5·75, 7·00	adjusted[a]	0·079	-0·111	0·268	0·41

Results are presented from the 12-month assessment. p25=25th centile. p75=75th centile. [a]The adjusted model included for age, sex, asthma severity and centre as covariates.

Table S3. Mean percent predicted forced expiratory volume in 1 second (FEV_1) for participants in the intervention and standard care arms of RAACENO. Results are presented from baseline and the four subsequent follow up points. The unadjusted overall mean difference over time was +0·37% [95% CI -1·60, +2·34] p=0·71· The difference adjusted for age, sex, asthma severity and centre was +0·24% [95% CI -1·68, +2·16] p=0·81.

Time point		Intervention	Standard care
Baseline	Total	234	219
	Mean	89·8	89·3
	SD	17·8	18·3
3 months	Total	210	188
	Mean	93·3	91·9
	SD	18·4	16·8
6 months	Total	193	183
	Mean	93·0	93·4
	SD	16·3	16·8
9 months	Total	179	162
	Mean	93·2	92·7
	SD	16·5	16·3
12 months	Total	156	137
	Mean	92·2	91·0
	SD	16·0	17·4

Table S4. Median fractional exhaled nitric oxide, in parts per billion, for participants in the intervention and standard care arms of RAACENO. Results are presented from baseline and the four subsequent follow up points. The unadjusted overall mean difference over time was +2·59ppb [95% CI -1·16, +6·35] p=0·18. The difference adjusted for age, sex, asthma severity and centre was +2·75ppb [95% CI -0·97, +6·47] p=0·15.

Time point		Intervention	Standard care
Baseline	Total N	255	254
	Median	20·0	22·5
	p25, p75	11, 45	10, 51
3 months	Total N	219	209
	Median	17·0	15·0
	p25, p75	10, 34	9, 33
6 months	Total N	207	202
	Median	17·0	17·0
	p25, p75	9, 40	9, 30
9 months	Total N	190	181
	Median	19·0	17·0
	p25, p75	10, 44	11, 37
12 months	Total N	163	147
	Median	19·0	22·0
	p25, p75	10, 47	11, 39

p25=25th centile· p75=75th centile.

Table S5. Median dose of inhaled corticosteroids, micrograms budesonide or equivalent, for participants in the intervention and standard care arms of RAACENO. Results are presented from baseline and the four subsequent follow up points. The unadjusted overall mean difference over time was -10·6 micrograms [95% CI -71·1, 49·9] p=0·73· The difference adjusted for age, sex, asthma severity and centre was -10·9 micrograms [95% CI -70·8, 49·1] p=0·72.

Time point		Intervention	Standard care
Baseline	Total N	255	251
	Median	400·0	400·0
	p25, p75	400, 1000	400, 1000
3 months	Total N	228	216
	Median	800·0	500·0
	p25, p75	400, 1000	400, 1000
6 months	Total N	211	210
	Median	500·0	400·0
	p25, p75	400, 1000	400, 1000
9 months	Total N	209	198
	Median	500·0	400·0
	p25, p75	400, 1000	400, 1000
12 months	Total N	224	208
	Median	500·0	400·0
	p25, p75	400, 1000	400, 1000

p25=25th centile· p75=75th centile.

Table S6. Median Asthma Control Test or Children's Asthma Control Test score for participants in the intervention and standard care arms of RAACENO. Results are presented from baseline and the four subsequent follow up points· The unadjusted overall mean difference over time was +0·04 [95% CI -0·50, +0·57] p=0·90. The difference adjusted for age, sex, asthma severity and centre was +0·05 [95% CI -0·47, +0·58] p=0·84.

Time point		Intervention	Standard care
Baseline	Total N	255	251
	Median	19·0	18·0
	p25, p75	14, 22	14, 21
3 months	Total N	231	224
	Median	20·0	21·0
	p25, p75	16, 24	17, 23
6 months	Total N	214	215
	Median	21·0	20·0
	p25, p75	17, 24	17, 23
9 months	Total N	213	204
	Median	22·0	22·0
	p25, p75	18, 24	18, 24
12 months	Total N	222	208
	Median	22·0	21·0
	p25, p75	18, 24	18, 24

p25=25th centile. p75=75th centile.

Table S7. Recommendations made by the algorithm at each clinical assessment.

	Intervention		Standard care		Overall	
	N	**%**	**N**	**%**	**N**	**%**
Algorithm recommendation at baseline						
Total	255		251		506	
Step down	57	22·4	0[a]	0·0	57	11·3
Remain the same	24	9·4	101	40·2	125	24·7
Step up	174	68·2	150	59·8	324	64·0
Algorithm recommendation at 3 months						
Total	226		216		442	
Step down	105	46·5	69	31·9	174	39·4
Remain the same	16	7·1	68	31·5	84	19·0
Step up	105	46·5	79	36·6	184	41·6
Algorithm recommendation at 6 months						
Total	211		209		420	
Step down	87	41·2	84	40·2	171	40·7
Remain the same	29	13·7	43	20·6	72	17·1
Step up	95	45·0	82	39·2	177	42·1
Algorithm recommendation at 9 months						
Total	205		199		404	
Step down	92	44·9	92	46·2	184	45·5
Remain the same	39	19·0	52	26·1	91	22·5
Step up	74	36·1	54	27·1	128	31·7
Missing	0	0·0	1	0·5	1	0·2
Algorithm recommendation at 12 months						
Total	219		206		425	
Step down	107	48·9	108	52·4	215	50·6
Remain the same	47	21·5	39	18·9	86	20·2
Step up	63	28·8	57	27·7	120	28·2

Missing	2	0·9	2	1·0	4	0·9

Table S8. Compliance with algorithm recommendation at each clinical assessment.

	Baseline			3-month follow-up			6-month follow-up			9-month follow-up		
	Intervention	**Standard care**	**Total**	**Intervention**	**Standard care**	**Total**	**Intervention**	**Standard care**	**Total**	**Intervention**	**Standard care**	**Total**
Step up												
Total N	174	150	324	105	79	184	95	82	177	74	54	128
N not followed	42	34	76	24	22	46	25	24	49	19	12	31
% not followed	24·1	22·7	23·5	22·9	27·8	25·0	26·3	29·3	27·7	25·7	22·2	24·2
Step down												
Total N	57	n/a[a]	57	105	69	174	87	84	171	92	92	184
N not followed	19	n/a[a]	19	24	16	40	24	27	51	19	30	49
% not followed	33·3	n/a[a]	33·3	22·9	23·2	23·0	27·6	32·1	29·8	20·7	32·6	26·6
Remain the same												
Total N	24	101	125	16	68	84	29	43	72	39	52	91
N not followed	2	4	6	0	7	7	0	1	1	2	0	2
% not followed	8·3	4·0	4·8	0·0	10·3	8·3	0·0	2·3	1·4	5·1	0·0	2·2
All algorithm recommendations												
Total N	255	251	506	226	216	442	211	209	420	205	198	403
N not followed	63	38	101	48	45	93	49	52	101	40	42	82
% not followed	24·7	15·1	20·0	21·2	20·8	21·0	23·2	24·9	24·0	19·5	21·2	20·3

Table S9. Comparison of characteristics of RAACENO participants with children recruited to hospital asthma clinics across Scotland for the Paediatric Asthma Gene Environment Study (PAGES)[2]. Data for PAGES are not complete for all outcomes.

	RAACENO	**PAGES**
Mean age (SD), y	10·1 (2·6) n=509	10·7 (2·8) n=483
% Male sex (n)	61% (308/509)	60% (266/447)
Eczema	36% (183/509)	38% (184/462)
White ethnic group	76% (385/509)	96% (362/377)
CACT or ACT >19	50% (256/509)	32% (96/3010)
Median overall PAQLQ score [p25, p75]	5·7 [4·4, 6·5] n=508	5·5 [4·0, 6·6] n=252
Any exacerbation in the last year	100%	50% (240/440)
Mean %FEV_1 (SD), n	90 (18) n=455	94 (16) n=173
Median FeNO (p25, p75), n	21 [10, 48] n=509	21 [12, 51] n=184
Mean bronchodilator response (SD), n	10 (9·1) n=160	4 (7·7) n=150
Median ICS (p25, p75) microgram budesonide equivalent	400 [400, 1000] n=509	200 [200, 500] n=415
Treated with LABA	76% (386/509)	61% (294/462)
% BTS treatment step 2	15·1% (77/509)	19% (87/457)
% BTS treatment step 3	43·0% (219/509)	59% (268/457)
% BTS treatment step 4	41·8% (213/509)	14% (66/457)

Table S10. Methodological details of earlier randomised clinical trials (recruiting from hospital setting) which have intervened with FeNO to guide asthma treatment.

	Primary outcome(s)	**Mean age (SD)**	**Number of participants**	**Atopy as inclusion criteria?**	**FEV_1 <80% also used in treatment algorithm?**	**FeNO cut off(s) used (ppb)**	**Follow up periods after baseline**	**What did the trial find? (FeNO treatment compared to standard care)**
RAACENO	Exacerbation	10·1 (2·6)	509	No	No	>50% change	3, 6, 9 and 12 months	
Fritsch[3]	FEV_1	11·5 (3·1)	47	Yes	Yes	20	6, 12, 18 and 24 weeks	Higher mid expiratory flow, higher dose of ICS
Peirsman[4]	Symptom free days	10·7 (2·1)	99	Yes	Yes	20	3, 6, 9 and 12 months	Reduced exacerbations, increased LTRA and ICS dose· No difference in primary outcome
Petsky[5]	Exacerbations	10·0 (3·2)	63	No	No	10 for non atopic, 12 with one PSPT[a], 20 for >1 PSPT[a]	1, 2, 3, 4, 6, 8, 10 and 12 months	Reduced exacerbation, increased ICS dose
Pijnenburg[6]	Cumulative ICS dose	12·3 (2·8)	85	No	No	30	3, 6, 9 and 12 months	Reduced FeNO and bronchial hyper-responsiveness· No increase in ICS dose
Pike[7]	ICS dose and exacerbation frequency	10·9 (2·6)	90	No	No	≤15 and ≥25	2, 4, 6, 8, 10 and 12 months	No differences in outcomes
Szefler[8]	Days with asthma symptoms	14·4 (2·1)	546	Yes	Yes	20, 30 and 40	6, 14, 22, 30, 38 and 46 weeks	Reduced exacerbations, increased ICS dose· No difference in primary outcome·
Voorend-van Bergen[9]	Proportion of symptom free days	10·2 (3·0)	181[a]	Yes	No	20 and 50	4, 8 and 12 months	Increased asthma control but not the primary outcome

[a] PSPT, positive skin prick test

[b] details of participants in a third trial arm (a web-based intervention) are not included.

Table S11. Baseline characteristics of participants in RAACENO and other relevant randomised clinical trials.

	% male (n)	Median FeNO (p25, p75), ppb	Mean % predicted FEV_1 (SD)	% with allergy[a]	% obese (n/N)	% prescribed LTRA (n)	% prescribed LABA (n)	Median dose of ICS (p25, p75)	% (number) > 400 microgram BUD	% White ethnic group	% controlled (n)
RAACENO	61% (308)	21 (10, 48)	89·6 (17·8) n=445	not determined	9% (46/505)	59% (302/509)	76% (386/509)	400 (400, 1000)	44% (223/509)	76% (385)	50% (256/509)
Fritsch[3]	60% (28)	34 (19, 59) n=46	93·5 (15·7) n=47	100%	8% (4/47)	28% (13/47)	38% (18/47)	400 (0, 800)	30% (14/47)	Not stated	49% (23/47)
Peirsman[4]	67% (66)	31 (14, 69) n=49	91·4 (15·7) n=98	100%	1% (1/99)	60% (59/99)	32% (32/99)	320 (200, 400)	15% (15/99)	82% (69/84)	75% (49/65)
Petsky[5]	49% (31)	26 (12, 48) n=61	90·7 (15·6) n=54	38% (24/63)	2% (1/58)	10% (6/58)	67% (39/58)	400 (250, 500)	49% (31/63)	Not stated	72% (41/57)
Pijnenburg[6]	65% (56)	32 (17, 53) n=85	97·5 (17·5) n=85	100%	4% (4/85)	0% (0/85)	39% (33/85)	800 (400, 1000)	67% (57/85)	Not stated	57% (44/77)
Pike[7]	57% (51)	26 (10, 48) n=90	89·2 (14·3) n=90	76% (68/90)	8% (7/89)	51% (46/90)	76% (68/90)	800 (400, 1000)	59% (53/90)	92% (83/90)	97% (87/90)
Szefler[8]	53% (288)	20 (11, 41) n=546	90·9 (16·6) n=546	88% (467/531)	31% (165/526)	15% (80/546)	66% (360/546)	1000 (400, 2000)	53% (287/546)	0% (0/526)	80% (421/528)
Voorend-van Bergen[9]	68% (123)	18 (10, 30) n=179	93·8 (13·0) n=157	100%	3% (5/181)	13% (23/181)	46% (84/181)	400 (400, 800)	33% (59/181)	89% (160/179)	67% (122/181)

[a] confirmed by skin prick test or allergen specific IGE test

Figure S1. Forest plot showing sub-group analyses of primary outcome. Results are presented as odds ratio and (in brackets) the 95% confidence intervals for each subgroup. LTRA=Leukotriene receptor antagonist. BTS=British Thoracic Society.

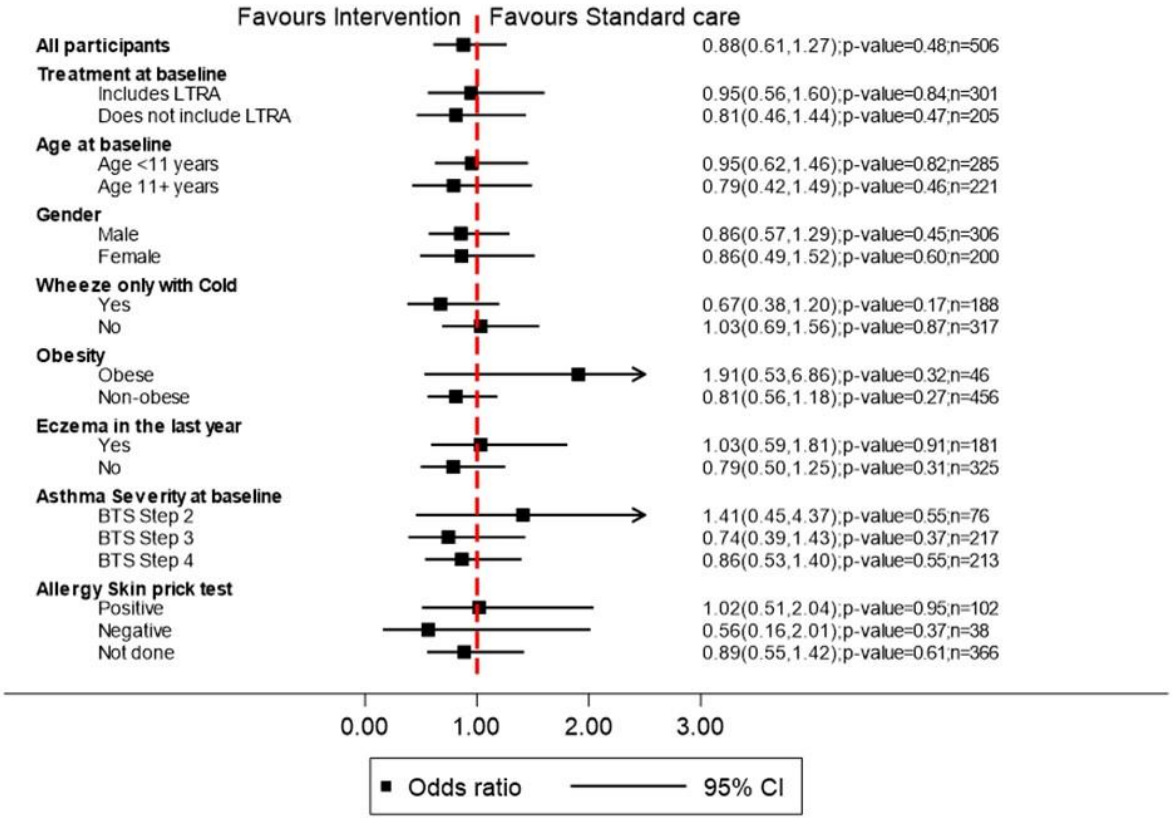
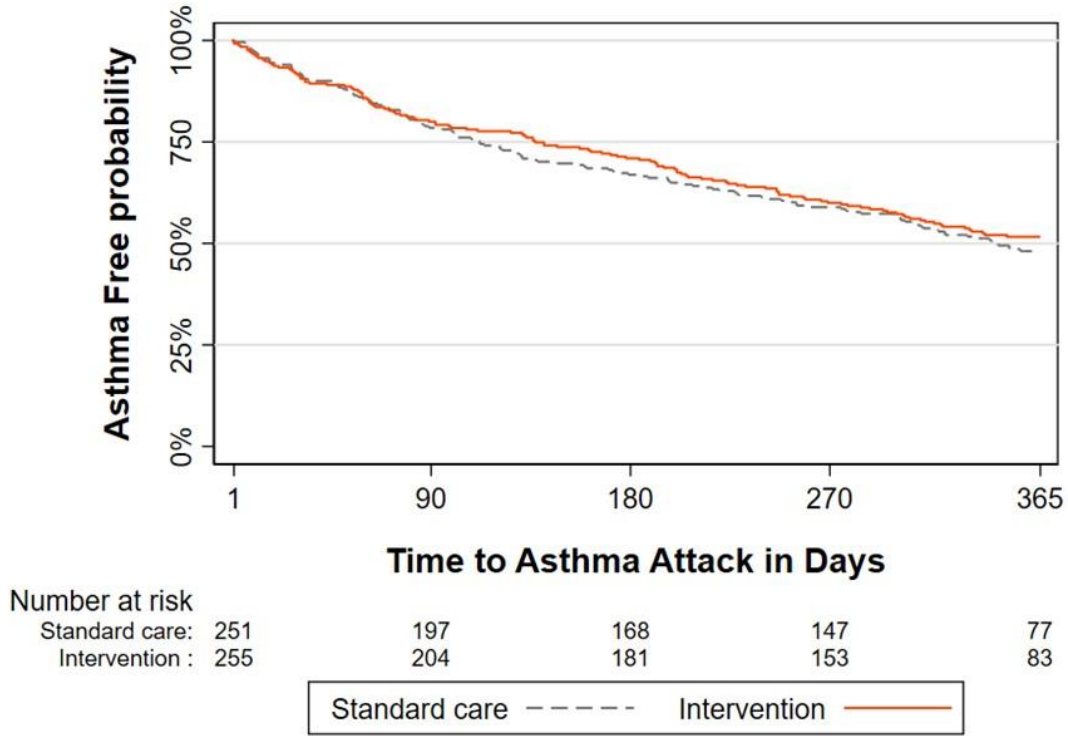


Figure S2. Kaplan-Meier plot for time to first exacerbation. Log-rank X^2 =0.31, p=0.58.



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