Received: 1 August 2020 | Accepted: 23 February 2021

DOI: 10.1111/resp.14055

ORIGINAL ARTICLE

Official Journal of the Asian Pacific Society of Respirology
Respirology APSR WILEY

A low exhaled nitric oxide level excludes a short-term benefit from inhaled corticosteroids in suspected asthma: A randomized placebo-controlled trial

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Funding information
Research for Patient Benefit Programme, Grant/Award Number: PB-PG-0614-34063

Associate Editor: Vanessa McDonald; **Senior Editor:** Fanny Ko

Abstract

Background and objective: Fractional exhaled nitric oxide (FeNO) is a non-invasive biomarker that reflects IL-4/IL-13 production and therefore represents T2 allergic inflammation. FeNO has previously been used to guide inhaled corticosteroid (ICS) treatment in asthma. The purpose of this study was to determine if a low FeNO (≤27 ppb) could be used to reliably identify patients with symptoms suggestive of asthma who would not benefit from initiating treatment with an ICS.

Methods: A total of 180 steroid-naïve adults with healthcare professional suspected asthma and an FeNO of ≤27 ppb were randomized to receive either 400 mcg of budesonide or placebo daily for 3 months. The primary outcome was the difference in the Asthma Control Questionnaire 7 (ACQ7) between treatment groups and the study was powered to determine equivalence. Secondary outcomes were the difference in FEV_1, Medical Research Council and Leicester Cough Questionnaire scores.

Results: One hundred and thirty-four patients (68 budesonide and 66 placebo) completed the study and were included in the analysis. The between-group mean difference in ACQ7 from baseline to the end of the study was −0.25 and the 95% CI around this difference was −0.004 to 0.495 confirming equivalence ($p < 0.05$). Differences in forced expiratory volume over 1 s and other secondary outcomes were also small and clinically unimportant.

Conclusion: The results of this study suggest that steroid-naïve patients with symptoms suggestive of asthma and an FeNO ≤ 27 ppb are unlikely to benefit from initiating treatment with an ICS over 3 months. However, further research is recommended to confirm these findings before withholding ICS treatment.

KEYWORDS
asthma, biomarker, fractional exhaled nitric oxide, inhaled corticosteroid, steroid naïve

INTRODUCTION

Asthma is a common chronic inflammatory airway disease that is often over-diagnosed[1] due to the non-specific nature of the typical symptoms including cough, wheeze, chest tightness and shortness of breath. Inhaled corticosteroid (ICS) treatment is now recommended for all but the mildest cases of asthma meaning many patients are prescribed medication they do not require and, as such, are at risk of developing unnecessary side effects such as oral candidiasis or dysphonia. A simple test that could be used to guide clinicians in prescribing or not prescribing therapeutic interventions, following the treatable traits concept,[2] could improve patient care and help to reduce unnecessary healthcare costs.

Fractional exhaled nitric oxide (FeNO) is a non-invasive biomarker produced in bronchial epithelial cells that reflects IL-4/IL-13 production and is, therefore, a proxy marker of T2 allergic inflammation in the airways.[3,4] Elevated FeNO levels have been used to identify patients with T2 high airway inflammation who are likely to respond to an ICS,[5] and we have previously shown in an open-label study that an FeNO level less than 27 parts per billion (ppb) is highly predictive of a negative response to ICS treatment.[6] In the current study, patients with symptoms suggestive of asthma and an FeNO ≤ 27 ppb were randomized to receive either an ICS or placebo for 3 months to determine if a low FeNO level could be used to reliably identify patients who are unlikely to benefit from initiating treatment with an ICS in the short term.

SUMMARY AT A GLANCE

We conducted a randomized, double-blind placebo-controlled trial and demonstrated that steroid-naïve patients with symptoms suggestive of asthma and a fractional exhaled nitric oxide level ≤ 27 parts per billion (ppb) are unlikely to benefit from treatment with an inhaled corticosteroid over 3 months.

METHODS

Study design and participants

This 12-week randomized, double-blind, placebo-controlled, single-centre study recruited participants aged 18 years and over from primary care practices in and around Nottingham and from poster advertisements between May 2016 and March 2018. Primary care practice registries were screened for patients with healthcare professional suspected asthma who were using a short-acting beta-agonist (SABA) as required as their only asthma-related medication. To enter the study, patients must have had symptoms that required them to use their SABA no less than monthly. All participants were also required to have a prebronchodilator forced expiratory volume over 1 s (FEV_1) > 70% predicted and an FeNO ≤ 27 ppb (mean of two consecutive measurements). Participants were excluded from the study if they had received any asthma medications other than a SABA within the previous 6 months, had any significant co-morbidities, had a hypersensitivity to budesonide or its excipients, as well as any pregnant or breastfeeding mothers. Participants identified via screening were contacted by phone by one of the study team and invited to attend a study visit at their general practioner (GP) surgery or at the Nottingham Respiratory Research Unit, where written informed consent was obtained before any study related procedures.

Study protocol

Participants were randomized to receive either 200 mcg budesonide (Pulmicort) via a Turbuhaler (AstraZeneca) or placebo inhaler identical in shape, colour and appearance (AstraZeneca) one puff twice-daily for 12 weeks. Study inhalers were stored in a secure locker in the Clinical Trials Pharmacy at Nottingham City Hospital and were dispensed by authorized pharmacy personnel. Randomization was conducted in blocks of eight according to smoking status: current (or smoked within the past 12 months) or never/ex (never or quit more than 12 months ago). Randomization sequences were generated by the Respiratory Research Unit using an online pseudo-random number generator service (sealedenvelope.com).

During the randomization visit, a medical history was recorded and an average of two FeNO readings was obtained consecutively. Participants with an FeNO ≤ 27 ppb also completed the Asthma Control Questionnaire 7 (ACQ7),[7] Leicester Cough Questionnaire (LCQ)[8] and Medical Research Council (MRC) dyspnoea questionnaires.[9] The ACQ7 consisted of seven questions, overall scores were obtained by averaging the score from each question, a change of ≥0.5 was required for the difference to be considered clinically significant.[10] The LCQ consisted of 19 questions encompassing three domains, the final score was the sum of each domain score which was determined by adding together the scores of the questions in each domain and dividing by the number of questions in that domain. The possible scores ranged from 3 to 21, where 3 represented the worst cough and 21 no cough and an increase of ≥1.3 was required for the difference to be considered clinically significant.[11] The MRC consisted of five questions alongside a 1–5 stage scale to ascertain the grade of perceived clinical breathlessness on activity. Stage 1 represented no breathlessness while stage 5 represented a disabling level of breathlessness.[9] There is no accepted interval of change that represents a clinically significant improvement for this test.

FeNO was performed at a constant flow rate of 50 mL/s (NIOX VERO®; Aerocrine, Solna, Sweden) followed by spirometry, performed according to the British Thoracic Society (BTS) criteria using either Carefusion or Vitalograph spirometers.[12] Venepuncture was conducted on participants if scheduled transport could be arranged to get the sample to a pathology department for a full blood count the same day. Finally, participants were instructed on the correct use of the Turbuhaler. Participants were seen for follow-up visits every 4 weeks for 12 weeks during which FeNO, spirometry and questionnaires were repeated, and at each visit were asked about their medication adherence.

Information storage

Clinical information obtained during the study visits from the research nurses was recorded in the participants case report form and then stored in the online database Medrio.

Outcome measures

The primary outcome was the mean difference in change in ACQ7 score over the 12-week period between the budesonide and placebo groups. Secondary outcomes included the mean difference in the change in FEV_1, MRC and LCQ scores between the two groups and the number of ACQ7, FEV_1 and LCQ responders (defined as decrease of ≥0.5 points, an increase of ≥200 ml and decrease of ≥1.3 points, respectively) over 12 weeks within each group over 12 weeks.

Statistical analysis

It was determined that 150 patients would be required to give 90% power to demonstrate equivalence based on a difference in ACQ7 of ≥0.5 being clinically important and an SD of 0.9.[6] The initial goal was to recruit 165 patients to allow for drop-outs but this figure was subsequently increased to 180 due to more drop-outs than expected. All patients who completed the 12 weeks were included in the final analysis.

All analysis was conducted in Stata/SE 15.0 (2017; StataCorp, TX). Minitab (2010; Minitab Inc., PA) was used to generate the equivalence graph. Results are given in mean and SD where the data were normally distributed. In cases where the data were not normally distributed, the median and interquartile range are given.

Statistical analysis of equivalence of the primary outcome was assessed using a two, one-sided equivalence test (TOST) as the null hypothesis was that there would not be a difference between the treatment groups. The TOST was conducted with a minimal clinically significant difference (δ) of 0.5 in ACQ score,[13–15] and a type 1 error rate of 0.05. TOSTs were also conducted for the secondary outcomes LCQ and FEV_1, δ 1.3 and δ 0.2 L, respectively. The secondary outcomes were assessed within tertiles of FeNO levels using chi-square and unpaired *t*-tests to evaluate how differences between responders and non-responders in the budesonide and placebo groups change with FeNO.

RESULTS

A total of 4700 patients were contacted. Of these, 236 responded and were screened with 180 randomized. Forty-six participants failed to complete all visits, 23 from each group. In total, 134 patients completed all study visits and were included in the analysis. A post hoc calculation indicated 84% power at alpha 0.05 for equivalence of primary outcome (Figure 1).

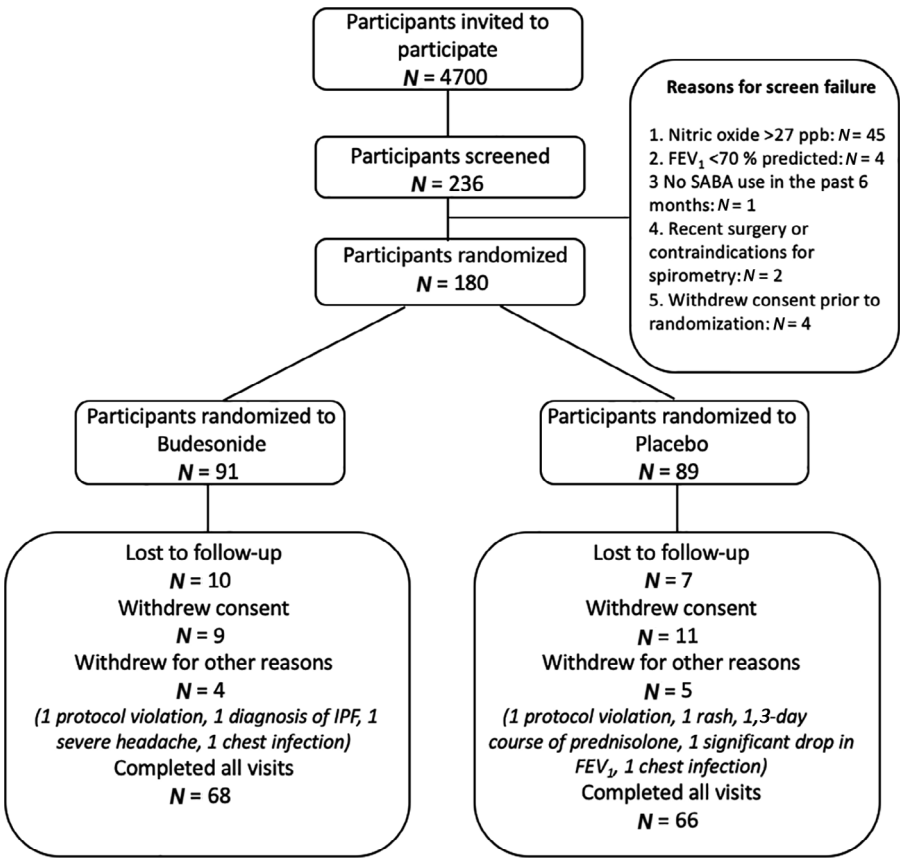

FIGURE 1 Study flow diagram

TABLE 1 Baseline demographics

Variable	Budesonide *n* = 91	Placebo *n* = 89
Age (years), mean (SD)	42.40 (17.82)	45.80 (18.20)
BMI, kg/m^2, median (IQR)	28.20 (23.53–33.80)	26.67 (23.32–31.60)
Duration of asthma symptoms (months), median (IQR)	1.30 (0.20–84.00)	2.00 (0.20–89.00)
Sex – female, *n* (%)	64.00 (70)	66.00 (74)
Ethnicity, *n* (%)		
Caucasian	80 (88)	78 (88)
Asian	2 (2)	3 (3)
Black	2 (2)	5 (6)
Other	7 (8)	3 (3)
Smoking status, *n* (%)		
Never	71 (78)	72 (80)
Current	20 (21)	17 (20)
Presenting symptoms, *n* (%)		
Cough	74.00 (83)	69.00 (80)
Wheeze	58.00 (65)	62.00 (69)
SOB	65.00 (73)	69.00 (80)
Questionnaires, median (IQR)		
ACQ7	1.28 (0.85–2.00)	1.28 (0.57–1.86)
LCQ	17.46 (12.93–20.07)	17.36 (13.43–19.96)
MRC	2.00 (1.00–2.00)	2.00 (1.00–2.00)
Lung function		
FEV_1 (L), mean (SD)	3.02 (0.78)	2.73 (0.72)
FEV_1 % predicted, mean (SD)	95.00 (13.79)	93.11 (14.74)
FVC (L), mean (SD)	3.81 (20.91)	3.52 (0.87)
FEV_1/FVC, mean (SD)	79.24 (8.20)	77.41 (8.50)
FeNO (ppb), mean (SD)	16.31 (6.24)	16.46 (6.75)
Blood eosinophils (cells × 10^9/L), median (IQR)	*N* = 59 0.16 (0.10–0.24)	*N* = 56 0.20 (0.10–0.30)

Abbreviations: ACQ, Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume over 1 s; FVC, forced vital capacity; IQR, interquartile range; LCQ, Leicester Cough Questionnaire; MRC, Medical Research Council; ppb, parts per billion; SOB, shortness of breath.

Baseline characteristics

The baseline demographics and clinical characteristics for all 180 participants who were randomized and completed visit 1 are presented in Table 1. Participants were well matched between the groups at baseline. The majority of patients were female (70% and 74%), non-smokers (78% and 80%) and Caucasian (88% and 88%) in the budesonide and placebo groups, respectively.

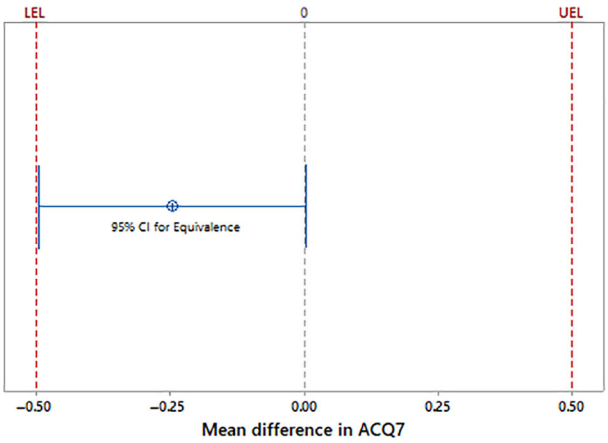

FIGURE 2 Two, one-sided equivalence test Asthma Control Questionnaire 7 mean difference and 95% CI (−0.495 to 0.004) showing the upper and lower equivalence interval (≤0.01, $p = 0.04$). LEL, lower equivalence limit; UEL, upper equivalence limit

Primary outcome

The mean changes in ACQ7 score were 0.53 (SD ±0.79) and 0.29 (SD ±0.95) in the budesonide and placebo groups, respectively. The between-group mean difference in ACQ7 was −0.25 with 95% CI of −0.004 to 0.495 which fell within the equivalence interval of −0.5 to 0.5, demonstrating equivalence ($p < 0.001$, $p = 0.047$) (Figure 2). A total of 53 participants, 29 (42%) in the budesonide and 24 (36%) in the placebo group, had an improvement in ACQ7 of ≥0.5 following 12 weeks of treatment ($p = 0.4$).

Secondary outcomes

Mean FEV_1 values decreased from 2.92 to 2.90 L in the budesonide group and remained at 2.69 L throughout the study in the placebo group. The between-group mean difference in FEV_1 was 0.01 with 95% CI of −0.06 to 0.06 which fell within the equivalence interval of −0.2 to 0.2, demonstrating equivalence ($p < 0.001$, $p < 0.001$). Following 12 weeks, 13 (10%) participants had a significant improvement in FEV_1 of ≥200 ml, four of them also had a ≥12% increase in FEV_1 % predicted. Of these, nine (13%) were in the budesonide group and four (6%) were in the placebo group ($p = 0.161$).

LCQ increased by 1.85 and 1.97 points in the budesonide and placebo groups, respectively, throughout the study. The between-group mean difference in LCQ was −0.12 with 95% CI of −1.06 to 1.31 which fell just outside the equivalence interval of −1.3 to 1.3 ($p = 0.02$, $p = 0.05$). A total of 57 participants, 27 (40%) and 30 (45%) in the budesonide and placebo groups, respectively, had a significant improvement in LCQ of ≥1.3 ($p = 0.501$).

Twenty-two (32%) and 19 (30%) of participants had an improvement in MRC score in the budesonide and placebo

groups with mean changes of 0.30 and 0.23, respectively (between-group mean difference 0.67; $p = 0.52$).

Baseline FeNO levels and response to treatment

A post hoc analysis was performed on baseline FeNO levels divided into tertile subgroups (low, ≤5–12 ppb; moderate, >12–20 ppb; and high, >20–27 ppb) to determine if there was a relationship with response to treatment (ACQ7). The number of responders in the low and moderate subgroups were independent of treatment (χ^2 $p = 0.15$ and χ^2 $p = 0.81$, respectively). Statistical significance was observed in the number of responders within the higher FeNO subgroup, suggesting the difference may be dependent on treatment when FeNO is greater than 20 ppb (63.6% budesonide, 20.0% placebo; χ^2 $p = 0.0043$) (Figure 3). Mean baseline ACQ7 scores and blood eosinophil levels were similar between treatment groups within FeNO subgroups (Table 2). The maximum FeNO level observed increased to 66.5 and 73 ppb in the budesonide and placebo groups, respectively, by the end of the study. However, the median values remained similar (17–16.75 ppb in the budesonide group and 15–17.50 ppb in the placebo group).

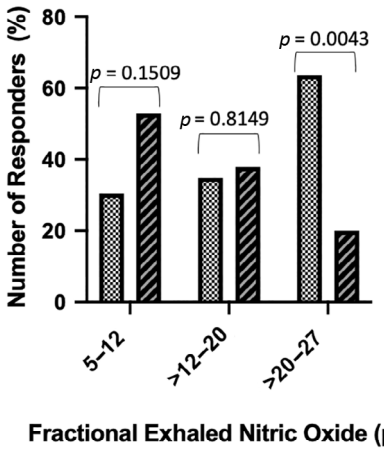

FIGURE 3 Response to intervention according to baseline fractional exhaled nitric oxide tertiles. Budesonide ▩, Placebo ▨

DISCUSSION

This study demonstrated that the between-group mean difference in ACQ7 and FEV_1 fell within their respective equivalence intervals suggesting that initiating treatment with an ICS in steroid-naïve patients with symptoms suggestive of asthma, FeNO ≤ 27 ppb and $FEV_1 > 70\%$ predicted is equivalent to treatment with placebo over 12 weeks. Mean differences in LCQ and MRC were also very similar between groups, although LCQ was marginally outside of the equivalence interval, favouring placebo. This finding builds on our previous findings which determined that baseline FeNO levels ≤ 27 ppb had a negative predictive value of 93% to starting ICS treatment.[6]

As there is no definite test to diagnose or exclude asthma, or to determine which treatments will be beneficial, the decision to initiate corticosteroids is typically driven by a compatible history with or without objective evidence of airflow obstruction. This is not ideal as symptoms are non-specific and do not necessarily reflect the type or severity of inflammation in the airways,[16,17] and spirometry is often normal when patients are asymptomatic. Several studies have shown that asthma is overdiagnosed,[1] and there is growing evidence that up to 25%–35% of patients with confirmed asthma do not benefit from ICS treatment.[18,19] FeNO is non-invasive, easy to perform, requires minimal effort and provides almost immediate results. As such, FeNO has the potential to facilitate treatment decisions by identifying patients who are unlikely to benefit from initiating an ICS.

Numerous studies have evaluated the utility of FeNO to predict response to corticosteroids. Smith et al. determined that regardless of the patient's diagnosis, those with an FeNO level > 47 ppb had a greater response to ICS than patients with low FeNO levels (<15 ppb).[20] Hahn et al. determined that patients with chronic cough and an FeNO of >35 ppb were more likely to respond to an ICS than patients with an FeNO < 35 ppb[21] and Martin et al. determined that the optimal FeNO cut-off point to predict ICS response was >33 ppb.[6] Therefore, although the cut-off points for high, moderate and low FeNO levels vary between studies, it has been well documented that higher FeNO levels are predictive of a positive response to an ICS.[22] To our knowledge, this is the first study to demonstrate that people with suspected asthma and a low FeNO (≤27 ppb)

TABLE 2 Baseline features based on FeNO tertiles

	FeNO (5–12)			FeNO (>12–20)			FeNO (>20–27)		
	Budesonide	Placebo	*p*	Budesonide	Placebo	*p*	Budesonide	Placebo	*p*
Total	23	17		23	29		22	20	
Responders (%)	7 (30.4)	9 (52.9)	0.151	8 (34.8)	11 (37.9)	0.815	14 (63.6)	4 (20.0)	0.004
Mean ACQ7 (SD)	1.73 (1.04)	1.76 (1.12)	0.924	1.31 (0.83)	1.23 (0.93)	0.738	1.31 (0.81)	1.24 (0.74)	0.757
Mean eosinophils (SD)	0.13 (0.12)	0.28 (0.21)	0.024	0.15 (0.12)	0.15 (0.09)	0.974	0.24 (0.13)	0.27 (0.17)	0.616

Abbreviations: ACQ7, Asthma Control Questionnaire 7; FeNO, fractional exhaled nitric oxide.

do not receive a short-term benefit to initiating treatment with an ICS.

When considering the clinical implications of our findings, it is important to recognize that we did not study patients with confirmed asthma and a low FeNO, but patients presenting with symptoms considered by a healthcare professional to be suggestive of asthma. We have therefore studied a group of patients with symptoms caused by a mixture of mild asthma and other problems. We are not, therefore, suggesting that a low FeNO identifies a group of steroid non-responsive asthma patients but a group of patients who either do not have asthma or have steroid non-responsive asthma. It is also possible that the latter group could still benefit from an ICS in terms of exacerbation prevention if studied over a longer time period as shown previously.[23] Therefore, we suggest that patients with symptoms suggestive of asthma and an FeNO ≤ 27 ppb and especially those with an FeNO < 20 ppb should undergo further investigation to confirm or dispute the diagnosis of asthma, ideally before starting an ICS. If these further investigations support a diagnosis of asthma, then ICS treatment is probably still indicated to prevent asthma exacerbations, something which may be best achieved by using a combination of bronchodilator with ICS as required, rather than regular ICS, as recommended in Golbal Initiative For Asthma (GINA) 2019.[22] This approach overcomes poor adherence with regular ICS which is likely to be common in patients who obtain no symptomatic benefit as shown in this study.

Our study has several limitations which also need to be considered. First, we had a low response rate from our invitation to take part. This is a common finding in clinical studies but it does raise the possibility that we have studied a population not typical of the overall population of interest and which could have introduced bias into our findings. For example, 20% of our population were smokers and smoking is known to lower FeNO levels. Second, we had no formal way of assessing adherence with the inhaled medication, although participants were asked about this at each visit. Corticosteroids are known to suppress FeNO and this has previously been used to assess treatment adherence.[23] In this study, we noted a general increase in FeNO throughout the study. This could suggest poor adherence in some participants and could be a reason why some participants failed to respond; however, this could also represent a regression to the mean, as the study population was at the bottom end of the possible values at baseline. Third, difficulties in transporting blood samples from primary care clinics back to the laboratory for processing in a timely manner resulted in baseline blood eosinophil levels only being determined for 115 participants, 92 of whom completed all study visits. Finally, FeNO is affected by many individual factors such as age, height and gender as well as external factors such as cigarette smoking, nitrate-rich foods, allergens, viral infections, exercise and air pollution.[5] As such, FeNO readings taken at one point in time may not accurately reflect airway inflammation throughout the year and longitudinal changes also need to be performed.

Our findings demonstrate that, in steroid-naïve patients with symptoms suggestive of asthma, FeNO levels ≤ 27 ppb and FEV_1 > 70% predicted, ICSs are no more effective than placebo over 3 months. Such patients are likely to benefit from further investigation rather than simply initiating treatment with an ICS, but further research is needed to confirm these findings.

ACKNOWLEDGEMENTS

This study presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0614-34063). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care, and not an official position of the institution or funder.

AUTHOR CONTRIBUTIONS

Lissa Sutherland: Data curation; formal analysis; investigation; project administration; writing-original draft; writing-review & editing. **Tim Harrison:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; supervision; validation; visualization; writing-original draft; writing-review & editing. **Dominic Shaw:** Conceptualization; investigation; methodology; writing-review & editing. **Matthew Martin:** Conceptualization; methodology; writing-review & editing. **Clair Parrish:** Investigation; project administration. **Tricia McKeever:** Data curation; formal analysis; methodology; writing-review & editing. **Karen Shaw:** Investigation; project administration. **Nicola Singleton:** Investigation. **Iain Stewart:** Data curation; formal analysis; writing-original draft; writing-review & editing.

CONFLICT OF INTEREST

This study was previously presented at the Primary Care Respiratory Society (PCRS) Conference 2019. Tim Harrison reports grants and personal fees from AstraZeneca and personal fees from GSK, outside the submitted work. Dominick Shaw reports grants from GSK and personal fees from AZ, Cheisi and Novartis, outside the submitted work. The other authors declare that they have no conflicts of interest.

HUMAN ETHICS APPROVAL DECLARATION

The study was approved by a local Research Ethics Committee (Ref 16/EM/0073) and written informed consent was obtained before the start of any study-related procedures. The study was registered as a clinical trial (NCT02771717) at clinicaltrials.gov

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Sutherland L, Shaw K, Parrish C, et al. A low exhaled nitric oxide level excludes a short-term benefit from inhaled corticosteroids in suspected asthma: A randomized placebo-controlled trial. *Respirology*. 2021;1–7. https://doi.org/10.1111/resp.14055