British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN Makes sense of evidence

Draft for Consultation

Asthma: diagnosis, monitoring and chronic asthma management (update)

Evidence reviews for clinical and cost-effectiveness of FeNO measures to monitor asthma

BTS/NICE/SIGN collaborative guideline <number>

Evidence reviews underpinning recommendation 1.5.4 in the BTS/NICE/SIGN guideline

June 2024

Draft for Consultation

This evidence review was developed by NICE

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1.1 Review question

In people with asthma, what is the clinical and cost-effectiveness of using fractional exhaled nitric oxide (FeNO) measures for monitoring asthma control?

1.1.1 Introduction

FeNO can give an indication of the levels of inflammation in the airways of people with asthma. High levels of inflammation can be associated with poor asthma control, and an increased risk of asthma attacks. It is important to evaluate the evidence around whether this leads to improved asthma control, because this would have implications for how regular asthma reviews are conducted and could require investment in healthcare resources (including equipment and staff time).

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	People with asthma. Not including severe asthma. All ages, stratified into the following 2 different groups: • Children and young people (5-16 years old) • Adults (17 years old and above) <u>Strata</u> Population of current smokers greater than 20%.
Intervention	Monitoring FeNO and adjustment of management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring) Only use validated methods of measuring FeNO (i.e. 50ml/s flow rate). *
Comparisons	Comparison of adjustment of asthma therapy based on FeNO to: • Usual care: e.g. clinical symptoms (with or without PEF) according to guidelines (including BTS/SIGN, GINA) • Asthma control questionnaires or QOL questionnaires • Lung function tests (spirometry or PEFv) • Blood eosinophils
Outcomes	• Mortality (both asthma related and all-cause) • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Severe asthma exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use)

	• Time off school or work • Inflammatory markers (FeNO)
Study design	• RCTs • Systematic reviews of RCTs

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Twenty-two randomised controlled trials were included in the review; (Bernholm, et al., 2018, Calhoun, et al., 2012, de Jongste, et al., 2009, Fang, et al., 2022, Fritsch, et al., 2006, Garg, et al., 2020, Honkoop, et al., 2015, Morphew, et al., 2019, Murphy, et al., 2022, Peirsman, et al., 2014, Petsky, et al., 2015, Pijnenburg, et al., 2005, Pike, et al., 2013, Powell, et al., 2011, Shaw, et al., 2007, Smith, et al., 2005, Syk, et al., 2013, Szefler, et al., 2008, Truong-Thanh, et al., 2020, Turner, et al., 2022, Voorend-van Bergen, et al., 2015, Wang, et al., 2019). These are summarised in Table 2 below. Eleven of these studies were conducted in children and young people, with another eleven studies conducted in adults. Evidence comparing FeNO monitoring to asthma control questionnaires was identified and combined with the usual care comparison at the discretion of the committee. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 3, Table 4 and Table 5).

No relevant clinical studies comparing FeNO monitoring with lung function tests or blood eosinophils were identified.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

Two Cochrane systematic reviews were identified. These reviews were excluded from the present review due to differences between the protocol outcomes and time frames reported, mainly due to specifying a 12-week minimum duration whereas we did not specify a minimum duration. The inclusion lists of these reviews were cross-referenced to ensure all relevant studies were included in the present review.

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Bernholm 2018(Bernhol	FeNO monitoring vs usual care	Adult patients recruited from asthma clinics	Asthma control (ACQ)	Note difference in current smokers between FeNO

Study	Intervention and comparison	Population	Outcomes	Comments
m et al., 2018) FeNO-based asthma management results in faster improvement of airway hyperresponsiveness		(median age 42, 30 years) N=80 Strata: adults, >20% current smokers Denmark	Quality of life (AQLQ) Lung function (FEV_1, litres and % predicted) Dose of regular asthma therapy (ICS dose) Inflammatory markers (FeNO) 28 weeks follow-up	monitoring group (30%) and usual care group (14%)
Calhoun 2012 (Calhoun et al., 2012) Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial	FeNO monitoring vs usual care	Adult patients aged ≥18 years with mild-moderate persistent asthma recruited concurrently with the Asthma Clinical Research Network (ACRN) trial N=343 Strata: adults, smokers excluded USA	Unscheduled healthcare utilisation (hospital admissions) Asthma control questionnaires (ACQ) Quality of life (AQLQ) Lung function (morning/evening PEF, FEV_1, litres and % predicted) Rescue medication 36 weeks follow-up	Two study arms (one based on NHBLI guideline-based monitoring, other symptom based) combined to make 'usual care' for this review
de Jongste 2009(de Jongste et al., 2009) Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma	FeNO monitoring vs usual care	Children aged 6-18 years recruited from academic centres and general hospitals with stable mild-moderate asthma N=151 Strata: children and young people, smokers excluded The Netherlands	Severe asthma exacerbations Lung function (FEV_1% predicted) 30 weeks follow-up	Mean ±SD age is within children and young people strata
Fang 2022(Fang et al., 2022) A Clinical	FeNO monitoring vs usual care	Children aged 6-12 years, newly diagnosed with asthma	Asthma control (c-ACT)	

Study	Intervention and comparison	Population	Outcomes	Comments
investigation into the usefulness of fractional exhaled nitric oxide in guiding glucocorticoid therapy in children with bronchial asthma		N=133 Strata: children, smoking stats not recorded China	Lung function (FEV1, PEF) Inflammatory markers (FeNO) 6 months follow-up	
Fritsch 2006(Fritsch et al., 2006) Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study	FeNO monitoring vs usual care	Children aged 6-18 years attending the outpatient department of a children's hospital N=47 Strata: children and young people, smoking status not reported Austria	Severe asthma exacerbations 6 months follow-up	Mean ±SD age is within children and young people strata
Garg 2020(Garg et al., 2020) Exhaled nitric oxide as a guiding tool for bronchial asthma: A randomised controlled trial	FeNO monitoring vs usual care	Adult patients aged 12- 70 years with asthma N=100 Strata: adults, smokers excluded India	Severe asthma exacerbations Dose of regular asthma therapy 12 months follow-up	Mean ±SD age is within adults strata
Honkoop 2015(Honkoop et al., 2015) Symptom- and fraction of exhaled nitric oxide-driven strategies for asthma control: A cluster-randomized trial in primary care	FeNO monitoring vs usual care	Adult patients aged 18-50 years from 44 clusters (general practices) with diagnosed asthma. N=647 Strata: adults <20% current smokers Netherlands	Unscheduled healthcare utilisation (ED visits and hospitalisation) Severe asthma exacerbations Asthma control questionnaires (ACQ) Quality of life (AQLQ) Lung function (FEV_1, % predicted) Dose of regular asthma therapy	Clustered RCT Two study arms (one aiming for partially controlled asthma, other aiming for full control) combined to make 'usual care' for this review.

Study	Intervention and comparison	Population	Outcomes	Comments
			12 months follow-up	
Morphew 2019(Morphew et al., 2019) Phenotypes favoring fractional exhaled nitric oxide discordance vs guideline-based uncontrolled asthma	FeNO monitoring vs usual care	Children with asthma (mean age, 11.2, 103 years) recruited from a health insurance database N=88 Strata: children and young people, smoking status not reported USA	Unscheduled healthcare utilisation (ED visits and hospitalisation) Severe asthma exacerbations Time off school or work Dose or regular asthma therapy 12 months follow-up	Mean ±SD age is within children and young people strata
Murphy 2022(Murphy et al., 2022) Effect of asthma management with exhaled nitric oxide versus usual care on perinatal outcomes	FeNO monitoring vs usual care	Pregnant women with doctor-diagnosed asthma (mean gestational age: 18.7 weeks) N=1200 Strata: adults, <20% current smokers Australia	Unscheduled healthcare utilisation (ED visits, hospital admissions) Severe asthma exacerbations Follow-up 2-6 weeks post-partum (approx. 25 weeks in total)	Note intervention arm also included adjustment of LABA based on symptom scores.
Peirsman 2014(Peirsman et al., 2014) Exhaled nitric oxide in childhood allergic asthma management: a randomised controlled trial	FeNO monitoring vs usual care	Children with mild to severe persistent asthma selected from 7 hospitals (mean age 10.6, 10.7 years) N=99 Strata: children and young people, smoking status not reported Belgium	Unscheduled healthcare utilisation (ED visits and hospitalisation) Severe asthma exacerbations Lung function (FEV_1 % predicted) Time off school 12 months follow-up	Mean ±SD age is within children and young people strata
Petsky 2015(Petsky et al., 2015)	FeNO monitoring vs usual care	Children receiving their asthma care at participating	Unscheduled healthcare utilisation	Median (IQR) age is within children and young people strata

Study	Intervention and comparison	Population	Outcomes	Comments
Management based on exhaled nitric oxide levels adjusted for atopy reduces asthma exacerbations in children: A dual centre randomized controlled trial		hospitals (median age 10.1 years) N=63 Strata: children and young people, smoking status not reported Australia and China	(hospital admissions) Severe asthma exacerbations 12 months follow-up	
Pijnenburg 2005(Pijnenburg et al., 2005) Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial	FeNO monitoring vs usual care	Children recruited from an outpatient clinic of a children's hospital (mean age 11.9, 12.6 years) N=85 Strata: children and young people, smoking status not reported Netherlands	Severe asthma exacerbations (12 months follow-up) Dose of regular asthma therapy (3 months follow-up)	Mean ±SD age is within children and young people strata
Pike 2013(Pike et al., 2013) Exhaled nitric oxide monitoring does not reduce exacerbation frequency or inhaled corticosteroid dose in paediatric asthma: a randomised controlled trial	FeNO monitoring vs usual care	Children aged 6-17 years recruited from outpatient clinics (mean age 10.5, 11.4 years) N=90 Strata: children and young people, smokers excluded UK	Unscheduled healthcare utilisation (hospital admissions) Inflammatory markers (FeNO) 12 months follow-up	Mean ±SD age is within children and young people strata
Powell 2011(Powell et al., 2011) Management of asthma in pregnancy guided by measurement of fraction of	FeNO monitoring vs usual care	220 pregnant women (aged >18 years) attending antenatal clinics N=220	Quality of life Lung function (FEV_1, litres and % predicted) Follow-up until delivery (mean of 18 weeks)	

Study	Intervention and comparison	Population	Outcomes	Comments
exhaled nitric oxide: a double-blind, randomised controlled trial		Strata: adults, smokers excluded Australia		
Shaw 2007(Shaw et al., 2007) The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial	FeNO monitoring vs usual care	Adult asthma patients recruited from registers held in general practices (aged >18 years) N=118 Strata: adults, smokers excluded UK	Severe asthma exacerbations Dose of regular asthma therapy 12 months follow-up	
Smith 2005(Smith et al., 2005) Use of exhaled nitric oxide measurements to guide treatment in chronic asthma	FeNO monitoring vs usual care	Asthmapatients (aged 12-73 years) having their treatment managed in primary care N=97 Strata: adults, smokers excluded New Zealand	Severe asthma exacerbations Lung function (FEV_1 % predicted, PEF) Dose of regular asthma therapy Rescue medication use Inflammatory markers (FeNO) 18 months follow-up	Standard deviation of age not reported, committee agreed to place in adult strata: (mean age 44.8, range 12-73)
Syk 2013 (Syk et al., 2013) Anti-inflammatory treatment of atopic asthma guided by exhaled nitric oxide: a randomized, controlled trial	FeNO monitoring vs usual care	Adult asthma patients (18-64 years) recruited from primary health centres N=181 Strata: adults, smokers excluded Sweden	Severe asthma exacerbations Lung function (FEV1, L) Inflammatory markers (FeNO) 12 months follow-up	
Szefler 2008(Szefler et al., 2008) Management of asthma based on exhaled nitric	FeNO monitoring vs usual care	Young people with uncontrolled asthma (mean 14.4 years) N=546	Unscheduled healthcare utilisation (unscheduled ER or clinic visits, hospital admissions)	Mean ±SD age is within children and young people strata

Study	Intervention and comparison	Population	Outcomes	Comments
oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial		Strata: children and young people, smokers excluded USA	Severe asthma exacerbations Asthma control questionnaires Lung function (FEV_1 % predicted) Time off school or work 46 weeks follow-up	
Truong-Thanh 2020(Truong-Thanh et al., 2020) The beneficial role of FeNO in association with GINA guidelines for titration of inhaled corticosteroids in adult asthma: A randomized study	FeNO monitoring vs usual care	Adults >18 yearswith uncontrolled asthma N=176 Strata: adults, <20% current smokers Vietnam	Asthma control questionnaires Lung function (FEV_1 and PEF % predicted) Dose of regular asthma therapy Inflammatory markers (FeNO) 9 months follow-up	
Turner 2022 (Turner et al., 2022) Reducing asthma attacks in children using exhaled nitric oxide (RAACENO) as a biomarker to inform treatment strategy: a multicentre, parallel, randomised, controlled, phase 3 trial	FeNO monitoring vs usual care	Children aged 6-15 years recruited from asthma hospital clinics and primary care practices N=515 Strata: children and young people, smoking status not reported UK	Mortality Severe asthma exacerbations 12 months follow-up	
Voorend-van Bergen 2015(Voorend-van Bergen et al., 2015) Monitoring strategies in	FeNO monitoring vs usual care	Children recruited by their paediatrician from general hospitals and tertiary referral centres	Asthma control questionnaires Lung function (FEV_1 % predicted) Dose of regular asthma therapy	Mean ±SD age is within children and young people strata

Study	Intervention and comparison	Population	Outcomes	Comments
children with asthma: a randomised controlled trial		(mean age 10.3, 10.4 years) N=272 Strata: children and young people, smokers excluded Netherlands	Rescue medication use Symptoms 12 months follow-up	
Wang 2019(Wang et al., 2019) The Reliability of Adjusting Stepped Care Based on FeNO Monitoring for Patients with Chronic Persistent Asthma	FeNO monitoring vs usual care	Adult patients with chronic persistent asthma (18-65 years) N=160 Strata: adults, smoking status not reported China	Asthma control questionnaires Lung function (PEF % predicted) 12 months follow-up	

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary for FeNO monitoring vs usual care in children and young people

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in children and young people	Risk difference with FeNO monitoring	Comments
Mortality (final values, lower is better)	506 (1 RCT) Follow-up: 12 months	⊕⊕◯◯ Low[a]	**RD 0.00** (-0.01 to 0.01)	0 per 1,000	**0 fewer per 1,000** (10 fewer to 10 more) No clinical difference	MID (clinical importance) = 1 per 1000 (imprecision) based on sample size: <70= very serious, 70-350= serious, >350= not serious

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in children and young people	Risk difference with FeNO monitoring	Comments
Unscheduled healthcare utilisation (ED/A&E visits, final values, lower is better)	179 (2 RCTs) Follow-up: 12 months	⊕◯◯◯ Very low[b,c]	**RR 0.53** (0.19 to 1.52)	102 per 1,000	**48 fewer per 1,000** (83 fewer to 53 more) Clinically important benefit for FeNO monitoring	MID (clinical importance) = 30 per 1000 (imprecision) = 0.8-1.25
Unscheduled healthcare utilisation (unscheduled ER and clinic visits, final values, lower is better)	546 (1 RCT) Follow-up: 46 weeks	⊕◯◯◯ Very low[b,c]	**RR 0.95** (0.69 to 1.30)	226 per 1,000	**11 fewer per 1,000** (70 fewer to 68 more) No clinical difference	MID (clinical importance) = 100 per 1000 (imprecision) = 0.8-1.25
Unscheduled healthcare utilisation (hospital admissions, final values, lower is better)	873 (5 RCTs) Follow-up: mean 51 weeks	⊕⊕⊕◯ Moderate[b]	not estimable	35 per 1,000	**35 fewer per 1,000** (35 fewer to 35 fewer) Clinically important benefit for FeNO monitoring	MID (clinical importance) = 30 per 1000 (imprecision) = 0.8-1.25
Severe asthma exacerbations (requiring oral corticosteroids, final values, lower is better)	1581 (8 RCTs) Follow-up: mean 45 weeks	⊕⊕◯◯ Low[d,e]	**RR 0.83** (0.72 to 0.94)	374 per 1,000	**64 fewer per 1,000** (105 fewer to 22 fewer) Clinically important benefit for FeNO monitoring	MID (clinical importance) = 30 per 1000 (imprecision) = 0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in children and young people	Risk difference with FeNO monitoring	Comments
Asthma control questionnaires at ≥3 months (Asthma Control Test (childrens and adults version), final values, higher is better)	897 (3 RCTs) Follow-up: mean 41 weeks	⊕◯◯◯ Very low[d,f]	-	The mean asthma control questionnaires at ≥3 months (Asthma Control Test (childrens and adults version), final values, higher is better) was **21.46**	MD **0.77 higher** (0.3 lower to 1.84 higher) No clinical difference	MID=2 for C-ACT (Szefler unclear which ACT used)
Lung function (FEV1 % predicted, final values, higher is better)	1137 (5 RCTs) Follow-up: mean 41 weeks	⊕⊕◯◯ Low[d,g]	-	The mean lung function (FEV1 % predicted, final values, higher is better) was **91.61**	MD **2.01 higher** (0.17 lower to 4.19 higher) No clinical difference	MID=6.75 (baseline SDs for control group/2)
Lung function (PEF, % of predicted, final values, higher is better)	133 (1 RCT) Follow-up=6 months	⊕⊕⊕◯ Moderate[d]	-	The mean lung function (PEF, % of predicted, final values, higher is better) was **80.35**	MD **6.21 higher** (3.97 higher to 8.45 higher) Clinically important benefit for FeNO monitoring	MID=2.82 (baseline SDs for control group/2)
Symptoms (% symptom free days over 4 weeks, final values, higher is better)	268 (1 RCT) Follow-up=12 months	⊕⊕⊕◯ Moderate[h]	-	The mean symptoms (% symptom free days over 4 weeks, final values, higher is better) was **59**	MD **3 higher** (5.85 lower to 11.85 higher) No clinical difference	MID=17 (baseline SDs for control group/2)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in children and young people	Risk difference with FeNO monitoring	Comments
Dose of regular asthma therapy (mean daily ICS dose, final values, lower is better)	441 (3 RCTs) Mean follow-up=9 months	⊕⊕⊕◯ Moderate [b]	-	The mean dose of regular asthma therapy (mean daily ICS dose, final values, lower is better) was **250** ug/day	MD **52.86 ug/day higher** (43.29 higher to 62.43 higher) No clinical difference	MID=137.5 (follow-up SDs for control group/2)
Reliever/rescue medication at ≥3 months (SABA use, puffs per day, final values, lower is better)	268 (1 RCT) Follow-up=12 months	⊕⊕⊕⊕ High	-	The mean reliever/rescue medication at ≥3 months (SABA use, puffs per day, final values, lower is better) was **0.3**	MD **0.1 higher** (0.15 lower to 0.35 higher) No clinical difference	MID=0.81 (established MID)
Time off school (number of participants who missed any school day, final values, lower is better)	185 (2 RCTs) Follow-up=12 months	⊕◯◯◯ Very low[b,c]	**RR 0.82** (0.49 to 1.38)	261 per 1,000	**47 fewer per 1,000** (133 fewer to 99 more) No clinical difference	MID (clinical importance) = 100 per 1000 (imprecision) = 0.8-1.25
Time off school (school days missed in last 2 weeks, final values, lower is better)	496 (1 RCT) Follow-up=46 weeks	⊕⊕⊕◯ Moderate [b]	-	The mean time off school (school days missed in last 2 weeks, final values, lower is better) was **0.23**	MD **0.04 lower** (0.13 lower to 0.05 higher) No clinical difference	MID=0.25 (follow-up SDs for control group/2)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in children and young people	Risk difference with FeNO monitoring	Comments
Inflammatory markers at ≥8 weeks (FeNO, ppb, mixed values, lower is better)	223 (2 RCTs) Mean follow-up=9 months	⊕⊕⊕◯ Moderate[d]	-	The mean inflammatory markers at ≥8 weeks (FeNO, ppb, mixed values, lower is better) was **20.08**	MD **1.69 lower** (3.19 lower to 0.18 lower) No clinical difference	MID=10.05 (follow-up SDs for control group/2)

a. Downgraded by two increments because the evidence is at high risk of bias (inadequate adherence to the monitoring strategies reported: 64.7% compliance in the FeNO group, 61% in the usual care group)

b. Downgraded by one increment for risk of bias because of some concerns about lack of information on adherence to monitoring strategies and treatments

c. Downgraded by two increments for imprecision because the 95% confidence interval crosses both MIDs (0.8-1.25)

d. Downgraded by one increment because there were some concerns about risk of bias for the majority of the evidence (adherence to monitoring strategies and treatments, and randomisation method not reported)

e. Downgraded by one increment for imprecision because the 95% confidence interval crosses one MID (0.8-1.25)

f. Downgraded by two increments for inconsistency (I squared=76%)

g. Downgraded by one increment for inconsistency (I squared=69%)

h. Downgraded by one increment because of some concerns about risk of bias (self-reported outcome and participants unblinded to intervention)

Table 4: Clinical evidence summary for FeNO monitoring vs usual care in adults

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in adults	Risk difference with FeNO monitoring	Comments
Unscheduled healthcare utilisation (ED/A&E visits, final values, lower is better)	1728 (2 RCTs) Mean follow-up=38.5 weeks	⊕⊕◯◯ Low[a]	RR 1.13 (0.69 to 1.84)	31 per 1,000	**4 more per 1,000** (10 fewer to 26 more) No clinical difference	MID (clinical importance) = 30 per 1000, (imprecision) = 0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in adults	Risk difference with FeNO monitoring	Comments
Unscheduled healthcare utilisation (hospital admissions, final values, lower is better)	2070 (3 RCTs) Mean follow-up: 37.7 weeks	⊕⊕⊕◯ Moderate[b]	RR 0.50 (0.21 to 1.23)	17 per 1,000	**9 fewer per 1,000** (14 fewer to 4 more) No clinical difference	MID (clinical importance) = 30 per 1000, (imprecision) = 0.8-1.25
Severe asthma exacerbations at ≥6 months (final values, lower is better)	2221 (6 RCTs) Mean follow-up: 52 weeks	⊕⊕◯◯ Low[b,c]	RR 0.81 (0.68 to 0.96)	218 per 1,000	**41 fewer per 1,000** (70 fewer to 9 fewer) Clinically important benefit for FeNO monitoring	MID (clinical importance) = 30 per 1000, (imprecision) = 0.8-1.25
Asthma control questionnaires at ≥3 months (Asthma Control Questionnaire, scale range: 0-6, mixed values, lower is better)	1113 (3 RCTs) Mean follow-up: 47 weeks	⊕⊕⊕◯ Moderate[d]	-	The mean asthma control questionnaires at ≥3 months (Asthma Control Questionnaire, scale range: 0-6, mixed values, lower is better) was **1.22**	MD **0.05 lower** (0.14 lower to 0.03 higher) No clinical difference	MID = 0.5 (established MID)
Asthma control questionnaires at ≥3 months (Asthma Control Test, scale range: 5-25, final values, higher is better)	176 (1 RCT) Follow-up= 9 months	⊕⊕◯◯ Low[e]	-	-	SMD **0.18 lower** (0.48 lower to 0.12 higher) No clinical difference	MID = 3 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in adults	Risk difference with FeNO monitoring	Comments
Quality of life at ≥3 months (Asthma Quality of Life Questionnaire, scale range: 1-7, mixed values, higher is better)	953 (2 RCTs) Mean follow-up: 44 weeks	⊕⊕⊕◯ Moderate[c]	-	The mean quality of life at ≥3 months (Asthma Quality of Life Questionnaire, scale range: 1-7, mixed values, higher is better) was **5.95**	MD **0.02 higher** (0.1 lower to 0.15 higher) No clinical difference	MID = 0.5 (established MID)
Quality of life at ≥3 months (Marks' Asthma Quality of Life Questionnaire, scale range: 0-10, final values, lower is better)	220 (1 RCT) Follow-up=18 weeks	⊕⊕⊕◯ Moderate[c]	-	The mean quality of life at ≥3 months (Marks' Asthma Quality of Life Questionnaire, scale range: 0-10, final values, lower is better) was **0.81**	MD **0.06 lower** (1.01 lower to 0.89 higher) No clinical difference	MID=2.16 (follow-up SD ofcontrol group/2)
Lung function (FEV1, litres, mixed values, higher is better)	726 (3 RCTs) Mean follow-up: 35 weeks	⊕⊕⊕◯ Moderate[c]	-	The mean lung function (FEV1, litres, mixed values, higher is better) was **3.01**	MD **0.02 higher** (0.04 lower to 0.08 higher) No clinical difference	MID=0.23 (established MID)
Lung function (FEV1 % predicted, mixed values, higher is better)	1443 (5 RCTs) Mean follow-up: 51 weeks	⊕⊕⊕◯ Moderate[c]	-	The mean lung function (FEV1 % predicted, mixed values, higher is better) was **87.5**	MD **1.1 higher** (0.13 lower to 2.32 higher) No clinical difference	MID=6.75 (follow-up SD of control group/2)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in adults	Risk difference with FeNO monitoring	Comments
Lung function (PEF % predicted, final values, higher is better)	336 (2 RCTs) Mean follow-up: 45.5 weeks	⊕⊕⊕◯ Moderate[f]	-	The mean lung function (PEF % predicted, final values, higher is better) was **85.15**	MD **1.4 lower** (4.73 lower to 1.93 higher) No clinical difference	MID=7.8 (baseline SD control group/2)
Lung function (PEF, litres/minute, change scores, higher is better)	436 (2 RCTs) Mean follow-up: 57 weeks	⊕⊕◯◯ Low[c,g]	-	The mean lung function (PEF, litres/minute, change scores, higher is better) was **403**	MD **7.59 higher** (4.21 lower to 19.39 higher) No clinical difference	MID=18.79 (established MID)
Dose of regular asthma therapy (ICS dose, mcg/day, mixed values, lower is better)	981 (5 RCTs) Mean follow-up: 54.6 weeks	⊕◯◯◯ Very low[f,h,i]	-	The mean dose of regular asthma therapy (ICS dose, mcg/day, mixed values, lower is better) was **625**	MD **84.73 lower** (184.19 lower to 14.73 higher) Clinically important benefit of FeNO monitoring	MID=65.5 (follow-up SD of control group/2)
Rescue medication use at ≥3 months (average bronchodilator use over previous 7 days, final values, lower is better)	94 (1 RCT) Follow-up=18 months	⊕⊕⊕◯ Moderate[f]	-	The mean rescue medication use at ≥3 months (average bronchodilator use over previous 7 days, final values, lower is better) was **0.4** puff/d	MD **0 puff/d** (0.41 lower to 0.41 higher) No clinical difference	MID=0.81 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in adults	Risk difference with FeNO monitoring	Comments
Rescue medication at ≥3 months (non-exercise preventative SABA use, change scores, lower is better)	342 (1 RCT) Follow-up=36 weeks	⊕⊕⊕◯ Moderate[c]	-	The mean rescue medication at ≥3 months (non-exercise preventative SABA use, change scores, lower is better) was **0** puff/d	MD **0.04 puff/d lower** (0.1 lower to 0.02 higher) No clinical difference	MID=0.81 (established MID)
Inflammatory markers at ≥8 weeks (FeNO, ppb, mixed values, lower is better)	434 (3 RCTs) Mean follow-up: 13 months	⊕⊕◯◯ Low[f,j]	-	The mean inflammatory markers at ≥8 weeks (FeNO, ppb, mixed values, lower is better) was **12.8**	MD **1.2 lower** (4.91 lower to 2.52 higher) No clinical difference	MID=5.5 (follow-up SD of control group/2)

a. Downgraded by two increments for imprecision because the 95% confidence interval crosses both MIDs (0.8-1.25)

b. Downgraded by one increment for imprecision because the 95% confidence interval crosses one MID (0.8-1.25)

c. Downgraded by one increment because of some concerns about risk of bias (adherence to monitoring strategies and treatments not reported)

d. Downgraded by one increment because of some concerns about risk of bias (adherence to interventions not reported and subjective outcome measure assessed by unblinded participants)

e. Downgraded by two increments because the evidence is at high risk of bias (randomisation method and adherence to monitoring strategies not reported; subjective outcome assessed by unblinded participant)

f. Downgraded by one increment because of some concerns about risk of bias (randomisation method and adherence to intervention not reported)

g. Downgraded by one increment for imprecision because the 95% confidence interval crosses one MID (established MID =18.79 L/min)

h. Downgraded by two increments for inconsistency (I squared = 80%)

i. Downgraded by one increment for imprecision because the 95% confidence interval crosses one MID (calculated as follow-up SDs of control group /2=65.5)

j. Downgraded by one increment for inconsistency (I squared=68%)

Table 5: Clinical evidence summary for FeNO monitoring vs usual care in adults (>20% smokers)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in adults (smokers >20%)	Risk difference with FeNO monitoring	Comments
Asthma control questionnaires at ≥3 months (Asthma Control Questionnaire, scale range: 0-6, change scores, lower is better)	72 (1 RCT) Follow-up=28 weeks	⊕◯◯◯ Very low[a,b]	-	The mean asthma control questionnaires at ≥3 months (Asthma Control Questionnaire, scale range: 0-6, change scores, lower is better, 24 weeks) was **-0.2**	MD **0.1 higher** (0.58 lower to 0.78 higher) No clinical difference	MID = 0.5 (established MID)
Quality of life at ≥3 months (Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)	72 (1 RCT) Follow-up=28 weeks	⊕◯◯◯ Very low[a,b]	-	The mean quality of life at ≥3 months (Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better, 24 weeks) was **0.2**	MD **0.1 lower** (0.72 lower to 0.52 higher) No clinical difference	MID = 0.5 (established MID)
Lung function (FEV1, litres, change scores, higher is better)	72 (1 RCT) Follow-up=28 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean lung function (FEV1, litres, change scores, higher is better, 24 weeks) was **0.08**	MD **0.01 lower** (0.13 lower to 0.11 higher) No clinical difference	MID = 0.23 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care in adults (smokers >20%)	Risk difference with FeNO monitoring	Comments
Lung function (FEV1 % predicted, change scores, higher is better)	72 (1 RCT) Follow-up=28 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean lung function (FEV1 % predicted, change scores, higher is better, 24 weeks) was **2.5**	MD **0.2 lower** (4.02 lower to 3.62 higher) No clinical difference	MID=4.14 (follow-up SD of control group/2)
Dose of regular asthma therapy (ICS dose, mcg/day, change scores, lower is better)	72 (1 RCT) Follow-up=28 weeks	⊕⊕◯◯ Low[a,c]	-	The mean dose of regular asthma therapy (ICS dose, mcg/day, change scores, lower is better, 24 weeks) was **-25**	MD **30 higher** (241.7 lower to 301.7 higher) No clinical difference	MID=294 (follow-up SD of control group/2)
Inflammatory markers at ≥8 weeks (FeNO, ppb, change scores, lower is better)	72 (1 RCT) Follow-up=28 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean inflammatory markers at ≥8 weeks (FeNO, ppb, change scores, lower is better, 24 weeks) was **-17**	MD **4 higher** (15.55 lower to 23.55 higher) No clinical difference	MID=28.1 (follow-up SD of control group/2)

a. Downgraded by one increment because of some concerns about risk of bias (adherence to intervention not reported)

b. Downgraded by one increment for imprecision because the 95% confidence interval crosses both MIDs (established MIDs: ACQ=0.5; AQLQ=0.5)

c. Downgraded by one increment for imprecision because the 95% confidence interval crosses one MID (calculated as final SD of control group/2=294)

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

Two health economic studies with the relevant comparison were included in this review (Harnan, et al., 2015, Yang, et al., 2021). These are summarised in the health economic evidence profile below (Table 6) and the health economic evidence tables in Appendix H.

1.1.7.2 Excluded studies

Nine economic studies relating to this review question were identified but were excluded due to a combination of limited applicability and methodological limitations [OR] the availability of more applicable evidence. (Berg, et al., 2008), (Buendia, et al., 2021), (Buendia, et al., 2021), (Buendia, et al., 2022),(Beerthuizen, et al., 2016), (Darba, et al., 2021), (Honkoop et al., 2015), (Sabatelli, et al., 2017), (Price, et al., 2009)

These are listed in Appendix J, with reasons for exclusion given.

See also the health economic study selection flow chart in **Error! Reference source not found.**.

1.1.8 Summary of included economic evidence

Table 6: Health economic evidence profile: Guidelines-based monitoring versus FeNO monitoring

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Harnan 2015 (Harnan et al., 2015) (UK)	Directly applicable	Potentially serious limitations[a]	• A cost-utility analysis based on Szefler 2008 (children) and Shaw 2006 (adults) to estimate clinical outcomes • Cost-utility analysis (QALYs) • Population: People treated for diagnosed asthma. Divided into: ○ Adults: 18 years old ○ Children: 5 years old • Comparators: ○ BTS/SIGN guidelines-based monitoring ○ FeNO[b] monitoring • Time horizon: Lifetime	**Adults:** £211[c] **Children:** £2,425[c]	**Adults:** 0.04 **Children:** 0.05	**Adults:** £5,567 per QALY **Children:** £47,924 per QALY	**Adults** Probability FeNO monitoring cost effective (£20/£30K threshold): 82%/87% **Children** Probability FeNO monitoring cost effective (£20/£30K threshold): 1%/9% The results were sensitive to the time horizon and assumptions on duration of benefits and ICS use with FeNO. In the adult model, longer time-horizon improved the cost-effectiveness of FeNO. In the children model, assumptions of a short impact of FeNO monitoring on dose titration and exacerbations improved cost-effectiveness.
Yang 2022 (Yang et al., 2021) (UK)	Partially applicable[d]	Potentially serious limitations[e]	• A cost-consequence analysis on CHAMPIONS, a before-	**CHAMPIONS**[f]**:** -£20.5[h]	**Asthma control** ACT = 1.1	n/a	No probabilistic sensitivity analysis was performed. The authors offered two different estimations for

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			and-after observational cohort study evaluating the impact of implementing spirometry and FeNO testing in children asthma review • Cost-consequence analysis (asthma control status and quality of life) • Population: Children in the asthma register and children with suspected asthma who were prescribed asthma medications in the previous 12 months. • Comparators: ○ Before implementing spirometry and FeNO guided asthma review (where asthma reviews included no objective tests) ○ After implementing spirometry and FeNO guided asthma review Follow-up: 1 year	**Real-world**[g]: £12.8[h]	CACT =1.3 **Quality of life** CHU9D = -0.03 PAQLQ Overall Score = 0.1 PAQLQ Activity Score = 0.17 PAQLQ Symptom Score = 0.1 M PAQLQ Emotional Score = 0.07 **Mean ICS dose** +27 mcg		equipment costs: one based on the low costs recorded in CHAMPIONS study where two spirometers were rotated between 10 GP practices and FeNO devices were received by the manufacturers free of charge; the second based on a real-world situation where each GP practices is required to purchase their own equipment. The incremental costs calculated using both estimations are reported in the table.

Abbreviations: ACT= Asthma Control Test; FeNO= Fractional exhaled nitric oxide; CHU9D= Child's Health Utility; ICER= incremental cost-effectiveness ratio; ICS= Inhaled corticosteroid; PAQLQ= Paediatric Asthma Quality of Life Questionnaire; QALY= quality-adjusted life years; RCT= randomised controlled trial

(a) Clinical effectiveness from two studies (one for children, one for adult), not meta-analyses. The study informing the analysis on children (Szefler et al.) was undertaken in the US and does not match BTS/SIGN on dose titration. No long-term evidence on the duration of FeNO impact dose titration. Exacerbations are assumed to affect only quality of life and does not increase mortality. Strong assumptions imposed regarding extrapolating treatment effects over a lifetime horizon.

(b) All three FeNO devices (NIOX MINO, NIOX VERO and NObreath) were included in a single comparator using their average cost. Accuracy was assumed to be the same.

(c) 2012/2013 UK pounds. Cost components incorporated: FeNO monitoring visits, marginal per-test costs for FeNO device, Inhaler Corticosteroids (ICS), severe hospitalised exacerbation, severe non-hospitalised exacerbation (one GP appointment and course of oral steroids).

(d) Cost-consequence analysis. QALYs were not calculated as EQ-5D were not collected during the study.

(e) The evidence is based on a before-and-after study so the results might be biased by confounding factors. The impact on pharmaceutical cost was not explored despite a statistically significant difference in the number of asthma medication prescriptions and median dose of ICS before and after the test-guided asthma reviews. A dropout statistical analysis was not attempted so it is unclear if high dropouts biased the estimation of quality of life after implementing test-guided asthma reviews. The CHAMPIONS estimation of equipment cost is a clear underestimation of real-world costs as the same devices were rotated between 10 different practices and FeNO devices were received free of charge. The real-world estimation is likely to be an overestimation of costs as the capital investment for 10 spirometers and 10 calibration syringes was not distributed among all patients, for instance adults, who would use the devices as well if purchased. No sensitivity analysis (bootstrapping) was conducted.

(f) Excluding implementation costs (development of training package, face-to-face teaching and practice training) and including the low equipment cost in CHAMPIONS consisting in two spirometrers only as FeNO devices were given for free.

(g) Excluding implementation costs (development of training package, face-to-face teaching and practice training) and including the equipment costs suggested by NICE for 10 spirometers and 10 calibration syringes and 612 FeNO tests.

(h) 2017/2018 UK pounds. Cost components incorporated: unplanned healthcare attendance, unplanned hospital admission, purchase of the equipment (test devices), implementing and delivering test-guided asthma review.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Unit costs

Table 7 shows the figures used to calculate the mean per-test cost of FeNO. For the cost analysis, we focused only on NIOX VERO as this is, currently, the most purchased device across NHS trusts. Cost provided directly by manufacturer, Circassia. A discounting factor of 3.5% was used to calculate the annuatisation factor over the lifetime of the device.

Table 7: Mean per-test cost of FeNO (NIOX VERO)

Characteristics	Low volume centre (Jersey Allergy Clinic)	Assumed average across NHS	High volume centre (Alder Hey Children's)	Source
Device lifetime (years)	5	5	5	Circassia
Use of FeNO	100% diagnosis	NA	30% diagnosis, 70% monitoring	Personal communication
No. of tests per year	100	300	450	Personal communication
Cost of device	£1,250	£1,250	£1,250	Circassia
Cost of test kits: 300	NA	£1,645	£1,645	Circassia
Cost of test kits: 100	£890	NA	NA	Circassia
Shipping cost per order	£75	£50	£0	Personal communication
Annuatisation factor for specific device lifetime	4.67	4.67	4.67	Calculation
Annuatised mean per-test cost	**£12.32**	**£6.54**	**£6.08**	**Calculation**
Annuatised mean per-test cost (excluding shipping cost)	**£11.57**	**£6.37**	**£6.08**	**Calculation**

Note: All prices are VAT-exclusive

The mean per-tests costs of a NIOX VERO FeNO device was calculated in three different scenarios varying for their testing volume. Jersey Allergy Clinic is a relatively small specialist clinic (106,000 population) dealing only in part with asthma and using FeNO only for diagnostic purposes. Hence, they report only 100 FeNO tests a year. With such a small volume, the mean per-test cost of FeNO is the highest amounting to around £11.57 excluding shipping costs. By contrast, Alder Hey Children's NHS Foundation Trust is a large and specialized centre, which uses FeNO both for diagnosis (30%) and monitoring (70%). Hence, they report a larger number of FeNO tests done every year, approximately 450. With this volume, the mean per-test cost of FeNO is the lowest and equal to £6.08. A third scenario using an average of 300 tests per years and a mean cost of £6.37 is also reported. This is based on Committee's expert opinion and reflects the figures used in Harnan 2015(Harnan et al., 2015).

Table 8 shows the cost of delivering a FeNO test including the cost of staff required. The committee were aware that FeNO is a relatively easy test to deliver and would not require more than 15 minutes of a GP practice nurse time.

Table 8: Cost of delivering the test

Resource	Quantity	Unit cost[(a)]	Total cost	Source
GP practice nurse	15 minutes	£63.38 per hour[(a)]	£15.84	PSSRU 2022(Jones, et al.)
Mean cost of FeNO	1 test	£6.37 (£6.08 to £11.57)	£6.37 (£6.08 to £11.57)	Table 7
Total			**£22.21 (£21.92 to £27.41)**	

a) Costs included qualification costs

1.1.11 Evidence statements

Economic

- One cost–utility analysis found that FeNO monitoring was cost effective compared to guidelines-based monitoring for adults with asthma (ICER: £5,567 per QALY gained). The same analysis found that FeNO monitoring was not cost effective compared to guidelines-based monitoring for children with asthma (ICER: £47,924 per QALY gained) This analysis was assessed as directly applicable with potentially serious limitations.
- A cost consequence analysis found that implementing spirometry and FeNO guided asthma reviews was less costly than before implementing this review when using low cost estimations but more costly when using 'real-world' cost estimations. Asthma control and quality of life improved after implementing these asthma reviews. This analysis was assessed as partially applicable with potentially serious limitations.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The Committee considered the outcomes of mortality, unscheduled healthcare utilisation, asthma exacerbations, asthma control, quality of life, lung function, symptoms, dose of regular asthma therapy/preventer medication, reliever/rescue medication use, time off school or work and inflammatory markers (FeNO).

All outcomes were deemed to be of equal importance and were rated as critical in GRADE. However, upon presentation of the evidence the committee agreed that exacerbations are an especially important and relevant outcome in the context of this review because they have a major effect on a person's quality of life and may result in hospitalisation which has a significant economic impact. The purpose of monitoring strategies is to guide healthcare professionals and people with asthma towards the optimal level of maintenance therapy and therefore reduce the risk of exacerbations as well as improving symptoms and lung function.

1.1.12.2 The quality of the evidence

There were 22 RCTs included in the clinical evidence for this review. The review was stratified by population age [adults (≥17 years) and children and young people (5-16 years)] and smoking status (proportion of current smokers >20%).

All evidence was assessed using GRADE criteria and was graded as high, moderate, low or very low quality depending upon the certainty of the evidence.

Children and Young People

Evidence was identified for all outcomes, except quality of life, and ranged from high to very low quality.

Downgrading of the evidence due to risk of bias occurred due to concerns arising from the randomisation process, deviations from the intended interventions, concerns about adherence to interventions, missing outcome data, and the measurement of the outcome. On a number of occasions evidence was downgraded due to imprecision, and on two occasions due to inconsistency arising from heterogeneity that could not be explained by pre-planned subgrouping of the data.

Severe asthma exacerbations was viewed as an especially important outcome by the committee. This outcome was graded as low-quality evidence because of some concerns about the risk of bias for (non-adherence to monitoring strategies and treatments, and randomisation method not reported) and imprecision resulting from the overlapping of the 95%CI with the minimally important difference..

Adults

Evidence was identified for all outcomes, except mortality, symptoms and time off work, and ranged from moderate to very low quality.

Downgrading of the evidence due to risk of bias occurred due to concerns arising from the randomisation process, concerns about adherence to interventions and subjective outcomes assessed by unblinded participants. On a number of occasions evidence was downgraded due to imprecision and/or due to inconsistency arising from heterogeneity that could not be explained by pre-planned subgrouping of the data.

Severe asthma exacerbations was viewed as a particularly important outcome by the committee. This was graded as low quality evidence due to imprecision resulting from the overlapping of the 95%CI with the minimally important difference and some concerns about risk of bias (no information reported about adherence to interventions).

Adults >20% smokers

One RCT provided moderate to very low quality evidence on asthma control, quality of life, lung function, dose of regular asthma therapy and inflammatory markers (FeNO).

1.1.12.3 Benefits and harms

When assessing the clinically significant impact of the evidence included, the GC agreed an approach for use of MIDs. For continuous outcomes, published MIDs were applied for: asthma control (asthma control test MID =2 for children, 3 for adults; asthma control questionnaire MID=0.5), quality of life (asthma quality of life questionnaire MID=0.5), rescue/reliever medication use (0.81 puffs/day) and lung function (PEF in L/min MID=18.79, FEV1 in L MID=0.23). In the absence of published MIDs for other continuous outcomes default calculations for MID were applied based on baseline SD (where available). For dichotomous outcomes, a threshold of 100/1000 people for changes in absolute effects was applied when assessing the following outcomes: unscheduled ER and clinic visits (combined) and time off school/work. A threshold of 30/1000 people for changes in absolute effects was applied when assessing the following outcomes: severe asthma exacerbations; emergency department visits; and hospital admissions. This is because the committee considered small differences between the intervention and comparison groups likely to be important.

Children and Young People

The evidence showed a clinically important benefit for FeNO monitoring for the outcomes: severe asthma exacerbations, hospital admissions, ER visits and lung function (PEF % predicted). The evidence on severe exacerbations was provided by 8 RCTs and low quality.

The evidence on hospital admissions was based on 5 RCTs and moderate quality. The evidence on ER visits was based on 2 RCTs and very low quality.

The dosage of regular asthma therapy across the studies was higher at the end of the study period, consistent with the hypothesis that regular FeNO monitoring helps to identify when it is necessary to increase therapy in individual people, with this in turn leading to improvements in asthma control, notably a reduction in exacerbations.

There were no clinically important harms of FeNO monitoring for any outcome; no clinically important difference was found for the remainder of outcomes.

The committee noted that several of the studies in children and young adults were conducted in secondary or tertiary care, and that the study population was therefore likely to have more severe asthma than an average group of people with asthma. However, some community-based studies were also included and the committee interpreted the evidence as showing a generalisable benefit of regular FeNO monitoring.

Adults

The evidence showed a clinically important benefit for FeNO monitoring for the outcomes: severe asthma exacerbations and dose of regular asthma therapy. The evidence on severe exacerbations was provided by 6 RCTs and was low quality. The evidence on dose of regular asthma therapy was based on 5 RCTs and was very low quality.

There were no clinically important harms of FeNO monitoring for any outcome; no clinically important difference was found for the remainder of outcomes.

Adults >20% smokers

There were no clinically important harms or benefits for FeNO monitoring for any outcome.

Although differences between FeNO monitoring and control groups were less marked in adults than in children, the committee nonetheless regarded the evidence as favouring the use of FeNO. They noted that the populations included were more likely to be primary care based in the adult studies, and therefore would tend to have less severe asthma with less scope for big improvements in outcome measures. Despite this a fall in exacerbation rate was found, coupled with an overall reduction in the amount of maintenance therapy used. This suggests more efficient use of maintenance therapy. Those people who were on inadequate doses and at risk of exacerbations had their treatment increased; those who were having more treatment than currently required were able to reduce their maintenance doses under FeNO guidance.

1.1.12.4 Cost effectiveness and resource use

Two health economic studies were identified for this review. One was a cost-consequence analysis based on a before-and-after study (CHAMPIONS) designed to evaluate the impact of implementing spirometry and FeNO in asthma reviews of children with asthma or suspected asthma. The study was assessed as partially applicable as no quality-of-life weights were estimated and with potentially serious limitations as it was based on a non-randomised evidence, excluded impact on pharmaceutical costs, did not conduct a dropout analysis despite high dropouts, and underestimated equipment purchase costs. The study found that test-guided review resulted in NHS savings due to less unplanned healthcare usage although it is unclear whether the savings would offset implementation costs. Asthma control was found to be higher after introducing spirometry and FeNO although general quality of life (CHU9D) was lower.

The second economic evaluation was a cost-utility analysis of FeNO for monitoring compared to BTS/SIGN guideline-based monitoring in children and adults that was

developed by an Evidence Assessement Group (EAG), an external academic organisation independent of NICE, to provide evidence on FeNO for NICE guideline on asthma NG80.

Their analysis was assessed as directly applicable but with potentially serious limitations as the analysis relied on strong assumptions to extrapolate short-term findings from clinical trials over the lifetime of people with asthma. In particular, the choice of using a lifetime horizon for the analysis on children was criticised by the committee as they were aware that asthma will resolve in around 50% of children with asthma before entering adulthood. Moreover, the committee aknowledged that once children moved to adult care, findings based on trials that enrolled children might not be applicable anymore.The analysis reached two different conclusions in adults and children: in adults, the analysis found FeNO for monitoring was cost-effective with a cost per QALY of £5,567 whereas in children the intervention was not cost-effective with a cost per QALY of £47,924 well beyond NICE thresholds of £20,000 and £30,000. This was explained by differences in dose titration of inhaled corticosteroid (ICS) following FeNO that were observed in children and adults.

In adults, although FeNO monitoring initially increases average ICS dose, the average dose observed at the last follow-up (12 months) is lower in people who received FeNO monitoring compared to those who did not. The opposite was observed in trials on children, including the US trial used in the model and the more recent UK trial Turner 2022, which found that FeNO monitoring increased ICS average dose in the long-term (12 months). The different directions in dose titration in children and adults with FeNO monitoring were also confirmed by a published meta-analysis (Petsky 2012) and interpreted by the committee as caused by differences in asthma phenotypes (asthma in children is more likely to respond to an ICS treatment compared to adults whose asthma could be resistent to ICS) or in the underlying severity of the asthma in the study participants (studies in children were more likely to be based on a secondary/tertiary care population). This means that, whereas FeNO monitoring reduces pharmaceutical spending in adults, the opposite is true in children whose average pharmaceutical expenditure increases. This explains the differing results for children and adults in the EAG cost-utility analysis.

Although the committee aknowledged that dose titration would have an impact on healthcare expenditure, they raised concerns on the length of the time horizon assumed in the analysis on children. They agreed that a shorter time horizon of 10 years would be more appropriate as asthma will resolve in approximately half of the children by the end of this period and the remaining half would be moved to adult care where evidence on dose titration is different. The EAG analysis included a scenario that uses a 10 year time horizon in children and is associated with a cost per QALY of £27,660 which would make FeNO monitoring potentially cost-effective in children at a £30,000 threshold. This scenario was considered more appropriate by the committee.

The committee discussed the clinical evidence on FeNO monitoring in children and adults. Exacerbations were viewed as an important outcome by the committee. Although graded as low-quality and with a confidence interval overalapping the minimally important difference, the committee agreed that FeNO for monitoring showed a clinically important effect in reducing the risk of people having exacerbations over a period of 12 months. Other benefits were observed in some of the outcomes such as lung function. As the economic analysis found FeNO to be cost-effective in adults at a £20,000 threshold but in children at a £30,000 the committee decided to make a “consider” recommendation on FeNO monitoring to people with asthma at regular reviews. This will include those who have a PRN therapy, such as ICS/LABA as needed.

This recommendation represents a change in practice. The previous guideline on asthma NG80 did not recommend routine use of FeNO monitoring but instead as an option for people who are symptomatic despite using ICS, so it is likely that the recommendation would require more people to be tested with FeNO annually. The cost-analysis on FeNO showed that the cost per test in high volume centre would be around £6. The cost of delivering FeNO

including the time of a respiratory nurse was estimated to be around £22. According to the British Lung Foundation, around 5.4 milion people (1.1 milion of children and 4.3 milion of adults) are receiving treatment for asthma in the UK. It is uncertain how many of these already receive regular monitoring, but if this figures goes up, new NHS resources will be required to implement FeNO in centres where it is not available and new staff will need to be trained.

The committee were aware that most of the asthma reviews in the UK are currently done over the phone. If routine FeNO is recommended, asthma assessment will need to be attended face to face. This could increase the length of the reviews and consequently the average cost per review. Included evidence showed that implementing routine FeNO monitoring would likely reduce the risk of exacerbations in adults and children, and reduce the average ICS dose in adults. This should increase the quality of life of people with asthma and reduce healthcare spending associated with asthma exacerbations and ICS prescribing. Lower ICS doses could also have other positive impacts, for instance, to the environment.

Of note, the clinical and cost-effectiveness evidence are based on trials where people were tested with FeNO multiple times a year (around three times), so it is unclear whether annual visits would be associated with similar benefits in terms of reducing exacerbations and achieving lower ICS doses. It is possible that, although less expensive, annual FeNO reviews would be associated with smaller benefits and smaller costs than observed in the trials and estimated in health economic analysis.

1.1.12.5 Other factors the committee took into account

The committee were aware that FeNO monitoring devices are currently not widely used in primary care in the UK. This was a significant area of discussion with much debate around the availability of the devices, and the likelihood of their future availability. The committee consensus was that this guidance would create an impetus for the addition of FeNO monitoring devices to centres around the UK.

The committee considered the additional time requirement of monitoring FeNO on healthcare professionals. In the committee's experience most people with asthma can perform the test easily and it can be completed in around 5 minutes, particularly if it is not the first time the person has done the test which would become the case if FeNO was monitored routinely. Some people with asthma find the test more difficult to perform and this will increase the time needed to employ FeNO monitoring routinely, but the committee believe that the advantages of knowing the FeNO measurement outweigh this disadvantage.

Part of the committee's reasoning behind recommending FeNO monitoring was due to the multifaceted benefits such devices can provide. The committee described the use of FeNO monitors as a tool to monitoring adherence to maintenance treatment, with high values often reflecting poor adherence. The committee agreed that FeNO could be used as an educational tool, whereby patients are able to objectively see the benefit of adhering to their maintenance mediation through the reduction of their FeNO values.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendation 1.5.4.

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for clinical effectiveness of FeNO measures for monitoring asthma control

ID	Field	Content
0.	PROSPERO registration number	CRD42023443285
1.	Review title	FeNO measures to monitor asthma
2.	Review question	In people with asthma, what is the clinical and cost-effectiveness of using fractional exhaled nitric oxide (FeNO) measures for monitoring asthma control?
3.	Objective	To evaluate the clinical and cost-effectiveness of using fractional exhaled nitric oxide (FeNO) for monitoring asthma control?
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies

		Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. MEDLINE search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details). The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.
5.	Condition or domain being studied	Asthma
6.	Population	People with asthma. Not including severe asthma or children aged < 5 years. All ages, stratified into the following 2 different groups: • Children and young people (5-16 years old) • Adults (17 years old and above) <u>Strata</u> • Population of current smokers greater than 20%
7.	Intervention	Monitoring FeNO and adjustment of management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring) Only use validated methods of measuring FeNO (i.e. 50ml/s flow rate).*
8.	Comparator	Comparison of adjustment of asthma therapy based on FeNO to:

		• Usual care: eg clinical symptoms (with or without PEF) according to guidelines (including BTS/SIGN, GINA) • Asthma control questionnaires or QOL questionnaires • Lung function tests (spirometry or PEFv) • Blood eosinophils
9.	Types of study to be included	RCTs SR of RCTs
10.	Other exclusion criteria	• Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Occupational asthma
11.	Context	Primary and secondary care settings
12.	Primary outcomes (critical outcomes)	• Mortality (both asthma related and all-cause) • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Severe asthma exacerbations (defined as need for course of oral steroids; dichotomous outcome at ≥6 months) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3; continuous outcome at ≥3 months) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire; continuous outcome at ≥3 months) • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) (continuous outcome at ≥3 months) • Time off school or work • Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks)
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.

		This review will make use of the priority screening functionality within the EPPI-reviewer software. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For this monitoring review, the Randomised Controlled Trial: Cochrane RoB (2.0) checklist will be used. For included systematic reviews, the Risk of Bias in Systematic Reviews (ROBIS) checklist will be used.
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences.

		Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. WinBUGS will be used for network meta-analysis, if possible given the data identified.	
16.	Analysis of sub-groups	• Subgroup according to the aim of the treatment in the study i.e. studies containing people with controlled asthma looking to step down ICS vs studies containing people with uncontrolled looking to step up ICS • Monitored adherence vs didn't	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☒	Other – monitoring

18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date			
21.	Anticipated completion date	31 July 2024		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐

		Data analysis	☐	☐
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail asthmachronicmanagement@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
24.	Review team members	From the National Guideline Centre: Bernard Higgins Sharon Swain Melina Vasileiou Toby Sands Alfredo Mariani Lina Gulhane Amy Crisp		
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee		

		Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10186	
28.	Other registration details		
29.	Reference/URL for published protocol	31 July 2024	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	N/A	
32.	Details of existing review of same topic by same authors	N/A	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	N/A	

35.	Details of final publication	www.nice.org.uk

Health economic review protocol

Table 9: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).(National Institute for Health and Care Excellence) **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:*

	• UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

Review question: In people with asthma, what is the clinical and cost-effectiveness of using fractional exhaled nitric oxide (FeNO) measures for monitoring asthma control?

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 10: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 28 Dec 2023	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 28 Dec 2023	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (conference abstracts, animal studies, letters, comments, editorials, case studies/reports) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2023 Issue 12 of 12 CENTRAL to 2023 Issue 12 of 12	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 28 Dec 2023	Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/

6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	biological markers/
25.	breath tests/
26.	exhalation/
27.	24 or 25 or 26
28.	Nitric oxide/
29.	27 and 28
30.	Fractional Exhaled Nitric Oxide Testing/
31.	((FE or exhal* or fraction*) adj3 (NO or nitric or nitrogen)).ti,ab,kf.
32.	FENO.ti,ab,kf.
33.	or/29-32
34.	23 and 33
35.	exp "sensitivity and specificity"/
36.	(sensitivity or specificity).ti,ab.
37.	((pre test or pretest or post test) adj probability).ti,ab.
38.	(predictive value* or PPV or NPV).ti,ab.
39.	likelihood ratio*.ti,ab.
40.	likelihood function/
41.	((area under adj4 curve) or AUC).ti,ab.
42.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
43.	gold standard.ab.
44.	exp Diagnostic errors/
45.	(false positiv* or false negativ*).ti,ab.
46.	Diagnosis, Differential/
47.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
48.	or/35-47

49.	randomized controlled trial.pt.
50.	controlled clinical trial.pt.
51.	randomi#ed.ab.
52.	placebo.ab.
53.	randomly.ab.
54.	clinical trials as topic.sh.
55.	trial.ti.
56.	or/49-55
57.	Meta-Analysis/
58.	Meta-Analysis as Topic/
59.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
60.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
61.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
62.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
63.	(search* adj4 literature).ab.
64.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
65.	cochrane.jw.
66.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
67.	or/57-66
68.	Epidemiologic studies/
69.	Observational study/
70.	exp Cohort studies/
71.	(cohort adj (study or studies or analys* or data)).ti,ab.
72.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
73.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
74.	Controlled Before-After Studies/
75.	Historically Controlled Study/
76.	Interrupted Time Series Analysis/
77.	(before adj2 after adj2 (study or studies or data)).ti,ab.
78.	exp case control study/
79.	case control*.ti,ab.
80.	Cross-sectional studies/
81.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
82.	or/68-81
83.	34 and (48 or 56 or 67 or 82)

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/

5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	*biological marker/
24.	*breath analysis/
25.	*exhalation/
26.	23 or 24 or 25
27.	*nitric oxide/
28.	26 and 27
29.	nitric oxide breathanalyzer/
30.	((FE or exhal* or fraction*) adj3 (NO or nitric or nitrogen)).ti,ab,kf.
31.	FENO.ti,ab,kf.
32.	or/28-31
33.	22 and 32
34.	exp "sensitivity and specificity"/
35.	(sensitivity or specificity).ti,ab.
36.	((pre test or pretest or post test) adj probability).ti,ab.
37.	(predictive value* or PPV or NPV).ti,ab.
38.	likelihood ratio*.ti,ab.
39.	((area under adj4 curve) or AUC).ti,ab.
40.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
41.	diagnostic accuracy/
42.	diagnostic test accuracy study/
43.	gold standard.ab.
44.	exp diagnostic error/
45.	(false positiv* or false negativ*).ti,ab.
46.	differential diagnosis/

47.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
48.	or/34-47
49.	Clinical study/
50.	Observational study/
51.	Family study/
52.	Longitudinal study/
53.	Retrospective study/
54.	Prospective study/
55.	Cohort analysis/
56.	Follow-up/
57.	cohort*.ti,ab.
58.	56 and 57
59.	(cohort adj (study or studies or analys* or data)).ti,ab.
60.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
61.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	(before adj2 after adj2 (study or studies or data)).ti,ab.
63.	exp case control study/
64.	case control*.ti,ab.
65.	cross-sectional study/
66.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
67.	or/49-55,58-66
68.	random*.ti,ab.
69.	factorial*.ti,ab.
70.	(crossover* or cross over*).ti,ab.
71.	((doubl* or singl*) adj blind*).ti,ab.
72.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
73.	crossover procedure/
74.	single blind procedure/
75.	randomized controlled trial/
76.	double blind procedure/
77.	or/68-76
78.	Systematic Review/
79.	Meta-Analysis/
80.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
81.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
82.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
83.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
84.	(search* adj4 literature).ab.
85.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
86.	cochrane.jw.

87.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
88.	or/78-87
89.	33 and (48 or 67 or 72 or 88)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Asthma] explode all trees
#2.	asthma*:ti,ab
#3.	#1 or #2
#4.	conference:pt or (clinicaltrials or trialsearch):so
#5.	#3 not #4
#6.	MeSH descriptor: [Biomarkers] this term only
#7.	MeSH descriptor: [Breath Tests] explode all trees
#8.	MeSH descriptor: [Exhalation] this term only
#9.	#6 or #7 or #8
#10.	MeSH descriptor: [Nitric Oxide] explode all trees
#11.	#9 and #10
#12.	MeSH descriptor: [Fractional Exhaled Nitric Oxide Testing] explode all trees
#13.	((FE or exhal* or fraction*) near/3 (NO or nitric or nitrogen)):ti,ab
#14.	FENO:ti,ab
#15.	#11 or #12 or #13 or #14
#16.	#5 and #15

Epistemonikos search terms

1.	(title:("Fractional Exhaled Nitric Oxide" OR FENO OR ((FE OR exhal* OR fraction*) AND (nitric OR nitrogen))) OR abstract:("Fractional Exhaled Nitric Oxide" OR FENO OR ((FE OR exhal* OR fraction*) AND (nitric OR nitrogen))))

B.2 Health economic literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Asthma population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies and modelling.

Table 11: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling

Database	Dates searched	Search filters and limits applied
	Quality of Life 1946 – 29 Dec 2023	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Modelling 1946 – 29 Dec 2023	
Embase (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 Dec 2023	
	Modelling 1974 – 29 Dec 2023	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 Dec 2023	English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/

11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	quality-adjusted life years/
25.	sickness impact profile/
26.	(quality adj2 (wellbeing or well being)).ti,ab.
27.	sickness impact profile.ti,ab.
28.	disability adjusted life.ti,ab.
29.	(qal* or qtime* or qwb* or daly*).ti,ab.
30.	(euroqol* or eq5d* or eq 5*).ti,ab.
31.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
32.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
33.	(hui or hui1 or hui2 or hui3).ti,ab.
34.	(health* year* equivalent* or hye or hyes).ti,ab.
35.	discrete choice*.ti,ab.
36.	rosser.ti,ab.
37.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
38.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
39.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
40.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
41.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
42.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
43.	or/24-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/

50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	Economics/
55.	Value of life/
56.	exp "Costs and Cost Analysis"/
57.	exp Economics, Hospital/
58.	exp Economics, Medical/
59.	Economics, Nursing/
60.	Economics, Pharmaceutical/
61.	exp "Fees and Charges"/
62.	exp Budgets/
63.	budget*.ti,ab.
64.	cost*.ti.
65.	(economic* or pharmaco?economic*).ti.
66.	(price* or pricing*).ti,ab.
67.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
68.	(financ* or fee or fees).ti,ab.
69.	(value adj2 (money or monetary)).ti,ab.
70.	or/54-69
71.	23 and 43
72.	23 and 53
73.	23 and 70

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract or conference paper).pt.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/

14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	quality adjusted life year/
24.	"quality of life index"/
25.	short form 12/ or short form 20/ or short form 36/ or short form 8/
26.	sickness impact profile/
27.	(quality adj2 (wellbeing or well being)).ti,ab.
28.	sickness impact profile.ti,ab.
29.	disability adjusted life.ti,ab.
30.	(qal* or qtime* or qwb* or daly*).ti,ab.
31.	(euroqol* or eq5d* or eq 5*).ti,ab.
32.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
33.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
34.	(hui or hui1 or hui2 or hui3).ti,ab.
35.	(health* year* equivalent* or hye or hyes).ti,ab.
36.	discrete choice*.ti,ab.
37.	rosser.ti,ab.
38.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
39.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
40.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
41.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
42.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
43.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
44.	or/23-43
45.	statistical model/
46.	exp economic aspect/
47.	45 and 46
48.	*theoretical model/
49.	*nonbiological model/
50.	stochastic model/
51.	decision theory/
52.	decision tree/

53.	monte carlo method/
54.	(markov* or monte carlo).ti,ab.
55.	econom* model*.ti,ab.
56.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
57.	or/47-56
58.	health economics/
59.	exp economic evaluation/
60.	exp health care cost/
61.	exp fee/
62.	budget/
63.	funding/
64.	budget*.ti,ab.
65.	cost*.ti.
66.	(economic* or pharmaco?economic*).ti.
67.	(price* or pricing*).ti,ab.
68.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
69.	(financ* or fee or fees).ti,ab.
70.	(value adj2 (money or monetary)).ti,ab.
71.	or/58-70
72.	22 and 44
73.	22 and 57
74.	22 and 71

NHS EED and HTA (CRD) search terms

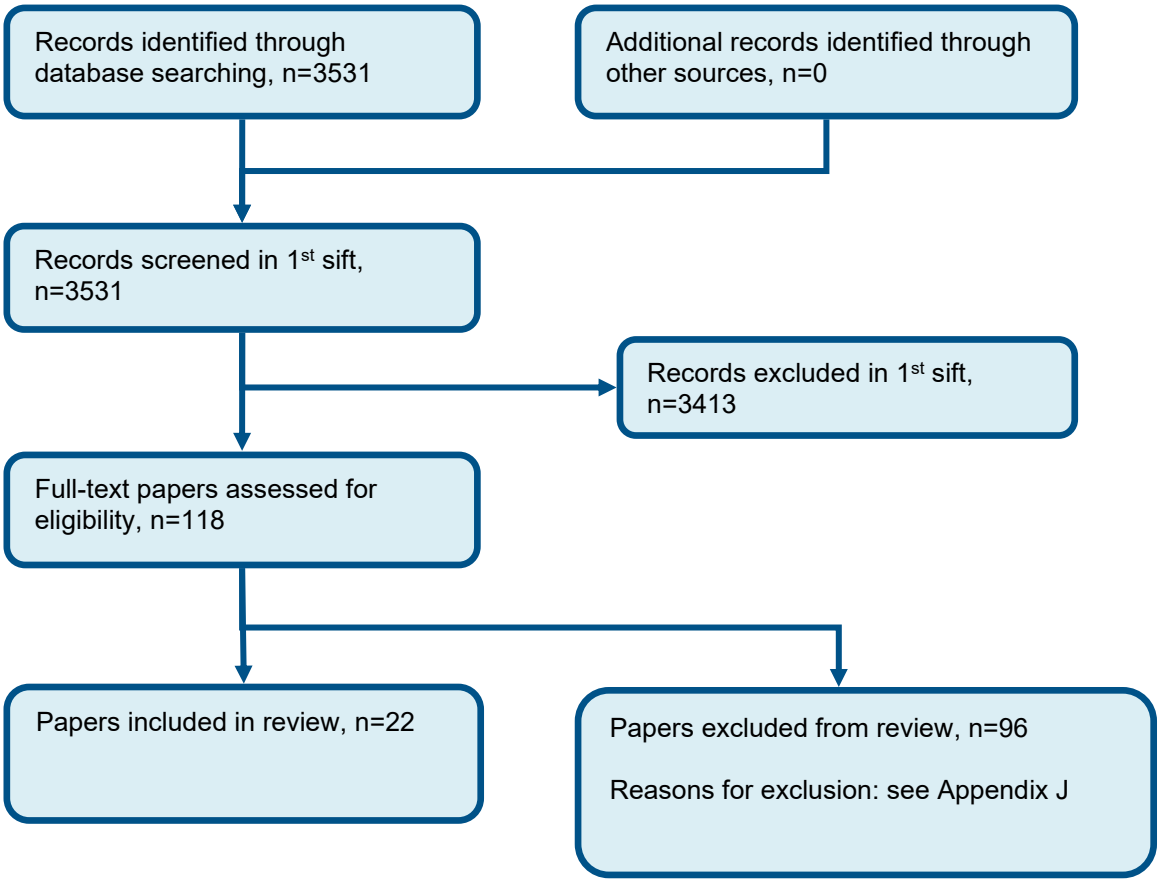
#1.	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES
#2.	(asthma*)
#3.	#1 OR #2

INAHTA search terms

1.	(Asthma)[mh] OR (asthma*)[Title] OR (asthma*)[abs]

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of clinical effectiveness of FeNO measures for monitoring asthma control



Appendix D – Effectiveness evidence

Bernholm, 2018

Bibliographic Reference	Bernholm, Katrine Feldballe; Homoe, Anne-Sophie; Meteran, Howraman; Jensen, Camilla Bjorn; Porsbjerg, Celeste; Backer, Vibeke; F eNO-based asthma management results in faster improvement of airway hyperresponsiveness; ERJ open research; 2018; vol. 4 (no. 4)

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Clinicaltrials.gov (NCT01978678) and EudraCT (2013-004905-15).
Study type	Randomised controlled trial (RCT)
Study location	Denmark
Study setting	No additional information
Study dates	Inclusion took place from September 2012 to June 2015
Sources of funding	No additional information
Inclusion criteria	Patients with a doctor’s diagnosis of asthma, including AHR (i.e. a provocative dose causing a 15% fall in forced expiratory volume in 1 s (PD15) <635 mg) to mannitol and asthma symptoms were included

Exclusion criteria	Participants could not have other pulmonary diseases and female participants should be using contraception and not be pregnant.
Recruitment / selection of participants	Patients were recruited either from a private asthma clinic outside the hospital or from the hospital-based outpatient clinic
Intervention(s)	Participants were started on different dosages of ICS, depending on their current treatment at randomisation. Steroid-naïve participants were initially treated with budesonide turbohaler (200 µg twice per day) and short-acting β2-agonist (terbutalin 0.5 mg as needed) from V1 to the following visit at V2 (baseline), after which regulation was established based on the algorithm. Similarly, all participants already being treated with ICS at randomisation were continued on their current dosage for 8 weeks, after which they were regulated due to the algorithm. Thus, the treatment algorithms were introduced at V2. The initial dosage of ICS determined which treatment step each participant was regulated from at V2. Only participants already being treated with LABA prior to inclusion were continued on this treatment. In both treatment algorithms, the current dosage of ICS and β2-agonist determined which treatment step each patient was on at every visit. The follow-up visits took place 8 (V2), 24 (V3) and 36 (V4) weeks after V1. In case of unscheduled visits due to exacerbations, the following visits were postponed by 2 weeks from last day of intake of the exacerbation treatment. In both treatment algorithms, the current dosage of ICS and β2-agonist determined which treatment step each patient was on at every visit. The regulation in treatment (decrease, increase or no change) was determined from this step (tables 1–3) Participants randomised to this treatment algorithm were regulated in two sequences. First, their visit specific FeNO value determined the regulation of ICS, and secondly their visit specific ACQ score determined the regulation of LABA. If a participant had a FeNO concentration <29 ppb as well as an ACQ score >1.5, 4.5 µg formoterol was added. The ICS steps and LABA steps were independent from each other. For patients taking LABA in the FeNO group, ICS was never reduced to zero, but remained at 100 µg twice daily. **Treatment Levels** Level 1 FeNO concentration: >29 = ↑ 1 ICS step; ACQ Score: ⩽1.5 = No change in beta-agonist dose

	Level 2 FeNO concentration: 16–29 = No change; ACQ Score: >1.5 = ↑ 1 LABA step Level 3 FeNO concentration: <16 = ↓ 1 ICS step; ACQ Score: NA (FeNO >29 ppb) = No change in beta-agonist dose **ICS Treatment Steps (adjusted based on FeNO levels)** Step 1: 0 Step 2: budesonide 100 µg twice daily Step 3: budesonide 200 µg twice daily Step 4: budesonide 400 µg twice daily Step 5: budesonide 800 µg twice daily **Beta-2-agonist Treatment Steps (adjusted based on ACQ score)** Step 1: terbutalin as required Step 2: formoterol 4.5 µg twice daily Step 3: formoterol 9 µg twice daily Step 4: formoterol 2×9 µg twice daily
Population subgroups	**Strata**

	Children or adults Adults **Population of current smokers (>20% vs ≤20%)** 22.2% current smokers **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** No
Comparator	Participants randomised to this algorithm were only regulated based on their visit specific ACQ. The algorithm did not contain regulations based on the participants visit specific FeNO value. After a doubling of ICS, if a participant had a further increase in ACQ 4.5 µg formoterol was added. **Treatment Levels** Level 1: ACQ Score >1.5 = ↑ 1 step Level 2: ACQ Score 0.75-1.5 = No change

	Level 3: ACQ score <0.75 = ↓ 1 step **Treatment Steps** Step 1: Terbutalin as required Step 2: Budesonide 200 µg twice daily Step 3: Budesonide 400 µg twice daily Step 4: Budesonide 400 µg and formoterol 9 µg twice daily Step 5: Budesonide 800 µg and formoterol 18 µg twice daily
Number of participants	80 randomised 40 in FeNO group, 36 at 8 weeks, 30 at 24 weeks, 29 at 36 weeks 40 in questionnaire group, 36 at 8 weeks, 29 at 24 weeks, 29 at 36 weeks
Duration of follow-up	36 weeks
Indirectness	None
Additional comments	Available case analysis

Study arms

FeNO monitoring (N = 36)

Usual care (N = 36)
Management based on the level of symptoms indicated by the Asthma Control Questionnaire

Characteristics

Study-level characteristics

Characteristic	Study (N = 72)
% Female Sample size	n = 46 ; % = 58
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Arm-level characteristics

Characteristic	FeNO monitoring (N = 36)	Usual care (N = 36)
Mean age (SD) Median (IQR)	42 (27 to 52)	30 (24 to 46)

Outcomes

Study timepoints

- Baseline
- 28 week (From V2 (8 weeks) to V4 (36 weeks))

Continuous Outcomes

Outcome	FeNO monitoring , Baseline, N = 36	FeNO monitoring , 28 week, N = 36	Usual care, Baseline, N = 36	Usual care, 28 week, N = 36
Lung Function (FEV1) (Litres) Change scores Mean (95% CI)	NR (NR to NR)	0.07 (-0.02 to 0.16)	NA (NA to NA)	0.08 (-0.01 to 0.17)
Lung function (FEV1 %) Change scores Mean (95% CI)	NR (NR to NR)	2.3 (-0.5 to 5)	NA (NA to NA)	2.5 (-0.3 to 5.2)

Outcome	FeNO monitoring , Baseline, N = 36	FeNO monitoring , 28 week, N = 36	Usual care, Baseline, N = 36	Usual care, 28 week, N = 36
Asthma control (Asthma Control Questionnaire) Scale range: 0-6, change scores Mean (95% CI)	NR (NR to NR)	-0.1 (-0.6 to 0.3)	NR (NR to NR)	-0.2 (-0.7 to 0.3)
Quality of life (Asthma Quality of Life Questionnaire) Scale range: 1-7, change scores Mean (95% CI)	NR (NR to NR)	0.1 (-0.3 to 0.6)	NR (NR to NR)	0.2 (-0.3 to 0.6)
Dose of regular asthma therapy (ICS dose) (µg/day) Change scores Mean (95% CI)	NR (NR to NR)	5 (-194 to 204)	NR (NR to NR)	-25 (-224 to 174)
Inflammatory markers (FeNO) (ppb) Change scores Mean (95% CI)	NR (NR to NR)	-13 (-20 to -5)	NR (NR to NR)	-17 (-36 to 2)

Lung Function (FEV1) - Polarity - Higher values are better
Lung function (FEV1 %) - Polarity - Higher values are better
Asthma control (Asthma Control Questionnaire) - Polarity - Lower values are better
Quality of life (Asthma Quality of Life Questionnaire) - Polarity - Higher values are better
Dose of regular asthma therapy (ICS dose) - Polarity - Lower values are better
Inflammatory markers (FeNO) - Polarity - Lower values are better

Transform

Continuous Outcomes

Outcome	FeNO monitoring , Baseline, N = 36	FeNO monitoring , 28 week, N = 36	Usual care, Baseline, N = 36	Usual care, 28 week, N = 36

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes -Lung Function (FEV1)-Mean Nine Five Percent CI-FeNO monitoring -Usual care-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes-Lung function (FEV1%)-Mean Nine Five Percent CI-FeNO monitoring -Usual care-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Asthma control (Asthma Control Questionnaire)-Mean Nine Five Percent CI-FeNO monitoring -Usual care-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes- Quality of life (Asthma Quality of Life Questionnaire)-Mean Nine Five Percent CI-FeNO monitoring -Usual care-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes-Dose of regular asthma therapy (ICS dose)-Mean Nine Five Percent CI-FeNO monitoring -Usual care-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes-Inflammatory markers (FeNO)-Mean Nine Five Percent CI- FeNO monitoring -Usual care-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Calhoun, 2012

Bibliographic Reference	Calhoun, William J.; Ameredes, Bill T.; King, Tonya S.; Icitovic, Nikolina; Bleecker, Eugene R.; Castro, Mario; Cherniack, Reuben M.; Chinchilli, Vernon M.; Craig, Timothy; Denlinger, Loren; DiMango, Emily A.; Engle, Linda L.; Fahy, John V.; Grant, J. Andrew; Israel, Elliot; Jarjour, Nizar; Kazani, Shamsah D.; Kraft, Monica; Kunselman, Susan J.; Lazarus, Stephen C.; Lemanske, Robert F.; Lugogo, Njira; Martin, Richard J.; Meyers, Deborah A.; Moore, Wendy C.; Pascual, Rodolfo; Peters, Stephen P.; Ramsdell, Joe; Sorkness, Christine A.; Sutherland, E. Rand; Szefler, Stanley J.; Wasserman, Stephen I.; Walter, Michael J.; Wechsler, Michael E.; Boushey, Homer A.; Asthma Clinical Research Network of the National Heart, Lung; Blood, Institute; Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial; JAMA; 2012; vol. 308 (no. 10); 987-97

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	The BASALT (Best Adjustment Strategy for Asthma in the Long Term) Study (clinicaltrials.gov Identifier: NCT00495157)
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Secondary care
Study dates	Not reported

Sources of funding	Support by the Institute for Translational Sciences at the University of Texas Medical Branch, supported in part by a Clinical and Translational Science Award UL1TR000071 from the National Center for Advancing Translational Sciences, National Institutes of Health. The study was also supported by the following National Institutes of Health grants U10 HL074225, U10 HL074227, U10 HL074231, U10 HL074204, U10 HL074212, U10 HL074073, U10 HL074206, U10 HL074208, and U10 HL074218 that were awarded by the National Heart, Lung, and Blood Institute. Teva Pharmaceuticals provided the study drug and matching placebo.
Inclusion criteria	Aged 18 and older, clinical history consistent with asthma, FEV1 >40% predicted, asthma confirmed by either beta-agonist reversibility to 4 puffs albuterol ≥ 12% OR PC20 FEV(1) methacholine of ≤8 mg/ml NOT on an inhaled corticosteroid, or ≤16 mg/ml ON an inhaled corticosteroid, need for daily controller therapy (i.e., inhaled corticosteroids, leukotriene modifiers, and/or long-acting beta-agonists), if on inhaled steroids, subject must have been on a stable dose for at least 2 weeks, non-smoker (total lifetime smoking history <10 pack-years; no smoking for at least 1 year), acceptable control of asthma (i.e. a score of 0 or 1 on each of the 3 questions on the Asthma Evaluation Questionnaire and predicted bronchodilator FEV1 >70%), and patients who demonstrated at least 75% adherence (i.e. those patients that could tolerate 2 puffs twice daily of beclomethasone HFA (40 mch/puff)) during the run-in period
Exclusion criteria	Poorly controlled, severe asthma, lung disease other than asthma, established or suspected diagnosis of vocal cord dysfunction, significant medical illness other than asthma, history of respiratory tract infection within the previous 4 weeks, history of a significant exacerbation of asthma in the previous 4 weeks, history of life-threatening asthma requiring treatment with intubation and mechanical ventilation within the past 5 years, hyposensitization therapy other than an established maintenance regimen, inability, in the opinion of the investigator or clinical coordinator, to coordinate use of the delivery devices used in the study, pregnant or if potentially able to bear children, not using an acceptable form of birth control.
Recruitment / selection of participants	**Strata** **Children or adults** Adults **Population of current smokers (>20% vs ≤20%)**

	Smokers excluded **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** Yes
Intervention(s)	The dose of inhaled corticosteroids was adjusted by measurement of exhaled nitric oxide. Dose adjustments of inhaled corticosteroids were made at the time of clinic visits (every 6 weeks). Patients were treated with 2 puffs twice daily of beclomethasone HFA (40 µg/puff) during the run-in period, and if their asthma was acceptably controlled (a score of 0 or 1 on each of 3 questions on the Asthma Evaluation Questionnaire and predicted bronchodilator FEV1 >70%), they were enrolled in the BASALT trial. During the prerandomization period, patients were given 3 inhalers coded as A, B, and C. Inhaler A contained beclomethasone HFA (40 µg/puff) and inhalers B and C contained placebo. An albuterol inhaler was provided for use as needed for asthma symptoms. Participants were instructed to use 2 puffs twice daily from inhalers A and B, and to use 2 puffs from inhaler C each time they used 2 puffs of albuterol for symptom relief. All metered dose inhalers were equipped with a Doser device (Meditrack Products) to measure adherence during the trial. Patients who demonstrated at least 75% adherence were randomized to 1 of 3 adjustment strategies. Beclomethasone HFA was provided at a dosage of 2 puffs twice daily (40 µg/puff) before randomization, corresponding to level 3 treatment. Hence, inhaled corticosteroid therapy could be intensified or deintensified during the trial. Following randomization, beclomethasone HFA was contained only in inhaler A for PABA participants, only in inhaler B for BBA participants, and only in inhaler C for SBA participants. Thereafter, inhaler B was adjusted according to exhaled nitric oxide measurements. Participants were instructed to use inhaler C only at the time of albuterol use. Subsequent visits occurred 2, 4, 6, 12, 18, 24, 30, and 36 weeks after randomization.

Comparator	The dose of inhaled corticosteroids was adjusted by measurement of exhaled nitric oxide. Dose adjustments of inhaled corticosteroids were made at the time of clinic visits (every 6 weeks). Patients were treated with 2 puffs twice daily of beclomethasone HFA (40 µg/puff) during the run-in period, and if their asthma was acceptably controlled (a score of 0 or 1 on each of 3 questions on the Asthma Evaluation Questionnaire and predicted bronchodilator FEV1 >70%), they were enrolled in the BASALT trial. During the prerandomization period, patients were given 3 inhalers coded as A, B, and C. Inhaler A contained beclomethasone HFA (40 µg/puff) and inhalers B and C contained placebo. An albuterol inhaler was provided for use as needed for asthma symptoms. Participants were instructed to use 2 puffs twice daily from inhalers A and B, and to use 2 puffs from inhaler C each time they used 2 puffs of albuterol for symptom relief. All metered dose inhalers were equipped with a Doser device (Meditrack Products) to measure adherence during the trial. Patients who demonstrated at least 75% adherence were randomized to 1 of 3 adjustment strategies. Beclomethasone HFA was provided at a dosage of 2 puffs twice daily (40 µg/puff) before randomization, corresponding to level 3 treatment. Hence, inhaled corticosteroid therapy could be intensified or deintensified during the trial. Following randomization, beclomethasone HFA was contained only in inhaler A for PABA participants, only in inhaler B for BBA participants, and only in inhaler C for SBA participants. Thereafter, inhaler A was adjusted by an investigator according to guidelines closely resembling the National Heart, Lung, and Blood Institute National Asthma Expert Panel. Participants were instructed to use inhaler C only at the time of albuterol use. In the symptom-control group (SBA), dose adjustment of inhaled corticosteroids was performed by matching inhaled steroid use on a puff-per-puff basis with as-needed albuterol use. Subsequent visits occurred 2, 4, 6, 12, 18, 24, 30, and 36 weeks after randomization.
Number of participants	342 randomised 115 allocated to FeNO monitoring group, 92 completed 114 allocated to usual care (guideline-based) group, 101 completed 113 allocated to usual care (symptom-based) group, 97 completed
Duration of follow-up	36 weeks
Indirectness	None

Additional comments	ITT

Study arms

FeNO monitoring (N = 115)

Usual care (N = 227)
Combined 2 study arms into 1 for this analysis. Study group 1 was based on National Heart, Lung and Blood Institute guidelines (PABA group). Study group 3 was based on symptoms prompting use of SABA (SBA group)

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 115)	Usual care (N = 227)
% Female Sample size	n = 82 ; % = 71.3	n = 155 ; % = 68.3
Mean age (SD) Mean (SD)	34.8 (11.3)	35.1 (12.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	FeNO monitoring (N = 115)	Usual care (N = 227)
American Indian/Alaska Native Sample size	n = 0 ; % = 0	n = 1 ; % = 0.4
Asian/Pacific islander Sample size	n = 2 ; % = 1.7	n = 11 ; % = 4.8
Black Sample size	n = 28 ; % = 24.3	n = 43 ; % = 18.9
White Sample size	n = 71 ; % = 61.7	n = 145 ; % = 63.9
Hispanic Sample size	n = 13 ; % = 11.3	n = 25 ; % = 11
Other Sample size	n = 1 ; % = 0.9	n = 4 ; % = 1.8
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline

- 36 week

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 115	FeNO monitoring, 36 week, N = 115	Usual care, Baseline, N = 227	Usual care, 36 week, N = 227
Lung function (morning PEF) (litres/minute) change scores Mean (SD)	NA (NA)	-14.4 (54.58)	NA (NA)	-22.52 (54.82)
Rescue medication (non-exercise preventative albuterol use) (puffs/day) change scores Mean (SD)	NA (NA)	-0.04 (0.29)	NA (NA)	0 (0.26)
Lung Function (FEV1) (Litres) change scores Mean (SD)	NA (NA)	-0.08 (0.55)	NA (NA)	-0.14 (0.52)
Lung function (FEV1 % predicted) change scores Mean (SD)	NA (NA)	-2.45 (7.56)	NA (NA)	-3.44 (7.3)
Quality of life (Asthma Quality of Life Questionnaire) scale range: 1-7, change scores Mean (SD)	NA (NA)	0.02 (0.77)	NA (NA)	0.02 (0.74)

Outcome	FeNO monitoring, Baseline, N = 115	FeNO monitoring, 36 week, N = 115	Usual care, Baseline, N = 227	Usual care, 36 week, N = 227
Asthma control questionnaires (Asthma Control Questionnaire) scale range: 0-6, change scores Mean (SD)	NA (NA)	-0.01 (0.65)	NA (NA)	0.03 (0.62)

Lung function (morning PEF) - Polarity - Higher values are better
Rescue medication (non-exercise preventative albuterol use) - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (FEV1 % predicted) - Polarity - Higher values are better
Quality of life (Asthma Quality of Life Questionnaire) - Polarity - Higher values are better
Asthma control questionnaires (Asthma Control Questionnaire) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 115	FeNO monitoring, 36 week, N = 115	Usual care, Baseline, N = 227	Usual care, 36 week, N = 227
Unscheduled health utilisation (hospitalisation) Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 7 ; % = 3.1

Unscheduled health utilisation (hospitalisation) - Polarity - Lower values are better

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 115	FeNO monitoring, 36 week, N = 115	Usual care, Baseline, N = 227	Usual care, 36 week, N = 227
Lung function (morning PEF) (litres/minute) change scores Mean (SD)	NA (NA)	-14.4 (54.58)	NA (NA)	-22.52 (54.82)
Rescue medication (non-exercise preventative albuterol use) (puffs/day) change scores Mean (SD)	NA (NA)	-0.04 (0.29)	NA (NA)	0 (0.26)
Lung Function (FEV1) (Litres) change scores Mean (SD)	NA (NA)	-0.08 (0.55)	NA (NA)	-0.14 (0.52)
Lung function (FEV1 % predicted) change scores Mean (SD)	NA (NA)	-2.45 (7.56)	NA (NA)	-3.44 (7.3)
Quality of life (Asthma Quality of Life Questionnaire) scale range: 1-7, change scores Mean (SD)	NA (NA)	0.02 (0.77)	NA (NA)	0.02 (0.74)

Outcome	FeNO monitoring, Baseline, N = 115	FeNO monitoring, 36 week, N = 115	Usual care, Baseline, N = 227	Usual care, 36 week, N = 227
Asthma control questionnaires (Asthma Control Questionnaire) scale range: 0-6, change scores Mean (SD)	NA (NA)	-0.01 (0.65)	NA (NA)	0.03 (0.62)

Arm based : Data distribution : Not set

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 115	FeNO monitoring, 36 week, N = 115	Usual care, Baseline, N = 227	Usual care, 36 week, N = 227

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Lung function (morning PEF)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Rescue medication (non-exercise preventative albuterol use)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Lung Function (FEV1)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Lung function (FEV1% predicted)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Quality of life (Asthma Quality of Life Questionnaire)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Asthma control questionnaires (Asthma Control Questionnaire)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Unscheduled health utilisation (hospitalisation) – No Of Events - FeNO monitoring-Usual care-t36

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

de Jongste, 2009

Bibliographic Reference	de Jongste, Johan C.; Carraro, Silvia; Hop, Wim C.; Group, Charism Study; Baraldi, Eugenio; Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma; American journal of respiratory and critical care medicine; 2009; vol. 179 (no. 2); 93-7

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	5 academic centres and 12 general hospitals
Study dates	No additional information
Sources of funding	Authors had received travel grants and lectured at scientific meetings for GlaxoSmithKline, Merck Sharp & Dohme, Altana Pharma, Aerocrine, and Roche. The Department of Pediatrics/Erasmus MC Holding received research grants from GlaxoSmithKline, AstraZeneca, Aerocrine, Roche, Freisland Foods, Transave, Chiron, and Pfizer. Also received a research grant from Aerocrine and travel grants from Merck Sharp & Dohme and Chiesi, received a research grant from Aerocrine in

	the past 3 years and also received travel grants and lectured at scientific meetings for GlaxoSmithKline, Merck Sharp & Dohme, Abbott, and Valeas.
Inclusion criteria	Aged 6–18 years; stable mild–moderate asthma, diagnosed according to Global Initiative for Asthma (GINA) guidelines; treatment with 200–1,000 mg of inhaled budesonide or equivalent daily for 2 months before randomization; and RAST class 2 or higher or a positive skin prick test for at least one airborne allergen.
Exclusion criteria	Active smoking, previous admission to an intensive care unit for asthma, and concomitant disease that might affect FeNO
Recruitment / selection of participants	Children were recruited from 5 academic centers and 12 general hospitals.
Intervention(s)	Children in the FeNO group received an airway inflammation monitor (NIOX MINO; Aerocrine, Solna, Sweden). Measurements were performed daily. Measurement time was recorded by the device for later review. Data were transmitted to the coordinating center. All parents were phoned every 3 weeks between visits, and medication was adapted according to geometric mean FeNO over the preceding 3 weeks and cumulative symptom scores. All children recorded asthma symptoms in a palmtop electronic diary (PalmOne Tungsten W PDA equipped with TrialMax software; CRF Inc., Helsinki, Finland). Entries were transmitted daily to the coordinating center. **Treatment Algorithm** High symptom score + High FeNO = Increase ICS High symptom score + Low FeNO = No change to ICS Low symptom score + High FeNO = Increase ICS Low symptom score + Low FeNO = Decrease or discontinue ICS Cut-off for high symptom score: >60, low score: ≤60 cumulative across three weeks.

	Cut-offs for FeNO: 20 ppb for children aged 6-10 years and 25 ppb for older children. Doses were changed according to predefined steps for each type of ICS (e.g., budesonide at 100, 200, 400, 800 and 1200 mg) If a combination of LABA and ICS was used, the LABA was stopped whenever a decrease was required at the lowest ICS dose, before stopping ICS.
Population subgroups	**Strata** **Children or adults** Children **Population of current smokers (>20% vs ≤20%)** No current smokers included **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** No
Comparator	All children recorded asthma symptoms in a palmtop electronic diary (PalmOne Tungsten W PDA equipped with TrialMax software; CRF Inc., Helsinki, Finland). Entries were transmitted daily to the coordinating center. All parents were phoned every 3 weeks between visits, and medication was adapted according to cumulative symptom scores.

	Treatment Algorithm Symptom score above range = Increase ICS Symptom score in range = No change Symptom score below range = Reduce ICS Normal range was 10-60. Doses were changed according to predefined steps for each type of ICS (e.g., budesonide at 100, 200, 400, 800 and 1200 mg) If a combination of LABA and ICS was used, the LABA was stopped whenever a decrease was required at the lowest ICS dose, before stopping ICS.
Number of participants	151 randomised 77 in FeNO monitoring group 74 in usual care group
Duration of follow-up	30 weeks
Indirectness	None
Additional comments	ITT - four participants, two from each arm, excluded due to severe non-compliance, inappropriate inclusion or moving away from study site

Study arms

FeNO monitoring (N = 77)

Usual care (N = 74)
Symptom scores submitted via an electronic diary

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 77)	Usual care (N = 74)
% Female Sample size	n = 31 ; % = 40	n = 20 ; % = 27
Mean age (SD) Mean (SD)	11.6 (2.6)	11.8 (4.3)
Ethnicity White Sample size	n = 70 ; % = 91	n = 65 ; % = 88
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 30 week

Continuous Outcomes

Outcome	FeNO monitoring , Baseline, N = 77	FeNO monitoring , 30 week, N = 75	Usual care, Baseline, N = 74	Usual care, 30 week, N = 72
Lung function (FEV1 % predicted) final values Mean (SD)	88 (15)	95 (14)	88 (13)	94 (14)

Lung function (FEV1 % predicted) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	FeNO monitoring , Baseline, N = 77	FeNO monitoring , 30 week, N = 75	Usual care, Baseline, N = 74	Usual care, 30 week, N = 72
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 9 ; % = 12	n = NA ; % = NA	n = 12 ; % = 16.6

Severe asthma exacerbations - Polarity - Lower values are better

Continuous Outcomes

Outcome	FeNO monitoring , Baseline, N = 77	FeNO monitoring , 30 week, N = 75	Usual care, Baseline, N = 74	Usual care, 30 week, N = 72
Lung function (FEV1 % predicted) final values Mean (SD)	88 (15)	95 (14)	88 (13)	94 (14)

Arm based : Data distribution : Not set

Dichotomous Outcomes

Outcome	FeNO monitoring , Baseline, N = 77	FeNO monitoring , 30 week, N = 75	Usual care, Baseline, N = 74	Usual care, 30 week, N = 72
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 9 ; % = 12	n = NA	n = 12 ; % = 16.6

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Lung function (FEV1% predicted)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Exacerbations (number of children who received ≥1 prednisone course)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Fang, 2022

Bibliographic Reference	Fang, C; Yang, L-J; Chen, X-J; Li, D-M; Li, D-X; Liang, L-T; Lu, Z-N; Li, Q; A clinical investigation into the usefulness of fractional exhaled nitric oxide in guiding glucocorticoid therapy in children with bronchial asthma.; Journal of physiology and pharmacology : an official journal of the Polish Physiological Society; 2022; vol. 73 (no. 4)

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	No additional information
Study dates	October 2018 - June 2020
Sources of funding	No external funding
Inclusion criteria	Newly diagnosed asthma

	Aged 6-12 years Received no glucocorticoids, leukotriene receptor antagonists, or other drugs prior to the study
Exclusion criteria	Chronic or underlying comorbidities Diseases affecting pulmonary function
Recruitment / selection of participants	Consecutive patients newly diagnosed with asthma
Intervention(s)	Those allocated to the intervention received adjustment of their ICS dose based upon the level of asthma control, pulmonary function, and FeNO levels
Population subgroups	**Strata** **Children or adults** Children **Population of current smokers (>20% vs ≤20%)** N/A **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring**

	Yes
Comparator	Those allocated to the comparator received adjustment of their ICS dose based upon the level of asthma control and pulmonary function
Number of participants	133 randomised 68 allocated to FeNO monitoring 65 allocated to usual care
Duration of follow-up	6 months
Indirectness	None
Additional comments	Unclear, no dropouts or switches between groups reported

Study arms

FeNO monitoring (N = 68)

Usual care (N = 65)
Treatment adjusted based on asthma control and pulmonary function

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 68)	Usual care (N = 65)
% Female Sample size	n = 26 ; % = 38	n = 26 ; % = 40
Mean age (SD) Mean (SD)	8.14 (1.71)	7.94 (2.01)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Moderate Sample size	n = 53 ; % = 78	n = 52 ; % = 80
Severe Sample size	n = 15 ; % = 22	n = 13 ; % = 20

Outcomes

Study timepoints

- Baseline

- 6 month

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 68	FeNO monitoring, 6 month, N = 68	Usual care, Baseline, N = 65	Usual care, 6 month, N = 65
Asthma control (Childhood Asthma Control Test) Scale range: 0-27, final values Mean (SD)	NR (NR)	23.38 (4.52)	NR (NR)	20.75 (5.96)
Lung Function (FEV1) (% of predicted) Final values Mean (SD)	56.17 (4.43)	85.43 (5.61)	56.73 (6.12)	80.75 (4.49)
Lung function (PEF) (% of predicted) Final values Mean (SD)	58.34 (4.37)	86.56 (5.67)	57.66 (5.63)	80.35 (7.38)
Inflammatory markers (FeNO) (ppb) Final values Mean (SD)	55.79 (9.41)	18.37 (3.32)	53.96 (8.86)	20.08 (5.32)

Asthma control (Childhood Asthma Control Test) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better
Inflammatory markers (FeNO) - Polarity - Lower values are better
Asthma control values reported as three separate values depending on level of control - combined by analyst for this review

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes-Asthma control (Childhood Asthma Control Test) - Mean SD - FeNO monitoring-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Method of randomisation not reported, and adherence to monitoring strategy and drug treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1)- Mean SD-FeNO monitoring-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Method of randomisation not reported, and adherence to monitoring strategy and drug treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes - Lung function (PEF)-Mean SD- FeNO monitoring-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Method of randomisation not reported, and adherence to monitoring strategy and drug treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes - Inflammatory markers (FeNO)-Mean SD-FeNO monitoring-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Method of randomisation not reported, and adherence to monitoring strategy and drug treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Fritsch, 2006

Bibliographic Reference	Fritsch, Maria; Uxa, Sabine; Horak, Friedrich, Jr.; Putschoegl, Bettina; Dehlink, Eleonora; Szepfalusi, Zsolt; Frischer, Thomas; Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study; Pediatric pulmonology; 2006; vol. 41 (no. 9); 855-62

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Austria
Study setting	Secondary care
Study dates	No additional information
Sources of funding	Aerocrine thanked for their continuous technical support and help with data analyses.
Inclusion criteria	Patients aged 6-18 years, with mild to moderate persistent asthma. All participants had a positive skin prick test or radioallergosorbent test (RAST >1) to at least one of seven common aeroallergens (cat, dog, house dust mite, alternaria, birch-, hazelnut-, and mixed grass-pollen) in their past medical history or at the time of recruitment.

Exclusion criteria	Participants who had received oral or IV steroid treatment 4 weeks prior to the first visit were excluded from the study
Recruitment / selection of participants	Recruited from the Paediatric Pulmonology outpatient clinic of the University Children's Hospital Vienna.
Intervention(s)	Therapy was based on symptoms, beta agonist use, lung function, and FeNO. A step down in therapy was performed if FEV1 % predicted was ≥80% and there was no or mild symptoms over the last 4 weeks and beta agonist use was <6 puffs over the last 14 days. A step up was performed in every other case. Treatment was further adjusted according the FeNO cut-off point, >20 ppb. In participants with stable asthma increased FeNO was considered a sign of insufficient anti-inflammatory treatment. These patients were provided with 2-week diary cards to record daily symptoms, beta agonists use and controller medication requirement, and telephone calls were regularly performed to check adherence to therapy. Asymptomatic patients on therapy with beta-agonist on demand only, with normal lung function but increased FeNO were prescribed low dose steroids. Step up was performed irrespective of FeNO level if FEV1% predicted was <80% and/or there were severe symptoms over the last 4 weeks and/or beta-agonist use was ≥6 puffs over the last 14 days. If FeNO was raised in these patients, they received 2-week diary cards as well. Step down was performed if FEV1% predicted was ≥80% and there were no or mild symptoms over the last 4 weeks and betaagonist use was <6 puffs over the last 14 days and FeNO was ≤20 ppb.. Duration 6 months. Concurrent medication/care: Following a run-in period of 4 weeks participants were randomly assigned to a control group or a FeNO group at the first visit. The trail included five visits (6 weeks intervals) over a period of 6 months. **Treatment Steps** Low dose ICS: (2X 100 mcg fluticasone or 2x 200 mcg budesonide) Low dose ICS + leukotriene receptor agonists: (2x 100 mcg fluticasone or 2x 200 mcg budesonide + 5 mg montelukast once daily p.o. Low dose ICS + long acting betaagonist (2x 100 mcg fluticasone + 2x 50 mcg salmeterol or 2x 200 mcg Budesonide + 2x 12 mcg formeterol)

	High dose ICS + leukotriene receptor agonist (2x 250 mcg fluticasone or budesonide 2x 400 mcg + 1 daily 5 mg montelukast p.o.) High dose ICS + long acting beta-agonist (2x 250 mcg fluticasone + 2x 50 mcg salmeterol or 2x 400 mcg budesonide + 2x 12 mcg formeterol).
Population subgroups	**Strata** **Children or adults** Children **Population of current smokers (>20% vs ≤20%)** Not reported **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** Yes in FeNO group in certain circumstances (e.g., step up in treatment and elevated FeNO), no in usual care
Comparator	Treated considering parameters of asthma control (symptoms, short-acting beta agonist use, and lung function) recommended in current asthma guidelines. A step down in therapy was performed if FEV1 % predicted was ≥80% and there was no or mild symptoms over the last 4 weeks and beta agonist use was <6 puffs over the last 12 days. A step up was performed in every other case.

	Treatment Steps Low dose ICS: (2X 100 mcg fluticasone or 2x 200 mcg budesonide) Low dose ICS + leukotriene receptor agonists: (2x 100 mcg fluticasone or 2x 200 mcg budesonide + 5 mg montelukast once daily p.o. Low dose ICS + long acting betaagonist (2x 100 mcg fluticasone + 2x 50 mcg salmeterol or 2x 200 mcg Budesonide + 2x 12 mcg formeterol) High dose ICS + leukotriene receptor agonist (2x 250 mcg fluticasone or budesonide 2x 400 mcg + 1 daily 5 mg montelukast p.o.) High dose ICS + long acting beta-agonist (2x 250 mcg fluticasone + 2x 50 mcg salmeterol or 2x 400 mcg budesonide + 2x 12 mcg formeterol).
Number of participants	52 randomised, 47 completed 22 in FeNO monitoring group 25 in usual care group
Duration of follow-up	6 months
Indirectness	None
Additional comments	Complete case analysis

Study arms

FeNO monitoring (N = 22)

Usual care (N = 25)
Adjustment of treatment according to parameters of asthma control as recommended in a German consensus paper (1999)

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 22)	Usual care (N = 25)
% Female Sample size	n = 8 ; % = 36	n = 11 ; % = 44
Mean age (SD) Mean (SD)	11.3 (3.4)	12.1 (2.8)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 6 month

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 22	FeNO monitoring, 6 month, N = 22	Usual care, Baseline, N = 25	Usual care, 6 month, N = 25
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 2 ; % = 9	n = NA ; % = NA	n = 2 ; % = 8

Severe asthma exacerbations - Polarity - Lower values are better

Transform

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 22	FeNO monitoring, 6 month, N = 22	Usual care, Baseline, N = 25	Usual care, 6 month, N = 25
Severe asthma exacerbations final values	n = NA ; % = NA	n = 2 ; % = 9	n = NA ; % = NA	n = 2 ; % = 8

Outcome	FeNO monitoring, Baseline, N = 22	FeNO monitoring, 6 month, N = 22	Usual care, Baseline, N = 25	Usual care, 6 month, N = 25
No of events				

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Exacerbations (requiring oral steroid course)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Garg, 2020

Bibliographic Reference	Garg, Yadvir; Kakria, Neha; Katoch, C. D. S.; Bhattacharyya, D.; Exhaled nitric oxide as a guiding tool for bronchial asthma: A randomised controlled trial; Medical journal, Armed Forces India; 2020; vol. 76 (no. 1); 17-22

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Tertiary care
Study dates	No additional information
Sources of funding	Armed Forces Medical Research Committee Project No. 4385/2013 granted by the office of the Directorate General Armed Forces Medical Services and Defence Research Development Organization, Government of India.
Inclusion criteria	Patients aged 12–70 years who were diagnosed with Bronchial Asthma as per Global Initiative for Asthma (GINA) guidelines

Exclusion criteria	History of smoking, severe asthma cases, ≥ 2 exacerbations in preceding year, requiring oral prednisolone for asthma exacerbation in two months of pre-allocation period and pregnant females
Recruitment / selection of participants	No additional information
Intervention(s)	FeNO values were measured with an electrochemical analyzer (NO breath FeNO monitor; Bedfont Scientific Limited, Maidstone, United Kingdom) at an expiratory flow rate of 50 ml/s as per ATS/European Respiratory Society recommendation. Through out the study period Metered Dose Inhaler (MDI) Fluticasone propionate was used as standard ICS in strength of multiples of 125 µg/puff. ICS dose was stepwise upregulated or downregulated by 125 µg/daily, based on FeNO values as per ATS recommendations (2011). Increase in FeNO was considered as significant when it increased by greater than 20% for values over 50 ppb or more than 10 ppb for values lower than 50 ppb from one visit to the next. A significant response to anti-inflammatory medication was deemed as a reduction of at least 20% in FeNO for values over 50 ppb or more than 10 ppb for values lower than 50 ppb. ICS dose was increased for significant increase in FeNO and decreased for its significant fall.
Population subgroups	**Strata** **Children or adults** Adults **Population of current smokers (>20% vs ≤20%)** No current smokers included **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed

	Included adherence monitoring Yes in usual care, no in FeNO
Comparator	During the study period, dose adjustment of ICS in Group A (conventional therapy control group) was primarily based on clinical symptoms, signs and spirometry (FEV1). ICS dose adjustment was done as per step up-step down recommendations of GINA guidelines after reviewing the medication technique, compliance and avoidance of risk factors
Number of participants	100 randomised 50 in FeNO group 50 in usual care group
Duration of follow-up	12 months
Indirectness	None
Additional comments	No additional information

Study arms

FeNO monitoring (N = 50)

Usual care (N = 50)
GINA guided treatment strategy

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 50)	Usual care (N = 50)
% Female Sample size	n = 27 ; % = 54	n = 28 ; % = 56
Mean age (SD) Mean (SD)	40.96 (14.16)	38.28 (11.68)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 50	FeNO monitoring, 12 month, N = 50	Usual care, Baseline, N = 50	Usual care, 12 month, N = 50
Dose of regular asthma therapy (mean fluticasone dose) (µg/day) change scores Mean (SD)	NA (NA)	107.5 (121.14)	NA (NA)	75 (131.22)

Dose of regular asthma therapy (mean fluticasone dose) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 50	FeNO monitoring, 12 month, N = 50	Usual care, Baseline, N = 50	Usual care, 12 month, N = 50
Exacerbations (requiring oral prednisolone) final values, number of participants with one or more exacerbations No of events	n = NA ; % = NA	n = 13 ; % = 26	n = NA ; % = NA	n = 17 ; % = 34

Exacerbations (requiring oral prednisolone) - Polarity - Lower values are better

Transform

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 50	FeNO monitoring, 12 month, N = 50	Usual care, Baseline, N = 50	Usual care, 12 month, N = 50
Dose of regular asthma therapy (mean fluticasone dose) (µg/day) change scores Mean (SD)	NA (NA)	107.5 (121.14)	NA (NA)	75 (131.22)

Arm based : Data distribution : Not set

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 50	FeNO monitoring, 12 month, N = 50	Usual care, Baseline, N = 50	Usual care, 12 month, N = 50
Exacerbations (requiring oral prednisolone) final values, number of participants with one or more exacerbations No of events	n = NA ; % = NA	n = 13 ; % = 26	n = NA ; % = NA	n = 17 ; % = 34

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dose of regular asthma therapy (mean fluticasone dose, change scores)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Exacerbations (requiring oral prednisolone)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Honkoop, 2015

Bibliographic Reference	Honkoop, Persijn J.; Loijmans, Rik J. B.; Termeer, Evelien H.; Snoeck-Stroband, Jiska B.; van den Hout, Wilbert B.; Bakker, Moira J.; Assendelft, Willem J. J.; ter Riet, Gerben; Sterk, Peter J.; Schermer, Tjard R. J.; Sont, Jacob K.; Asthma Control Cost-Utility Randomized Trial Evaluation Study, Group; Symptom- and fraction of exhaled nitric oxide-driven strategies for asthma control: A cluster-randomized trial in primary care; The Journal of allergy and clinical immunology; 2015; vol. 135 (no. 3); 682-8.e11

Study details

Study type	Cluster randomised controlled trial
Duration of follow-up	

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information

Trial name / registration number	www.trialregister.nl (NTR 1756).
Study type	Cluster randomised controlled trial
Study location	The Netherlands
Study setting	Primary care
Study dates	September 2009 - January 2012
Sources of funding	Funded by the Netherlands Organization for Health Research and Development and the Netherlands Asthma Foundation and received nonfinancial support from Aerocrine. Authors held stock in Grace Bros and received consultancy fees from AstraZeneca, GlaxoSmithKline, and Novartis, as well as grant funding from ACME Pharmaceutical. Additionally have received research grants from Boehringer Ingelheim, GlaxoSmithKline, Chiesi, and Fonds NutsOhra (1101-081), as well as nonfinancial support from AstraZeneca (3.4.07.044).
Inclusion criteria	Aged 18 to 50 years, doctor-diagnosed asthma according to the Dutch national guidelines, a prescription for ICS for at least 3 months in the previous year, and asthma being managed in primary care.
Exclusion criteria	Significant comorbidity (at the general practitioner discretion), inability to understand Dutch, and a prescription for oral corticosteroids in the previous month
Recruitment / selection of participants	General practices from both rural and urban areas in The Netherlands were invited to participate
Intervention(s)	In all strategies, patients visited the practice nurse of their general practice every 3 months over the course of 1 year. During these visits, the practice nurse assessed current medication use and asthma control status by using the 7-item asthma control questionnaire that includes lung function. In addition, FeNO measurement was performed in the intervention group. Concurrent medication/care: At each visit, a patient's asthma control status was classified based on the ACQ: controlled (score ≤0.75), partly controlled (score 0.75 - 1.5), or uncontrolled (score>1.5) and additionally as 3 subcategories of FeNO: low/absence of airway inflammation (≤25 ppb), intermediate (26 - 50 ppb), and high/presence of airway inflammation (>50 ppb).

	Treatment Algorithm **Low FeNO (<25 ppb)** + asthma controlled (ACQ ≤0.75): step down, treatment choice open + asthma partly controlled (0.75 > ACQ ≤1.5): 3 mo: no change/change within current step to LABA, 6mo: step down to ICS + asthma uncontrolled (ACQ >1.5): 3 mo: step up LABA, 6mo: revise asthma diagnosis **Intermediate FeNO (25 -50 ppb)** + asthma controlled (ACQ ≤0.75): no change + asthma partly controlled (0.75 > ACQ ≤1.5): step up, treatment choice open + asthma uncontrolled (ACQ >1.5): step up, treatment choice open **High FeNO (>50 ppb)** = + asthma controlled (ACQ ≤0.75): step up/change within current step to ICS + asthma partly controlled (0.75 > ACQ ≤1.5): step up, 1 X ICS + asthma uncontrolled (ACQ >1.5): step up, 2 X ICS Current medication use and all measurements were entered into an online decision support tool, which subsequently automatically generated treatment advice based on the appropriate algorithm for each of the treatment strategies. Patients' current medication use was classified as an asthma treatment step ranging from 0 (only short -acting beta agonists) to 5 (oral prednisone) based on the US National Asthma Education and Prevention Program guideline. In the intervention arm, guidance was given as to adding/removing ICS and LABA at each treatment stage.

Population subgroups	**Strata** **Children or adults** Adults **Population of current smokers (>20% vs ≤20%)** <20% (13, 16 and 14% in treatment arms) **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** No
Comparator	In all strategies, patients visited the practice nurse of their general practice every 3 months over the course of 1 year. During these visits, the practice nurse assessed current medication use and asthma control status by using the 7-item asthma control questionnaire that includes lung function. At each visit, a patient's asthma control status was classified based on the ACQ: controlled (score ≤0.75), partly controlled (score 0.75 - 1.5), or uncontrolled (score >1.5). Two separate groups were present in the study, aiming at controlled and partly controlled asthma. **Controlled Asthma Treatment Algorithm** **ACQ**

	Controlled (score ≤0.75): 3mo: No change, 6mo: step down Partly controlled (score 0.75 - 1.5): step up, treatment choice open Uncontrolled (score >1.5): Step up, treatment choice open **Partly controlled Asthma Treatment Algorithm** **ACQ** Controlled (score ≤0.75): step down, treatment choice open Partly controlled (score 0.75 - 1.5): No change Uncontrolled (score >1.5): Step up, treatment choice open When treatment was to be adjusted, professionals and patients could choose any (combination of) type or types of asthma medication they preferred within a certain treatment step
Number of participants	647 randomised 232 (44 clusters) allocated to partly controlled group (219 analysed), 210 (43 clusters) allocated to controlled group (203 analysed), combined into 'Asthma control questionnaires' for analysis in this review (422 analysed) 205 (44 clusters) allocated to FeNO monitoring (189 analysed)
Duration of follow-up	12 months
Indirectness	None
Additional comments	ITT

Study arms

FeNO monitoring (N = 189)

Asthma control questionnaires (N = 422)
Combined two study arms aiming for 1) controlled asthma (2 partly controlled asthma

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 189)	Asthma control questionnaires (N = 422)
% Female Sample size	n = 137 ; % = 72.3	n = 284 ; % = 67.3
Mean age (SD) Mean (SD)	39.5 (9.3)	39.4 (9.6)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 189	FeNO monitoring, 12 month, N = 189	Asthma control questionnaires , Baseline, N = 422	Asthma control questionnaires , 12 month, N = 422
Asthma control questionnaires (Asthma Control Questionnaire-7) scale range: 0-6, final values Mean (SD)	0.99 (0.73)	0.78 (0.74)	1 (0.82)	0.8 (0.8)
Quality of life (Asthma Quality of Life Questionnaire) scale range: 1-7, final values Mean (SD)	NR (NR)	6 (1.05)	NR (NR)	5.95 (0.93)
Lung function (FEV1 % predicted) final values Mean (SD)	93.1 (17)	92.4 (17.18)	92.69 (17.11)	90.56 (80.04)
Dose or regular asthma therapy (Beclomethasone patient-reported mean daily use) (µg/day) final values	853 (642)	778 (722)	828 (672)	810 (752)

Outcome	FeNO monitoring, Baseline, N = 189	FeNO monitoring, 12 month, N = 189	Asthma control questionnaires , Baseline, N = 422	Asthma control questionnaires , 12 month, N = 422
Mean (SD)				

Asthma control questionnaires (Asthma Control Questionnaire-7) - Polarity - Lower values are better
Quality of life (Asthma Quality of Life Questionnaire) - Polarity - Higher values are better
Lung function (FEV1 % predicted) - Polarity - Higher values are better
Dose or regular asthma therapy (Beclomethasone patient-reported mean daily use) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 189	FeNO monitoring, 12 month, N = 189	Asthma control questionnaires , Baseline, N = 422	Asthma control questionnaires , 12 month, N = 422
Unscheduled healthcare utilisation (hospitalisation) final values No of events	n = NA ; % = NA	n = 1 ; % = 0.53	n = NA ; % = NA	n = 8 ; % = 1.9
Unscheduled healthcare utilisation (ED visits) final values No of events	n = NA ; % = NA	n = 2 ; % = 1.06	n = NA ; % = NA	n = 6 ; % = 1.42
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 34 ; % = 17.98	n = NA ; % = NA	n = 107 ; % = 25.36

Unscheduled healthcare utilisation (hospitalisation) - Polarity - Lower values are better
Unscheduled healthcare utilisation (ED visits) - Polarity - Lower values are better
Severe asthma exacerbations - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cluster randomised trials

Asthma control questionnaires (Asthma Control Questionnaire-7)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Subjective outcome measure assessed by participants with knowledge of the intervention received)*
Overall bias and Directness	Overall Directness	Directly applicable

Quality of life (Asthma Quality of Life Questionnaire)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Subjective outcome measure assessed by participants with knowledge of the intervention received)*
Overall bias and Directness	Overall Directness	Directly applicable

Lung function (FEV1 % predicted)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dose of regular asthma therapy (Beclomethasone patient-reported mean daily use)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Unscheduled healthcare utilisation (hospitalisation)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Unscheduled healthcare utilisation (ED visits)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Exacerbations (requiring oral prednisolone)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Morphew, 2019

Bibliographic Reference	Morphew, Tricia; Shin, Hye-Won; Marchese, Sara; Pires-Barracosa, Naomi; Galant, Stanley P.; Phenotypes favoring fractional exhaled nitric oxide discordance vs guideline-based uncontrolled asthma; Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology; 2019; vol. 123 (no. 2); 193-200

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Tertiary care
Study dates	No additional information
Sources of funding	Supported by a grant from Aerocrine (since acquired by Circassia Pharmaceuticals Inc). Primary author supported by an ongoing consultancy arrangement with Children's Hospital of Orange County (CHOC).
Inclusion criteria	Physician-diagnosed persistent asthma with moderate to high risk as defined by a history of 2 emergency room visits, 1 hospitalization, or 2 oral corticosteroid courses in the previous 12 months, receiving inhaled corticosteroids therapy for at

	least 3 months, atopy as defined by positive skin prick test to 1 or more allergens (dog, cat, feather, cockroach, mites, mold mix, tree mix, weed mix, and grass mix) in the CHOC Breathmobile clinic and receiving Medicaid insurance.
Exclusion criteria	Other lung disease, a record of poor adherence documented in the clinical notes, and inability to take inhaled corticosteroids or bronchodilators
Recruitment / selection of participants	A list of eligible patients was provided by CHOC Health Alliance (Medicaid program).
Intervention(s)	The FeNO levels were measured using an FDA-approved handheld nitric oxide analyzer (NIOX VERO, Circassia Pharmaceuticals Inc [formerly Aerocrine]). Using the American Thoracic Society (ATS) guidelines for children younger than 12 years, FeNO levels were categorized as low, <20 ppb; intermediate, 20 to 35 ppb; or high, >35 ppb. Consideration of ICS titration was based on the worst level of control determined by both NHBLI guidelines (very poorly controlled, not well controlled, or well controlled) and corresponding FeNO guidelines (high, intermediate, or low). The FeNO levels were also monitored in the control group but were not available to the provider. In assessment of discord between FeNO and NHLBI guidelines determined asthma control, FeNO level greater than 35 ppb was applied as an indicator of uncontrolled asthma.
Population subgroups	**Strata** **Children or adults** Children **Population of current smokers (>20% vs ≤20%)** Not reported **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed

	Included adherence monitoring Yes
Comparator	Therapeutic decisions for step up, no change, or step down of controller therapy were based on NHLBI guideline impairment and risk domains appropriate for age, ACT for those ≥12 years of age, and cACT for 7- to 11-year-olds. Adherence to controller therapy was determined by the provider based on self-reported use of greater than or equal to 5 days per week. Uncontrolled asthma was defined by ACT greater than 20, and by NHLBI guidelines as any of the following events: day symptoms (>2 d/wk), night symptoms (>1/month), limitations with normal activities, short-acting beta 2 agonists (SABA) use for symptom control (>2 d/wk), oral corticosteroid (OCS) use (≥1/yr), and age- and performance-dependent additional criteria of FEV1 of 80% or greater than predicted and FEV1/FVC of 80% or less.
Number of participants	88 randomised 46 in FeNO group 42 in usual care group
Duration of follow-up	1-year
Indirectness	None
Additional comments	Not reported

Study arms

FeNO monitoring (N = 46)

Usual care (N = 42)
National Heart, Lung, and Blood Institute (NHLBI) guideline algorithm

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 46)	Usual care (N = 42)
% Female Sample size	n = 15 ; % = 32.6	n = 21 ; % = 50
Mean age (SD) Mean (SD)	11.2 (2.9)	10.3 (2.5)
Ethnicity % Hispanic Sample size	n = 44 ; % = 95.7	n = 38 ; % = 90.5
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 1 year

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 46	FeNO monitoring, 1 year, N = 46	Usual care, Baseline, N = 42	Usual care, 1 year, N = 42
Unscheduled healthcare utilisation (hospitalisation) final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Unscheduled healthcare utilisation (ED visits) final values No of events	n = NA ; % = NA	n = 3 ; % = 6.5	n = NA ; % = NA	n = 5 ; % = 11.9
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 9 ; % = 19.6	n = NA ; % = NA	n = 11 ; % = 26.2
Time off school or work (number with any school days missed) final values No of events	n = NA ; % = NA	n = 10 ; % = 21.7	n = NA ; % = NA	n = 12 ; % = 28.6

Unscheduled healthcare utilisation (hospitalisation) - Polarity - Lower values are better
Unscheduled healthcare utilisation (ED visits) - Polarity - Lower values are better
Severe asthma exacerbations - Polarity - Lower values are better
Time off school or work (number with any school days missed) - Polarity - Lower values are better

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 46	FeNO monitoring, 1 year, N = 46	Usual care, Baseline, N = 42	Usual care, 1 year, N = 42
Dose of regular asthma therapy (ICS dose/day) (µg/day) Mean (95% CI)	NR (NR to NR)	333 (326 to 340)	NR (NR to NR)	280 (273 to 287)

Dose of regular asthma therapy (ICS dose/day) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 46	FeNO monitoring, 1 year, N = 46	Usual care, Baseline, N = 42	Usual care, 1 year, N = 42
Unscheduled healthcare utilisation (hospitalisation) final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Unscheduled healthcare utilisation (ED visits) final values No of events	n = NA ; % = NA	n = 3 ; % = 6.5	n = NA ; % = NA	n = 5 ; % = 11.9
Severe asthma exacerbations final values	n = NA ; % = NA	n = 9 ; % = 19.6	n = NA ; % = NA	n = 11 ; % = 26.2

Outcome	FeNO monitoring, Baseline, N = 46	FeNO monitoring, 1 year, N = 46	Usual care, Baseline, N = 42	Usual care, 1 year, N = 42
No of events				
Time off school or work (number with any school days missed) final values No of events	n = NA ; % = NA	n = 10 ; % = 21.7	n = NA ; % = NA	n = 12 ; % = 28.6

Arm based : Data distribution : Not set

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 46	FeNO monitoring, 1 year, N = 46	Usual care, Baseline, N = 42	Usual care, 1 year, N = 42
Dose of regular asthma therapy (ICS dose/day) (µg/day) Mean (95% CI)	NR (NR to NR)	333 (326 to 340)	NR (NR to NR)	280 (273 to 287)
Data transformations	Mean/SD not calculated from Mean/95% CI - empty data	Mean/SD not calculated from Mean/95% CI - no distribution type set	Mean/SD not calculated from Mean/95% CI - empty data	Mean/SD not calculated from Mean/95% CI - no distribution type set

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Unscheduled healthcare utilisation (hospitalisation)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes-Unscheduled healthcare utilisation (ED visits)- No Of Events-FeNO monitoring-Usual care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes -Severe asthma exacerbations -No Of Events-FeNO monitoring-Usual care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes-Time off school or work (number with any school days missed)- No Of Events - FeNO monitoring- Usual care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes-Dose of regular asthma therapy(ICSdose/day)-Mean Nine Five Percent CI -FeNO monitoring- Usual care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Murphy, 2022

Bibliographic Reference	Murphy, Vanessa E; Jensen, Megan E; Holliday, Elizabeth G; Giles, Warwick B; Barrett, Helen L; Callaway, Leonie K; Bisits, Andrew; Peek, Michael J; Seeho, Sean K; Abbott, Alistair; Robijn, Annelies L; Colditz, Paul B; Searles, Andrew; Attia, John; McCaffery, Kirsten; Hensley, Michael J; Mattes, Joerg; Gibson, Peter G; Effect of asthma management with exhaled nitric oxide versus usual care on perinatal outcomes.; The European respiratory journal; 2022; vol. 60 (no. 5)

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	ACTRN12613000202763
Study type	Randomised controlled trial (RCT)
Study location	Australia
Study setting	Antenatal clinics
Study dates	March 2013 - June 2019
Sources of funding	Funding received from The National Health and Medical Research Council of Australia, University of Newcastle, John Hunter Hospital Charitable Trust, Hunter Medical Research Institute, Singleton Foundation and the Woodend Foundation

Inclusion criteria	Doctor-diagnosed asthma Symptoms of asthma and/or asthma medication use in the past 12 months Aged ⩾18 years Between 12 and <23 weeks gestation at randomisation
Exclusion criteria	Chronic lung disease other than asthma Use of oral corticosteroids for >14 days in the past 3 months Concomitant chronic illness which may affect participation Inability to perform FENO or spirometry Drug or alcohol dependence
Recruitment / selection of participants	No additional information
Intervention(s)	In both groups, brief asthma self-management education was provided by the research nurse/midwife, including assessment and correction of inhaler technique, assessment and discussion of medication knowledge, assessment of written asthma action plan and discussion of asthma triggers. A consumer-focused pamphlet on asthma in pregnancy was provided. A letter to the woman's general practitioner informed them of the woman's participation in the trial and women in both groups continued with separate and usual antenatal care. Women randomised to the intervention group also received FENO-based asthma management for the remainder of pregnancy. Women attended visits every 3–6 weeks during pregnancy aligned with antenatal appointments, where self-management education was reinforced, and asthma control, lung function and FENO assessed. Asthma treatment was adjusted at the first visit, and every second visit thereafter (every 6– 12 weeks). Women received an equivalent dose of budesonide or budesonide/eformoterol. FENO was used to adjust ICS dose (when levels were above the high cut-point,

	ICS dose was increased, while ICS dose was decreased when levels were below the low cut-point), while LABA was added when symptoms based on the ACQ (ACQ7/ACQ6 >1.5) remained uncontrolled, unless FENO was high, when only the ICS dose was adjusted. A custom mobile application allowed algorithm application in the clinical setting using an iPad.
Population subgroups	**Strata** **Children or adults** Adults **Proportion of current smokers (>20 vs ≤20%)** ≤20% **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed
Comparator	In both groups, brief asthma self-management education was provided by the research nurse/midwife, including assessment and correction of inhaler technique, assessment and discussion of medication knowledge, assessment of written asthma action plan and discussion of asthma triggers. A consumer-focused pamphlet on asthma in pregnancy was provided. A letter to the woman's general practitioner informed them of the woman's participation in the trial and women in both groups continued with separate and usual antenatal care.
Number of participants	1200 randomised 601 allocated to FeNO monitoring, 511 completed 599 allocated to usual care, 523 completed

Duration of follow-up	Not reported, mean gestational age was 18.7 weeks and participants were followed-up 2-6 weeks post-partum
Indirectness	None
Additional comments	Intention to treat and complete case analysis assuming data missing completely at random

Study arms

FeNO monitoring (N = 554)
Treatment adjusted based on FeNO levels and ACQ score

Usual care (N = 543)

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 554)	Usual care (N = 543)
% Female Sample size	n = 601 ; % = 100	n = 599 ; % = 100
Mean age (SD) Mean (SD)	30.2 (5.4)	30.4 (5.5)

Characteristic	FeNO monitoring (N = 554)	Usual care (N = 543)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
European Sample size	n = 477 ; % = 80	n = 473 ; % = 82
Aboriginal or Torres Strait Islander Sample size	n = 31 ; % = 5.2	n = 27 ; % = 4.7
Maori/Polynesian Sample size	n = 11 ; % = 1.9	n = 11 ; % = 1.9
Indian/Pakistani Sample size	n = 9 ; % = 1.5	n = 2 ; % = 0.3
Asian Sample size	n = 21 ; % = 3.5	n = 20 ; % = 3.4
African Sample size	n = 4 ; % = 0.7	n = 3 ; % = 0.5
Other Sample size	n = 41 ; % = 6.9	n = 44 ; % = 7.6
Comorbidities Nominal	NA	NA

Characteristic	FeNO monitoring (N = 554)	Usual care (N = 543)
Current smokers Sample size	n = 80 ; % = 13	n = 74 ; % = 12
Lung function (% of predicted) FEV1 Mean (SD)	89.6 (13.4)	89.3 (14.1)
ICS dose (µg/day) Mean (range) BDP equivalent Nominal	400	400
ICS dose (µg/day) Mean (range) BDP equivalent Range	200 to 500	250 to 800
GINA asthma control classification Sample size	n = NA ; % = NA	n = NA ; % = NA
Well controlled Sample size	n = 116 ; % = 19	n = 132 ; % = 23
Partly controlled Sample size	n = 262 ; % = 44	n = 253 ; % = 44
Uncontrolled Sample size	n = 219 ; % = 37	n = 184 ; % = 32

Outcomes

Study timepoints

- Baseline
- End of follow-up

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 554	FeNO monitoring, End of follow-up, N = 554	Usual care, Baseline, N = 543	Usual care, End of follow-up, N = 543
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 89 ; % = 16.1	n = NA ; % = NA	n = 104 ; % = 19.2
Unscheduled health utilisation (hospitalisation) Final values No of events	n = NA ; % = NA	n = 6 ; % = 1.1	n = NA ; % = NA	n = 6 ; % = 1.1
Unscheduled health utilisation (hospital/ED presentation) Final values No of events	n = NA ; % = NA	n = 30 ; % = 5.4	n = NA ; % = NA	n = 25 ; % = 4.6

Severe asthma exacerbations - Polarity - Lower values are better
Unscheduled health utilisation (hospitalisation) - Polarity - Lower values are better
Unscheduled health utilisation (hospital/ED presentation) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous Outcomes – Severe asthma exacerbations – No Of Events-FeNO monitoring-Usual care-tEnd of follow-up

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Unscheduled health utilisation (hospitalisation)- No Of Events - FeNO monitoring-Usual care-tEnd of follow-up

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Unscheduledhealthutilisation(hospital/EDpresentation)-NoOfEvents-FeNO monitoring-Usual care-tEndoffollow-up

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Peirsman, 2014

Bibliographic Reference	Peirsman, Eva J.; Carvelli, Thierry J.; Hage, Pierre Y.; Hanssens, Laurence S.; Pattyn, Luc; Raes, Marc M.; Sauer, Kate A.; Vermeulen, Francoise; Desager, Kristine N.; Exhaled nitric oxide in childhood allergic asthma management: a randomised controlled trial; Pediatric pulmonology; 2014; vol. 49 (no. 7); 624-31

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Clinicaltrials.gov: NCT00562991.
Study type	Randomised controlled trial (RCT)
Study location	Belgium
Study setting	Secondary care
Study dates	October 2007 - November 2009
Sources of funding	Supported in part by a research grant from the Investigator Initiated Studies Program of Merck & Co., Inc. NO analysers used in this study were provided by Aerocrine, Solna, Sweden
Inclusion criteria	Mild to severe persistent asthma according to GINA guidelines, for a period of at least 6 months, and allergic sensitization (i.e., a positive skin prick test and/or specific IgE antibodies against inhalant allergens)

Exclusion criteria	Significant comorbidity, an acute exacerbation or the administration of experimental medication 4 weeks prior to the screening visit, hospitalization and/or systemic corticosteroids 12 weeks prior to the screening visit or oral corticosteroid dependence
Recruitment / selection of participants	Patients were selected from 7 Belgian hospitals
Intervention(s)	FeNO measurements were primarily used to adjust the treatment. The treatment goal was to keep FeNO <20 ppb. FeNO measurements were conducted at a constant flow of 50 ml/sec using the single-breath online technique with the FeNO analyser NIOX MINO; Aerocrine, Solna, Sweden **Treatment algorithms** **FeNO ≤20 ppb and controlled** ICS (dosage in budesonide or equivalent): ICS step down by 100 mcg/day, if below 100 mcg/day --> stop ICS and add LTRA LTRA: maintain ICS+LTRA: ICS step down by 100 mcg/day, if below 100 mcg/day --> stop ICS ICS+LABA: Stop LABA **FeNO ≤20 ppb and partly controlled or uncontrolled** ICS (dosage in budesonide or equivalent): Consider adding LTRA LTRA: Consider adding ICS at 100 mcg/day (maximum of 200 mcg/day)

	ICS+LTRA: Consider ICS step up by 100 mcg/day (maximum of 400 mcg/day, then add LABA) ICS+LABA: Consider adding LTRA **FeNO >20 ppb, regardless of symptoms** ICS (dosage in budesonide or equivalent): Add LTRA LTRA: Add ICS at 100 mcg/day (maximum of 200 mcg/day) ICS+LTRA: Step up ICS by 100 mcg/day (maximum of 400 mcg/day, then add LABA) ICS+LABA: Replace LABA with LTRA
Population subgroups	**Strata** **Children or adults** Children **Population of current smokers (>20% vs ≤20%)** Not reported **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed

	Included adherence monitoring No
Comparator	Asthma control and treatment adjustments during each visit were determined by the reporting of symptoms (i.e., limitation of activities, daytime and nocturnal symptoms), the need for rescue treatment during the two preceding weeks and spirometry (FEV1), based on the GINA guidelines. **Treatment algorithms** **Controlled asthma** ICS (dosage in budesonide or equivalent): ICS step down by 100 mcg/day, if below 100 mcg/day --> stop ICS and add LTRA LTRA: maintain ICS+LTRA: ICS step down by 100 mcg/day, if below 100 mcg/day --> stop ICS ICS+LABA: Stop LABA **Partly controlled asthma** ICS (dosage in budesonide or equivalent): Consider adding LTRA LTRA: Consider adding ICS at 100 mcg/day (maximum of 200 mcg/day) ICS+LTRA: Consider ICS step up by 100 mcg/day (maximum of 400 mcg/day, then add LABA) ICS+LABA: Consider adding LTRA

	Uncontrolled asthma ICS (dosage in budesonide or equivalent): Add LTRA LTRA: Add ICS at 100 mcg/day (maximum of 200 mcg/day) ICS+LTRA: Step up ICS by 100 mcg/day (maximum of 400 mcg/day, then add LABA) ICS+LABA: Replace LABA with LTRA
Number of participants	99 randomised 50 allocated to usual care group (46 completed) 49 allocated to FeNO monitoring (47 completed)
Duration of follow-up	1-year
Indirectness	None
Additional comments	Not reported

Study arms

FeNO monitoring (N = 49)

Usual care (N = 50)
Adjustment to treatment based on symptoms, need for rescue treatment and FEV1 based on GINA guidelines

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 49)	Usual care (N = 50)
% Female Sample size	n = 16 ; % = 33	n = 17 ; % = 34
Mean age (SD) Mean (SD)	10.6 (2.2)	10.7 (2.1)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 1 year

Continuous Outcomes

Outcome	FeNO monitoring , Baseline, N = 49	FeNO monitoring , 1 year, N = 47	Usual care, Baseline, N = 50	Usual care, 1 year, N = 46
Lung function (FEV1 % predicted) final values Mean (SD)	92.9 (12.2)	93.9 (15.5)	89 (16.2)	91.2 (12.3)

Lung function (FEV1 % predicted) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	FeNO monitoring , Baseline, N = 49	FeNO monitoring , 1 year, N = 49	Usual care, Baseline, N = 50	Usual care, 1 year, N = 50
Unscheduled healthcare utilisation (number of children who had ≥1 ED visits) final values (FeNO n=45, UC n=46) No of events	n = NA ; % = NA	n = 2 ; % = 4.4	n = NA ; % = NA	n = 4 ; % = 8.7
Unscheduled healthcare utilisation (number of children who had ≥1 hospitalisation) final values (FeNO n=43, UC n=43) No of events	n = NA ; % = NA	n = 1 ; % = 2.3	n = NA ; % = NA	n = 1 ; % = 2.3
Time off school (number of children who missed school over 1-year) final values (FeNO n=46, UC n=46) No of events	n = NA ; % = NA	n = 10 ; % = 21.7	n = NA ; % = NA	n = 12 ; % = 26.1

Outcome	FeNO monitoring , Baseline, N = 49	FeNO monitoring , 1 year, N = 49	Usual care, Baseline, N = 50	Usual care, 1 year, N = 50
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 2 ; % = 4.1	n = NA ; % = NA	n = 3 ; % = 6

Unscheduled healthcare utilisation (number of children who had ≥1 ED visits) - Polarity - Lower values are better
Unscheduled healthcare utilisation (number of children who had ≥1 hospitalisation) - Polarity - Lower values are better
Time off school (number of children who missed school over 1-year) - Polarity - Lower values are better
Severe asthma exacerbations - Polarity - Lower values are better

Continuous Outcomes

Outcome	FeNO monitoring , Baseline, N = 49	FeNO monitoring , 1 year, N = 47	Usual care, Baseline, N = 50	Usual care, 1 year, N = 46
Lung function (FEV1 % predicted) final values Mean (SD)	92.9 (12.2)	93.9 (15.5)	89 (16.2)	91.2 (12.3)

Arm based : Data distribution : Not set

Dichotomous Outcomes

Outcome	FeNO monitoring , Baseline, N = 49	FeNO monitoring , 1 year, N = 49	Usual care, Baseline, N = 50	Usual care, 1 year, N = 50
Unscheduled healthcare utilisation (number of children who had ≥1 ED visits) final values (FeNO n=45, UC n=46) No of events	n = NA ; % = NA	n = 2 ; % = 4.4	n = NA ; % = NA	n = 4 ; % = 8.7
Unscheduled healthcare utilisation (number of children who had ≥1 hospitalisation) final values (FeNO n=43, UC n=43) No of events	n = NA ; % = NA	n = 1 ; % = 2.3	n = NA ; % = NA	n = 1 ; % = 2.3
Time off school (number of children who missed school over 1-year) final values (FeNO n=46, UC n=46) No of events	n = NA ; % = NA	n = 10 ; % = 21.7	n = NA ; % = NA	n = 12 ; % = 26.1
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 2 ; % = 4.1	n = NA ; % = NA	n = 3 ; % = 6

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Unscheduled healthcare utilisation (number of children who had ≥1 ED visits)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (FEV1%predicted)- Mean SD - FeNO monitoring -Usual care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Unscheduled healthcare utilisation (number of children who had ≥ 1 hospitalisation)-No Of Events-FeNO monitoring -Usual care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes-Time off school (number of children who missed school over 1- year)- No Of Events - FeNO monitoring -Usual care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations – No Of Events - FeNO monitoring -Usual care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Petsky, 2015

Bibliographic Reference	Petsky, Helen L.; Li, Albert M.; Au, Chun T.; Kynaston, Jennifer A.; Turner, Catherine; Chang, Anne B.; Management based on exhaled nitric oxide levels adjusted for atopy reduces asthma exacerbations in children: A dual centre randomized controlled trial; Pediatric pulmonology; 2015; vol. 50 (no. 6); 535-43

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Australia New Zealand Clinical Trials Registry (ACTRN012605000321640
Study type	Randomised controlled trial (RCT)
Study location	Australia and China
Study setting	Secondary care
Study dates	February 2006 - April 2008
Sources of funding	Funded by Asthma Foundation of Queensland 2008 and Royal Children's Hospital Foundation. AstraZeneca and GlaxoSmithKline supplied the medications. Authors are supported by the NHMRC (grant number 545216) and a QCMRI program grant

Inclusion criteria	Children aged >4 years with persistent asthma, prescribed anti-inflammatory asthma treatment, and receiving their care primarily through the clinical service at Royal Children's Hospital, Brisbane or Prince of Wales Hospital, Hong Kong
Exclusion criteria	Children who had underlying cardio-respiratory illness such as bronchiectasis or tracheomalacia, inability to take ICS or long acting beta-2-agonists (LABA) or previous poor adherence to medications
Recruitment / selection of participants	Children receiving their care at the participating hospitals were recruited
Intervention(s)	Management based on FeNO levels and atopic status. If FeNO was low for two consecutive visits, medications were stepped down. Elevated FeNO was defined as ≥10ppb in children with no positive skin prick test (SPT), ≥12ppb in children with one positive SPT, and ≥20ppb in children with ≥2 positive SPT. Treatment steps were modified from the Australian National Asthma Council guidelines and GINA guidelines.
Population subgroups	**Strata** **Children or adults** Children **Population of current smokers (>20% vs ≤20%)** Not reported **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** Yes

Comparator	Management based on clinical symptoms. Treatment decisions were made on symptoms as recorded on the asthma symptom diary card. Control was considered inadequate and treatment increased if scores increased by more than or equal to 15% since the previous visit. Treatment was stepped down if the child's scores totaled <10 in recent week. Treatment steps were modified from the Australian National Asthma Council guidelines and GINA guidelines.
Number of participants	63 randomised 31 allocated to FeNO monitoring group, 27 completed 32 allocated to usual care group, 28 completed
Duration of follow-up	12 months
Indirectness	None
Additional comments	ITT

Study arms

FeNO monitoring (N = 31)

Usual care (N = 32)

Treatment adjusted based on asthma diary card that monitored symptoms

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 31)	Usual care (N = 32)
% Female Sample size	n = 13 ; % = 41.94	n = 19 ; % = 59.38
Mean age (SD) Median (IQR)	10.17 (6.56 to 12.69)	10.08 (6.25 to 12.44)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 31	FeNO monitoring, 12 month, N = 31	Usual care, Baseline, N = 32	Usual care, 12 month, N = 32
Unscheduled healthcare utilisation (hospitalisation) final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 6 ; % = 19.35	n = NA ; % = NA	n = 15 ; % = 46.88

Unscheduled healthcare utilisation (hospitalisation) - Polarity - Lower values are better
Severe asthma exacerbations - Polarity - Lower values are better

Transform

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 31	FeNO monitoring, 12 month, N = 31	Usual care, Baseline, N = 32	Usual care, 12 month, N = 32
Unscheduled healthcare utilisation (hospitalisation) final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Outcome	FeNO monitoring, Baseline, N = 31	FeNO monitoring, 12 month, N = 31	Usual care, Baseline, N = 32	Usual care, 12 month, N = 32
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 6 ; % = 19.35	n = NA ; % = NA	n = 15 ; % = 46.88

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Unscheduled healthcare utilisation (hospitalisation)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Exacerbations (number of children that had ≥1 course of oral corticosteroids)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Pijnenburg, 2005

Bibliographic Reference	Pijnenburg, Marielle W.; Bakker, E. Marije; Hop, Wim C.; De Jongste, Johan C.; Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial; American journal of respiratory and critical care medicine; 2005; vol. 172 (no. 7); 831-6

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	Secondary care
Study dates	Not reported
Sources of funding	Department of Paediatrics at Erasmus University has received research grants and payments for consultancy services from Aerocrine (manufacturer of NO analyser)
Inclusion criteria	Children aged 6-18 years with atopic asthma, defined as RAST class 2 or higher for at least 1 airborne allergen, and using a constant dose of ICS for at least 3 months prior to the study

Exclusion criteria	None reported
Recruitment / selection of participants	Children were recruited from the outpatient clinic of Erasmus MC - Sophia Children's Hospital. Children were randomly allocated to 1 of 2 groups stratified for baseline FeNO (≥30 or < 30 ppb) and ICS dose (≥400 or < 400 µg budesonide or equivalent daily)
Intervention(s)	FeNO was measured according to ERS/ ATS guidelines. Patients performed 3 on-line maneuvers on the NIOX NO-analyzer (Aerocrine, Solna, Sweden) and the mean of these 3 measurements was recorded. Symptom scores were obtained from diary cards. Coughing, wheezing and dyspnoea were scored twice daily (day and night) on a four-point scale (0-3), with 3 as a maximal score. The maximum possible 2-weekly cumulative symptom score therefore was 252 (maximal daily score of 18). Cut-off for dose adaptation was a 2-weekly cumulative score of 14 or higher. Beta-2 agonist use was recorded daily. **Treatment algorithm** FeNO >30 ppb, regardless of symptoms = ⇑ ICS FeNO ≤30 ppb and symptoms >14 = No change FeNO ≤30 ppb and symptoms ≤14 = ⇓ ICS Step-up/down of ICS dose was dependent upon starting dose: Initial dose: 100µg, increase if indicated = 100µg, decrease if indicated = 100µg Initial dose: 200µg, increase if indicated = 200µg, decrease if indicated = 100µg Initial dose: 400µg, increase if indicated = 400µg, decrease if indicated = 200µg

	Initial dose: 500µg, increase if indicated = 500µg, decrease if indicated = 250µg Initial dose: 800µg, increase if indicated = 400µg, decrease if indicated = 400µg Initial dose: 1000µg, increase if indicated = 500µg, decrease if indicated = 500µg Initial dose: 1200µg, increase if indicated = 400µg, decrease if indicated = 400µg Initial dose: 1600µg, increase if indicated = 400µg, decrease if indicated = 400µg Initial dose: 2000µg (maximum dose), increase if indicated = 0µg, decrease if indicated = 1000µg
Population subgroups	**Strata** **Children or adults** Children **Population of current smokers (>20% vs ≤20%)** Not reported **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** Mixed, in patients using dry powder fluticasone or fluticasone/salmeterol yes, in all others no

Comparator	Symptom scores were obtained from diary cards. Coughing, wheezing and dyspnoea were scored twice daily (day and night) on a four-point scale (0-3), with 3 as a maximal score. The maximum possible 2-weekly cumulative symptom score therefore was 252 (maximal daily score of 18). Cut-off for dose adaptation was a 2-weekly cumulative score of 14 or higher. Beta-2 agonist use was recorded daily. **Treatment algorithm** Symptoms >14 = ⇑ ICS Symptoms ≤14 (first time) = No change Symptoms ≤14 (second time) = ⇓ ICS Step-up/down of ICS dose was dependent upon starting dose: Initial dose: 100µg, increase if indicated = 100µg, decrease if indicated = 100µg Initial dose: 200µg, increase if indicated = 200µg, decrease if indicated = 100µg Initial dose: 400µg, increase if indicated = 400µg, decrease if indicated = 200µg Initial dose: 500µg, increase if indicated = 500µg, decrease if indicated = 250µg Initial dose: 800µg, increase if indicated = 400µg, decrease if indicated = 400µg Initial dose: 1000µg, increase if indicated = 500µg, decrease if indicated = 500µg Initial dose: 1200µg, increase if indicated = 400µg, decrease if indicated = 400µg

	Initial dose: 1600µg, increase if indicated = 400µg, decrease if indicated = 400µg Initial dose: 2000µg (maximum dose), increase if indicated = 0µg, decrease if indicated = 1000µg
Number of participants	89 randomised 42 allocated to FeNO monitoring group, 39 completed 47 allocated to symptom monitoring group, 46 completed
Duration of follow-up	1-year
Indirectness	None
Additional comments	Complete case analysis

Study arms

FeNO monitoring (N = 39)
Treatment adjustment was influenced by FeNO and symptoms

Usual care (N = 46)
Treatment adjustment was influenced only by symptoms

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 39)	Usual care (N = 46)
% Female Sample size	n = 14 ; % = 36	n = 16 ; % = 35
Mean age (SD) Mean (SD)	11.9 (2.9)	12.6 (2.8)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 3 month
- 12 month

Continuous Outcomes

Outcome	FeNO monitoring , Baseline, N = 39	FeNO monitoring , 3 month, N = 39	FeNO monitoring , 12 month, N = 39	Usual care, Baseline, N = 46	Usual care, 3 month, N = 46	Usual care, 12 month, N = 46
Dose of regular asthma therapy (ICS dose) (µg/day) change scores Mean (SD)	NA (NA)	169 (285)	NR (NR)	NA (NA)	172 (275)	NR (NR)

Dose of regular asthma therapy (ICS dose) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	FeNO monitoring , Baseline, N = 39	FeNO monitoring , 3 month, N = 39	FeNO monitoring , 12 month, N = 39	Usual care, Baseline, N = 46	Usual care, 3 month, N = 46	Usual care, 12 month, N = 46
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = NR ; % = NR	n = 7 ; % = 18	n = NA ; % = NA	n = NR ; % = NR	n = 10 ; % = 22

Severe asthma exacerbations - Polarity - Lower values are better

Continuous Outcomes

Outcome	FeNO monitoring , Baseline, N = 39	FeNO monitoring , 3 month, N = 39	FeNO monitoring , 12 month, N = 39	Usual care, Baseline, N = 46	Usual care, 3 month, N = 46	Usual care, 12 month, N = 46
Dose of regular asthma therapy (ICS dose) (µg/day) change scores Mean (SD)	NA (NA)	169 (285)	NR (NR)	NA (NA)	172 (275)	NR (NR)

Arm based : Data distribution : Not set

Dichotomous Outcomes

Outcome	FeNO monitoring , Baseline, N = 39	FeNO monitoring , 3 month, N = 39	FeNO monitoring , 12 month, N = 39	Usual care, Baseline, N = 46	Usual care, 3 month, N = 46	Usual care, 12 month, N = 46
Severe asthma exacerbations final values No of events	*empty data*	*empty data*	n = 7 ; % = 18	*empty data*	*empty data*	n = 10 ; % = 22

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dose of regular asthma therapy (ICS dose)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Exacerbations (number of children with course of oral prednisone prescribed)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Pike, 2013

Bibliographic Reference	Pike, Katharine; Selby, Anna; Price, Sophie; Warner, John; Connett, Gary; Legg, Julian; Lucas, Jane S. A.; Peters, Sheila; Buckley, Hannah; Magier, Krzysztof; Foote, Keith; Drew, Kirsty; Morris, Ruth; Lancaster, Nikki; Roberts, Graham; Exhaled nitric oxide monitoring does not reduce exacerbation frequency or inhaled corticosteroid dose in paediatric asthma: a randomised controlled trial; The clinical respiratory journal; 2013; vol. 7 (no. 2); 204-13

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Secondary care
Study dates	Not reported
Sources of funding	Funding for the study was provided by Sparks

Inclusion criteria	Aged 6-17 years, clinical diagnosis of asthma and treatment with ≥400 mcg/day beclomethasone/budesonide or ≥200 mcg/day fluticasone. Asthma diagnosis was based upon a history of typical symptoms, ≥15% increase in forced expiratory volume in 1 second (FEV1) with bronchodilator or diurnal peak expiratory flow (PEF) variability ≥15%
Exclusion criteria	Inability to perform spirometry or FeNO measurement, cigarette smoking, poor treatment adherence, life-threatening exacerbation or need for maintenance oral prednisolone
Recruitment / selection of participants	Participants were recruited from outpatient clinics at Southampton University Hospital, St Mary's Hospital, Portsmouth, St Mary's Hospital, Isle of Wight and the Royal Hampshire County Hospital, Winchester
Intervention(s)	At each visit, a single measure of FeNO (blinded to the patient, family and assessing clinician) was taken by a research nurse according to ATS/ERS guidelines, using a portable monitor (NIOX MINO; Aerocrine, Solna, Sweden). Therapy decisions were taken by a clinician independent of participant assessment following a simple algorithm reflecting symptom control for standard management subjects, and FeNO measurements in addition to symptom control for the FENO group. ICS was decreased if FENO ≤15ppb and symptoms were controlled or well controlled for 3 months. Where asthma was poorly controlled and FeNO was <25ppb, long-acting beta-agonist (LABA) therapy was maximised before ICS were increase. ICS was increased if FeNO ≥25ppb or FeNO doubled from baseline. If FeNO remained raised after increasing by two SIGN/BTS steps, ICS was not further increased unless participants were poorly controlled. **Treatment algorithm** FeNO ≥25 ppb or more than twice baseline + poorly controlled asthma = Increase ICS or add LTRA if already at BTS/SIGN Step 4. If after increasing by 2 Steps FeNO remains high, do not increase therapy further FeNO ≥25 ppb or more than twice baseline + controlled/well controlled asthma = Increase ICS or add LTRA if already at BTS/SIGN Step 4 FeNO >15 and <25 ppb + poorly controlled asthma = Increase LABA therapy. If LABA at maximum dose, increase ICS or add LTRA if already at BTS/SIGN Step 4 FeNO >15 and <25 ppb + controlled/well controlled asthma = Continue current treatment

	FeNO ≤15 ppb + poorly controlled asthma = Increase LABA. If LABA at maximum dose, increase ICS of add LTRA if already at BTS/SIGN Step 4 FeNO ≤15 ppb + controlled/well controlled asthma = If asthma controlled for 3 months, reduce ICS. If dose ≤400 mcg, reduce LABA **Treatment steps** 1 No inhaled corticosteroid 2 Beclometasone 50mcg twice a day via spacer Budesonide 50mcg twice a day via spacer (or turbohaler) Fluticasone 50mcg once a day via spacer (or accuhaler) 3 Beclometasone 100mcg twice a day via spacer OR Budesonide 100mcg twice a day via spacer (or turbohaler) OR Fluticasone 50mcg twice a day via spacer (or accuhaler) 4 Beclomethasone 200mcg twice a day via spacer OR Budesonide 200mcg twice a day via spacer (or turbohaler) OR Fluticasone 100mcg twice a day via spacer (or accuhaler) 5 Trial of LABA. If ineffective, consider trial of LTRA. 6 Fluticasone 125mcg twice a day via spacer OR Fluticasone 125mcg twice a day via spacer OR Fluticasone 125mcg twice a day via spacer 7 Fluticasone 250mcg twice a day via spacer OR Fluticasone 250mcg twice a day via spacer OR Fluticasone 250mcg twice a day via spacer 8 Consider short course of prednisolone or other therapeutic options
Population subgroups	**Strata**

	Children or adults Children **Population of current smokers (>20% vs ≤20%)** Smokers excluded **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** Yes
Comparator	Therapy decisions were taken by a clinician independent of participant assessment following a simple algorithm reflecting symptom control. Therapy was increased if symptoms were poorly controlled and decreased if symptoms were well controlled for 3 months as per the SIGN/BTS guidelines. **Treatment algorithm** Poorly controlled asthma = Increase ICS or add LABA and/or LTRA as directed by stepwise approach to therapy Asthma controlled = No change in ICS

	Well controlled asthma = If well controlled for 3 months, reduce ICS. If dose ≤400 mcg, reduce LABA **Treatment steps** 1 No inhaled corticosteroid 2 Beclometasone 50mcg twice a day via spacer Budesonide 50mcg twice a day via spacer (or turbohaler) Fluticasone 50mcg once a day via spacer (or accuhaler) 3 Beclometasone 100mcg twice a day via spacer OR Budesonide 100mcg twice a day via spacer (or turbohaler) OR Fluticasone 50mcg twice a day via spacer (or accuhaler) 4 Beclomethasone 200mcg twice a day via spacer OR Budesonide 200mcg twice a day via spacer (or turbohaler) OR Fluticasone 100mcg twice a day via spacer (or accuhaler) 5 Trial of LABA. If ineffective, consider trial of LTRA. 6 Fluticasone 125mcg twice a day via spacer OR Fluticasone 125mcg twice a day via spacer OR Fluticasone 125mcg twice a day via spacer 7 Fluticasone 250mcg twice a day via spacer OR Fluticasone 250mcg twice a day via spacer OR Fluticasone 250mcg twice a day via spacer 8 Consider short course of prednisolone or other therapeutic options
Number of participants	90 randomised 44 allocated to FeNO management group, 34 completed 46 allocated to usual care group, 43 completed

Duration of follow-up	12 months
Indirectness	None
Additional comments	ITT

Study arms

FeNO monitoring (N = 44)
Treatment adjustment based on FeNO and symptoms

Usual care (N = 46)
Treatment adjustment based on symptoms alone as per SIGN/BTS guidelines

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 44)	Usual care (N = 46)
% Female Sample size	n = 23 ; % = 52.3	n = 16 ; % = 34.8
Mean age (SD) Mean (SD)	10.51 (2.62)	11.42 (2.69)

Characteristic	FeNO monitoring (N = 44)	Usual care (N = 46)
Ethnicity Caucasian Sample size	n = 41 ; % = 93.2	n = 44 ; % = 95.7
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 44	FeNO monitoring, 12 month, N = 44	Usual care, Baseline, N = 46	Usual care, 12 month, N = 46
Inflammatory markers (FeNO) (ppb) change scores Mean (95% CI)	NA (NA to NA)	3.1 (-5.5 to 11.6)	NA (NA to NA)	3.3 (-8.5 to 15.1)

Inflammatory markers (FeNO) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 44	FeNO monitoring, 12 month, N = 44	Usual care, Baseline, N = 46	Usual care, 12 month, N = 46
Unscheduled healthcare utilisation (severe exacerbations requiring hospitalisation for ≥8 hours) final values No of events	n = NA ; % = NA	n = 5 ; % = 11.4	n = NA ; % = NA	n = 3 ; % = 6.5

Unscheduled healthcare utilisation (severe exacerbations requiring hospitalisation for ≥8 hours) - Polarity - Lower values are better

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 44	FeNO monitoring, 12 month, N = 44	Usual care, Baseline, N = 46	Usual care, 12 month, N = 46
Inflammatory markers (FeNO) (ppb) change scores Mean (95% CI)	NA (NA to NA)	3.1 (-5.5 to 11.6)	NA (NA to NA)	3.3 (-8.5 to 15.1)
Data transformations	Mean/SD not calculated from Mean/95% CI - empty data	Mean/SD not calculated from Mean/95% CI - no distribution type set	Mean/SD not calculated from Mean/95% CI - empty data	Mean/SD not calculated from Mean/95% CI - no distribution type set

Arm based : Data distribution : Not set

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 44	FeNO monitoring, 12 month, N = 44	Usual care, Baseline, N = 46	Usual care, 12 month, N = 46
Unscheduled healthcare utilisation (severe exacerbations requiring hospitalisation for ≥8 hours) final values No of events	n = NA ; % = NA	n = 5 ; % = 11.4	n = NA ; % = NA	n = 3 ; % = 6.5

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Inflammatory markers (FeNO)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence to monitoring strategies and treatments not reported, and 14% dropout rate with large difference in rates between arms (10 from FeNO, 3 from usual care))*
Overall bias and Directness	Overall Directness	Directly applicable

Unscheduled healthcare utilisation (severe exacerbations requiring hospitalisation for ≥8 hours)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence to monitoring strategies and treatments not reported, and 14% dropout rate with large difference in rates between arms (10 from FeNO, 3 from usual care))*
Overall bias and Directness	Overall Directness	Directly applicable

Powell, 2011

Bibliographic Reference	Powell, Heather; Murphy, Vanessa E.; Taylor, D. Robin; Hensley, Michael J.; McCaffery, Kirsten; Giles, Warwick; Clifton, Vicki L.; Gibson, Peter G.; Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial; Lancet (London, England); 2011; vol. 378 (no. 9795); 983-90

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Australian and New Zealand Clinical Trials Registry, number 12607000561482.
Study type	Randomised controlled trial (RCT)
Study location	Australia
Study setting	Secondary care
Study dates	June 2007 - December 2010
Sources of funding	Funded by the National Health and Medical Research Council of Australia. Authors were recipients of a National Health and Medical Research Council (NHMRC) Australian Research Training Fellowship (part time, 455626), a NHMRC Senior Research Fellowship (510703) and a NHMRC Practitioner Fellowship recipient. Authors declared receiving payment for

	reimbursement of meeting/travel expenses from GlaxoSmithKline, AstraZeneca, Novartis, and Boehringer Ingelheim and reciept of lecture fees from Aerocrine
Inclusion criteria	Non-smoking pregnant women (aged >18 years) with asthma attending antenatal clinics between weeks 12 and 20 of gestation. Women had a doctor's diagnosis of asthma and were using inhaled therapy for asthma within the past year. The diagnosis was confirmed by a respiratory physician's diagnostic interview. Non-smoking status was validated by normal exhaled carbon monoxide (<10 ppm; piCO Smokerlyzer Breath CO Monitor, Bedfont, UK), and urinary cotinine
Exclusion criteria	None specified
Recruitment / selection of participants	Women attending antenatal clinics were recruited
Intervention(s)	The FENO algorithm used a sequential process: first, the FeNO concentration was used to adjust the dose of inhaled corticosteroids; and second, the ACQ score was used to adjust the dose of longacting β2 agonist. The cutoff points for the FeNO algorithm were derived from a prospective cohort study of asthma in pregnancy. The cutoff used for dose reduction was 16 ppb. The cutoff for dose increase was derived from pregnant asthmatic women with unstable eosinophilic asthma (ACQ score >1·5, FENO >16 ppb). Steroid-naïve patients who needed inhaled corticosteroids started with budesonide 100 µg twice per day. **Treatment algorithm** Level 1 FeNO: >29 = ↑ ICS × 1 step, No change LABA Level 2 FeNO: 16–29, ACQ ≤1·5 = No change to ICS or LABA Level 3 FeNO: 16–29, ACQ >1·5 = No change to ICS ↑ LABA × 1 step Level 4 FeNO: <16, ACQ ≤1·5 = ↓ ICS × 1 step, No change LABA Level 5 FeNO: <16, ACQ >1·5 = ↓ ICS × 1 step, ↑ LABA × 1 step

	Treatment steps Step 1 No ICS, Salbutamol as required Step 2 Budesonide 100 µg twice per day + Formoterol 6 µg twice per day Step 3 Budesonide 200 µg twice per day + Formoterol 12 µg twice per day Step 4 Budesonide 400 µg twice per day + Formoterol 2 × 12 µg twice per day Step 5 Budesonide 800 µg twice per day + Formoterol 2 × 12 µg twice per day
Population subgroups	**Strata** **Children or adults** Adults **Population of current smokers (>20% vs ≤20%)** Smokers excluded **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed

	Included adherence monitoring No
Comparator	The clinical algorithm was based on asthma control, which was assessed with the Juniper ACQ17 with cutoff points defined as: well controlled asthma (ACQ score <0·75), partially controlled asthma (0·75–1·50), and uncontrolled asthma (>1·5) **Treatment algorithm** Level 1: ACQ score >1.5 = ↑ ICS 1 step Level 2: ACQ score 0.75-1.5 = No change Level 3: ACQ score <0.75 = ↓ ICS 1 step **Treatment steps** Step 1: Salbutamol as required Step 2: Budesonide 200 µg twice per day Step 3: Budesonide 400 µg twice per day Step 4: Budesonide 400 µg + formoterol 12 µg twice per day Step 5: Budesonide 800 µg + formoterol 24 µg twice per day
Number of participants	220 randomised

	111 allocated to FeNO monitoring group, 100 completed 109 assigned to Asthma control questionnaires group, 103 completed
Duration of follow-up	Until individual delivery. Mean treatment length 17.8 (5.5) and 18.8 (3.8) weeks in FeNO and Asthma control questionnaire groups, respectively
Indirectness	None
Additional comments	ITT

Study arms

FeNO monitoring (N = 111)

Usual care (N = 109)
Treatment adjusted based on asthma control (ACQ)

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 111)	Usual care (N = 109)
% Female Sample size	n = 111 ; % = 100	n = 109 ; % = 100

Characteristic	FeNO monitoring (N = 111)	Usual care (N = 109)
Mean age (SD) Mean (95% CI)	28.1 (27.1 to 29.1)	28.8 (27.7 to 29.8)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 18 week (All outcomes reported at end of treatment (delivery). Mean treatment length 17.8 (5.5) and 18.8 (3.8) weeks in FeNO and Asthma control questionnaire groups, respectively.)

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 111	FeNO monitoring, 18 week, N = 111	Usual care, Baseline, N = 109	Usual care, 18 week, N = 109
Quality of life (Marks' Asthma Quality of Life Questionnaire) scale range: 0-10, final values	0.8 (0.4 to 1.5)	0.75 (0.38 to 1.25)	1 (0.5 to 1.6)	0.81 (0.38 to 1.63)

Outcome	FeNO monitoring, Baseline, N = 111	FeNO monitoring, 18 week, N = 111	Usual care, Baseline, N = 109	Usual care, 18 week, N = 109
Mean (95% CI)				
Lung Function (FEV1) (Litres) final values Mean (95% CI)	3.05 (2.96 to 3.15)	3.09 (3 to 3.17)	3.06 (2.96 to 3.15)	3.01 (2.91 to 3.1)
Lung function (FEV1 % predicted) final values Mean (95% CI)	95.1 (92.76 to 97.44)	96.4 (94.31 to 98.46)	96.12 (93.49 to 98.73)	94.4 (91.84 to 96.96)

Quality of life (Marks' Asthma Quality of Life Questionnaire) - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (FEV1 % predicted) - Polarity - Higher values are better

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 111	FeNO monitoring, 18 week, N = 111	Usual care, Baseline, N = 109	Usual care, 18 week, N = 109
Quality of life (Marks' Asthma Quality of Life Questionnaire) scale range: 0-10, final values Mean (95% CI)	0.8 (0.4 to 1.5)	0.75 (0.38 to 1.25)	1 (0.5 to 1.6)	0.81 (0.38 to 1.63)
Data transformations	Mean/SD not calculated from Mean/95% CI - no distribution type set	Mean/SD not calculated from Mean/95% CI - no distribution type set	Mean/SD not calculated from Mean/95% CI - no distribution type set	Mean/SD not calculated from Mean/95% CI - no distribution type set

Outcome	FeNO monitoring, Baseline, N = 111	FeNO monitoring, 18 week, N = 111	Usual care, Baseline, N = 109	Usual care, 18 week, N = 109
Lung Function (FEV1) (Litres) final values Mean (95% CI)	3.05 (2.96 to 3.15)	3.09 (3 to 3.17)	3.06 (2.96 to 3.15)	3.01 (2.91 to 3.1)
Data transformations	Mean/SD not calculated from Mean/95% CI - no distribution type set	Mean/SD not calculated from Mean/95% CI - no distribution type set	Mean/SD not calculated from Mean/95% CI - no distribution type set	Mean/SD not calculated from Mean/95% CI - no distribution type set
Lung function (FEV1 % predicted) final values Mean (95% CI)	95.1 (92.76 to 97.44)	96.4 (94.31 to 98.46)	96.12 (93.49 to 98.73)	94.4 (91.84 to 96.96)
Data transformations	Mean/SD not calculated from Mean/95% CI - no distribution type set	Mean/SD not calculated from Mean/95% CI - no distribution type set	Mean/SD not calculated from Mean/95% CI - no distribution type set	Mean/SD not calculated from Mean/95% CI - no distribution type set

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Quality of life (Asthma Quality of Life Questionnaire)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Lung Function (FEV1)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Lung function (FEV1 % predicted)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Shaw, 2007

Bibliographic Reference	Shaw, Dominick E.; Berry, Mike A.; Thomas, Mike; Green, Ruth H.; Brightling, Chris E.; Wardlaw, Andrew J.; Pavord, Ian D.; The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial; American journal of respiratory and critical care medicine; 2007; vol. 176 (no. 3); 231-7

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Primary care
Study dates	January 2004 - December 2004
Sources of funding	Authors had previously received a travel grant from GlaxoSmithKline (GSK) and lecture fees from AstraZeneca and had participated as a speaker in scientific meetings or courses organized and financed by various pharmaceutical companies (GSK, AstraZeneca); as well asv being in receipt of an unrestricted grant from GSK for research into refractory asthma

Inclusion criteria	>18 years old, diagnosis of asthma recorded in their GP's notes, received at least one prescription for any antiasthma medication in the last 12 months
Exclusion criteria	Current smokers with a past smoking history of >10 pack-years, considered by their physician to be poorly compliant or had had a severe asthma exacerbation, requiring a course of prednisolone, within 4 weeks of study entry
Recruitment / selection of participants	Participants were identified from registers held in general practices around Leicester, United Kingdom
Intervention(s)	Participants were seen monthly for the first 4 months and every 2 months thereafter. At each visit, the patient's asthma control was determined using the validated Juniper asthma control questionnaire, which scores asthma control from 0 to 6; a score of greater than 1.57 was used to identify poorly controlled asthma. Treatment was adjusted following a set protocol according to both the FeNO and Juniper scores. If FeNO was greater than 26 ppb, inhaled corticosteroid treatment was increased; if it was less than 16 ppb or less than 26 ppb on two consecutive occasions, treatment was decreased. Bronchodilator therapy was increased if symptoms were uncontrolled, despite an FeNO of less than 26 ppb. **Treatment algorithm** FeNO <16 on first occasion, or 16-26 on second occasion + Juniper Asthma Control Score ≤1.57 = Step down anti-inflammatory treatment. Step down bronchodilator treatment once off ICS FeNO <16 on first occasion, or 16-26 on second occasion + Juniper Asthma Control Score >1.57 = Step down anti-inflammatory treatment. Step up bronchodilator treatment FeNO >26 + Juniper Asthma Control Score ≤1.57 = Step up anti-inflammatory treatment. No change in bronchodilator treatment FeNO >26 + Juniper Asthma Control Score >1.57 = Step up anti-inflammatory treatment. Step up bronchodilator treatment once on maximum anti-inflammatory treatment

	Treatment steps (anti-inflammatory) 1) Low dose inhaled steroid (100-200µg BDP bd) 2) Moderate dose inhaled steroid (200-800µg BDP bd) 3) High dose inhaled steroid (800-2000µg BDP bd) 4) High dose inhaled steroid (800-2000µg BDP bd) plus leukotriene antagonist 5) Higher dose inhaled steroid (2000µg BDP bd) plus leukotriene antagonist 6) Higher dose inhaled steroid (2000µg BDP bd) plus leukotriene antagonist plus oral Prednisolone 30mg 2/52, then titrating dose reducing by 5mg/week **Treatment steps (bronchodilator)** 1) PRN short acting β2-agonists 2) Long acting β2 agonist 3) Long acting β2 agonist plus theophylline 4) Long acting β2-agonist plus theophylline plus nebulised bronchodilator
Population subgroups	**Strata** **Children or adults** Adults

	Population of current smokers (>20% vs ≤20%) Smokers excluded **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** No
Comparator	Participants were seen monthly for the first 4 months and every 2 months thereafter. At each visit, the patient's asthma control was determined using the validated Juniper asthma control questionnaire, which scores asthma control from 0 to 6; a score of greater than 1.57 was used to identify poorly controlled asthma. Treatment was doubled if the score was more than 1.57, and treatment was halved if the score was less than 1.57 for 2 consecutive months **Treatment steps (step increase if JACS >1.57, step decrease if ≤1.57)** Step 1 = inhaled short acting beta agonist as required Step 2 = Add ICS 200-800 mcg/day BDP equivalent Step 3 = Add LABA Step 4 = Increase ICS up to 2000 mcg/day and add a fourth drug e.g., leukotriene modifier, theophylline, beta agonist tablet

	Step 5 = Oral prednisolone (lowest dose providing adequate control), maintain ICS at 2000 mcg/day, refer patient for specialist care
Number of participants	118 randomised 58 allocated to FeNO monitoring group, 52 completed 60 allocated to usual care group, 51 completed
Indirectness	None
Additional comments	ITT

Study arms

FeNO monitoring (N = 58)

Usual care (N = 60)

Treatment adjusted based on conventional stepwise asthma management plan from BTS/SIGN guideline (2003)

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 58)	Usual care (N = 60)
% Female	n = 31 ; % = 53	n = 33 ; % = 55

Characteristic	FeNO monitoring (N = 58)	Usual care (N = 60)
Sample size		
Mean age (SD) Median (range) Median (IQR)	50 (20 to 75)	52 (24 to 81)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 58	FeNO monitoring, 12 month, N = 58	Usual care, Baseline, N = 60	Usual care, 12 month, N = 60
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 12 ; % = 20.68	n = NA ; % = NA	n = 19 ; % = 31.66

Severe asthma exacerbations - Polarity - Lower values are better

Contrast Outcomes

Outcome	FeNO monitoring vs Usual care, Baseline, N2 = 60, N1 = 58	FeNO monitoring vs Usual care, 12 month, N2 = 60, N1 = 58
Dose of regular asthma therapy (µg/day) Final values Mean (95% CI)	NA (NA to NA)	-338 (-640 to -37)

Dose of regular asthma therapy - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 58	FeNO monitoring, 12 month, N = 58	Usual care, Baseline, N = 60	Usual care, 12 month, N = 60
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 12 ; % = 20.68	n = NA ; % = NA	n = 19 ; % = 31.66

Arm based : Data distribution : Not set

Contrast Outcomes

Outcome

Contrast : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Exacerbations (number of patients with an exacerbation requiring course of oral steroids or antibiotics)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence to monitoring strategies and treatments not reported and 13% dropout rate)*
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Dose of regular asthma therapy – Mean Nine Five Percent CI-FeNO monitoring-Usual care-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence to monitoring strategies and treatments not reported and 13% dropout rate)*
Overall bias and Directness	Overall Directness	Directly applicable

Smith, 2005

Bibliographic Reference	Smith, Andrew D.; Cowan, Jan O.; Brassett, Karen P.; Herbison, G. Peter; Taylor, D. Robin; Use of exhaled nitric oxide measurements to guide treatment in chronic asthma; The New England journal of medicine; 2005; vol. 352 (no. 21); 2163-73

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	New Zealand
Study setting	Primary care
Study dates	No additional information
Sources of funding	Funded by the Otago Medical Research Foundation, the Dean’s Fund of the Dunedin School of Medicine, and a grant from the University of Otago. Supplies of fluticasone were provided by GlaxoSmithKline (New Zealand). Equipment for the analysis of nitric oxide in other studies was provided by Aerocrine
Inclusion criteria	12 to 75 years of age with chronic asthma, managed in primary care, regular inhaled corticosteroids for six months or more with no change in dose in last 6 weeks

Exclusion criteria	Four or more courses of oral prednisone in the previous 12 months; admission to the hospital because of asthma in the previous 6 months or to the intensive care unit because of asthma at any time in the past; and cigarette smoking, either current or past, with a history of more than 10 pack-years
Recruitment / selection of participants	Patients having their treatment managed in primary care were approached
Intervention(s)	**Phase 1** The dose of inhaled fluticasone was titrated downward in a stepwise manner until the optimal dose was deemed to have been achieved. Subjects received 750 μg per day to start (or 500 μg per day if their inhaled-corticosteroid requirement before enrollment was less than 200 μg per day of fluticasone or the equivalent). Subjects returned after four weeks and were randomly assigned to one of the two management groups. The FeNO-group algorithm was based solely on FeNO measurements, with 15 parts per billion (ppb) of nitric oxide (at an exhaled flow rate of 250 ml per second) used as the cutoff point, above which an increase in the dose of inhaled corticosteroid was prescribed. At each study visit the patient's asthma was deemed to be controlled or uncontrolled. The dose of inhaled fluticasone was decreased or increased (to a maximum of 1000 μg per day) accordingly. Titration downward was repeated one step at a time every four weeks until the FeNO was greater than 15 ppb or until asthma became uncontrolled, at which point the dose of fluticasone was increased — again, one step at a time, at four-week intervals, until the FeNO level was less than 15 ppb or until asthma was again controlled. Once the FeNO level had decreased to less than 15 ppb, or asthma control had been reestablished, the final dose (which possibly included placebo among patients in whom asthma control was not lost at a dose of 0 μg of fluticasone per day) was deemed to be the optimal dose for that person. **Phase 2** During phase 2, which lasted for 12 months, maintenance treatment with inhaled fluticasone was continued at the optimal dose, although further upward adjustments in the dose were permitted if asthma control was lost. Subjects were evaluated on six occasions at intervals of two months. At each visit, FeNO measurements were obtained in the same way as during phase 1. If the FeNO was greater than 15 ppb at any visit during phase 2, treatment was increased by one step in accordance with the assigned algorithm. Thereafter, if the FeNO level remained at less than 15 ppb or if the asthma was controlled for two consecutive visits (i.e., for four months), the dose was titrated back down one step. However, treatment

	was not decreased below the optimal dose (below which each patient had previously demonstrated instability) or to placebo during phase 2. **Back-up strategy for FeNO monitoring (due to uncertainty of FeNO as a sole monitoring strategy)** Subjects in the FeNO group had a predetermined “safety buffer” by which an upward (one-step) adjustment in the dose was provided to deal with deteriorating asthma in the absence of a rise in measured FeNO. All subjects had a personalized self-management plan, which instructed them to take oral prednisone, 40 mg per day, when morning peak flows fell below 70 percent of mean run-in values; they continued this dose until peak flows increased above 85 percent, at which time they were to take 20 mg per day for the same number of days. Participants had 24- hour access to the study investigators.
Population subgroups	**Strata** **Children or adults** Adults (mean age 44.8, range 12-73 years) **Population of current smokers (>20% vs ≤20%)** Smokers excluded **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** Yes via inhaler weighing

Comparator	**Phase 1** The dose of inhaled fluticasone was titrated downward in a stepwise manner until the optimal dose was deemed to have been achieved. Subjects received 750 µg per day to start (or 500 µg per day if their inhaled-corticosteroid requirement before enrollment was less than 200 µg per day of fluticasone or the equivalent). Subjects returned after four weeks and were randomly assigned to one of the two management groups. The control-group algorithm was derived from criteria established by the Global Initiative for Asthma 2002 for the control of asthma. Dose adjustments were based on predetermined thresholds in regard to symptoms, bronchodilator use, diurnal peak flows, and spirometry. . At each study visit, with the use of the appropriate algorithm, the patient's asthma was deemed to be controlled or uncontrolled. The dose of inhaled fluticasone was decreased or increased (to a maximum of 1000 µg per day) accordingly. Titration downward was repeated one step at a time every four weeks until asthma became uncontrolled, at which point the dose of fluticasone was increased — again, one step at a time, at four-week intervals, until asthma was again controlled. Once asthma control had been reestablished, the final dose (which possibly included placebo among patients in whom asthma control was not lost at a dose of 0 µg of fluticasone per day) was deemed to be the optimal dose for that person. **Phase 2** During phase 2, which lasted for 12 months, maintenance treatment with inhaled fluticasone was continued at the optimal dose, although further upward adjustments in the dose were permitted if asthma control was lost. Subjects were evaluated on six occasions at intervals of two months. At each visit, asthma control was assessed in the same way as during phase 1. If asthma was uncontrolled at any visit during phase 2, treatment was increased by one step in accordance with the assigned algorithm. Thereafter, if asthma was controlled for two consecutive visits (i.e., for four months), the dose was titrated back down one step. However, treatment was not decreased below the optimal dose (below which each patient had previously demonstrated instability) or to placebo during phase 2. **Treatment algorithm** Asthma symptoms: asthma controlled if present ≤2 days/week, uncontrolled if present >2 days/week with 24-hour asthma score ≥2

	Night time waking: asthma controlled if ≤1 night/week, uncontrolled if >1 night/week Bronchodilator use: asthma controlled if ≤4 occasions/week and ≤2 days/week, uncontrolled if >4 occasions/week and >2 days/week Variation in PEFR (amplitude % of mean, previous 7 days): asthma controlled if ≤20%, uncontrolled if >20% FEV1 (% of baseline): asthma controlled if ≥90%, uncontrolled if <90%
Number of participants	110 entered study, 97 randomised 48 allocated to FeNO monitoring group, 44 completed 49 allocated to usual care group, 45 completed
Duration of follow-up	Phase 1 mean duration 22 and 25 weeks in the two groups, phase 2 = 12 months
Indirectness	None
Additional comments	ITT

Study arms

FeNO monitoring (N = 48)

Usual care (N = 49)
Treatment adjusted based on algorithm derived from criteria established by GINA (2002) for asthma control

Characteristics

Study-level characteristics

Characteristic	Study (N = 110)
% Female Sample size	n = 69 ; % = 63
Mean age (SD) Mean (range) Mean (95% CI)	44.8 (12 to 73)
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Outcomes

Study timepoints

- Baseline
- 18 month (End of study phase 2: 12 months after end of phase 1)

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 48	FeNO monitoring, 18 month, N = 46	Usual care, Baseline, N = 49	Usual care, 18 month, N = 48
Lung function (FEV1 % predicted) final values Mean (95% CI)	86.4 (80.6 to 92.2)	86.1 (80.6 to 91.6)	83.1 (76.5 to 89.7)	82.3 (75.8 to 88.8)
Inflammatory markers (FeNO) (ppb) final values, reported as geometric mean Mean (95% CI)	7.8 (6.6 to 9.3)	8.6 (7.5 to 9.9)	6.4 (5.5 to 7.5)	7.6 (6.4 to 9.1)
Rescue medication (average bronchodilator use in previous 7 days) (acctuations per day) final values Mean (95% CI)	0.5 (0.2 to 0.8)	0.4 (0.1 to 0.7)	0.6 (0.3 to 0.8)	0.4 (0.1 to 0.6)
Lung function (morning peak flow, mean of previous 7 days) final values Mean (95% CI)	394 (363 to 424)	404 (373 to 436)	395 (365 to 424)	403 (371 to 435)
Dose of regular asthma therapy (ICS dose) (µg/day) final values Mean (95% CI)	411 (344 to 478)	370 (263 to 477)	491 (402 to 579)	641 (526 to 756)

Lung function (FEV1 % predicted) - Polarity - Higher values are better
Inflammatory markers (FeNO) - Polarity - Lower values are better
Rescue medication (average bronchodilator use in previous 7 days) - Polarity - Lower values are better
Lung function (morning peak flow, mean of previous 7 days) - Polarity - Higher values are better
Dose of regular asthma therapy (ICS dose) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 48	FeNO monitoring, 18 month, N = 46	Usual care, Baseline, N = 49	Usual care, 18 month, N = 48
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 13 ; % = 28.26	n = NA ; % = NA	n = 15 ; % = 31.25

Severe asthma exacerbations - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Lung function (FEV1 % predicted)2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and unclear adherence to monitoring strategies)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Inflammatory markers (FeNO)- Mean Nine Five Percent CI-FeNO monitoring-Usual care-t18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and unclear adherence to monitoring strategies)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Rescue medication (average bronchodilator use in previous 7 days) – Mean Nine Five Percent CI- FeNO monitoring-Usual care-t18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and unclear adherence to monitoring strategies)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (morning peak flow, mean of previous 7 days)- Mean Nine Five Percent CI- FeNO monitoring -Usual care-t18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and unclear adherence to monitoring strategies)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Dose of regular asthma therapy (ICS dose)- Mean Nine Five Percent CI- FeNO monitoring-Usual care-t18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and unclear adherence to monitoring strategies)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations – No Of Events - FeNO monitoring-Usual care-t18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and unclear adherence to monitoring strategies)*
Overall bias and Directness	Overall Directness	Directly applicable

Syk, 2013

Bibliographic Reference	Syk, Jorgen; Malinovschi, Andrei; Johansson, Gunnar; Unden, Anna-Lena; Andreasson, Anna; Lekander, Mats; Alving, Kjell; Anti-inflammatory treatment of atopic asthma guided by exhaled nitric oxide: a randomized, controlled trial; The journal of allergy and clinical immunology. In practice; 2013; vol. 1 (no. 6); 639-8

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NOAK study
Study type	Randomised controlled trial (RCT)
Study location	Sweden
Study setting	Primary care
Study dates	November 2006 - March 2010
Sources of funding	None reported
Inclusion criteria	Aged 18-64 years old with physician's diagnosis of asthma, on prescribed ICS treatment for at least 6 months, and had confirmed IgE sensitisation to at least 1 major airborne perennial allergen (dog, cat, or mite), non-smokers for at least 1-year and with a smoking history of <10 packs years

Exclusion criteria	Not reported
Recruitment / selection of participants	Patients were recruited from 17 primary health care centres in 7 regions of Central and Southern Sweden
Intervention(s)	Anti-inflammatory treatment (ICS and leukotriene receptor antagonist [LTRA]) was adjusted according to an algorithm based on exhaled NO levels and 6 fixed treatment steps. **Treatment algorithm** (FeNO <19ppb (men), <21ppb (women) - decrease one step FeNO 19 -23 (men), 21 -25 (women) - no change FeNO ≥24ppb (men), ≥26ppb (women) - increase one step (no change in treatment step if on step 4 or 5 and using ≤2 inhalations of short -acting beta2 agonist per week) FeNO ≥30ppb (men), ≥32ppb (women) - increase two steps (only if one treatment step 1) **Treatment steps** 6 possible fixed treatment steps with 3 different steroids: Budesonide (mcg/day): 0, 200, 400, 800, 800+LTRA, 1600+LTRA Fluticasone (mcg/day): 0, 100, 250, 500, 500+LTRA; 1000+LTRA Mometasone (mcg/day): 0, 100, 200, 400, 400+LTRA, 800+LTRA

Population subgroups	**Strata** **Children or adults** Adults **Population of current smokers (>20% vs ≤20%)** Smokers excluded **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** No
Comparator	Treatment was adjusted according to usual care, that is, based on patient -reported symptoms, SABA use, physical examination, and results of pulmonary function tests. Changes in treatment steps were entirely at the discretion of the treating physician, and immediate changes over several steps were allowed. Permissible treatment steps basically followed the prevailing national guidelines at the time of the study start, issued in 2002 by the Swedish Medical Product Agency, with the exception that only LTRA was used as an add on treatment. **Treatment steps** 6 possible fixed treatment steps with 3 different steroids:

	Budesonide (mcg/day): 0, 200, 400, 800, 800+LTRA, 1600+LTRA Fluticasone (mcg/day): 0, 100, 250, 500, 500+LTRA; 1000+LTRA Mometasone (mcg/day): 0, 100, 200, 400, 400+LTRA, 800+LTRA
Number of participants	181 randomised 93 allocated to FeNO monitoring group 88 allocated to usual care group
Duration of follow-up	12 months
Indirectness	None
Additional comments	Not reported

Study arms

FeNO monitoring (N = 93)

Usual care (N = 88)
Treatment adjusted based on patient-reported symptoms, SABA use, physical examination, and results of pulmonary function tests

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 93)	Usual care (N = 88)
% Female Sample size	n = 45 ; % = 48.4	n = 42 ; % = 47.7
Mean age (SD) Mean (SD)	40.9 (11.8)	41.1 (*empty data*)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 93	FeNO monitoring, 12 month, N = 86	Usual care, Baseline, N = 88	Usual care, 12 month, N = 78
Lung Function (FEV1) (Litres) change scores (follow up: n=88 in FeNO group, n=78 in usual care group) Mean (SD)	NR (NR)	-0.034 (0.28)	NR (NR)	-0.006 (0.28)
Inflammatory markers (FeNO) (ppb) change scores (follow up: n=87 in FeNO group, n=76 in usual care group) Mean (SD)	NR (NR)	-2.57 (20.94)	NR (NR)	-1.46 (23.86)

Lung Function (FEV1) - Polarity - Higher values are better
Inflammatory markers (FeNO) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 93	FeNO monitoring, 12 month, N = 93	Usual care, Baseline, N = 88	Usual care, 12 month, N = 88
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 8 ; % = 8.6	n = NA ; % = NA	n = 6 ; % = 6.8

Severe asthma exacerbations - Polarity - Lower values are better

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 93	FeNO monitoring, 12 month, N = 86	Usual care, Baseline, N = 88	Usual care, 12 month, N = 78
Lung Function (FEV1) (Litres) change scores (follow up: n=88 in FeNO group, n=78 in usual care group) Mean (SD)	NR (NR)	-0.034 (0.28)	NR (NR)	-0.006 (0.28)
Inflammatory markers (FeNO) (ppb) change scores (follow up: n=87 in FeNO group, n=76 in usual care group) Mean (SD)	NR (NR)	-2.57 (*empty data*)	NR (NR)	-1.46 (23.86)

Arm based : Data distribution : Not set

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 93	FeNO monitoring, 12 month, N = 93	Usual care, Baseline, N = 88	Usual care, 12 month, N = 88
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 8 ; % = 8.6	n = NA ; % = NA	n = 6 ; % = 6.8

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Lung Function (FEV1)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Inflammatory markers (FeNO)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Exacerbations (number of patients with ≥1 exacerbation requiring oral corticosteroids)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	*Low*
Overall bias and Directness	Overall Directness	Directly applicable

Szefler, 2008

Bibliographic Reference	Szefler, Stanley J.; Mitchell, Herman; Sorkness, Christine A.; Gergen, Peter J.; O'Connor, George T.; Morgan, Wayne J.; Kattan, Meyer; Pongracic, Jacqueline A.; Teach, Stephen J.; Bloomberg, Gordon R.; Eggleston, Peyton A.; Gruchalla, Rebecca S.; Kercsmar, Carolyn M.; Liu, Andrew H.; Wildfire, Jeremy J.; Curry, Matthew D.; Busse, William W.; Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial; Lancet (London, England); 2008; vol. 372 (no. 9643); 1065-72

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Not reported
Study dates	September 2004 - December 2005
Sources of funding	Funded through a contract with the Division of Allergy, Immunology, and Transplantation, NIAID/NIH

Inclusion criteria	Aged 12 to 20 years, with asthma; residents of urban census tracts in which at least 20 percent of households had incomes below the federal poverty threshold. Individuals receiving long-term control therapy were required to have symptoms of persistent asthma or evidence of uncontrolled disease. Individuals not receiving long-term control therapy were required to have both symptoms of persistent asthma and evidence of uncontrolled disease defined by NAEPP guidelines
Exclusion criteria	Smokers (urinary cotinine >100), participants were excluded after the run-in if controller treatment adherence was <25%
Recruitment / selection of participants	No additional information
Intervention(s)	Symptoms, rescue medication use, pulmonary function, adherence and FeNO were used to determine control level. FeNO was measured (flow rate 50 ml/s) with a rapid-response chemiluminescent analyzer (NIOX™ System, Aerocrine, Sweden) following American Thoracic Society guidelines at each visit. Control level and FeNO data were entered into a computer program which generated a treatment option. The treatment options were derived from protocol-defined treatment steps. Medication was adjusted based on control and adherence. Medication was only reduced after two consecutive visits with good control (Control level 1). When adherence was ≥50%, and FeNO was elevated, patients were eligible to receive an additional one step increase in treatment compared to what would be given to the Reference Group. For safety reasons, FeNO was not allowed to increase treatment on the third consecutive visit without elevated symptoms. Also low FeNO alone was not allowed to reduce therapy without a corresponding reduction in symptoms. **Treatment steps** Step 0: No controller medication; albuterol prn Step 1: Fluticasone DPI 100 mcg qd Step 2: Fluticasone DPI 100 mcg bid Step 3: Fluticasone 100 mcg / salmeterol 50 mcg bid Step 4: Fluticasone 250 mcg / salmeterol 50 mcg bid

	Step 5: Fluticasone 500 mcg/ salmeterol 50 mcg bid Step 6: Fluticasone 500 mcg/ salmeterol 50 mcg bid + either low dose theophylline or montelukast qd
Population subgroups	**Strata** **Children or adults** Children **Population of current smokers (>20% vs ≤20%)** Smokers excluded **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** Yes
Comparator	Symptoms, rescue medication use, pulmonary function, and adherence were used to determine control level. Control level was entered into a computer program which generated treatment options. The treatment options were derived from protocol-defined treatment steps. Medication was adjusted based on control and adherence. Medication was only reduced after two consecutive visits with good control.

	Treatment steps Step 0: No controller medication; albuterol prn Step 1: Fluticasone DPI 100 mcg qd Step 2: Fluticasone DPI 100 mcg bid Step 3: Fluticasone 100 mcg / salmeterol 50 mcg bid Step 4: Fluticasone 250 mcg / salmeterol 50 mcg bid Step 5: Fluticasone 500 mcg/ salmeterol 50 mcg bid Step 6: Fluticasone 500 mcg/ salmeterol 50 mcg bid + either low dose theophylline or montelukast qd
Number of participants	546 randomised 276 allocated to FeNO monitoring group, 250 completed 270 allocated to usual care group, 244 completed
Duration of follow-up	46 weeks
Indirectness	None
Additional comments	ITT

Study arms

FeNO monitoring (N = 276)
FeNO monitoring in addition to guideline-based care

Usual care (N = 270)
Treatment adjusted on guideline-based (NAEPP) care

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 276)	Usual care (N = 270)
% Female Sample size	n = 130 ; % = 47.1	n = 128 ; % = 48.4
Mean age (SD) Mean (SD)	14.4 (2.1)	14.4 (2.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Black Sample size	n = 183 ; % = 66.3	n = 164 ; % = 60.7
Hispanic Sample size	n = 62 ; % = 22.5	n = 63 ; % = 23.3
Other or mixed Sample size	n = 31 ; % = 11.2	n = 43 ; % = 15.9

Outcomes

Study timepoints

- Baseline
- 46 week

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 276	FeNO monitoring, 46 week, N = 250	Usual care, Baseline, N = 270	Usual care, 46 week, N = 246
Asthma control questionnaires (Asthma Control Test) scale range: 0-25, final values Mean (SD)	21.1 (3.6)	21.89 (1.99)	21.3 (3.2)	21.83 (1.97)
Lung function (FEV1 % predicted) final values Mean (SD)	95.9 (15.5)	96.3 (8.3)	95.7 (15.9)	95.5 (8.22)
Time off school or work (School days missed in last 2 weeks) final values Mean (SD)	NA (NA)	0.19 (0.5)	NA (NA)	0.23 (0.49)

Asthma control questionnaires (Asthma Control Test) - Polarity - Higher values are better
Lung function (FEV1 % predicted) - Polarity - Higher values are better
Time off school or work (School days missed in last 2 weeks) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 276	FeNO monitoring, 46 week, N = 276	Usual care, Baseline, N = 270	Usual care, 46 week, N = 270
Unscheduled healthcare utilisation (number of children who had ≥1 unscheduled ER or clinic visits) final values (unscheduled visit=unscheduled ER or clinic visit) No of events	n = NA ; % = NA	n = 59 ; % = 21.3	n = NA ; % = NA	n = 61 ; % = 22.7
Unscheduled healthcare utilisation (number of children who were hospitalised ≥1) final values No of events	n = NA ; % = NA	n = 9 ; % = 3.3	n = NA ; % = NA	n = 11 ; % = 4.1
Severe asthma exacerbations No of events	n = NA ; % = NA	n = 89 ; % = 32.1	n = NA ; % = NA	n = 113 ; % = 42

Unscheduled healthcare utilisation (number of children who had ≥1 unscheduled ER or clinic visits) - Polarity - Lower values are better
Unscheduled healthcare utilisation (number of children who were hospitalised ≥1) - Polarity - Lower values are better

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 276	FeNO monitoring, 46 week, N = 250	Usual care, Baseline, N = 270	Usual care, 46 week, N = 246
Asthma control questionnaires (Asthma Control Test) scale range: 0-25, final values Mean (SD)	21.1 (3.6)	21.89 (1.99)	21.3 (3.2)	21.83 (1.97)
Lung function (FEV1 % predicted) final values Mean (SD)	95.9 (15.5)	96.3 (8.3)	95.7 (15.9)	95.5 (8.22)

Arm based : Data distribution : Not set

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 276	FeNO monitoring, 46 week, N = 276	Usual care, Baseline, N = 270	Usual care, 46 week, N = 270
Unscheduled healthcare utilisation (number of children who had ≥1 unscheduled ER or clinic visits) final values (unscheduled visit=unscheduled ER or clinic visit) No of events	n = NA ; % = NA	n = 59 ; % = 21.3	n = NA ; % = NA	n = 61 ; % = 22.7
Unscheduled healthcare utilisation (number of children	n = NA ; % = NA	n = 9 ; % = 3.3	n = NA ; % = NA	n = 11 ; % = 4.1

Outcome	FeNO monitoring, Baseline, N = 276	FeNO monitoring, 46 week, N = 276	Usual care, Baseline, N = 270	Usual care, 46 week, N = 270
who were hospitalised ≥1) final values No of events				
Severe asthma exacerbations No of events	n = NA ; % = NA	n = 89 ; % = 32.1	n = NA ; % = NA	n = 113 ; % = 42

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Asthma control questionnaires (Asthma Control Test)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (FEV1%predicted)- Mean SD - FeNO monitoring-Usual care-t46

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes-Time off school or work (School days missed in last 2 weeks)-MeanSD-FeNO monitoring-Usual care-t46

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Unscheduled healthcare utilisation (number of children who had ≥ 1 unscheduled visits)- No Of Events - FeNO monitoring-Usual care-t46

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Unscheduled healthcare utilisation (number of children who were hospitalised ≥ 1)-No Of Events-FeNO monitoring-Usual care-t46

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations-No Of Events-FeNO monitoring-Usual care-t46

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Truong-Thanh, 2020

Bibliographic Reference	Truong-Thanh, Tung; Vo-Thi-Kim, Anh; Vu-Minh, Thuc; Truong-Viet, Dung; Tran-Van, Huong; Duong-Quy, Sy; The beneficial role of FeNO in association with GINA guidelines for titration of inhaled corticosteroids in adult asthma: A randomized study; Advances in medical sciences; 2020; vol. 65 (no. 2); 244-251

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Vietnam
Study setting	No additional information
Study dates	January 2016 - January 2019
Sources of funding	Supported by a Grant from the Lam Dong Medical College (LDMC.DTNC.005.16), Dalat City, Vietnam.
Inclusion criteria	Adult (>18 years) asthmatic patients who were not treated or discontinuously treated in the previous months were included in the study; they were able to perform lung function testing (LFT), FeNO measurement, skin prick test (SPT), and blood analysis (blood eosinophil count - BEC and total IgE quantifying).

Exclusion criteria	Asthmatic patients with one of the following features were excluded from the study: acute respiratory infection, severe asthma exacerbations needing systemic corticosteroid therapy at inclusion, severe chronic diseases (cirrhosis, diabetes, or kidney failure), coronary disease treated with nitroglycerin, severe airway obstruction without positive bronchial reversibility (forced expiratory volume in 1 s - FEV1 < 50%), unreproducible FEV1 and FeNO measurements, or unable to do laboratory testing.
Recruitment / selection of participants	Patients with uncontrolled asthma, from Clinical Research Center of Lam Dong Medical College (LMC).
Intervention(s)	Treatment modification was done according to GINA recommendations in addition to FeNO values. ICS response and asthma control were evaluated by physicians as recommended by GINA (controlled, partially controlled, or uncontrolled asthma). Asthma control test (ACT) was used as a self-assessment by asthmatic patients. The measurement of FeNO was done using an electrochemical analyzer HypAir FeNo+ (Medisoft; Sorinnes, Belgium). Technical measurement of FeNO, in order to assure expiratory flow of 50 mL/s and its level, were conducted according to manufacturer's instructions and as recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines for adults (< 25 ppb: normal; 25–50 ppb: increased; > 50 ppb: highly increased)
Population subgroups	**Strata** **Children or adults** Adults **Population of current smokers (>20% vs ≤20%)** 16.2 & 20% current smokers **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)**

	Mixed **Included adherence monitoring** No
Comparator	ICS response and asthma control were evaluated by physicians as recommended by GINA (controlled, partially controlled, or uncontrolled asthma). Asthma control test (ACT) was used as a self-assessment by asthmatic patients. The modification of treatment was based on daytime symptoms, limitation of activities, nocturnal symptoms or awakening, use of rescue treatment with short-acting beta-agonist, lung function variation (FEV1 or peak expiratory flow - PEF), and risk of acute asthma exacerbation
Number of participants	176 randomised 90 in FeNO group 86 in usual care group
Duration of follow-up	9 months
Indirectness	None
Additional comments	Not reported

Study arms

FeNO monitoring (N = 90)
FeNO monitoring in addition to GINA guideline-defined treatment

Usual care (N = 86)
Treatment according to GINA guideline-defined treatment

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 90)	Usual care (N = 86)
% Female Male:female ratio Nominal	1.6	1.4
Mean age (SD) Mean (SD)	36 (13)	34 (12)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 9 month

Continuous Outcomes

Outcome	FeNO monitoring , Baseline, N = 90	FeNO monitoring , 9 month, N = 90	Usual care, Baseline, N = 86	Usual care, 9 month, N = 86
Asthma control questionnaires (Asthma Control Test) scale range: 0-25, final values Mean (SD)	12 (5)	22 (6)	11 (4)	23 (5)
Lung function (FEV1 % predicted) final values Mean (SD)	67 (12)	82 (11)	68 (13)	83 (12)
Lung function (PEF % predicted) final values Mean (SD)	66 (11)	78 (14)	64 (12)	79 (14)
Inflammatory markers (FeNO) (ppb) final values Mean (SD)	56 (17)	14 (12)	53 (14)	18 (11)
Dose of regular asthma therapy (ICS treatment) (mcg/day) final values Mean (SD)	NA (NA)	375 (203)	NA (NA)	424 (221)

Asthma control questionnaires (Asthma Control Test) - Polarity - Higher values are better
Lung function (FEV1 % predicted) - Polarity - Higher values are better
Lung function (PEF % predicted) - Polarity - Higher values are better
Inflammatory markers (FeNO) - Polarity - Lower values are better
Dose of regular asthma therapy (ICS treatment) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Asthma control questionnaires (Asthma Control Test)2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to monitoring strategies and treatments not reported, and subjective outcome assessed by participant with knowledge of the intervention received)*
Overall bias and Directness	Overall Directness	Directly applicable

Lung function (FEV1 % predicted)2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF%predicted)-MeanSD-FeNO monitoring -Usual care-t9

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Inflammatory markers(FeNO)-MeanSD-FeNO monitoring -Usual care-t9

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes - Dose of regular asthma therapy(ICS treatment)-Mean SD-FeNO monitoring -Usual care-t9

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to monitoring strategies and treatments not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Turner, 2022

Bibliographic Reference	Turner, Steve; Cotton, Seonaidh; Wood, Jessica; Bell, Victoria; Raja, Edwin-Amalraj; Scott, Neil W.; Morgan, Heather; Lawrie, Louisa; Emele, David; Kennedy, Charlotte; Scotland, Graham; Fielding, Shona; MacLennan, Graeme; Norrie, John; Forrest, Mark; Gaillard, Erol A.; de Jongste, Johan; Pijnenburg, Marielle; Thomas, Mike; Price, David; Reducing asthma attacks in children using exhaled nitric oxide (RAACENO) as a biomarker to inform treatment strategy: a multicentre, parallel, randomised, controlled, phase 3 trial; The Lancet. Respiratory medicine; 2022

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	RAACENO (Reducing Asthma Attacks in Children using Exhaled Nitric Oxide) (ISRCTN 67875351)
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Secondary and tertiary care
Study dates	June 2017 - August 2019
Sources of funding	Circassia provided at no cost the apparatus to allow FeNO measurements to be made in the intervention. David Price has board membership with AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Sanofi

	Genzyme, Thermofisher; consultancy agreements with Airway Vista Secretariat, AstraZeneca, Boehringer Ingelheim, Chiesi, EPG Communication Holdings Ltd, FIECON Ltd, Fieldwork International, GlaxoSmithKline, Mylan, Mundipharma, Novartis, OM Pharma SA, PeerVoice, Phadia AB, Spirosure Inc, Strategic North Limited, Synapse Research Management Partners S.L., Talos Health Solutions, Theravance and WebMD Global LLC; grants and unrestricted funding for 20 investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Theravance and UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals and Sanofi Genzyme; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, Thermofisher; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 92.61% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp which develops adherence monitoring technology; is peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation programme, and Health Technology Assessment; and was an expert witness for GlaxoSmithKline
Inclusion criteria	Confirmed asthma diagnosis; aged 6-15 years; prescribed ICS inhaler; and at least one asthma exacerbation treated with a course of oral corticosteroids in the 12 months prior to recruitment
Exclusion criteria	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.
Recruitment / selection of participants	Children were recruited from asthma hospital clinics and primary care practices
Intervention(s)	Participants receiving the intervention had protocolised treatment decisions (based on the 2016 UK guideline) informed by current treatment, ACT/CACT score, adherence plus FeNO. For 63 treatment combinations, step up and step down options were agreed for participants in each trial arm. The FeNO result informed different treatment options where available (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. Subsequently reduced and elevated FeNO

	were defined as >50% fall or rise relative to the previous concentration. An ACT/CACT score of >19 was defined as fully control. Treatment was stepped up if symptoms were not controlled or if symptoms were controlled but FeNO had risen (limited to one increase for the duration of the trial). Treatment was stepped down if symptoms were controlled and FeNO had fallen. 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, the participant was referred to the local clinical team.
Population subgroups	**Strata** **Children or adults** Children **Population of current smokers (>20% vs ≤20%)** Not reported **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** Yes
Comparator	Treatment decisions for participants in the standard care arm were informed by current treatment, ACT/CACT score and adherence. Treatment was stepped up if symptoms were not controlled. Treatment was stepped down if symptoms were controlled on successive assessments.

Number of participants	515 randomised 255 in FeNO group 251 in usual care group
Duration of follow-up	1-year
Indirectness	None
Additional comments	ITT

Study arms

FeNO monitoring (N = 255)
FeNO and symptom based monitoring

Usual care (N = 251)
Treatment decisions informed by current treatment, ACT/CACT score and adherence

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 255)	Usual care (N = 251)
% Female Sample size	n = 99 ; % = 38.8	n = 102 ; % = 40.2
Mean age (SD) Mean (SD)	10 (2.6)	10.1 (2.5)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 1 year

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 255	FeNO monitoring, 1 year, N = 255	Usual care, Baseline, N = 251	Usual care, 1 year, N = 251
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 123 ; % = 48.2	n = NA ; % = NA	n = 129 ; % = 51.4
Mortality final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	FeNO monitoring, Baseline, N = 255	FeNO monitoring, 1 year, N = 255	Usual care, Baseline, N = 251	Usual care, 1 year, N = 251
Severe asthma exacerbations final values No of events	n = NA ; % = NA	n = 123 ; % = 48.2	n = NA ; % = NA	n = 129 ; % = 51.4
Mortality final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Exacerbations (requiring oral corticosteroids)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Inadequate adherence to the monitoring strategies reported: 64.7% compliance in the FeNO group, 61% in the usual care group)*
Overall bias and Directness	Overall Directness	Directly applicable

Mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Inadequate adherence to the monitoring strategies reported: 64.7% compliance in the FeNO group, 61% in the usual care group)*
Overall bias and Directness	Overall Directness	Directly applicable

Voorend-van Bergen, 2015

Bibliographic Reference	Voorend-van Bergen, Sandra; Vaessen-Verberne, Anja A.; Brackel, Hein J.; Landstra, Anneke M.; van den Berg, Norbert J.; Hop, Wim C.; de Jongste, Johan C.; Merkus, Peter J.; Pijnenburg, Marielle W.; Monitoring strategies in children with asthma: a randomised controlled trial; Thorax; 2015; vol. 70 (no. 6); 543-50

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Better Asthma Treatment: Monitoring with ACT and Nitric Oxide (Trial number NTR 1995)
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	General hospitals and tertiary referral centres
Study dates	February 2010 - November 2011
Sources of funding	Funded by Lung foundation Netherlands (grant no 3.4.08.039), the Netherlands Organization for Health Research (ZonMW) (grant no 171002101), and Fund Nuts Ohra (grant no 0901-023).
Inclusion criteria	Children aged 4–18 years, with atopic asthma (defined as a radioallergosorbent test class 2 or higher for at least one airborne allergen) based on clinical symptoms, a previous bronchodilator response of >9% increase in FEV1 of predicted

	(FEV1%) and/or previous airway hyperresponsiveness (AHR) to methacholine. Patients had been using inhaled corticosteroids (ICS) for at least 3 months before the study.
Exclusion criteria	active smoking, pulmonary diseases other than asthma, recent (<1 year) or multiple admissions to an intensive care unit for asthma, inability to perform FeNO measurements and/or the use of omalizumab.
Recruitment / selection of participants	Participants were recruited by their own paediatrician from general hospitals (n=5) and tertiary referral centres (n=2) in the Netherlands
Intervention(s)	Treatment was adapted at clinic visits every four months based on FeNO and ACT scores. Two FeNO cut-off points were used for decreasing (<25 ppb) or increasing (>50 ppb) treatment. **Treatment algorithm** ACT <20 + FeNO ≥25 ppb = step up treatment ACT <20 + FeNO <25 ppb = no change ACT ≥20 + FeNO <25 ppb = step down treatment ACT ≥20 + FeNO 25-50 ppb = no change ACT ≥20 + FeNO ≥50 ppb = step up treatment
Population subgroups	**Strata** **Children or adults** Children **Population of current smokers (>20% vs ≤20%)**

	Smokers excluded **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring** Yes
Comparator	Two study groups were combined for analysis in this review. Study group 1 was a web-based treatment group. Treatment was adapted monthly according to the web-based ACT score. Study group 3 was a standard care group where the ACT score during clinic visits (every 4 months) was used to direct treatment. Treatment was guided by the algorithm, but the clinician was allowed to alter treatment at their discretion. **Treatment algorithm (web-based group)** ACT <20 + good adherence, no cold = step up treatment ACT <20 + poor adherence, cold = no change ACT ≥20 for the first time = no change ACT ≥20 for a second time = step down

	Treatment algorithm (standard care group) ACT <20 = step up ACT ≥20 = no change or step down
Number of participants	272 randomised 92 allocated to FeNO monitoring group, 91 completed 91 allocated to web-based monitoring group, 90 completed 89 allocated to usual care group, 87 completed
Duration of follow-up	52 weeks
Indirectness	None
Additional comments	Complete case analysis

Study arms

FeNO monitoring (N = 92)

Usual care (N = 180)

Treatment adjusted via web-based ACT at monthly intervals (study group: web based monitoring) or through ACT at clinic visits with clinicians discretion (study group: usual care)

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 92)	Usual care (N = 180)
% Female Sample size	n = 30 ; % = 32.6	n = 59 ; % = 32.7
Mean age (SD) Mean (SD)	10.3 (2.9)	10.4 (3)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 91	FeNO monitoring, 12 month, N = 91	Usual care, Baseline, N = 177	Usual care, 12 month, N = 177
Symptoms (% symptom free days over 4 weeks) final values Mean (SD)	53 (34)	62 (35)	57 (34)	59 (35)
Asthma control questionnaires (Asthma Control Test of Children's Asthma Control Test) scale range: 0-25, final values Mean (SD)	20.7 (4.3)	22.4 (3.5)	21.6 (3.4)	21.8 (3.9)
Rescue medication (SABA use) (puffs/day) final values Mean (SD)	0.6 (1.2)	0.4 (1.1)	0.4 (0.8)	0.3 (0.7)
Dose of regular asthma therapy (ICS dose) (µg/day) final values Mean (SD)	400 (400)	400 (600)	400 (400)	298 (490)
Lung Function (FEV1) (Units not reported, but assumed be % predicted (L unfeasible)) final values Mean (SD)	95.2 (12.6)	97 (12.6)	96.1 (13.5)	96.6 (12.4)

Symptoms (% symptom free days over 4 weeks) - Polarity - Higher values are better
Asthma control questionnaires (Asthma Control Test of Children's Asthma Control Test) - Polarity - Higher values are better
Rescue medication (SABA use) - Polarity - Lower values are better
Dose of regular asthma therapy (ICS dose) - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better

Transform

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 91	FeNO monitoring, 12 month, N = 91	Usual care, Baseline, N = 177	Usual care, 12 month, N = 177
Symptoms (% symptom free days over 4 weeks) final values Mean (SD)	53 (34)	62 (35)	57 (34)	59 (35)
Asthma control questionnaires (Asthma Control Test of Children's Asthma Control Test) scale range: 0-25, final values Mean (SD)	20.7 (4.3)	22.4 (3.5)	21.6 (3.4)	21.8 (3.9)
Rescue medication (SABA use) (puffs/day) final values Mean (SD)	0.6 (1.2)	0.4 (1.1)	0.4 (0.8)	0.3 (0.7)
Dose of regular asthma therapy (ICS dose) (µg/day) final values Mean (SD)	400 (400)	400 (600)	400 (400)	298 (490)
Lung Function (FEV1) (Units not reported, but assumed be %	95.2 (12.6)	97 (12.6)	96.1 (13.5)	96.6 (12.4)

Outcome	FeNO monitoring, Baseline, N = 91	FeNO monitoring, 12 month, N = 91	Usual care, Baseline, N = 177	Usual care, 12 month, N = 177
predicted (L unfeasible)) final values Mean (SD)				

Arm based : Data distribution : Not set

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Symptoms (% symptom free days over 4 weeks)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Self-reported outcome and participants unblinded to intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Asthma control questionnaires (Asthma Control Test of Children's Asthma Control Test)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Rescue medication (SABA use)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dose of regular asthma therapy (ICS dose)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Lung Function (FEV1)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Wang, 2019

Bibliographic Reference	Wang, Xiaoru; Wu, Ling; Zhang, Zhi; Kong, Qinghua; Qi, Hui; Lei, Han; The Reliability of Adjusting Stepped Care Based on FeNO Monitoring for Patients with Chronic Persistent Asthma; Open medicine (Warsaw, Poland); 2019; vol. 14; 217-223

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Unclear
Study dates	January 2016 - December 2017
Sources of funding	Supported by Medical Science and Technology Project of Shanghai Xuhui District (SHXH201612).
Inclusion criteria	18-65 years old, met the GINA diagnostic criteria for asthma, in the stage of chronic persistence asthma according to clinical manifestations, severity of asthma slightly sustained or above, no inhalation or oral treatment of corticoids within 3 months before admission

Exclusion criteria	Acute respiratory infections within 4 weeks, comorbidity with other respiratory diseases, in the acute stage of asthma, severe liver and renal insufficiency and cardiac insufficiency, pregnant or lactating women, severe mental disorders, other diseases that might impact the results of the study, current smokers or former smokers who smoked more than 10 packs /year
Recruitment / selection of participants	Not reported
Intervention(s)	Patients were assessed every 3 months with an evaluation of symptoms, medications, lung function tests and a FeNO test. Step-down treatment was performed in patients with FeNO <25 ppb and complete control of clinical symptoms. The dose of ICS was doubled for patients with complete clinical control and FeNO ≥25ppb. Patients with partial control and uncontrolled asthma were given step-up treatment. If the patient's condition deteriorated during the step-down treatment, a readjustment was made to the original treatment program whereby a a higher level of treatment, or hospitalization is required.
Population subgroups	**Strata** **Children or adults** Adults **Population of current smokers (>20% vs ≤20%)** Smokers excluded **Subgroups** **Aim of the treatment in the study (step-up vs step-down ICS)** Mixed **Included adherence monitoring**

	No
Comparator	Treatment was adjusted according to symptoms over the past 4 weeks, medications and lung function tests. For the controlled group step-down treatment was given, and escalation therapy was given for partially controlled and uncontrolled patients.
Number of participants	160 randomised 80 allocated to FeNO management group 80 allocated to usual care group
Duration of follow-up	12 months
Indirectness	None
Additional comments	Not reported

Study arms

FeNO monitoring (N = 80)
Treatment adjusted according to GINA guidelines with additional FeNO input

Usual care (N = 80)
Treatment adjusted according to GINA (2014) guidelines

Characteristics

Arm-level characteristics

Characteristic	FeNO monitoring (N = 80)	Usual care (N = 80)
% Female Sample size	n = 34 ; % = 42.5	n = 36 ; % = 45
Mean age (SD) Mean (SD)	40.38 (9.85)	39.67 (9.34)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	FeNO monitoring, Baseline, N = 80	FeNO monitoring, 12 month, N = 80	Usual care, Baseline, N = 80	Usual care, 12 month, N = 80
Asthma control questionnaires (Asthma Control Questionnaire) scale range: 0-6, final values Mean (SD)	4.59 (1.07)	1.52 (0.56)	4.42 (1.14)	1.65 (0.51)
Lung function (PEF % predicted) final values Mean (SD)	70.32 (20.25)	89.18 (23.12)	73.56 (19.21)	91.31 (10.85)

Asthma control questionnaires (Asthma Control Questionnaire) - Polarity - Lower values are better
Lung function (PEF % predicted) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Asthma control questionnaires (Asthma Control Questionnaire)2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to monitoring strategies and treatments not reported, no information on missing outcome data or attrition rates and subjective outcome measure assessed by participants with knowledge of the interventions received)*
Overall bias and Directness	Overall Directness	Directly applicable

Lung function (PEF % predicted)2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence to monitoring strategies and treatments not reported, and no information on missing outcome data or attrition rates)*
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E – Forest plots

FeNO monitoring vs usual care in children and young people

Figure 2: Mortality (final values, lower is better, 12 months)

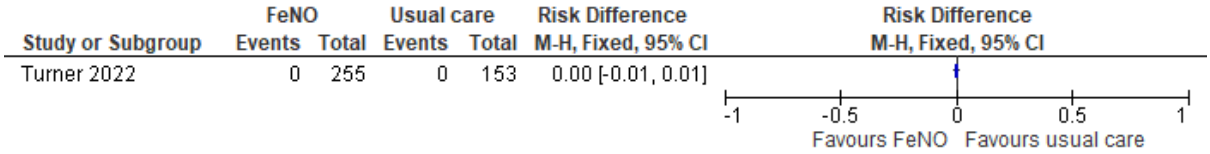


Figure 3: Unscheduled healthcare utilisation at >6 months (ED/A&E visits, final values, lower is better, 12 months)

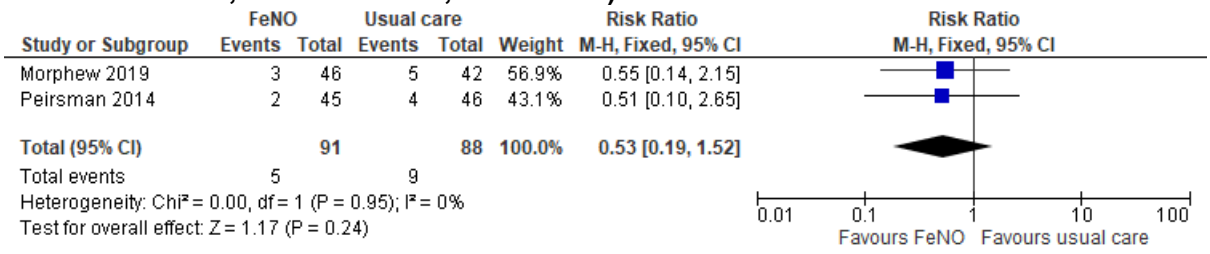


Figure 4: Unscheduled healthcare utilisation (unscheduled ER and clinica visits, final values, lower is better, 46 weeks)

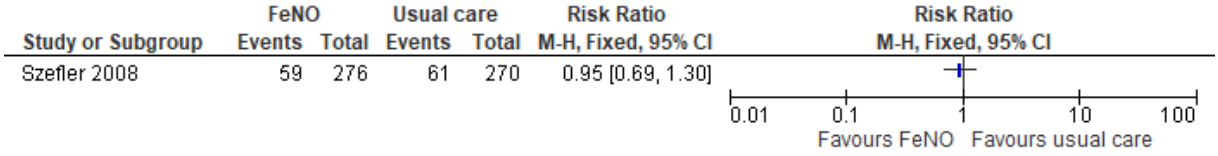


Figure 5: Unscheduled healthcare utilisation (hospital admissions, final values, lower is better, 46-52 weeks)

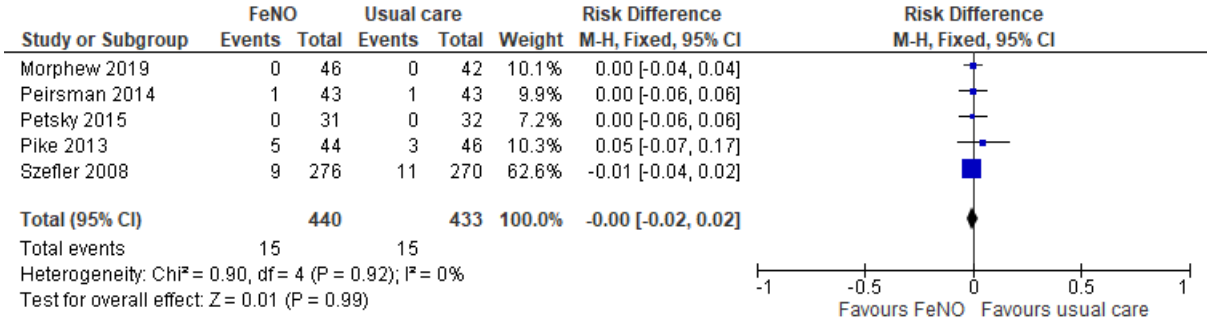


Figure 6: Severe asthma exacerbations (requiring oral corticosteroids, final values, lower is better, 26-52 weeks)

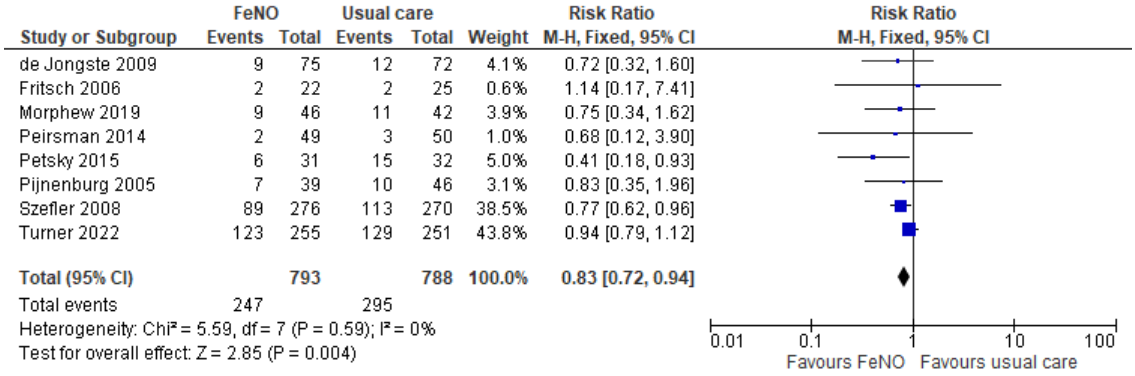


Figure 7: Asthma control questionnaires (Asthma Control Test, scale range: 0-25, final values, higher is better, 26-52 weeks)

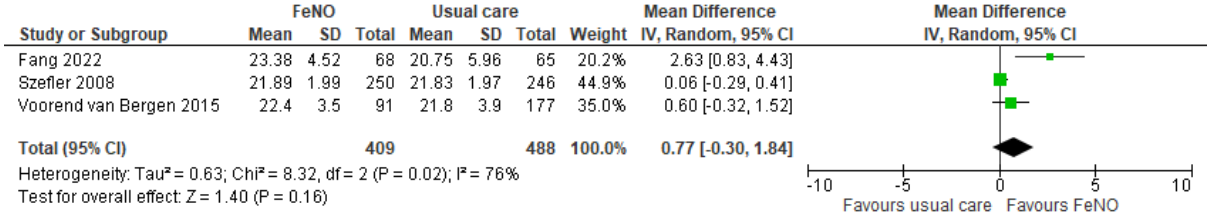


Figure 8: Lung function at (FEV1 % predicted, final values, higher is better, 6-12 monhts)

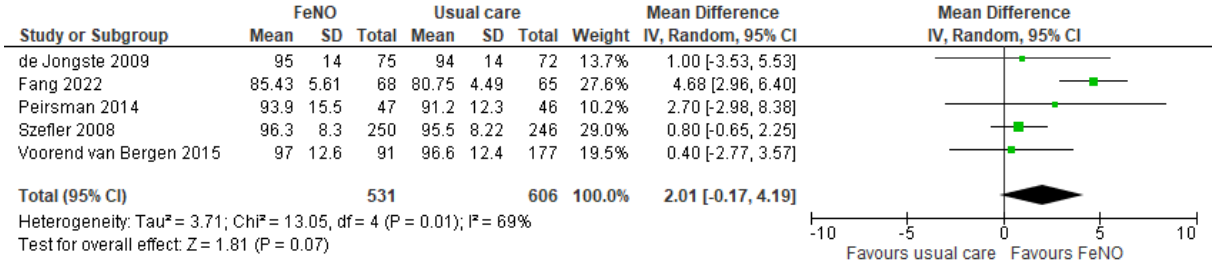


Figure 9: Lung function (PEF, % of predicted, final values, higher is better, 6 months)

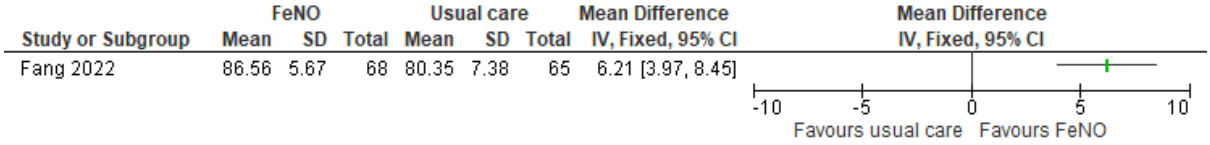


Figure 10: Symptoms (% symptom free days over 4 weeks, final values, higher is better, 12 months)

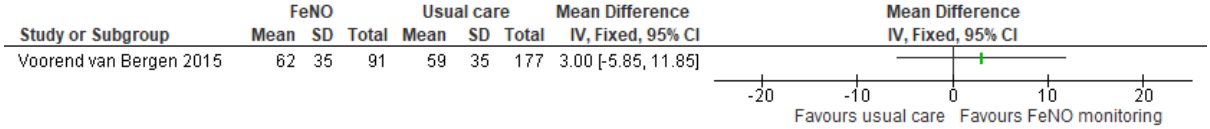


Figure 11: Dose of regular asthma therapy (mean daily ICS dose, final values, lower is better, 3-12 months)

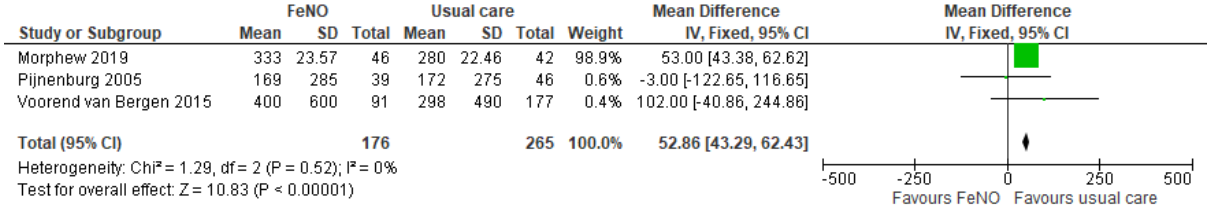


Figure 12: Rescue medication (SABA use, puffs per day, final values, lower is better, 12 months)

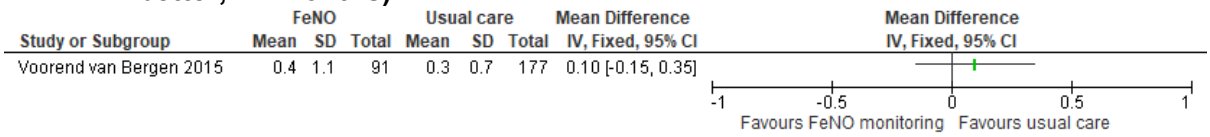


Figure 13: Time off school (school days missed in last 2 weeks, final values, lower is better, 46 weeks)

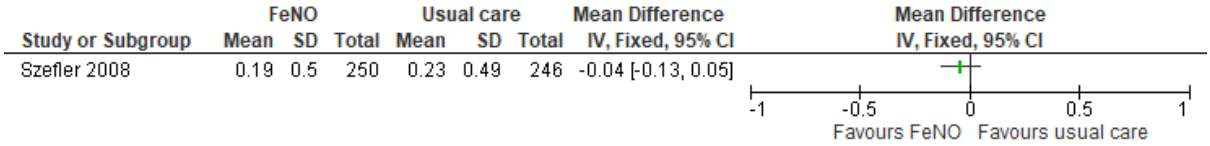
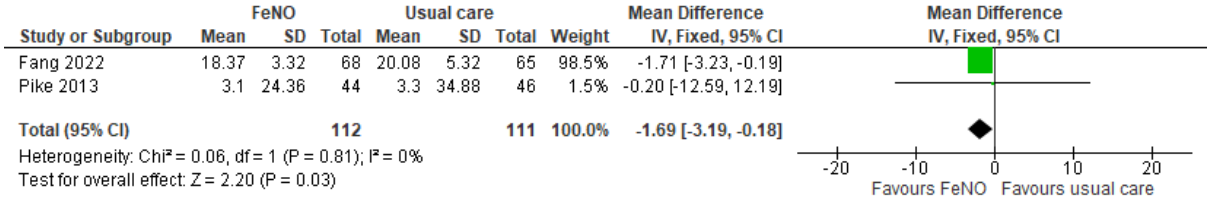


Figure 14: Time off school at >6 months (number of participants who missed any school day, final values, lower is better, 12 months)

Figure 15: Inflammatory markers (FeNO, ppb, mixed values, lower is better, 6-12 months)



FeNO monitoring vs usual care in adults

Figure 16: Unscheduled healthcare utilisation at A&E/ED visits, final values, lower is better, 25-52 weeks)

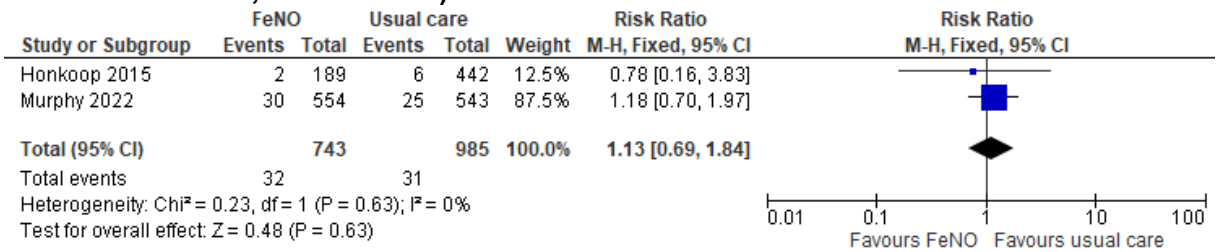


Figure 17: Unscheduled healthcare utilisation (hospital admissions, final values, lower is better, 25-52 weeks)

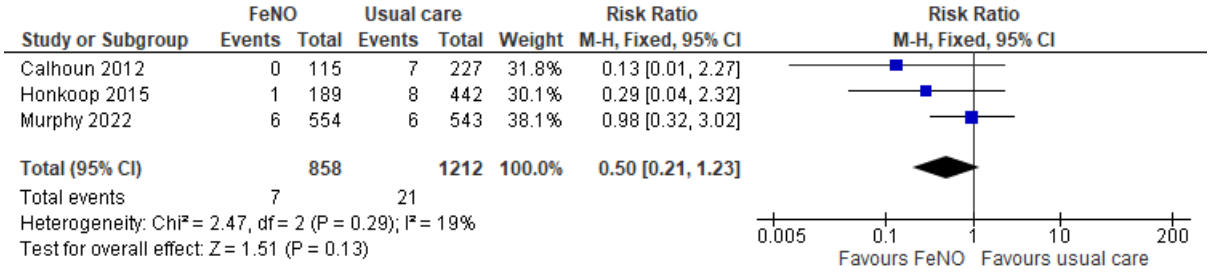


Figure 18: Severe asthma exacerbations (final values, lower is better, 25-78 weeks)

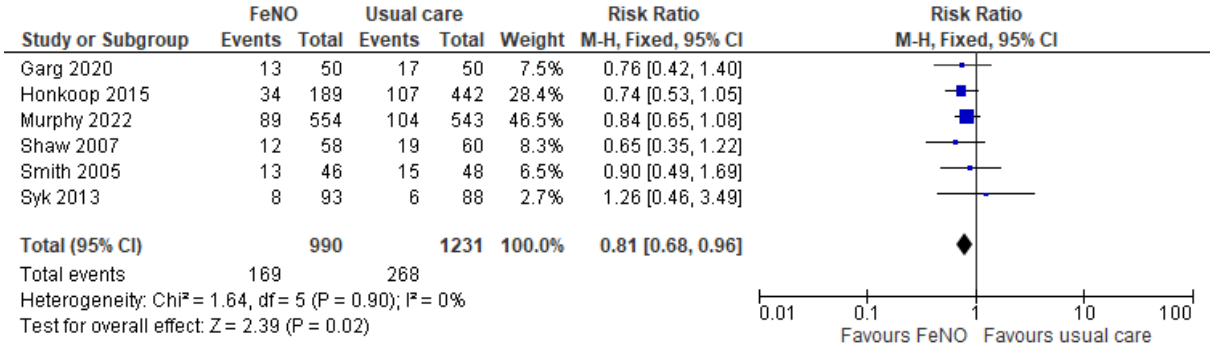


Figure 19: Asthma control questionnaires (Asthma Control Questionnaire, scale range: 0-6, mixed values, 36-52 weeks)

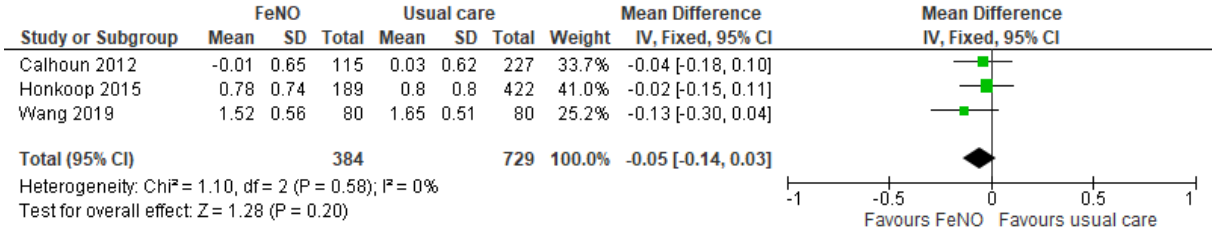


Figure 20: Asthma control questionnaires (Asthma Control Test, scale range 5-25, final values, higher is better, 9 months)

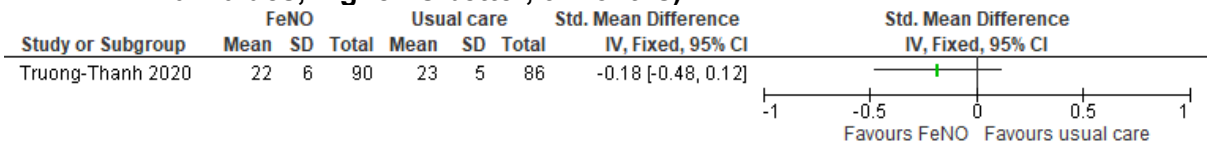


Figure 21: Quality of life (Mark's Asthma Quality of Life Questionnaire, scale range: 0-10, final values, lower is better, 18 weeks)

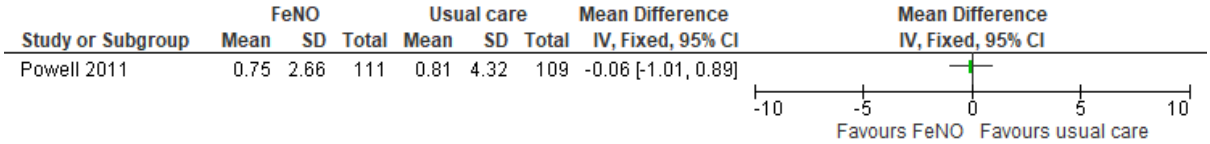


Figure 22: Quality of life (Asthma Quality of Life Questionnaire, scale range: 1-7, mixed values, higher is better, 36-52 weeks)

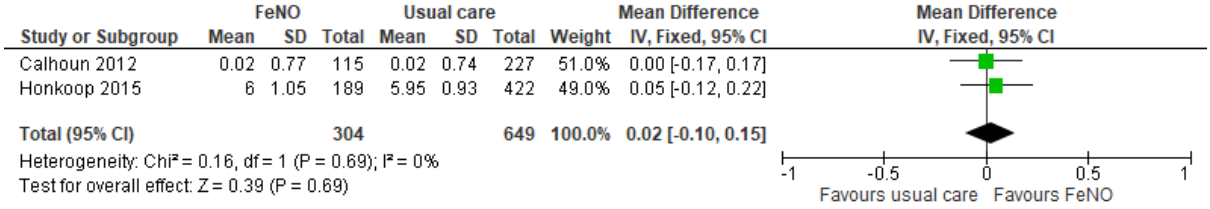


Figure 23: Lung function (FEV1, litres, mixed values, higher is better, 18-52 weeks)

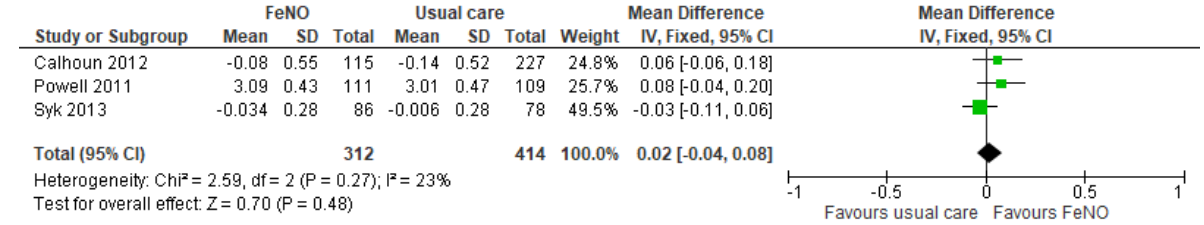


Figure 24: Lung function (FEV1 % predicted, mixed values, higher is better, 36-78 weeks)

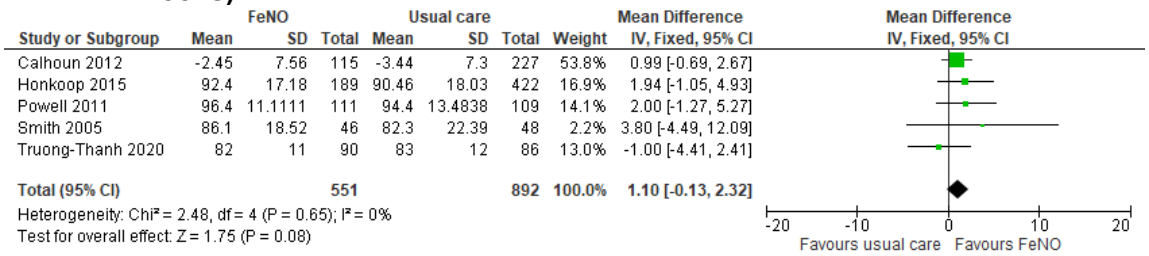


Figure 25: Lung function (PEF % predicted, final values, higher is better, 39-52 weeks)

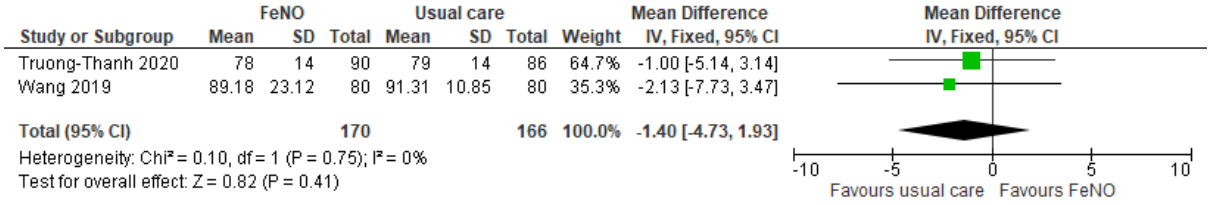


Figure 26: Lung function (PEF, litres/minute, change scores, higher is better, 36-78 weeks)

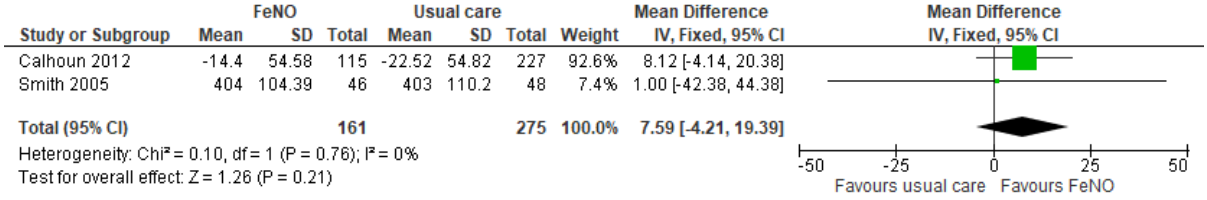


Figure 27: Dose of regular asthma therapy (ICS dose, mcg/day, mixed values, lower is better, 39-78 weeks)

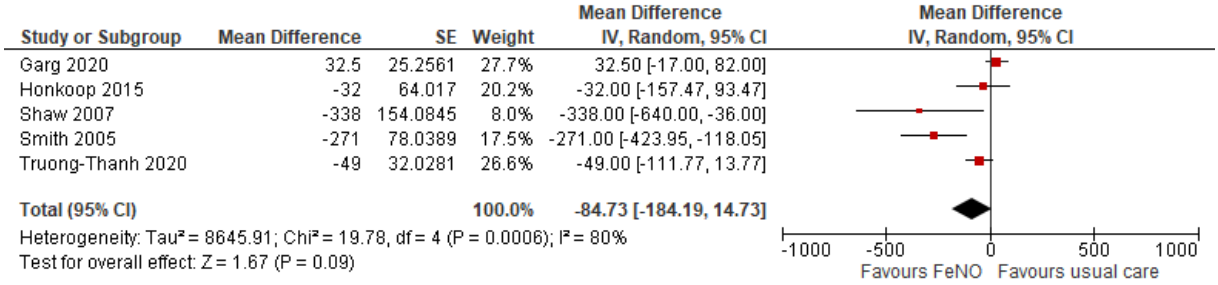


Figure 28: Rescue medication use (non-exercise preventative SABA use, change scores, lower is better, 36 weeks)

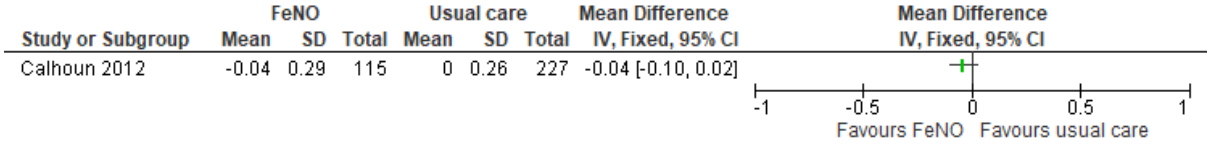


Figure 29: Rescue medication use (average bronchodilator use over previous 7 days, final values, lower is better, 18 months)

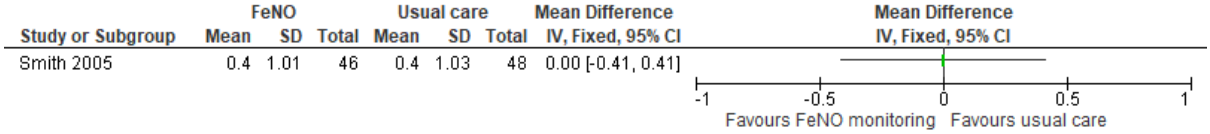
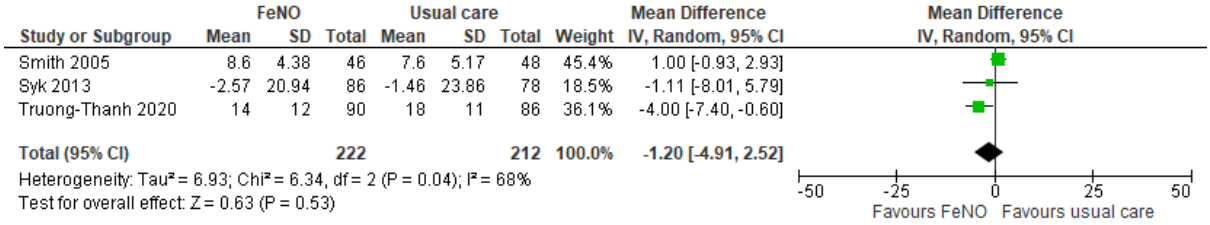


Figure 30: Inflammatory markers (FeNO, ppb, mixed values, lower is better, 9-18 months)



FeNO monitoring vs usual care in adults (smokers >20%)

Figure 31: Asthma control questionnaires (ACQ, scale range 0-6, change scores, lower is better, 28 weeks)

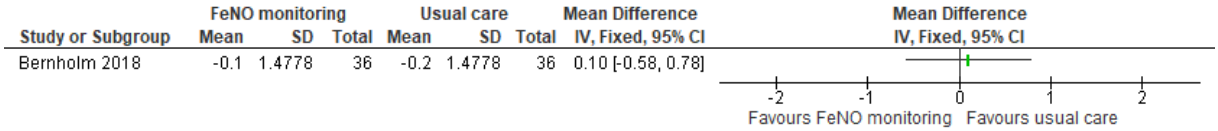


Figure 32: Quality of life (AQLQ, scale range 1-7, change scores, higher is better, 28 weeks)

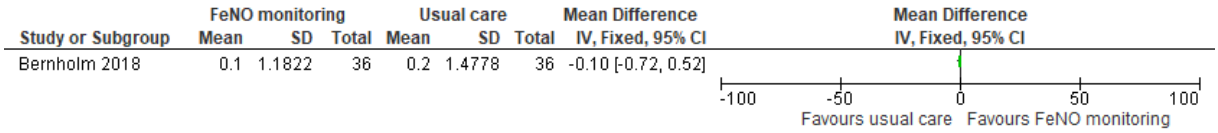


Figure 33: Lung function, FEV1, litres, change scores, higher is better, 28 weeks)

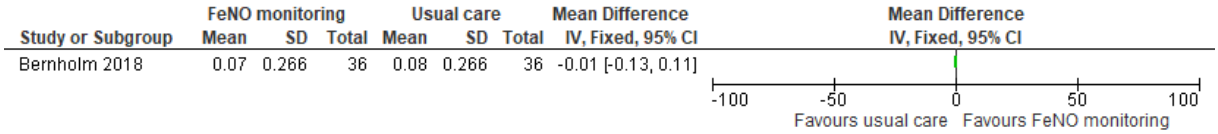


Figure 34: Lung function (FEV1 % predicted. change scores , higher is better, 28 weeks)

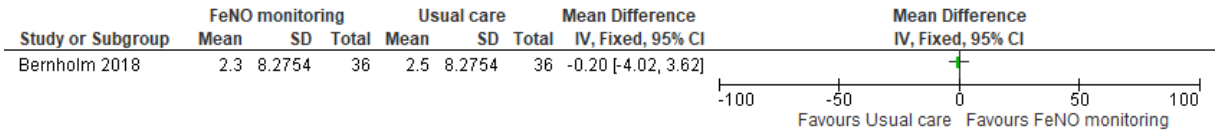


Figure 35: Dose of regular asthma therapy (ICS dose, mcg/day, change scores, lower is better, 28 weeks)

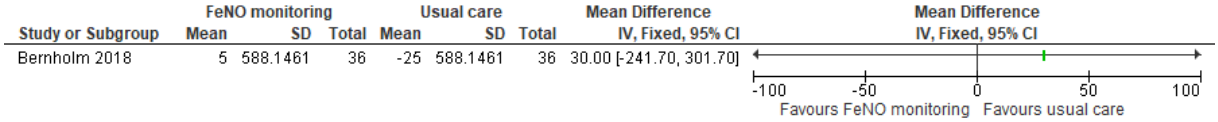
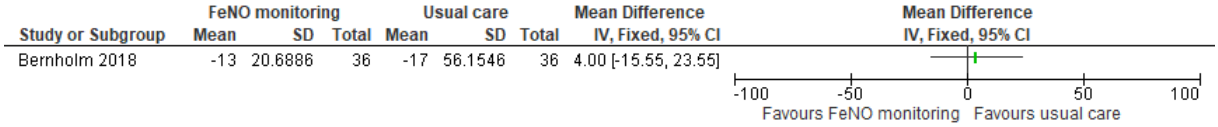


Figure 36: Inflammatory markers (FeNO, ppb, change scores, lower is better, 28 weeks)



Appendix F – GRADE tables

FeNO monitoring vs usual care in children and young people

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO monitoring	usual care in children and young people	Relative (95% CI)	Absolute (95% CI)		
Mortality (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	0/255 (0.0%)	0/251 (0.0%)	RD 0.00 (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	⨁⨁◯◯ Low	CRITICAL
Unscheduled healthcare utilisation (ED/A&E visits, final values, lower is better)												
2	randomised trials	serious[b]	not serious	not serious	very serious[c]	none	5/91 (5.5%)	9/88 (10.2%)	RR 0.53 (0.19 to 1.52)	**48 fewer per 1,000** (from 83 fewer to 53 more)	⨁◯◯◯ Very low	CRITICAL
Unscheduled healthcare utilisation (unscheduled ER and clinic visits, final values, lower is better)												
1	randomised trials	serious[b]	not serious	not serious	very serious[c]	none	59/276 (21.4%)	61/270 (22.6%)	RR 0.95 (0.69 to 1.30)	**11 fewer per 1,000** (from 70 fewer to 68 more)	⨁◯◯◯ Very low	CRITICAL
Unscheduled healthcare utilisation (hospital admissions, final values, lower is better)												
5	randomised trials	serious[b]	not serious	not serious	not serious	none	15/440 (3.4%)	15/433 (3.5%)	not estimable	**0 fewer per 1,000** (from 20 fewer to 20 more)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO monitoring	usual care in children and young people	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at ≥6 months (requiring oral corticosteroids, final values, lower is better)												
8	randomised trials	serious[d]	not serious	not serious	serious[e]	none	247/793 (31.1%)	295/788 (37.4%)	RR 0.83 (0.72 to 0.94)	**64 fewer per 1,000** (from 105 fewer to 22 fewer)	⨁⨁◯◯ Low	CRITICAL
Asthma control questionnaires at ≥3 months (Asthma Control Test (childrens and adults version), final values, higher is better)												
3	randomised trials	serious[d]	very serious[f]	not serious	not serious	none	409	488	-	MD **0.77 higher** (0.3 lower to 1.84 higher)	⨁◯◯◯ Very low	CRITICAL
Lung function (FEV1 % predicted, final values, higher is better)												
5	randomised trials	serious[d]	serious[g]	not serious	not serious	none	531	606	-	MD **2.01 higher** (0.17 lower to 4.19 higher)	⨁⨁◯◯ Low	CRITICAL
Lung function (PEF, % of predicted, final values, higher is better)												
1	randomised trials	serious[d]	not serious	not serious	not serious	none	68	65	-	MD **6.21 higher** (3.97 higher to 8.45 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Symptoms (% symptom free days over 4 weeks, final values, higher is better)												
1	randomised trials	serious[h]	not serious	not serious	not serious	none	91	177	-	MD **3 higher** (5.85 lower to 11.85 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Dose of regular asthma therapy (mean daily ICS dose, final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO monitoring	usual care in children and young people	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[b]	not serious	not serious	not serious	none	176	265	-	MD **52.86 ug/day higher** (43.29 higher to 62.43 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication at ≥3 months (SABA use, puffs per day, final values, lower is better)												
1	randomised trials	not serious	not serious	not serious	not serious	none	91	177	-	MD **0.1 higher** (0.15 lower to 0.35 higher)	⨁⨁⨁⨁ High	CRITICAL
Time off school (number of participants who missed any school day, final values, lower is better)												
2	randomised trials	serious[b]	not serious	not serious	very serious[c]	none	20/93 (21.5%)	24/92 (26.1%)	RR 0.82 (0.49 to 1.38)	**47 fewer per 1,000** (from 133 fewer to 99 more)	⨁◯◯◯ Very low	CRITICAL
Time off school (school days missed in last 2 weeks, final values, lower is better)												
1	randomised trials	serious[b]	not serious	not serious	not serious	none	250	246	-	MD **0.04 lower** (0.13 lower to 0.05 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Inflammatory markers at ≥8 weeks (FeNO, ppb, mixed values, lower is better)												
2	randomised trials	serious[d]	not serious	not serious	not serious	none	112	111	-	MD **1.69 lower** (3.19 lower to 0.18 lower)	⨁⨁⨁◯ Moderate	CRITICAL

a. Downgraded by two increments because the evidence is at high risk of bias (inadequate adherence to the monitoring strategies reported: 64.7% compliance in the FeNO group, 61% in the usual care group)

b. Downgraded by one increment for risk of bias because of some concerns about lack of information on adherence to monitoring strategies and treatments

c. Downgraded by two increments for imprecision because the 95% confidence interval crosses both MIDs (0.8-1.25)

d. Downgraded by one increment because there were some concerns about risk of bias for the majority of the evidence (adherence to monitoring strategies and treatments, and randomisation method not reported)

e. Downgraded by one increment for imprecision because the 95% confidence interval crosses one MID (0.8-1.25)

f. Downgraded by two increments for inconsistency (I squared=76%)

g. Downgraded by one increment for inconsistency (I squared=69%)

h. Downgraded by one increment because of some concerns about risk of bias (self-reported outcome and participants unblinded to intervention)

FeNO monitoring vs usual care in adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO monitoring	usual care in adults	Relative (95% CI)	Absolute (95% CI)		
Unscheduled healthcare utilisation (ED/A&E visits, final values, lower is better)												
2	randomised trials	not serious	not serious	not serious	very serious[a]	none	32/743 (4.3%)	31/985 (3.1%)	RR 1.13 (0.69 to 1.84)	**4 more per 1,000** (from 10 fewer to 26 more)	⨁⨁◯◯ Low	CRITICAL
Unscheduled healthcare utilisation (hospital admissions, final values, lower is better)												
3	randomised trials	not serious	not serious	not serious	serious[b]	none	7/858 (0.8%)	21/1212 (1.7%)	RR 0.50 (0.21 to 1.23)	**9 fewer per 1,000** (from 14 fewer to 4 more)	⨁⨁⨁◯ Moderate	CRITICAL
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
6	randomised trials	serious[c]	not serious	not serious	serious[b]	none	169/990 (17.1%)	268/1231 (21.8%)	RR 0.81 (0.68 to 0.96)	**41 fewer per 1,000** (from 70 fewer to 9 fewer)	⨁⨁◯◯ Low	CRITICAL
Asthma control questionnaires at ≥3 months (Asthma Control Questionnaire, scale range: 0-6, mixed values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO monitoring	usual care in adults	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[d]	not serious	not serious	not serious	none	384	729	-	MD **0.05 lower** (0.14 lower to 0.03 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Asthma control questionnaires at ≥3 months (Asthma Control Test, scale range: 5-25, final values, higher is better)												
1	randomised trials	very serious[e]	not serious	not serious	not serious	none	90	86	-	SMD **0.18 lower** (0.48 lower to 0.12 higher)	⨁⨁◯◯ Low	CRITICAL
Quality of life at ≥3 months (Asthma Quality of Life Questionnaire, scale range: 1-7, mixed values, higher is better)												
2	randomised trials	serious[c]	not serious	not serious	not serious	none	304	649	-	MD **0.02 higher** (0.1 lower to 0.15 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Quality of life at ≥3 months (Marks' Asthma Quality of Life Questionnaire, scale range: 0-10, final values, lower is better)												
1	randomised trials	serious[c]	not serious	not serious	not serious	none	111	109	-	MD **0.06 lower** (1.01 lower to 0.89 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (FEV1, litres, mixed values, higher is better)												
3	randomised trials	serious[c]	not serious	not serious	not serious	none	312	414	-	MD **0.02 higher** (0.04 lower to 0.08 higher)	⨁⨁⨁◯ Moderate	
Lung function (FEV1 % predicted, mixed values, higher is better)												
5	randomised trials	serious[c]	not serious	not serious	not serious	none	551	892	-	MD **1.1 higher** (0.13 lower to 2.32 higher)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO monitoring	usual care in adults	Relative (95% CI)	Absolute (95% CI)		
Lung function (PEF % predicted, final values, higher is better)												
2	randomised trials	serious[f]	not serious	not serious	not serious	none	170	166	-	MD **1.4 lower** (4.73 lower to 1.93 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (PEF, litres/minute, change scores, higher is better)												
2	randomised trials	serious[c]	not serious	not serious	serious[g]	none	161	275	-	MD **7.59 higher** (4.21 lower to 19.39 higher)	⨁⨁◯◯ Low	CRITICAL
Dose of regular asthma therapy (ICS dose, mcg/day, mixed values, lower is better)												
5	randomised trials	serious[f]	very serious[h]	not serious	serious[i]	none	375	606	-	MD **84.73 lower** (184.19 lower to 14.73 higher)	⨁◯◯◯ Very low	
Rescue medication use at ≥3 months (average bronchodilator use over previous 7 days, final values, lower is better)												
1	randomised trials	serious[f]	not serious	not serious	not serious	none	46	48	-	MD **0 puff/d** (0.41 lower to 0.41 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Rescue medication at ≥3 months (non-exercise preventative SABA use, change scores, lower is better)												
1	randomised trials	serious[c]	not serious	not serious	not serious	none	115	227	-	MD **0.04 puff/d lower** (0.1 lower to 0.02 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Inflammatory markers at ≥8 weeks (FeNO, ppb, mixed values, lower is better)												
3	randomised trials	serious[f]	serious[i]	not serious	not serious	none	222	212	-	MD **1.2 lower** (4.91 lower to 2.52 higher)	⨁⨁◯◯ Low	CRITICAL

a. Downgraded by two increments for imprecision because the 95% confidence interval crosses both MIDs (0.8-1.25)

b. Downgraded by one increment for imprecision because the 95% confidence interval crosses one MID (0.8-1.25)

c. Downgraded by one increment because of some concerns about risk of bias (adherence to monitoring strategies and treatments not reported)

d. Downgraded by one increment because of some concerns about risk of bias (adherence to interventions not reported and subjective outcome measure assessed by unblinded participants)

e. Downgraded by two increments because the evidence is at high risk of bias (randomisation method and adherence to monitoring strategies not reported; subjective outcome assessed by unblinded participant)

f. Downgraded by one increment because of some concerns about risk of bias (randomisation method and adherence to intervention not reported)

g. Downgraded by one increment for imprecision because the 95% confidence interval crosses one MID (published MID =18.79 L/min)

h. Downgraded by two increments for inconsistency (I squared = 80%)

i. Downgraded by one increment for imprecision because the 95% confidence interval crosses one MID (calculated as follow-up SDs of control group /2=65.5)j. Downgraded by one increment for inconsistency (I squared=68%)

FeNO monitoring vs usual care in adults (smokers >20%)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO monitoring	usual care in adults (smokers >20%)	Relative (95% CI)	Absolute (95% CI)		
Asthma control questionnaires at ≥3 months (Asthma Control Questionnaire, scale range: 0-6, change scores, lower is better, 24 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	36	36	-	MD **0.1 higher** (0.58 lower to 0.78 higher)	⨁◯◯◯ Very low	CRITICAL
Quality of life at ≥3 months (Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better, 24 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	36	36	-	MD **0.1 lower** (0.72 lower to 0.52 higher)	⨁◯◯◯ Very low	CRITICAL
Lung function (FEV1, litres, change scores, higher is better, 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO monitoring	usual care in adults (smokers >20%)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	not serious	none	36	36	-	MD **0.01 lower** (0.13 lower to 0.11 higher)	⨁⨁⨁◯ Moderate	CRITICAL

Lung function (FEV1 % predicted, change scores, higher is better, 24 weeks)

1	randomised trials	serious[a]	not serious	not serious	not serious	none	36	36	-	MD **0.2 lower** (4.02 lower to 3.62 higher)	⨁⨁⨁◯ Moderate	CRITICAL

Dose of regular asthma therapy (ICS dose, mcg/day, change scores, lower is better, 24 weeks)

1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	36	36	-	MD **30 higher** (241.7 lower to 301.7 higher)	⨁⨁◯◯ Low	CRITICAL

Inflammatory markers at ≥8 weeks (FeNO, ppb, change scores, lower is better, 24 weeks)

1	randomised trials	serious[a]	not serious	not serious	not serious	none	36	36	-	MD **4 higher** (15.55 lower to 23.55 higher)	⨁⨁⨁◯ Moderate	CRITICAL

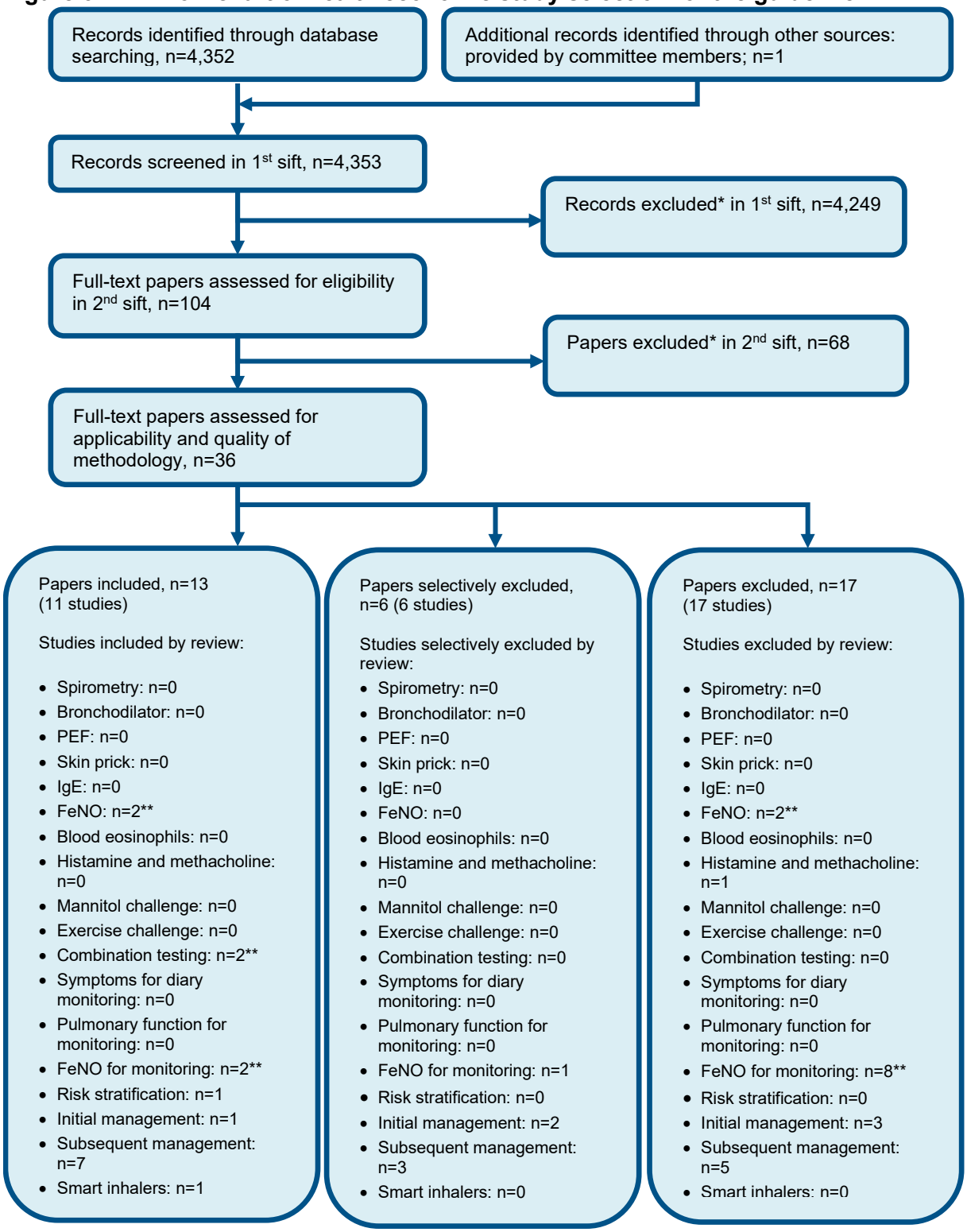
a. Downgraded by one increment because of some concerns about risk of bias (adherence to intervention not reported)

b. Downgraded by one increment for imprecision because the 95% confidence interval crosses both MIDs (established MIDs: ACQ=0.5; AQLQ=0.5)

c. Downgraded by one increment for imprecision because the 95% confidence interval crosses one MID (calculated as final SD of control group/2=294)

Appendix G – Economic evidence study selection

Figure 37: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language
** Includes studies that are in multiple reviews

Appendix H – Economic evidence tables

<table>
<tr><th>Study</th><th colspan="4">Harnan 2015(Harnan et al., 2015), also reported in NICE Diagnostics Guidance 12(National Institute for Health and Care Excellence, 2014)</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis: CUA (health outcome: QALYs)

Study design: Markov model
Approach to analysis: The model adopts two states: (1) alive with diagnosed asthma and (2) dead. The model assumes that exacerbation rate is used to determine proportion of people who have a disutility and hospitalisation cost/drug management cost. Two-year data was extrapolated over a lifetime horizon.

Perspective: UK NHS
Time horizon Lifetime
Treatment effect duration:[a] Lifetime

Discounting: Costs: 3.5%; Outcomes: 3.5%</td>
<td>Population:
People treated for diagnosed asthma.
Two distinct groups: adults and children.
Cohort settings:
Start age group ‘adults’: 18 years
Male: 40%

Start age group ‘children’: Children 5 years
Male: 55%

Intervention 1:
BTS/SIGN guidelines (standard care)

Intervention 2:
Guidelines plus FeNO monitoring at each visit plus four additional appointments with a practice nurse. FeNO measurement to titrate medication.(NObreath)</td>
<td>Total costs (mean per patient):

Adults Group Intervention (£)
1:7296
2:7378
3:7535
4:7609

Children Group Intervention (£)
1:5860
2:8149
3:8314
4:8392

For incremental analysis see cost effectiveness

Currency & cost year:
2012/2013 UK pounds

Cost components incorporated:</td>
<td>QALYs (mean per patient):

Adults group Intervention
1:21.9018
2:21.9397
3:21.9397
4:21.9397
4.21.9018

Children Group Intervention
1:23.6261
2:23.6767
3:23.6767
4:23.6767

For incremental analysis see cost effectiveness</td>
<td>Full incremental analysis (pa): [b] [c]

Adult group
<table>
<tr><th>Int</th><th>Cost (£)</th><th>QALY</th><th>Inc cost (£)</th><th>Inc QALY</th><th>ICER</th><th>% Most CE at £20K/£30K:</th></tr>
<tr><td>1</td><td>7296</td><td>21.9018</td><td colspan="3">Baseline</td><td>18%/13%</td></tr>
<tr><td>2</td><td>7378</td><td>21.9397</td><td>81.31</td><td>0.0379</td><td>2146</td><td>82%/87%</td></tr>
<tr><td>3</td><td>7535</td><td>21.9397</td><td colspan="3">Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>4</td><td>7609</td><td>21.9397</td><td colspan="3">Dominated by 2</td><td>0%/0%</td></tr>
</table>
Probability Intervention 2 (NObreath) cost effective (£20K/30K threshold): 82%/87%

Children group
<table>
<tr><th>Int</th><th>Cost (£)</th><th>QALY</th><th>Inc cost (£)</th><th>Inc QALY</th><th>ICER</th><th>% Most CE at £20K/£30K:</th></tr>
</table>
</td>
</tr>
</table>

Intervention 3:
Guidelines plus FeNO monitoring at each visit plus four additional appointments with a practice nurse. FeNO measurement to titrate medication (NIOX VERO)

Intervention 4:
Guidelines plus FeNO monitoring at each visit plus four additional appointments with a practice nurse. FeNO measurement to titrate medication (NIOX MINO)

FeNO monitoring visits (additional quarterly appointment with nurse),
Marginal per-test costs for FeNO devices,
Relative Dose Intensity of Inhaled Corticosteroids (RDI ICS);
Cost of severe hospitalised exacerbation,
Cost of severe non-hospitalised exacerbation (one GP appointment and course of oral steroids).

1	5860.06	23.6261	Baseline			99%/91%
2	8148.59	23.6767	2288.53	0.0506	45,213	1%/9%
3	8314.30	23.6767	Dominated by 2			0%/0%
4	8391.53	23.6767	Dominated by 2			0%/0%

Probability **Intervention 1 (guidelines only)** cost effective (£20K/30K threshold): 99%/91%

Analysis of uncertainty:
The marginal test cost of FeNO testing doesn't have a significant impact on the overall cost-effectiveness of FeNO monitoring compared with guidelines.
Discounting has little impact on the cost-effectiveness of FeNO monitoring.

Adult group
The result was most sensitive to how long the impacts of FeNO monitoring lasted. If the impacts on exacerbation rates and change in ICS dosage lasted less than 30 years then FeNO monitoring was no longer cost effective with an ICER of £29,707 per QALY gained. The result was also sensitive to different input parameters derived from different RCTs. Using alternative exacerbation rates from Syk et al. and Smith et al. has a substantial negative impact on
the cost-effectiveness of FeNO monitoring which has a significant ICER (£184,000) and dominated by guidelines respectively.
The cost-effectiveness of FeNO monitoring improves over longer time horizons, if the time horizon is less than 5 years all the results are over £163,000 per QALY gained. This is

				driven by observed differences in relative ICS use identified in data from trials. **Children group** The results in the child model are particularly sensitive to assumptions regarding changes in ICS use over time, the number of nurse visits for FeNO monitoring and the duration over which FeNO monitoring is assumed to impact on exacerbations and ICS use. The duration over which FeNO monitoring is assumed to impact on exacerbations and ICS use is a key parameter within the child subgroup. In the base-case the impact of FeNO monitoring on dose titration and exacerbations would be retained indefinitely over the patient's lifetime Shorter durations of impact improve the cost-effectiveness of FeNO monitoring compared to standard guidelines. If the impact is assumed to be 10 years or less then the ICER for NObreath + guidelines will remain below £30,000 per QALY gained. Changes in ICS use over time have a significant impact on the result however all results have a ICER of over £30,000.
Data sources				
Health outcomes: Systematic review conducted with studies selected based on applicability to reflect NHS practise. Annual exacerbation rates with and without FeNO testing were derived for children from the RCT reported by Szefler et al. (2008) (USA based selected as similar to UK practice) and for adults from the RCT reported by Shaw et al. (2005) which was selected as this was the only study that was UK based. Changes in ICS use with/without FeNO monitoring for the child and adult subgroups were also drawn from these trials. These studies had a follow up of 46 weeks and 52 weeks, respectively. **Quality-of-life weights:** Disutility associated with hospitalised and non-hospitalised exacerbations taken from Lloyd et al. (2007). This used EQ-5D questionnaire, patient population were classed as UK based with moderate to severe asthma (BTS levels 4 & 5). The duration of hospitalisations/length of exacerbation was taken from expert opinion. **Cost sources:** BTS/SIGN, Unit costs taken from NHS reference costs, PSSRU unit costs, FeNO manufacturers, Healthcare Resource Group, previous HTA reports, BNF, and published studies (drug management costs from Main et al. (2008)				
Comments				
Source of funding: NIHR **Limitations:** Effectiveness evidence, the study used to inform the model particularly children, (Szefler et al.) the study was undertaken in the USA and does not fully match BTS/SIGN guidelines on dose titration. Both analyses are based on single RCT trials. A further limitation is that there is uncertainty and lack of long-term evidence on the duration over which FeNO monitoring impacts on dose titration. This could change the cost effectiveness results. Only quality of life improvements from reduced exacerbations are considered and impacts on mortality are not considered, however these limitations are due to a lack of clinical				

evidence rather than methodological choices. Strong assumptions imposed regarding extrapolating treatment effects over a lifetime horizon. The costs may not reflect current prices whilst the effectiveness data may not reflect the clinical evidence.

Other: All FeNO tests (NIOX MINO, NIOX VERO and NObreath) are assumed to have equivalent diagnostic accuracy

Overall applicability:[d] Directly applicable **Overall quality:**[e] Potentially serious limitations

Abbreviations: BTS-SIGN= British Thoracic Society/Scottish Intercollegiate Guidelines Network, CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); FeNO= Fractional exhaled nitric oxide, HRQoL= Health related quality of life; ICER= incremental cost-effectiveness ratio; ICS= Inhaled corticosteroid, NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years, SA=sensitivity analysis

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Intervention number in order of least to most effective (in terms of QALYs)

(c) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Yang 2022(Yang et al., 2021)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcomes: asthma control status and quality of life) **Study design:** A within-trial analysis of CHAMPIONS, a before-and-after observational cohort study conducted in 10 general practices in England between 2016 and 2017 designed to evaluate the implementation of Spirometry and FeNO testing for children with diagnosed or suspected asthma. **Approach to analysis:** Healthcare costs and outcomes (asthma control status and quality of life) were collected 6 months before and after the implementation using GP records. Training and implementation costs were separately calculated and added. Healthcare utilisation and quality of life	**Population:** Children in the asthma register and children with suspected asthma who were prescribed asthma medications in the previous 12 months. **Cohort settings:** Mean age: 10 (3.3) Male: 54.2% Asthma register: 74.5% **Intervention 1:** Before implementing spirometry and FeNO guided asthma review (where asthma reviews included no objective tests) **Intervention 2:** After implementing spirometry and FeNO guided asthma review	**Total costs (mean per patient):** CHAMPIONS: Incremental[(a)] (2−1): -£20.5 (95% CI: NR; p=NR) Real-world Incremental[(b)] (2−1): £12.8 (95% CI: NR; p=NR) **Currency & cost year:** 2017 UK pounds **Cost components incorporated:** Unplanned healthcare attendance, unplanned hospital admission, purchase of the equipment (test devices), implementing and delivering test-guided asthma review	**Quality of life and asthma control (mean per patient):** Intervention 1: Mean ACT: 19.9 (4.0) Mean CACT: 20.8 (4.2) Mean CHU9D: 0.88 (0.16) Mean PAQLQ Overall Score: 5.92 (1.06) Mean PAQLQ Activity Score: 5.68 (1.31) Mean PAQLQ Symptom Score: 5.95 (1.18) Mean PAQLQ Emotional Score: 6.05 (1.08) Intervention 2: Mean ACT: 21.0 (3.8) Mean CACT: 22.1 (3.9) Mean CHU9D: 0.85 (0.18) Mean PAQLQ Overall Score: 6.02 (1.04) Mean PAQLQ Activity Score: 5.85 (1.22) Mean PAQLQ Symptom Score: 6.05 (1.17) Mean PAQLQ Emotional Score: 6.12 (1.08)	**ICER (Intervention 2 versus Intervention 1):** n/a **Analysis of uncertainty:** No probabilistic sensitivity analysis was performed. The authors offered two different estimations for equipment costs: one based on the low costs recorded in CHAMPIONS study where two spirometers were rotated between 10 GP practices and FeNO devices were received by the manufacturers free of charge; the second based on a real-world situation where each GP practices is required to purchase their own equipment. The incremental costs calculated using both estimation are reported in the table.

outcomes were compared before and after to estimate the impact of the intervention. **Perspective:** UK NHS **Follow-up :** 1 year **Discounting:** Costs: n/a; Outcomes: n/a			Incremental (2−1): Mean ACT: 1.1 Mean CACT: 1.3 Mean CHU9D: -0.03 Mean PAQLQ Overall Score: 0.1 Mean PAQLQ Activity Score: 0.17 Mean PAQLQ Symptom Score: 0.1 Mean PAQLQ Emotional Score: 0.07 **Mean dose of daily prescribed ICS** Intervention 1: 191.1 (218.9) Intervention 2: 218.2 (213.3) Incremental (2-1): 27.1 (95% CI: NR; p=NR)	
Data sources				
Health outcomes: Data on asthma-related quality of life were collected from all children recruited at baseline and those who provided data at 6 months-follow up. Asthma control status of each child was assessed using ACT and CACT. Asthma-related quality of life was assessed using PAQLQ ad general health-related quality of life was assessed using CHU9D. **Quality-of-life weights:** QALYs were not calculated in this analysis. **Cost sources:** Standard unit cost for each GP visit was obtain from Unit Cost of Health and Social Care (PSSRU) 2017. Standard unit cost for hospitalisation was obtained from NHS Reference Cost 2017.				
Comments				
Source of funding: This work was supported by grants provided by the Midlands Asthma and Allergy Research Association and Circassia Pharmaceuticals. **Limitations:** The evidence is based on a before-and-after study so the results might be biased by confounding factors. EQ-5D measures were not reported and quality-of-life weights were not calculated. The impact on pharmaceutical cost was not explored despite a statistically significant difference in the number of asthma medication prescriptions and median dose of ICS before and after the test-guided asthma reviews. Although data asthma-related quality of life were collected from all children at baseline, there was a high dropout in the end with only 37% of children providing data at 6 months' follow-up. A dropout statistical analysis was not attempted so it is unclear if dropouts biased the estimation of quality of life after implementing				

test-guided asthma reviews. The CAMPIONS estimation of equipment cost is a clear underestimation of real-world costs as the same devices were rotated between 10 different practices and FeNO devices were received free of charge. The real-world estimation is likely to be an overestimation of costs as the capital investment for 10 spirometers and 10 calibration syringes was not distributed among all patients, for instance adults, who would use the devices as well if purchased. No sensitivity analysis (bootstrapping) was conducted. **Other:** The manufacturer of FeNO devices (CIRCASSIA) directly sponsored the study and provided two FeNO devices to the authors free of charge	
Overall applicability: Partially applicable(c)	**Overall quality: Potentially serious limitations**(d)

Abbreviations: ACT= Asthma Control Test; CCA= cost–consequences analysis; 95% CI= 95% confidence interval; CHU9D= Child's Health Utility 9D; FeNO= Fractional Exhaled Nitric Oxide; ICER= incremental cost-effectiveness ratio; ICS= inhaled corticosteroids; NR= not reported; n/a= not available; PAQLQ= Paediatric Asthma Quality of Life Questionnaire; QALYs= quality-adjusted life years.

(a) Excluding implementation costs (development of training package, face-to-face teaching and practice training) and including the low equipment cost in CHAMPIONS consisting in two spirometers only as FeNO devices were given for free

(b) Excluding implementation costs (development of training package, face-to-face teaching and practice training) and including the equipment costs suggested by NICE for 10 spirometers and 10 calibration syringes and 612 FeNO tests

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Health economic model

This area was not prioritised for health economic modelling.

Appendix J – Excluded studies

Clinical studies

Table 12: Studies excluded from the clinical review

Study	Code [Reason]
Abba, Abdullah A. (2009) Exhaled nitric oxide in diagnosis and management of respiratory diseases. Annals of thoracic medicine 4(4): 173-81	- Review article but not a systematic review
Alahmadi, Fahad, Peel, Adam, Keevil, Brian et al. (2021) Assessment of adherence to corticosteroids in asthma by drug monitoring or fractional exhaled nitric oxide: A literature review. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 51(1): 49-62	- Study design not relevant to this review protocol *Review focused on adherence as outcome, not relevant to this protocol*
Araujo, L., Jacinto, T., Moreira, A. et al. (2012) Clinical efficacy of web-based versus standard asthma self-management. Journal of investigational allergology & clinical immunology 22(1): 28-34	- Study does not contain an intervention relevant to this review protocol *FeNO not included in either treatment arm*
Arnold, Renee J. G.; Layton, Andrew; Massanari, Marc (2018) Cost impact of monitoring exhaled nitric oxide in asthma management. Allergy and asthma proceedings 39(5): 338-344	- Study design not relevant to this review protocol *Retrospective observational study, not an RCT*
Arnold, Renee Jg, Massanari, Marc, Lee, Todd A. et al. (2018) A Review of the Utility and Cost Effectiveness of Monitoring Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management. Managed care (Langhorne, Pa.) 27(7): 34-41	- Study design not relevant to this review protocol *Systematic review of economic analyses, no information relevant to this review question*
Ashutosh, K. (2000) Nitric oxide and asthma: a review. Current opinion in pulmonary medicine 6(1): 21-5	- Review article but not a systematic review
Bayes, Hannah K. and Cowan, Douglas C. (2016) Biomarkers and asthma management: an update. Current opinion in allergy and clinical immunology 16(3): 210-7	- Review article but not a systematic review
Beerthuizen, Thijs, Voorend-van Bergen, Sandra, van den Hout, Wilbert B. et al. (2016) Cost-effectiveness of FENO-based and web-based monitoring in paediatric asthma	- Study design not relevant to this review protocol

Study	Code [Reason]
management: a randomised controlled trial. Thorax 71(7): 607-13	*Economic analysis of: Voorend-van Bergen S, Vaessen-Verberne AA, Brackel HJ, et al. Monitoring strategies in children with asthma: a randomised controlled trial. Thorax 2015;70:543–50*
Berg, Jenny and Lindgren, Peter (2008) Economic evaluation of FE(NO) measurement in diagnosis and 1-year management of asthma in Germany. Respiratory medicine 102(2): 219-31	- Study design not relevant to this review protocol *Economic analysis of multiple RCTs*
Boer, Suzanne, Honkoop, Persijn J., Loijmans, Rik J. B. et al. (2020) Personalised exhaled nitric oxygen fraction (F ENO)-driven asthma management in primary care: a F ENO subgroup analysis of the ACCURATE trial. ERJ open research 6(3)	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis of Honkoop 2015*
Brooks, Elizabeth A. and Massanari, Marc (2018) Cost-Effectiveness Analysis of Monitoring Fractional Exhaled Nitric Oxide (FeNO) in the Management of Asthma. Managed care (Langhorne, Pa.) 27(7): 42-48	- Study design not relevant to this review protocol *Economic model, not an RCT*
Buendia, J. A.; Acuna-Cordero, R.; Rodriguez-Martinez, C. E. (2021) Budget impact analysis of Fractional Exhaled Nitric Oxide Monitoring for the Management of Childhood Asthma: The Colombian National Health System perspective. Journal of investigational allergology & clinical immunology: 0	- Study design not relevant to this review protocol *Economic analysis*
Buendia, Jefferson Antonio; Acuna-Cordero, Ranniery; Rodriguez-Martinez, Carlos E. (2021) Cost utility of fractional exhaled nitric oxide monitoring for the management of children asthma. Cost effectiveness and resource allocation : C/E 19(1): 33	- Study design not relevant to this review protocol *Economic analysis*
Bush, Andrew and Eber, Ernst (2008) The value of FeNO measurement in asthma management: the motion for Yes, it's NO--or, the wrong end of the Stick!. Paediatric respiratory reviews 9(2): 127-31	- Review article but not a systematic review
Calhoun, Karen H. (2014) The role of fractional exhaled nitric oxide in asthma management. Otolaryngologic clinics of North America 47(1): 87-96	- Review article but not a systematic review

Study	Code [Reason]
Carroll, W. and Ruggins, N. (2014) Managing childhood asthma: Clinical experience with the measurement of fractional exhaled nitric oxide (FeNO). Paediatrics and Child Health (United Kingdom) 24(6): 260-263	- Review article but not a systematic review
Cloutier, Michelle M., Dixon, Anne E., Krishnan, Jerry A. et al. (2020) Managing Asthma in Adolescents and Adults: 2020 Asthma Guideline Update From the National Asthma Education and Prevention Program. JAMA 324(22): 2301-2317	- More recent systematic review included that covers the same topic
Cowan, Douglas C., Hewitt, Richard S., Cowan, Jan O. et al. (2010) Exercise-induced wheeze: Fraction of exhaled nitric oxide-directed management. Respirology (Carlton, Vic.) 15(4): 683-90	- Study does not contain an intervention relevant to this review protocol *No monitoring strategies included*
Dabbaghzadeh, Abbas; Tavakol, Marzieh; Gharagozlou, Mohammad (2019) The Role of FENO in Comparison to Spirometry and ACT in Control of Children Asthma Symptoms. Iranian journal of allergy, asthma, and immunology 18(5): 479-486	- Study design not relevant to this review protocol *Cross-sectional study, not an RCT*
de Abreu, Fernanda Cruvinel; da Silva Junior, Jose Laerte Rodrigues; Rabahi, Marcelo Fouad (2019) The Fraction Exhaled Nitric Oxide as a Biomarker of Asthma Control. Biomarker insights 14: 1177271919826550	- Study design not relevant to this review protocol *Cross-sectional study, not an RCT*
Delgado-Corcoran, Claudia, Kissoon, Niranjan, Murphy, Suzanne P. et al. (2004) Exhaled nitric oxide reflects asthma severity and asthma control. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 5(1): 48-52	- Study design not relevant to this review protocol *Cross-sectional study, not an RCT*
Deykin, Aaron, Lazarus, Stephen C., Fahy, John V. et al. (2005) Sputum eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids. The Journal of allergy and clinical immunology 115(4): 720-7	- Study does not contain an intervention relevant to this review protocol *Investigating different inhaler treatments, not monitoring strategies*
Diamant, N., Amirav, I., Armoni-Domany, K. et al. (2021) High fractional exhaled nitric oxide levels in asthma patients: Does size matter?. Pediatric Pulmonology 56(6): 1449-1454	- Study design not relevant to this review protocol *Cross-sectional study, not an RCT*

Study	Code [Reason]
Dinakar, C. (2009) Exhaled nitric oxide in pediatric asthma. Current allergy and asthma reports 9(1): 30-37	- Study not reported in English
Dinakar, Chitra (2004) Exhaled nitric oxide in the clinical management of asthma. Current allergy and asthma reports 4(6): 454-9	- Review article but not a systematic review
Dinh-Thi-Dieu, H., Vo-Thi-Kim, A., Tran-Van, H. et al. (2020) Study of the beneficial role of exhaled nitric oxide in combination with GINA guidelines for titration of inhaled corticosteroids in children with asthma. Journal of breath research 14(2): 026014	- Study does not contain an intervention relevant to this review protocol *Study uses ICS doses not applicable to current UK practice*
Dodig, Slavica; Richter, Darko; Zrinski-Topic, Renata (2011) Inflammatory markers in childhood asthma. Clinical chemistry and laboratory medicine 49(4): 587-99	- Review article but not a systematic review
Donohue, James F. and Jain, Neal (2013) Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates. Respiratory medicine 107(7): 943-52	- Review article but not a systematic review
Duong-Quy, S., Hua-Huy, T., Doan-Quynh, N. et al. (2015) A study of exhaled NO (FENO) measurement used to determine asthma control, dose of inhaled corticosteroid and cost in a developing country. European respiratory journal 46	- Full text paper not available
Duong-Quy, Sy (2019) Clinical Utility Of The Exhaled Nitric Oxide (NO) Measurement With Portable Devices In The Management Of Allergic Airway Inflammation And Asthma. Journal of asthma and allergy 12: 331-341	- Review article but not a systematic review
Essat, Munira, Harnan, Sue, Gomersall, Tim et al. (2016) Fractional exhaled nitric oxide for the management of asthma in adults: a systematic review. The European respiratory journal 47(3): 751-68	- More recent systematic review included that covers the same topic
Fang, C, Yang, L-J, Chen, X-J et al. (2022) A clinical investigation into the usefulness of fractional exhaled nitric oxide in guiding glucocorticoid therapy in children with bronchial asthma. Journal of physiology and	- Systematic review used as source of primary studies

Study	Code [Reason]
pharmacology : an official journal of the Polish Physiological Society 73(4)	
Ferrante, G., Malizia, V., Antona, R. et al. (2013) The value of FeNO measurement in childhood asthma: Uncertainties and perspectives. Multidisciplinary Respiratory Medicine 8(7): 50	- Review article but not a systematic review
Fielding, S. S., Pijnenburg, M., de Jongste, J. et al. (2020) Does treatment guided by fractional exhaled nitric oxide improve outcomes in subgroups of children with asthma?. The european respiratory journal	- Duplicate reference
Fielding, S., Pijnenburg, M., De Jongste, J. et al. (2017) FEV1 and FeNo as predictors of asthma outcomes in children? an individual patient data analysis using data from six FeNo trials. Thorax 72(supplement3): a37	- Conference abstract
Fielding, Shona S., Pijnenburg, Marielle, de Jongste, Johan et al. (2020) Does treatment guided by exhaled nitric oxide fraction improve outcomes in subgroups of children with asthma?. The European respiratory journal 55(5)	- Duplicate reference
Fielding, Shona, Pijnenburg, Marielle, de Jongste, Johan C. et al. (2019) Change in FEV1 and Feno Measurements as Predictors of Future Asthma Outcomes in Children. Chest 155(2): 331-341	- Study design not relevant to this review protocol *Individual patient data analysis of 6 RCTS all identified and included in this review*
Fielding, Shona, Pijnenburg, Marielle, de Jongste, Johan et al. (2020) What is a clinically meaningful change in exhaled nitric oxide for children with asthma?. Pediatric pulmonology 55(3): 599-606	- Study design not relevant to this review protocol *Individual patient data analysis of 6 RCTS all identified and included in this review*
Franklin, Peter J. and Stick, Stephen M. (2008) The value of FeNO measurement in asthma management: the motion against FeNO to help manage childhood asthma--reality bites. Paediatric respiratory reviews 9(2): 122-6	- Review article but not a systematic review
Galant, S. P., Morphew, T., Shin, H. W. et al. (2018) The role of fractional exhaled nitric oxide (FENO) in the asthma decision process: The discordant/concordant (D/C) ratio. American Journal of Respiratory and Critical Care Medicine 197(meetingabstracts)	- Conference abstract

Study	Code [Reason]
Garcia-Estepa, R., Praena, M., Ruiz-Canela, J. et al. (2011) Systematic review of the usefulness of exhaled nitric oxide in management of childhood and adolescence asthma. Allergy: European Journal of Allergy and Clinical Immunology: 667	- Conference abstract
Garcia-Marcos, L. and Brand, P. L. (2010) The utility of sputum eosinophils and exhaled nitric oxide for monitoring asthma control with special attention to childhood asthma. Allergologia et immunopathologia 38(1): 41-6	- More recent systematic review included that covers the same topic
Gibson, P. G. (2009) Using fractional exhaled nitric oxide to guide asthma therapy: design and methodological issues for ASthma TReatment ALgorithm studies. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 39(4): 478-90	- More recent systematic review included that covers the same topic
Gomersal, Tim, Harnan, Sue, Essat, Munira et al. (2016) A systematic review of fractional exhaled nitric oxide in the routine management of childhood asthma. Pediatric pulmonology 51(3): 316-28	- More recent systematic review included that covers the same topic
Gupta, Atul; Bhat, Gayathri; Pianosi, Paolo (2018) What is New in the Management of Childhood Asthma?. Indian journal of pediatrics 85(9): 773-781	- Review article but not a systematic review
Harnan, Sue E., Tappenden, Paul, Essat, Munira et al. (2015) Measurement of exhaled nitric oxide concentration in asthma: a systematic review and economic evaluation of NIOX MINO, NIOX VERO and NObreath. Health technology assessment (Winchester, England) 19(82): 1-330	- Study design not relevant to this review protocol *Comparison of FeNO measurement devices*
Hashimoto, S., Ten Brinke, A., Roldaan, A. C. et al. (2010) Monitoring exhaled nitric oxide (FENO) to tailor the lowest effective dose of oral corticosteroids in severe asthma (MONOSA-Study). American Journal of Respiratory and Critical Care Medicine 181(1meetingabstracts)	- Conference abstract
Hashimoto, Simone, Brinke, Anneke Ten, Roldaan, Albert C. et al. (2011) Internet-based tapering of oral corticosteroids in severe asthma: a pragmatic randomised controlled trial. Thorax 66(6): 514-20	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
	Intervention contained other forms of asthma monitoring not offered in the comparator arm e.g., ACQ, symptom monitoring
Hromis, S., Milutinov, S., Zvezdin, B. et al. (2012) Exhaled nitric oxide in assessing of asthma control in smoking patients-pilot study. Allergy 67: 461	- Full text paper not available
Jartti, Tuomas, Wendelin-Saarenhovi, Maria, Heinonen, Inka et al. (2012) Childhood asthma management guided by repeated FeNO measurements: a meta-analysis. Paediatric respiratory reviews 13(3): 178-83	- More recent systematic review included that covers the same topic
Khatri, Sumita B., Iaccarino, Jonathan M., Barochia, Amisha et al. (2021) Use of Fractional Exhaled Nitric Oxide to Guide the Treatment of Asthma: An Official American Thoracic Society Clinical Practice Guideline. American journal of respiratory and critical care medicine 204(10): e97-e109	- Systematic review used as source of primary studies
Khusial, R., Honkoop, P., Usmani, O. et al. (2019) Myaircoach: mHealth assisted self-management in patients with uncontrolled asthma, a randomized control trial. European Respiratory Journal 54(supplement63)	- Conference abstract
Khusial, Rishi J., Honkoop, Persijn J., Usmani, Omar et al. (2020) Effectiveness of myAirCoach: A mHealth Self-Management System in Asthma. The journal of allergy and clinical immunology. In practice 8(6): 1972-1979.e8	- Conference abstract
Klok, T. and Brand, P. L. P. (2017) Can exhaled nitric oxide fraction predict adherence to inhaled corticosteroids in atopic and nonatopic children with asthma?. Journal of Allergy and Clinical Immunology: In Practice 5(2): 521-522	- Study design not relevant to this review protocol *Longitudinal study, not an RCT*
Korevaar, Daniel A, Damen, Johanna A, Heus, Pauline et al. (2023) Effectiveness of FeNO-guided treatment in adult asthma patients: A systematic review and meta-analysis. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 53(8): 798-808	- Systematic review used as source of primary studies

Study	Code [Reason]
LaForce, Craig, Brooks, Elizabeth, Herje, Nancy et al. (2014) Impact of exhaled nitric oxide measurements on treatment decisions in an asthma specialty clinic. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 113(6): 619-23	- Study design not relevant to this review protocol *Cross-sectional, not an RCT*
Langendam, M, Pijnenburg, MW, de Jongste, JC et al. (2010) [Treatment of children with asthma based on exhaled nitrogen monoxide: added value of nitrogen monoxide measurements has not yet been demonstrated]. Nederlands tijdschrift voor geneeskunde 154: a1804	- Study not reported in English
Lee, Qun Ui (2015) Fractional exhaled nitric oxide-guided algorithm for children with asthma. Pediatric pulmonology 50(9): 932-3	- Study design not relevant to this review protocol *Editorial letter*
Lehtimaki, Lauri, Csonka, Peter, Makinen, Eeva et al. (2016) Predictive value of exhaled nitric oxide in the management of asthma: a systematic review. The European respiratory journal 48(3): 706-14	- More recent systematic review included that covers the same topic
Loewenthal, Lola and Menzies-Gow, Andrew (2022) FeNO in Asthma. Seminars in respiratory and critical care medicine	- Review article but not a systematic review
Lu, Min, Wu, Beirong, Che, Datian et al. (2015) FeNO and asthma treatment in children: a systematic review and meta-analysis. Medicine 94(4): e347	- More recent systematic review included that covers the same topic
Ludviksdottir, Dora, Diamant, Zuzana, Alving, Kjell et al. (2012) Clinical aspects of using exhaled NO in asthma diagnosis and management. The clinical respiratory journal 6(4): 193-207	- Review article but not a systematic review
Mahr, Todd A.; Malka, Jonathan; Spahn, Joseph D. (2013) Inflammometry in pediatric asthma: a review of fractional exhaled nitric oxide in clinical practice. Allergy and asthma proceedings 34(3): 210-9	- Review article but not a systematic review
Maniscalco, Mauro and Lundberg, Jon O. (2010) Hand-held nitric oxide sensor NIOX	- Review article but not a systematic review

Study	Code [Reason]
MINO R for the monitoring of respiratory disorders. Expert review of respiratory medicine 4(6): 715-21	
Moeller, Alexander, Carlsen, Kai-Hakon, Sly, Peter D. et al. (2015) Monitoring asthma in childhood: lung function, bronchial responsiveness and inflammation. European respiratory review : an official journal of the European Respiratory Society 24(136): 204-15	- Review article but not a systematic review
Murphy, V. E., Jensen, M., Robijn, A. et al. (2019) Influence of maternal body mass index and gestational weight gain, with asthma management on maternal and infant outcomes. European Respiratory Journal 54(supplement63)	- Conference abstract
Murphy, V. and Gibson, P. (2019) Stop, start or continue asthma medication: Use of a biomarker-based approach for adjusting asthma medication dose during pregnancy. Australian and New Zealand Journal of Obstetrics and Gynaecology 59(supplement1): 89-90	- Conference abstract
Murphy, V., Jensen, M., Holliday, E. et al. (2022) Asthma management in pregnancy and perinatal outcomes. Respirology 27(suppl1): 32-33	- Conference abstract
Murphy, Vanessa E.; Jensen, Megan E.; Gibson, Peter G. (2022) Exacerbations of asthma following step-up and step-down inhaled corticosteroid and long acting beta agonist therapy in the managing asthma in pregnancy study. The Journal of asthma : official journal of the Association for the Care of Asthma 59(2): 362-369	- Secondary publication of an included study that does not provide any additional relevant information *Secondary publication of Powell 2011*
Murphy, Vanessa E., Porsbjerg, Celeste M., Robijn, Annelies L. et al. (2020) Biomarker-guided management reduces exacerbations in non-eosinophilic asthma in pregnancy: A secondary analysis of a randomized controlled trial. Respirology (Carlton, Vic.) 25(7): 719-725	- Secondary publication of an included study that does not provide any additional relevant information *Secondary publication of Powell (2011)*
Oppenheimer, John and Sorkness, Christine A. (2009) Does exhaled nitric oxide measurement have a role in asthma care?. Annals of allergy, asthma & immunology : official publication of the	- Review article but not a systematic review

Study	Code [Reason]
American College of Allergy, Asthma, & Immunology 102(3): 253-5	
Paro-Heitor, Maria Luisa Z., Bussamra, Maria Helena C. F., Saraiva-Romanholo, Beatriz M. et al. (2008) Exhaled nitric oxide for monitoring childhood asthma inflammation compared to sputum analysis, serum interleukins and pulmonary function. Pediatric pulmonology 43(2): 134-41	- Study design not relevant to this review protocol *Cohort study, not an RCT*
Perez de Llano, Luis Alejandro (2012) Nitric oxide (NO) in managing asthma. Archivos de bronconeumologia 48(2): 35-6	- Review article but not a systematic review
Petsky, H. (2022) Randomised controlled trials utilising FENO to manage asthma: is it time to acknowledge that "one size does not fit all"?. European Respiratory Journal 60(5): 2201639	- Study design not relevant to this review protocol
Petsky, H. L. (2014) Dual-centre randomised trial on tailored asthma therapy based on exhaled nitric oxide (FeNO) vs routine clinical care. Pediatric Pulmonology 49(suppl37): 57	- Conference abstract
Petsky, H. L., Cates, C. J., Lasserson, T. J. et al. (2012) A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). Thorax 67(3): 199-208	- More recent systematic review included that covers the same topic *2015 Cochrane review on same topic*
Petsky, H., Kew, K., Turner, C. et al. (2016) Exhaled nitric oxide (FENO) levels to guide treatment for adults with asthma: A cochrane systematic review. Respirology 21(suppl2): 46	- Conference abstract
Petsky, H., Kew, K., Turner, C. et al. (2016) Exhaled nitric oxide (FeNO) levels to guide treatment for children with asthma: A Cochrane systematic review. European Respiratory Journal	- Systematic review used as source of primary studies
Petsky, H., Li, A. M., Kynaston, J. A. et al. (2010) Dual-center randomised trial on tailored asthma therapy based on exhaled nitric oxide (FENO) versus routine clinical care. American Journal of Respiratory and Critical Care Medicine 181(1meetingabstracts)	- Conference abstract

Study	Code [Reason]
Petsky, H., Li, A. M., Kynaston, J. A. et al. (2010) Dual-centre randomised trial on tailored asthma therapy based on exhaled nitric oxide (FeNO). Paediatric Respiratory Reviews 11(suppl1): S80-S81	- Conference abstract
Petsky, Helen L., Cates, Chris J., Kew, Kayleigh M. et al. (2018) Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils): a systematic review and meta-analysis. Thorax 73(12): 1110-1119	- More recent systematic review included that covers the same topic
Petsky, Helen L., Cates, Christopher J., Li, Albert et al. (2009) Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. The Cochrane database of systematic reviews: cd006340	- More recent systematic review included that covers the same topic *2015 Cochrane review on same topic*
Petsky, Hl; Kew, Km; Chang, Ab (2016) Exhaled nitric oxide levels to guide treatment for children with asthma. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies *Unable to use full review in this guideline due to differences between protocol outcomes*
Petsky, Hl, Kew, Km, Turner, C et al. (2016) Exhaled nitric oxide levels to guide treatment for adults with asthma. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies *Unable to use full review in this guideline due to differences between protocol outcomes*
Spahn, A.J.D., Malka, J., Mahr, T.A. et al. (2013) Meta analysis of asthma exacerbation rates in pediatric studies during asthma managed using fractional exhaled nitric oxide versus standard clinical parameters. Journal of Allergy and Clinical Immunology: ab194	- Conference abstract
Syk, J., Malinovschi, A., Johansson, G. et al. (2012) Lower incidence of asthma exacerbations with FENO-guided anti-inflammatory treatment: A randomised controlled trial. European Respiratory Journal 40(suppl56)	- Conference abstract
Turner, S., Cotton, S. C., Emele, C. D. et al. (2019) Reducing Asthma Attacks in Children using Exhaled Nitric Oxide as a biomarker to inform treatment strategy: a randomised trial (RAACENO). Trials 20(1): 573	- Study protocol

Study	Code [Reason]
Ulrik, Charlotte Suppli; Lange, Peter; Hilberg, Ole (2021) Fractional exhaled nitric oxide as a determinant for the clinical course of asthma: a systematic review. European clinical respiratory journal 8(1): 1891725	- Study design not relevant to this review protocol *Investigating FeNO as a prognostic marker of future asthma development*
Verini, Marcello, Consilvio, Nicola Pietro, Di Pillo, Sabrina et al. (2010) FeNO as a Marker of Airways Inflammation: The Possible Implications in Childhood Asthma Management. Journal of allergy 2010	- Data not reported in an extractable format or a format that can be analysed *No outcomes relevant to this review protocol*
Voorend-van Bergen, Sandra, Vaessen-Verberne, Anja A., Landstra, Anneke M. et al. (2015) Fractional Exhaled Nitric Oxide Monitoring Does Not Improve Asthma Management in Children with Concordant and Discordant Asthma Phenotypes. American journal of respiratory and critical care medicine 192(8): 1016-8	- Conference abstract
Wang, Kay, Verbakel, Jan Y., Oke, Jason et al. (2020) Using fractional exhaled nitric oxide to guide step-down treatment decisions in patients with asthma: a systematic review and individual patient data meta-analysis. The European respiratory journal 55(5)	- More recent systematic review included that covers the same topic
Wang, X. R., Wu, L., Zhang, Z. et al. (2019) Application of fractional exhaled nitric oxide in stepped treatment of chronic persistent asthma. Academic journal of second military medical university 40(6): 683-687	- Study not reported in English
Wang, Xia; Tan, Xiangsheng; Li, Qubei (2020) Effectiveness of fractional exhaled nitric oxide for asthma management in children: A systematic review and meta-analysis. Pediatric pulmonology 55(8): 1936-1945	- More recent systematic review included that covers the same topic
Wang, Z, Pianosi, P, Keogh, K et al. (2017) The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management. AHRQ Comparative Effectiveness Reviews	- Systematic review used as source of primary studies
Whalen, O., Campbell, L., Lane, A. et al. (2023) FENO management of asthma in pregnancy and infant developmental outcomes. Respirology 28(supplement2): 121	- Conference abstract

Study	Code [Reason]
Xepapadaki, Paraskevi, Adachi, Yuichi, Pozo Beltran, Cesar Fireth et al. (2023) Utility of biomarkers in the diagnosis and monitoring of asthmatic children. The World Allergy Organization journal 16(1): 100727	- Review article but not a systematic review

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 13: Studies excluded from the health economic review

Reference	Reason for exclusion
Berg 2008(Berg et al., 2008)	Excluded as rated not applicable. Sources used to estimate prices are older than 15 years.
Buendia 2021(Buendia et al., 2021)	Excluded as rated not applicable. The study is a budget impact analysis with the full cost-utility analysis available elsewhere(Buendia et al., 2021)
Buendia 2021(Buendia et al., 2021)	Excluded as rated not applicable. The analysis had a societal perspective and the settings of the analysis are of unclear generalisability to the UK NHS
Buendia 2022(Buendia et al., 2022)	Excluded as rated not applicable. The analysis had a societal perspective and the settings of the analysis are of unclear generalisability to the UK NHS.
Beerthuizen 2016(Beerthuizen et al., 2016)	Excluded as rated not applicable. Standard care includes 4-monthly ACT questionnaire which is not usual practice in the UK.
Darba 2021(Darba et al., 2021)	Excluded as rated not applicable. This is a budget analysis which does not report any health outcomes.
Honkoop 2015 (Honkoop et al., 2015)	Excluded due to a combination of applicability and methodological limitations. The analysis had a societal perspective and there are discrepancies in the reporting of the results.
Sabatelli 2017(Sabatelli et al., 2017)	The study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable recent UK analysis with fewer methodological limitations was available (Harnan et al., 2015) this study was selectively excluded.
Price 2009(Price et al., 2009)	This study was assessed as not applicable. Sources used to estimate prices are older than 15 years.