Study	Sample size	Participant Age	Description of intervention and control arms	Primary Outcome and definition of exacerbation	Duration	Funding and support
Calhoun 2012[35]	342 randomised; FeNO group N=115. Control group N=114.	FeNO group: mean age 35(SD 11), 33 males. Control group: mean age 34 (SD12), 42 males.	Control group: Treatment decisions based on National Heart, Lung and Blood Institute guidelines. FeNO group: <22ppb treatment stepped down 22 to 35 maintain treatment >35 increase treatment	Primary outcomes: Time to first treatment failure, a clinically important worsening of asthma Exacerbation: Increased asthma symptoms resulting in use of oral corticosteroids, increased ICS, or additional asthma medications.	Participants were seen at week 2, 4, 6 and then every 6 weeks for 9 months. Follow-up duration: 9 months	National Institutes of Health and by National Institutes of Health Grants awarded by the National Heart, Lung, and Blood Institute Teva Pharmaceuticals provided the study drug and matching placebo.
Cao 2007[22]	41 randomised; EOS strategy N=20. Control group N=21.	EOS strategy: age 41 (SD2), 11 males. Control group: age 43 (SD4), 11 males.	Control strategy: “Standard clinical guidelines” EOS strategy: decrease ICS if <1% eosinophils, keep ICS the same if 1-3% eosinophils, increase ICS if eosinophils >3%.	Primary outcome: Total number of acute exacerbations. Exacerbation: Unknown	Participants had a 2 week run-in, then visits at months 2, 4 and 6. Follow-up duration: 6 months	Capital Medical Development Foundation (No. 2002-3004)

Chlumsky 2006[23]	55 randomised; EOS strategy N=30. Standard strategy N=25.	EOS strategy: mean age 42(SD 19) 13 males Standard strategy: mean age 48 (SD 16)	Standard strategy arm: GINA guidelines EOS strategy: decrease ICS if ≤3%, keep same if 4-8%, increase ICS if ≥8%.	Primary outcome: Rate of asthma exacerbations Exacerbation: a doubling of the frequency of symptoms or number of puffs of rescue salbutamol or a reduction in morning PEF by 30% or more on at least two consecutive days or two of the aforementioned or all three.	Participants were assessed every 3 months for 18 months	Internal Grant Agency of the Ministry of Health of the Czech Republic (Grant No. 5866/3)
deJongste 2009[30]	151 children randomised; FeNO group N=75. Symptom group N=72.	FeNO group: mean age 11.6 (SD 2.6), 46 males. Symptom group: mean age 11.8 (SD 4.3), 54 males.	All participants scored asthma symptoms in an electronic diary over 30 weeks. FeNO group received a portable nitric oxide analyser. Aim to keep FeNo <20ppb Symptom group based on symptom score: Below range (< 10) = step down/discontinue, range 10 to 60 = no change and range > 60 = step up	Primary outcome: Proportion of symptom free days over the last 12 study weeks. Exacerbation: emergency visit, hospitalization or prednisolone course	Children were seen at 3, 12, 21 and 30 weeks. Groups had their medications changed every 3 weeks based on electronic diary and/or FeNO levels. Follow-up duration = 30 weeks.	The study was supported by Aerocrine AB, Sweden.
Fleming 2012[26]	55 children randomised;	Inflammatory group: median age 13.4 yrs	Symptom group: Based on number of major exacerbations in the	Primary outcome: Rate of major exacerbations and asthma control as assessed by	Children were seen 3 monthly for 12 months.	British Lung Foundation

	Inflammatory group N=27. Symptom group N=28.	(range 11-15.8), 16 males. Symptom group: median age 12.6yrs (range 10.2-14.7), 13 males.	preceding 3 months and SABA use in preceding 2 weeks. Inflammatory group: Treatment aimed to keep sputum eosinophil counts <2.5%.	symptom-free days and SABA use. Minor exacerbation: Use of bronchodilators >5 times/wk (excl. routine or pre-exercise). Major exacerbation: Deterioration requiring high dose oral corticosteroids (≥20 mg/day) for at least 2 days.		
Fritsch 2006[19]	52 patients entered the study; FeNO group N=22. Control group N=25.	FeNO group: mean age 11.3 (SD 3.4), 14 males. Control group: mean age 12.1 (SD 2.8), 14 males.	FeNO group: therapy was based on symptoms, beta-agonists use, lung function and FeNO. Control group: therapy based on symptoms, beta-agonists and lung function only.	Primary outcome: FEV_1 Exacerbation defined by 4 parameters: oral steroid courses, and/or off-scheduled visit because of asthma symptoms over the past 4 weeks, and/or increase of asthma symptoms from a symptom score 0 or 1 to a symptom score 2 and/or decline of FEV_1 (L) more than 10% compared to the previous visit.	Visits were at 6, 12, 18 and 24 weeks after 4 week run-in. Follow-up duration = 24 months.	Aerocrine (analyser manufacturer) assisted with data analysis.
Green 2002[24]	74 randomised; Sputum management group N=37. BTS	Sputum management group: median age 50, range 19-73, 19 males.	Sputum management group: anti-inflammatory treatment was based on maintenance of sputum eosinophil count below 3% with a minimum	1.Number of severe asthma exacerbations 2.Control of eosinophilic airway inflammation measured by the induced sputum eosinophil count	Study duration was for 12 months with visits at month 1, 2, 3, 4, 6, 8, 10, 12.	Trent NHS Regional Research Scheme.

	management group N=37.	BTS management group: median age 47, range 20-75, 21 males.	dose of anti-inflammatory treatment. BTS management group: treatment decisions were based on traditional assessments of symptoms, peak expiratory flow and use of beta-2-agonists.	3.Exhaled nitric oxide concentrations 4.Symptom scores (0 to 3 for daytime and nighttime symptoms) 5.Total asthma quality of life scores 6.Peak flow amplitude as a proportion of the mean 7.FEV1 8.Changes from baseline of methacholine PC20 9.Drug use 10.Admissions for asthma Severe exacerbations defined as a decrease in morning peak expiratory flow to more than 30% below baseline value on = 2 consecutive days, or deterioration in symptoms needing rescue course of oral corticosteroid.	Follow-up duration = 12 months.	
Hashimoto 2011[36]	95 adults were randomised; Internet strategy N=51. Conventional strategy N=38.	Internet strategy: mean age 48.5 yrs (SD12.5), 23 males. Conventional strategy: mean age 52.4 yrs	Internet strategy: Had steroid dose adjusted based on the 3 components: electronic diary, in-built algorithm (which includes FeNO levels), and monitoring support, e.g. coaching by study nurse and	Primary outcomes: Cumulative sparing OCS (actual cumulative dose minus the expected dose), ACT, and AQLQ. Exacerbations: Decrease in morning FEV_1 >10% compared to mean FEV_1 from week before, increase in	Monthly visits with follow-up duration of 6 months. Participants daily registered their dose of OCS, lung	Netherlands Organisation for Health Research and Development (ZonMw). Equipment for the analysis of nitric

		(SD11.7), 18 males.	monitoring data, which was entered. Conventional strategy: GINA guidelines for the treatment of severe asthma.	symptoms requiring increased prednisolone >10mg/day, or course of antibiotics, regardless of hospitalisations.	function and FEV_1.	oxide was provided by Aerocrine AB.
Honkoop 2014[37]	GP practices cluster randomisation including 647 adults in 3 arms; FeNO group N=189. Controlled asthma group N=203.	FeNO group: mean age 39 yrs (SD 9), 62 males. Control group: mean age 40 yrs (SD 10), 69 males.	FeNO strategy: Treatment targeted to keep FeNO <50ppb. Symptom strategy: ACT utilized including lung function	Primary outcomes: Societal costs per QALY gained Severe exacerbation: Hospitalisation, emergency department visit because of asthma, or use of OCS for >3 days.	Follow-up duration of 12 months with 3 monthly visits.	Netherlands Organisation for Health Research and Development and by the Netherlands Asthma Foundation. Aerocrine (Solna, Sweden) provided 20 of a total of 40 fraction of exhaled nitric oxide meters for free.
Jayaram 2006[31]	117 randomised; Sputum strategy group N=50. Clinical strategy group N=52.	Sputum strategy: group mean age 46 (SD 13.8), 15 males Clinical strategy: group mean age 43.5 (SD 13.9), 15 males	Sputum strategy: dose of inhaled steroid was guided solely by induced sputum eosinophils to keep <2%. Spirometry was used to identify clinical control, exacerbations and other treatment. Clinical strategy: guided by symptoms as per Canadian Asthma Consensus Group Guidelines.	1.Relative risk reduction for the first exacerbation 2.The length of time without exacerbations 3.Type and severity of exacerbations 4. The usefulness of monitoring sputum cell counts in relation to the overall serverity of asthma. Defined by the minimum dose of inhaled steroid to maintain control	2 year study duration with monthly visits in Phase 1 until control maintained with minimum treatment (variable duration) or at exacerbations. Phase 2: 3 monthly visits or at exacerbations.	Canadian Institutes of Health Research Clinical Trials Grant.

				5. The cumulative dose of inhaled steroid needed in Phase 2 adjusted for its duration. Exacerbation: Loss of symptomatic control requiring increased use of short acting beta2-agonists by = 4 extra puffs per day for a minimum of 48 hours, or by nocturnal symptoms, or early morning wakening due to respiratory symptoms two or more times in one week. Severe exacerbations were defined as requiring rescue courses of oral prednisone as defined by the investigator.		
Malerba 2015[25]	28 adults randomised; Sputum strategy N=14. Clinical strategy N=14.	Sputum strategy: mean age 45.2 yrs (SD31.2), 5 males. Clinical strategy: mean age 46.7 yrs (SD30.1), 6 males.	Sputum strategy: Treatment based on sputum eosinophil (%) and FeNO (ppb). Decrease ICS <2% & ≤10pbb Keep same 2-3% & 11-20ppb Increase ICS >3% & ≥20ppb Symptom strategy: Symptom scores, use of SABA and night time symptoms.	Primary outcome: Asthma exacerbations combined with changes in symptom score at end of study. Moderate exacerbations: Requiring an unscheduled visit with a course of OCS. Severe exacerbation: Course of OCS as determined by study investigator.	Follow-up duration was 24 months, with 6 monthly visits.	University of Brescia

Peirsman 2014[34]	99 children randomised; FeNO group N=49. Control group N=50.	FeNO group: mean age 10.6 yrs (SD 2.2), 33 boys. Control group: mean age 10.7 yrs (SD 2.1), 33 boys.	FeNO group: Treatment aimed to keep FeNO below 20ppb. Control group: Treatment adjusted according to GINA guidelines (i.e. reporting of symptoms, use of SABA and FEV_1)	Primary outcome: Symptom free days using the first 4 questions from childhood ACT. Exacerbation: As per GINA guidelines	Follow-up duration was 12 months with 3 monthly appointments.	Study funded partially by Merck & Co and FeNO analysers supplied by Aerocrine.
Petsky 2015[28]	63 randomised; FeNO group N=31. Symptom group N=32.	FeNO group: median age 10.2 yrs (IQR 6.6 to 12.7), 18 boys. Symptom group: median age 10.1 yrs (IQR 6.3 to 12.4), 13 boys.	FeNO group: Treatment adjusted based on FeNO level and atopy status. Elevated FeNO defined as: ≥ 10ppb with no positive SPT ≥ 12ppb with 1 positive SPT ≥ 20ppb with ≥ 2 positive SPT	Primary outcome: Severe exacerbations requiring course of OCS with or without hospitalization. Exacerbation: Respiratory events requiring OCS.	Study duration 12 months with visits month 1, 2, 3, 4, 6, 8, 10 and 12.	Asthma Foundation of Queensland
Pijnenburg 2005[18]	89 children randomised; FeNO group N=39 Symptom group N=46	FeNO group: median age 11.9 (SD 2.9), 25 males. Symptom group: mean age 12.6 (SD 2.8), 30 males.	FeNO group: FeNO guided ICS dosing according to predetermined algorithm. Symptom group: Symptom scores influenced ICS dosing.	Primary outcome: cumulative steroid dose (sum of mean daily steroid doses of visits 1 to 5) Exacerbation: Deterioration in symptoms requiring oral prednisone course.	Study duration was 12 months with 3 monthly visits.	Kroger Foundation/Sophia Children's Hospital Foundation

Pike 2013[32]	90 children randomised; FeNO group N=44. Standard management group N=46.	FeNO group: mean age 10.51 yrs (SD 2.62), 21 boys. Standard management group: mean age 11.42 yrs (SD 2.69), 30 boys.	FeNO group: FeNO measurements and symptom control. Standard management group: symptom control as per blinded clinician (reliever use, FEV_1).	Change in ICS dose, exacerbation frequency, FeNO measurements and lung function.	Study duration 12 months with study visits every 2 months.	Sparks
Powell 2011[27]	220 pregnant women randomised; FeNO group N=111. Control group N=109.	FeNO group: mean age 28 (range 27 to 29). Control group: mean age 29 (range 28 to 30).	FeNO group: Sequential process, first FeNO concentrations used to adjust ICS dose, and second ACT score used to adjust the LABA dose. Clinical group: Based on asthma control using Juniper ACT with cutoff points defined as: well-controlled asthma (ACT < 0.75), partially controlled asthma (0.75 to 1.50), and uncontrolled asthma (> 1.5)	Primary outcome: Total number of asthma exacerbations (i.e. moderate and severe). Secondary outcomes: QoL, asthma treatment, and fetal outcomes	Study duration was average of 4 months. Women were seen monthly until they delivered.	National Health and Medical Research Council of Australia
Shaw 2007[38]	118 adults were randomised;	FeNO group: median age 50	FeNO group: FeNO >26ppb, ICS was increased. If FeNO <16ppb or <26ppb	Primary outcome: Number of exacerbations	Study duration was 12 months with participants	Asthma UK

	FeNO group N=58 Control group N=60.	(range 20-75), 27 males. Control group: median age 52 (range 24-81), 27 males.	on 2 separate occasions, treatment was decreased. In Control Group treatment was doubled if Juniper Asthma Control Score (JACS) >1.57 and treatment halved if JACS <1.57 for 2 consecutive months.	Exacerbation: An increase in symptoms requiring oral steroids or antibiotics	being send at baseline, 2 weeks, months 1, 2, 3, 4, 6, 8, 10 and 12.	
Smith 2005[21]	97 patients randomised from 110 patients recruited.	N=46 in FeNO group achieved optimal dose in phase 1 and N=28 achieved optimal dose in control group. Mean age of randomised patients was 44.8 (range 12-73), 41 males.	Phase 1: Run-in period was for 6 weeks, after 2 weeks fluticasone 750ug/day was commenced. Visits were every 4 weeks until optimal dose was achieved. FeNO group: adjustment of dose of ICS was based soley to keep FeNO <15ppb at 250mL/sec. Control group: dose adjustment based on asthma symptoms, night-time waking, bronchodilator use, variation in PEFR and FEV1. Phase 2: visits every 2 months with upward adjustments made as per phase 1 but no downward adjustments would be made from optimal dose.	Primary outcome: Frequency of exacerbation Minor exacerbation was defined as a daily asthma score of 2 or more on 2 or more consecutive days, whereas a major exacerbation was a daily asthma score of 3 or more on 2 or more consecutive days.	2 phase study, with phase 1 varying in duration (3-12 months) depending when optimal dose was deemed to have been achieved. During phase 2 (12 months) optimal dose from phase 1 was continued and therapy stepped up if asthma control was lost.	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.

Syk 2013[39]	187 adults randomised; FeNO group N=87. Control group N=78.	FeNO group: mean age 40.9 yrs (SD 11.8), 48 males. Control group: mean age 41.1 yrs (SD 12.9), 46 males.	FeNO group: Keep FeNO level <24ppb for women, and <26ppb for men. Control group: Treatment adjusted based on patient reported symptoms, SABA use, physical examination and spirometry results.	Primary outcome: change in mAQLQ score during the study. Exacerbation: Increasing asthma symptoms requiring course of OCS.	Study duration was 12 months with visits at months 1, 2, 4, 8 & 12.	Stockholm county council (PickUP), Centre for Allergy Research, Karolinska Institute, and the Research Foundation of the Swedish Asthma and Allergy Association. Aerocrine AB (NIOX MINO instruments), Phadia AB (ImmunoCAP Rapid), Meda AB (Buventol Easyhaler), and MSD Sweden (small grant).
Szefler 2008[29]	546 participants randomised from 780 patients screened. FeNO group N=276. Control group N=270	FeNO group: mean age 14.4, 146 males. Control group: mean age 14.4, 142 males.	FeNO group: Standard treatment modified on the basis of measurements of FeNO Control group: Standard treatment based on the guidelines of National Asthma Education and Prevention Program (NAEPP).	Primary outcome: Number of days with asthma symptoms. Exacerbation: Combination of admissions to hospital, unscheduled visits and oral prednisone.	The study duration was 46 weeks with visits every 6-8 weeks.	US National Institute of Allergy and Infectious Diseases, US National Institutes of Health.

Verini 2010[20]	64 children randomised; FeNO group N=32. GINA group N=32.	FeNO group: mean age 10.7 yrs (SD 2.4), 18 boys. GINA group: mean age 11.3 yrs (SD 2.1), 18 boys.	FeNO group at 6 month visit only: step treatment up if >12ppb. Control group: As per GINA guidelines.	Primary outcome: No clear definition given of outcomes, however asthma severity score, asthma exacerbation frequency and asthma therapy score were the main items reported in results section. Exacerbation: According to ATS/ERS criteria and requiring SABA.	Study duration was 12 months with 6 monthly visits.	No information provided on funding
Voorend-van Bergen 2015[33]	272 children randomised into 3 arms; FeNO group N=92. Standard care group N=89.	FeNO group: mean age 10.3 yrs (SD 2.9), 62 boys. Standard care group: mean age 10.2 yrs (SD 3.2), 61 boys.	FeNO group: Treatment adjusted according to FeNO levels and ACT results. If ACT ≥ 20 and: FeNO < 25 = step down FeNO ≥ 25 to < 50 = no change FeNO ≥ 50 = step up If ACT < 20 and: FeNO ≥ 25 = step up FeNO < 25 = no change Control group: Treatment adjusted based on ACT results < 20 = step up ≥ 20 = no change or step down	Primary outcome: Changes from baseline of proportion of symptom-free days Exacerbation: No definition provided but OCS courses and hospitalization data included in the exacerbation results.	Children were run-in for 4 weeks, then 4 monthly visits for a total of 12 months.	Lung Foundation Netherlands, the Netherlands Organisation for Health Research (ZonMW) and Fund Nuts Ohra.